

SECOND EDITION

INFECTIOUS DISEASES

A GEOGRAPHIC GUIDE



Edited by
ESKILD PETERSEN,
LIN H. CHEN and
PATRICIA SCHLAGENHAUF-LAWLOR

#ZikaGlobal #EbolaAfrica #ChagasLatinAmerica #TBEEurope #JEAsia

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Infectious Diseases

Infectious Diseases: A Geographic Guide

Second Edition

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WILEY Blackwell

This edition first published 2011. © 2017 John Wiley & Sons Ltd
First edition published 2011 by John Wiley & Sons Ltd

Wiley-Blackwell is an imprint of John Wiley & Sons, formed by the merger of Wiley's global Scientific, Technical and Medical business with Blackwell Publishing.

Registered Office

John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Offices

9600 Garsington Road, Oxford, OX4 2DQ, UK

The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

111 River Street, Hoboken, NJ 07030-5774, USA

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Library of Congress Cataloging-in-Publication Data

Names: Petersen, Eskild, editor. | Chen, Lin H., editor. | Schlagenhauf-Lawlor, Patricia, editor.

Title: Infectious diseases : a geographic guide / [edited by] Eskild Petersen, Lin H. Chen, Patricia Schlagenhauf-Lawlor.

Other titles: Infectious diseases (Petersen)

Description: Second edition. | Chichester, West Sussex, UK ; Hoboken, NJ : John Wiley & Sons Inc., 2017. | Includes bibliographical references and index.

Identifiers: LCCN 2016058312 (print) | LCCN 2016059476 (ebook) | ISBN 9781119085720 (pbk.) | ISBN 9781119085737 (ePDF) | ISBN 9781119085751 (Wiley online library) | ISBN 9781119085744 (ePub) | ISBN 9781119085737 (Adobe PDF)

Subjects: | MESH: Communicable Diseases—epidemiology | Disease Outbreaks | Epidemiologic Methods | Topography, Medical—methods

Classification: LCC RA643 (print) | LCC RA643 (ebook) | NLM WC 100 | DDC 616.9—dc23

LC record available at <https://lccn.loc.gov/2016058312>

A catalogue record for this book is available from the British Library.

This book is published in the following electronic formats: ePDF 9781119085737; Wiley Online Library 9781119085751; ePub 9781119085744

Cover Design: Wiley

Cover Credit: alexaldo/Gettyimages (map); Joao Paulo Burini/Gettyimages (mosquito)

Set in 8/11pt StoneSerif by SPi Global, Pondicherry, India

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Foreword to the first edition

Where have you been? In the world of clinical medicine, this is a critical question that opens a treasure chest or sometimes a Pandora's box of epidemiological information often leading the infectious disease specialist to a correct diagnosis or intervention that otherwise might not be considered. When this key question is forgotten, a poor or preventable outcome may follow. But what happens when the experienced physician or travel medicine specialist, who unfailingly includes this question in his or her initial assessment, hears a patient respond with a lengthy discussion of a complex itinerary, multiple exposures, or unusual symptoms? Sometimes the destination is not familiar, the exposures trigger a distant memory of "something important" but one cannot recall exactly the connection, or a specific finding can generate a limited differential diagnosis. The physician or travel medicine specialist then attempts to locate the missing information in published papers, books, and online references.

Where are you going? In the pretravel setting, this book is an indispensable reference for travel medicine practitioners advising individual long-term travelers or making recommendations for expatriates who will stay for prolonged periods in a particular geographic area. Long-term travelers have been shown to have a higher risk of acquiring travel-associated illness because of their prolonged exposure, suboptimal adherence to preventive measures, and often a lack of knowledge on risks at the destination. The comprehensive regional disease profile presented in this volume will allow for tailored advice for this important group of travelers.

This important new book, *Infectious Diseases: A Geographic Guide* by Eskild Petersen, Lin H. Chen, and Patricia Schlagenhauf admirably fills the need for a single reference structured to assist the travel medicine practitioner to answer these questions.

Infectious Diseases: A Geographic Guide is organized by geographic regions of the world; for example, South Asia, Central Europe, South America, etc. Each chapter pertaining to a geographic region is then organized into an initial section on important regional infections, a series of very useful and easily scanned tables, a section on antibiotic resistance, a short section on vaccine-preventable diseases in the region, and finally a section on background data from the region. The tables are organized by presenting clinical syndromes, the way we actually encounter patients, subdivided where appropriate into those that usually occur within four weeks of exposure and those that occur greater than four weeks after exposure. Each table then divides infectious pathogens into those that are frequently encountered, uncommonly encountered, and rarely encountered. The sections on antibiotic resistance are unique and quite useful. This kind of antibiotic resistance information is usually not presented by geographic region but rather by pathogen with a secondary linkage to geographic regions. Having this regional perspective is novel and fits nicely with the evaluation of the ill returned traveler. There are several other very interesting and useful chapters in the introductory and closing sections of the book with inviting titles such as "An historical overview of global infectious diseases and geopolitics," "Detection of infectious diseases using unofficial sources," "Microbes on the move: prevention, curtailment, outbreak", "diagnostic tests and procedures", "the immunocompromised patient", "migration and the geography of disease," and "Climate change and the geographical distribution of infectious diseases."

The editors of this new text are leaders in the field of international travel medicine and have attracted a brilliant and luminous collection of chapter contributors. The regional chapters are written by individuals living in the region or expatriates with long-standing affiliations with the area. A strength of this book is the editorial oversight and vision of the editors who skillfully bring together a very diverse, international team to yield a cohesive, multiauthored, yet well-written textbook.

The global community of the twenty-first century is connected by ever growing bonds of communication, economic growth, shared aspirations, and increasingly, a globalized enterprise of international treaties, agreements, covenants, and structures. Global health is now part of the daily

lexicon of universities, governments, and multinational companies. The basis for this explosive growth over the last half century lies in the movement of people from one place to another. The motivation for movement is varied, but the most important questions that a travel medicine practitioner can ask are: “*Where are you going?*” in the pretravel setting or “*Where have you been?*” when seeing the ill returned traveler. *Infectious Diseases: A Geographic Guide* by Eskild Petersen, Lin H. Chen, and Patricia Schlagenhauf will be the first resource most of us reach for when those questions are fielded.

Alan J. Magill MD FACP FIDSA (deceased)
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Foreword to the second edition

The ancient Romans produced some of the most relevant and important questions pertaining to the field of geographic medicine. For those giving pretravel advice, “*Quo vadis?*” (Where are you going?) is the critical question that enables travel medicine advisors to complete an individual risk assessment to ensure the safety of international travelers. On the other hand, “*Ubi eras?*” (Where have you been?) is the crucial question for clinicians evaluating the ill returned traveler in order to develop an appropriate differential diagnosis and investigation strategy. Of course, my favorite Latin phrase could apply in almost any situation: “*Semper ubi sububi*”... always wear underwear!

Never before in human history has knowledge of infectious disease in a global context, the field of geographic medicine, been so important from personal, public health and clinical perspectives. In 2014, more than a billion tourists crossed the globe, an estimated 200 million individuals traveled internationally for business, and in 2013, 82 million migrants arrived in the North from developing countries. It now takes less than 36 hours to cross the globe, well within the incubation periods of many infectious diseases. Thus, global travel provides an excellent opportunity for the acquisition and spread of infectious diseases. In the past two decades, we have seen SARS spread from South-east Asia to North America, chikungunya virus from Africa through Asia to the Caribbean and Latin America, MERS co-virus throughout the Arabian peninsula, and, more recently, Zika virus from the South Pacific to Brazil and beyond in the Western hemisphere. Each of these infections has played havoc with the health of local populations and visitors.

So, what is a healthcare provider to do when faced with an ill traveler returned from some unfamiliar remote destination? How to counsel a volunteer planning to provide healthcare or education in some rural area of a developing country? Is there a single resource that will provide information on the risks of infectious diseases globally by geographic region that also includes an approach to clinical diagnosis by incubation period and presenting symptoms? Yes, in the following chapters of this book.

Infectious Diseases: A Geographic Guide is probably the only print publication that provides both the clinical and epidemiological approach to infectious diseases on a global basis. A passage from the Foreword of the first edition bears repeating: “The editors of this text are leaders in the field of international travel medicine and have attracted a brilliant and luminous collection of chapter contributors. The strength of this book is the editorial oversight and vision of the editors who skillfully bring together a very diverse, international team to yield a cohesive, multi-authored, yet well-written textbook.” I couldn’t have said it better than the author of this quote, the late Dr Alan McGill, one of the most accomplished and beloved tropical disease and travel medicine experts of this generation.

This book is divided into chapters by region of the world, written by credible and experienced authors who have worked in or have intimate knowledge of a particular geographic area. The chapters are organized into an initial section on important regional infections, a series of tables organized by presenting clinical syndromes, sections on antibiotic resistance and vaccine-preventable diseases, and finally a section on background data from the region. From the initial regional overview of infectious diseases, the travel medicine practitioner can readily obtain a perspective on some of the major infectious disease risks facing the traveler-to-be. The second and major portion of each chapter is designed for the clinician facing the ill returned traveler or migrant. Tables, organized by presenting clinical syndromes, are subdivided into those that usually occur within four weeks or greater than four weeks after exposure. Each table then divides infectious pathogens into those that are frequently encountered, uncommonly encountered, and rarely encountered. What more could a healthcare provider ask than being able to consult clinically relevant tables setting out key infections that might be responsible for a patient’s symptoms? It almost makes geographic medicine easy when the work of providing a differential diagnosis is laid out so clearly.

In addition to chapters by geographic region, the editors have included a number of excellent and eclectic chapters that provide the reader with a perspective on the epidemiology of travel-related infections such as infections by air and sea, climate change, and migration, as well as clinically oriented chapters pertaining to diagnostic algorithms, the immune-compromised patient and emerging infections. For the public health expert, very interesting chapters are included on surveillance systems, novel techniques for tracking infections, and outbreak curtailment. Essentially, *Infectious Diseases: A Geographic Guide* has something for everyone!

This book belongs on the shelf of every practitioner who provides pretravel health advice, public health officials responsible for outbreak control, and especially for clinicians caring for ill returned travelers and newly arrived migrants. I will have one on my shelf even if I don't receive a complimentary copy!

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Preface

The microbe is nothing; the terrain everything.

(Louis Pasteur)

We beg to differ with Louis Pasteur regarding this statement. Both the microbe *and* the terrain are important and this book is concerned with both. It is primarily concerned with global disease risk. The increasing mobility in populations has challenged the traditionally distinct specialties of tropical medicine, infectious diseases, public health, and travel medicine to address advising travelers visiting specific destinations and evaluating returning patients with distinct geographical travel histories.

For the clinician, this book is intended as a guide to generate differential diagnoses in consideration of the geographical history and in concert with presenting symptoms and duration of illness. Once a diagnosis has been made, classic textbooks on infectious diseases should be consulted for guidance on specific management and therapy.

In the pretravel setting, the book provides information on risks of different infections in the destination region and will be particularly useful in advising and assessing travelers visiting environments off the beaten path and for travelers visiting friends and relatives in their countries of origin.

The book can also be used by healthcare personnel from one area of the world practicing medicine in another area as a guide to distinguish the infections that are locally prevalent from those that occur in their home medical environment.

In addition to general background chapters, the book is divided according to United Nations (UN) world regions and addresses geographic disease profiles, presenting symptoms, and incubation periods of infections. Geographic childhood vaccination coverage is addressed. Vaccination is probably the most successful disease control tool ever, and diseases like tetanus and diphtheria, *Haemophilus influenzae* type b, measles, rubella and mumps are now very rare in countries with high vaccination coverage. Each chapter therefore contains a section on childhood vaccination programs in the countries included in that region.

The important topic of antibiotic resistance is addressed on a regional basis. The distribution of antimicrobial resistance in common bacteria is disparate worldwide, and with the increasing volume of travelers an increasing number will travel with or import multiresistant infections. Early reports of gram-negative Enterobacteriaceae with resistance to carbapenem conferred by the New Delhi metallo-β-lactamase-1 (NDM-1) imported into the UK by “medical tourists” (patients who traveled for medical interventions or operations) flashed the early warning lights. Now there are increasing numbers of studies on the colonization of travelers with multidrug-resistant pathogens. The situation has consequences for the returning travelers, their family contacts, and the healthcare systems encountered. This composite picture sketches a frightening, Orwellian scenario of the ease of the global travel of drug-resistant microbes.

Our book has a special focus on immigrants and those visiting friends and relatives. It is estimated that nearly 200 million people are refugees or permanently displaced persons. In Europe alone, 30 million inhabitants have an immigrant background, of which approximately one-third were born outside the industrialized countries. The current migration waves to Europe from Syria and countries in Africa create new challenges in preparation for screening and care of migrants. Individuals migrating from one country to another carry a history of exposures to infections not present in the destination country, and a sensible strategy for evaluating infections in this group requires knowledge of disease patterns in the country of origin and along the migration route. Information on childhood immunization coverage in the countries of origin is also most important. When a diagnosis or presumptive diagnosis is made, knowledge of the drug susceptibility patterns, including those for malaria, in the country of origin is crucial to determine the appropriate treatment.

Furthermore, exposures earlier in life should be included when diagnostic considerations are made, as tuberculosis, HIV, schistosomiasis, leishmaniasis, and onchocerciasis can remain undiagnosed for up to several decades.

Immigrants obtaining residency status through the UN program for refugees often originate in countries with rudimentary health systems, which are torn by civil strife, as is the case in Syria, and have spent years in refugee camps where healthcare facilities have limited resources. Health problems in this special group require specific knowledge of infections present in the countries of origin and the effect of civil war on the childhood vaccination program or disease control programs. The introduction of Chagas disease to Europe, in particular Spain, with immigrants from South America is another recent example of how migration can bring a health problem to the new country of residence.

This book also contains a number of fascinating background and general chapters. The riveting historical perspective on infectious diseases is key to understanding the present geopolitical distribution of infection. There are chapters describing infectious disease risks at sea and in the air. Another section addresses infection prevention, outbreak, and the role of the International Health Regulations (IHR) in the curtailment of disease. Data on disease epidemiology and changing disease patterns are provided by surveillance networks exemplified here by GeoSentinel and ProMED, that publish and rapidly disseminate information to the infectious disease and travel medicine communities. These networks utilize the development of electronic communication, which supports instantaneous publication of news on disease outbreaks worldwide.

Emerging infections is a key topic in a world where infected persons can travel half the globe in 12 hours. Newly emerging infections are very likely to emerge from a zoonotic reservoir whenever the contact between humans and the reservoir animal is altered. Like the recent outbreaks of Ebola and Zika virus, new emerging infections will be increasingly observed in the future and many will probably be zoonotic in origin.

Another chapter in this book addresses individuals with an impaired immune system who constitute a special risk group, including patients with transplants, HIV, and other conditions like immunoglobulin deficiency. These travelers will often have a decreased humoral and cellular immune response to vaccines and may be at higher risk of certain infections at their destination compared to immunocompetent individuals.

Climate change will affect the distribution of infectious diseases. Most obvious are effects on vector-borne infections, where changes in temperature, humidity, vegetation, and distribution of the zoonotic reservoirs influence the distribution of the infections. The recent introduction of chikungunya virus in Italy, dengue transmission in the south of France, and dengue outbreaks in Key West, Florida, are associated with the recent establishment of *Aedes albopictus* in these regions.

We hope that this book will be a useful aid for those involved in global infections and that you, the reader, will enjoy using and browsing this volume. We thank the Wiley-Blackwell team for their support and publishing expertise. Most of all, we are grateful to all the collaborators worldwide who contributed to this global project and who made it possible. Let's do it again!

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November 2016

Envoi

Knowledge is little; to know the right context is much; to know the right spot is everything. (Hugo von Hofmannsthal, 1874–1929)

Chapter 1

Historical overview of global infectious diseases and geopolitics

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Following the migration of *Homo sapiens* out of Africa, our species interbred with other archaic humans while spreading through present-day Europe, Africa, Asia, and Australia, ultimately arriving in the New Worlds of current-day North and South America. Over subsequent millennia, national boundaries have largely been shaped by discrete populations of our human species, through the retention or acquisition of strategically important land areas necessary to satisfy their needs for resources such as food, settled agriculture and trade. Wars and conquest, for which we have only relatively recent information covering the past few millennia, have played important roles in these events. However, a number of infectious diseases, including cholera, leprosy, typhoid, typhus, plague, tuberculosis, measles, smallpox, yellow fever, and malaria, have also played significant roles in important historical events that we know of. This chapter highlights ways in which infectious diseases have influenced the course of recent human history and often changed political maps of the world.

Introduction

Superimposed upon physical maps of the world are political maps that show not only natural boundaries, but also boundaries created by humans through their acquisition of territories by conquest and colonization or subjugation by force. Geopolitics, a term that has had many meanings, some politically extreme, is concerned with "... power relationships in international politics including, *inter alia*, the acquisition of natural boundaries, the control of strategically important land areas and access to sea routes" – Kjellén's original definition that will be adopted here [1,2].

The present-day political maps of the world have been determined largely by earlier human migrations, and ultimately both military successes and failures. Throughout history, civilian casualties and deaths have been regarded as unfortunate consequences of conflicts. The role played by disease among both armies and civilians is seldom acknowledged despite the fact that in virtually all wars, morbidity and loss of life from disease have massively exceeded losses caused by weapons [3,4]. It can, therefore, be argued that disease within civilian populations, during and as an aftermath of conflict, has been as important in shaping the political maps of the world as military successes or failures [5].

[†] In memoriam

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Most anthropologists agree that our species, *Homo sapiens*, emerged in Africa about 150–200 000 years ago and from c.70 000 BC dispersed in waves throughout the world until by the end of the last ice age, c.10 000 BC, we had occupied most of the inhabitable planet except New Zealand and some other isolated islands [6]. The world's population of modern humans was then about 1 million, but increasing and discrete populations began to covet territory that others already occupied, thus leading to conflict and occupancy – the beginnings of geopolitics. Acquisition of territory became more important as the population of the world grew to about 10 million by 3000 BC and nearly 500 million by AD 1500 when the political world as we know it today began to take shape [7]. Nearly all that we know about the epidemiology and effects of infectious diseases dates from about 1500.

The most important diseases in the past, as now, were those caused by microbial pathogens (broadly speaking, viruses, bacteria and protozoa) that multiply within their hosts, causing an immediate threat unless brought under control by an immune response. Individuals differ in their degree of susceptibility or resistance to infection and, over time, as more susceptible individuals die out, those who are more resistant pass on their genes. Thus whole populations develop “herd immunity” which protects them against diseases prevalent in their particular environment and communities [8]. When such individuals move into areas where there are infections to which they have not developed herd immunity, they rapidly succumb and, conversely, spread their own infections among susceptible local inhabitants. This is an oversimplification that takes no account of such factors as the role of nutrition, which markedly affects an individual's capacity to resist infection. It has been argued that improvements in nutrition have, over the centuries, enabled populations to withstand diseases that would have killed their ancestors [9]. This is a study in itself and will not be considered further in this chapter,

Of approximately 150 common infectious diseases, 28 that are caused by viruses, 35 by bacteria and six by protozoa are the most serious [10,11]. Of these, cholera, leprosy, typhoid, typhus, plague, tuberculosis, measles, smallpox, yellow fever, and malaria in particular have, in turn, markedly affected the course of history [12]. Region by region, the following sections will discuss ways in which some of these diseases exerted profound changes upon the history of the world. The topics covered are, of necessity, selective and for more information, particularly regarding the background, the reader is referred to the following references: [2,5,9,10,13–24], for historical continuity [25–27], and for more information on disease and geopolitics [28].

The Near East and North Africa

Human civilizations emerged somewhere between 12 000 and 10 000 years ago in this region and by 2000 BC there were great cities and populations that stretched over Mesopotamia, Egypt, North Africa and the Mediterranean. For nearly 30 centuries, great empires including Babylonian, Phoenician, Persian, Greek, and Roman came and went until the rise of Islam in the seventh century AD. We know both from military and civilian records and archaeological evidence that several infectious diseases, including tuberculosis, leprosy (brought from India by the troops of Alexander III), typhus, typhoid, and malaria, existed in the region, but there appear to have been no epidemics that could have significantly altered the course of history. There is, however, one intriguing possibility. Alexander III (the Great), having amassed a great empire and having conquered the Greek, Persian, Syrian, Phoenician, and Egyptian empires, was on the brink of bringing much of Asia and parts of Europe under his control when he died suddenly in 323 BC. He had successfully led his Macedonian troops in conquests but died following an 11-day illness contracted after sailing down the Euphrates River, while inspecting marshlands near the Arabian border. Although most commentators believe that he was poisoned, some feel that he died of typhoid or malaria [10,29]. Because he experienced continuous fevers during the illness, it is more compatible with typhoid. After Alexander's death, his empire was divided among his generals and began its terminal decline. If this decline resulted from Alexander's death caused by an infection, this could be the earliest documented example of an infectious disease changing the course of history. There is a need for some caution here because many historians believe that his death merely accelerated an historical process that would have inevitably occurred within the next decade or two.

The rise of Islam in the seventh century might also be traced back to the effects of an infectious disease. By 632AD most of the Arab world had converted to Islam and the next target for conversion was the Byzantine empire, the successor of the Roman West (see below), and its capital, Damascus, which fell after a siege in 634. The origins of this defeat can be traced back to 542 when the “Justinian Plague” (see below) frustrated plans to reunite the Roman empire after which neither the Roman nor Byzantine armies ever recovered. By 634 each was so weakened that Damascus surrendered with hardly a fight. What followed was an Islamic golden age during which Islam spread throughout the Mediterranean area and into Spain and southern France. It is tempting to speculate that if the fall of Damascus can be traced back to the Justinian Plague of 542, and had Damascus not fallen, the advance of Islam might have been halted.

Europe

By 7000 BC, farming was established in Europe and for the next 6000 years people lived in small tribes on farms or within small villages. Several infectious diseases must have been prevalent but, because of the scattered nature of the population, it is unlikely that there were any significant epidemics. This situation changed with the development of the first city states which brought people together in large numbers and witnessed the growth of military expeditionary forces. The first European city state, Athens, emerged as a major power in about 750 BC and flourished until it was defeated by its rival, Sparta, in the Peloponnesian wars (431–405 BC), after which it fell into decline [30].

The outcome of the wars was determined less by superior military achievements than by the arrival from Africa, via Egypt, Libya, and Persia, of the “Plague of Athens” that killed an estimated one-quarter to one-third of the population of Athens. Pericles, then ruler of Athens, attempted to hold back his troops and sit out a siege by the Spartans until they requested a truce. Having fortified and protected Athens, along with its port of Piraeus, inside wooden walls, the Athenians experienced an unexpected influx of refugees from the countryside as the Spartans advanced. The city rapidly became overcrowded, setting the stage for the oldest epidemic ever recorded. It was documented by Thucydides and included the loss of both Pericles and about a quarter of the Athenian frontline troops and cavalry [10]. The cause was possibly louse-borne typhus, for which besieged Athens’ crowded and humid conditions were ideal. Measles and smallpox have also been suggested but the actual cause will probably never be known [31]. We do know, however, that the Spartans were spared.

The next great power to emerge in Europe was the Roman empire. By the third century AD, its dominance had spread until it included nearly all of Western Europe, North Africa and the Near East [32]. Under a series of ambitious military emperors, however, the empire grew so large that it became almost ungovernable and by the beginning of the fourth century it had split into the West, centered on Rome, and the East, centered on Constantinople. By the end of the fifth century, the empire had begun to disintegrate. Most of the West had succumbed to the invading Visigoths, while the East became the precursor of the Byzantine empire. In 540, one final abortive attempt to restore the old Roman empire was begun by the Emperor Justinian. By then he had regained most of the former Mediterranean possessions and hoped to retrieve the more important Eastern section. He was, however, stopped in his tracks by the arrival of the “Plague of Justinian” (541–2). Because we have the writings of Procopius of Caesarea and his detailed descriptions of its signs and symptoms, most experts agree that this was bubonic plague that had spread from Alexandria to Constantinople, where it killed an estimated 5–10000 people *every day*. This may have been the first epidemic of bubonic plague in Europe that continued for 200 more years. Because of the “plague” Justinian could not raise the armies required for his campaign and was forced to abandon his ambitious plans. This eventually led to the terminal decline of the Roman empire. The estimated overall death toll in the two empires is estimated to have been 100 million [10].

Bubonic plague spread through Western Europe, beginning in 547, and continued to recur sporadically for the next 200 years until it virtually disappeared there for 600 years. However, plague returned

with a vengeance in 1347 as the “Black Death.” The origins of this epidemic are obscure, but it appears to have emerged around 1300 along the Caspian Sea and spread to both the Crimea and Constantinople by 1346–7. On the Black Sea, while the Tartar army was laying siege to Kaffa in the Crimea, it was caught up in the plague pandemic. The invaders catapulted the bodies of plague victims into the city – perhaps one of the first examples of germ warfare [33,34]. Beginning inconspicuously with the arrival of infected Genoese merchants from the Black Sea at the port of Messina, Sicily, the infection spread with amazing rapidity throughout Europe. In less than 10 years, it had reduced Europe’s population from about 75 million people to less than 50 million. The plague was particularly hard on the populations of great cities such as Venice, Florence, Genoa, London, Paris, and Barcelona, some of which lost half their population. Plague also affected even the most remote rural areas, taking with it princes, clergy, and peasants, leaving Europe in a state of chaos. Agriculture failed and millions who had survived the plague died of starvation. As a result of plague, the former feudal system fell into abeyance; a shortage of labour occurred and peasants realized that labourers were worth their wages – with implications that lasted for centuries. Other long-lasting effects included the irrevocable loss of whole villages, migration to larger conurbations and a diminution of the authority of Church and state which could not control the disease [34].

The cause of plague was unclear and the Church had very little to offer in terms of protection or therapy, so people turned on the Jews of central Europe, blaming them for plague. Persecution drove whole Jewish populations further east into Poland and Russia where their cultures flourished until World War II. The plague may have also delayed the further European discovery of North America by contributing to the extinction of the Norse on Greenland where they had farmed for 500 years. The fourteenth century had some of the coldest temperatures known in Greenland over the past 700 years. Short summers and the gradual loss of land productivity took their toll on these remote Norse Greenlanders who were then living at the edge of their sustainable existence. When Europeans arrived once again, there were no human colonies remaining at the former Norse eastern and western Greenland settlements following the introduction of plague [34]. Iceland was devastated twice in the fifteenth century when ships from England carried plague to this cold Arctic habitat that did not prevent it from spreading across the entire island. Plague continued to rumble on in waves across Europe about every 15–20 years from the mid-1550s until the 1670s, causing the deaths of over half the inhabitants of many cities, and it persisted at insignificant levels until about 1800 [35]. Like the Black Death, plague in Europe brought with it starvation and severely curtailed the economies of affected countries. The final outbreak of plague in Western Europe occurred during 1720 in southern France in the port city of Marseilles.

Influenza viruses that are adapted to humans circulate continuously among them but they can cause outbreaks that reach pandemic proportions. The last great epidemic to strike Europe was the 1918 influenza pandemic, also known as Spanish flu [36]. We do not know where that lethal strain of H1N1 originated in 1918 but it is clear that it had undergone at least 10 mutations that allowed it to both infect and proliferate in human cells. The first epidemic records are from the United States and Austria in 1917, the rest of Europe in 1918 and worldwide in two waves, the second more virulent than the first. Survivors of the first wave had some protection against the more dangerous form, but by the time the pandemic ended, in the summer of 1920, influenza had infected between one-quarter and one-fifth of the world’s population and killed 50–100 million people. This epidemic might also have affected the outcome of the final stages of the First World War (1914–18) as it seems to have adversely affected German and Austrian forces more than the Allies. The impact of this epidemic on the economies of European countries cannot be overestimated. It took decades before its effects wore off and it may even have influenced the advent of a worldwide economic depression during the 1930s.

The Americas

As the last Ice Age came to an end, the land bridges across the Bering Strait were lost to rising sea levels. The indigenous populations, descended from the original migrants who arrived approximately 14000 years ago, became isolated and cut off from the Old World. The first human arrivals had come

from northern Eurasia where the “cold filter” prevented many Old World diseases from reaching the continent. However, nowhere have the effects of infectious diseases on geopolitics been more marked than in the Americas [37].

When microbes from the Old World were introduced to the Americas in the fifteenth century, they encountered a population that lacked genetic resistance and they devastated the indigenous populations. We know very little about any of the diseases that afflicted these early peoples who had virtually no contact with the wider world. There is evidence of villages and permanent settlements from about 2000 BC, and civilizations that rivaled those of Mesopotamia, Egypt, and China existed over 2000 years ago in present-day Mexico, Peru, and Ecuador.

When Europeans first arrived in 1500, Central and South America were dominated by two advanced and powerful civilizations: the Aztecs in Mexico and the Incas in Peru and Ecuador. North America was occupied at that time by scattered and sparsely populated Native American tribes. From the beginning of the sixteenth century, successive waves of Spanish troops in small groups overcame the vastly larger Inca and Aztec armies and it is not at all clear why they succumbed so easily. Although infections played major roles, it has been suggested that nutritional, psychological, economic, and religious factors along with the fear of disease also contributed to their defeat.

Spanish conquistadors introduced smallpox into the Caribbean by 1507 and it was almost invariably accompanied by measles. Hernan Cortés was sent into Mexico by the Spanish governor of Cuba to corroborate fantastic stories of a thriving and opulent civilization in Mexico. His small group of 16 horsemen and 600 foot soldiers reached the Aztec capital, but relations quickly deteriorated between the Aztecs and his army. Cortés did not quite turn out to be the “white-skinned god” that Emperor Montezuma had expected and Cortés was forced to withdraw and return to the coast to regroup his forces. While he planned his strategy for counterattack in 1520, smallpox arrived in the Aztec capital, causing massive mortality wherever it appeared, killing between one-quarter and one-third of its victims. The pattern was nearly always the same: disease spread ahead of the invading armies, causing overwhelming mortality and morbidity, leaving the dispirited survivors at the mercy of the invaders, thus clearing the whole region and making it available for colonization by generations of Europeans. When Francisco Pizarro invaded the Inca empire in 1532, he had been aided by its first smallpox epidemic during the 1520s which killed a third of the population, including an absolute monarch worshipped as the Sun God, his family, and military leaders. Hence, “within fifty years of Cortés arrival in central Mexico only one in ten Native Americans survived and the population plummeted from 30 to 3 million” [10]. North America became “virgin territory” ready to be carved up and colonized by Portugal, Spain, Britain, Denmark, France, Sweden, and The Netherlands.

Waves of infected immigrants and slaves added to the disease burden and by the early seventeenth century, smallpox and measles had spread along the coast of North America as far as Massachusetts. By the nineteenth century, these diseases had reached the west and become endemic throughout the Americas. Infectious diseases continued to be significant into the nineteenth century as they spread along the Mississippi as a result of trade and settlement and during the Civil War (1861–5) the majority of deaths were caused by disease.

One disease in particular played an important role in the later history of North America. Yellow fever, carried from Africa by infected slaves, together with its mosquito vector, caused the first reported yellow fever epidemic in the New World in 1647 [38]. It arrived in Yucatan in 1649. From there it spread to Cuba, Hispaniola and across mainland America, reaching Philadelphia in 1793 [35]. By then, Philadelphia was the favored site for a new capital of the new United States that had been established in 1783. However, epidemics of yellow fever and dengue fever in 1793 and during subsequent years were partly responsible for George Washington’s decision in 1800 to locate the new capital elsewhere – within the state of Maryland at what is now Washington DC [39].

Meanwhile, that same year the Spanish West Indian colony of Haiti had been seized by the French against the wishes of the local population. By 1790, there were more than 500000 slaves living in Haiti, outnumbering the white population by a factor of 16 to 1. By 1791, the political events in both Europe and the Caribbean precipitated a slave revolt that led ultimately to independence. The French Emperor, Napoleon, sent massive reinforcements of French troops under General Le Clerc to quell the rebellion. This was disastrous for the French, who succumbed to yellow fever, and out of 40000

soldiers, only 3000 returned to France. By January 1804, Jean-Jacques Dessalines, a former slave, could sign an Act of Independence and be declared Emperor of Haiti. However, what followed was a century of geographic and cultural isolation during which there were few advances in the sciences or medicine [40]. It was also a major, but not fatal, setback for Napoleon's ambitions in the New World and in 1802 he sent an army to claim New Orleans for France. However, 29 000 out of 35 000 soldiers succumbed to yellow fever, effectively ending France's claims to New Orleans and French aspirations for New World dominance that had begun in the 1530s. It has even been suggested that were it not for yellow fever, Americans would probably be speaking French today [19]. As a result, with his ambitious plans ruined, Napoleon sold the French territories comprising Louisiana for 15 million dollars to the United States – territory that today essentially comprises the entire middle third of the country.

Yellow fever was to have one other major effect on the relationships between France and the United States. From 1879 to 1889, the French had tried to link the Pacific with the Atlantic via a Panama Canal, but had to abandon the scheme partly because of the devastating effects of yellow fever and malaria. The entire project cost the French over 300 million dollars and 28 000 lives. Following the discovery by American and Cuban scientists that mosquitoes transmitted yellow fever, the threat of disease was virtually eliminated and work on the Panama Canal was resumed. When it was opened in 1914, the Canal gave the United States unfettered dominance of the entire region [41].

Australasia

It is not certain when the first humans arrived in Australia and estimates range from 125 000 to 40–50 000 years ago. Written history of this area begins with sporadic visits by Europeans in the early sixteenth century. By 1650, Dutch explorers had mapped much of the coastline. When the British arrived in 1769, Australia was sparsely populated, with about 250 well-defined and scattered Aboriginal tribes, each with its own culture and language. The total population at that time was about 350 000. Shortly after the colonization of New South Wales in 1788, there was a major and well-documented epidemic of smallpox in Sydney. Thereafter, there were sporadic epidemics of smallpox and measles elsewhere on the continent. In 1798, one particularly severe epidemic of smallpox killed 90% of the Darug (Dharug, Daruk or Dharuk) tribe in the area now including Sydney [42]. Overall, however, disease played only a minor role in the decline of the Aboriginals to about 93 000 in 1900, a decline that was mainly due to deliberate killings, starvation, and forcible resettlement. The Aboriginals were largely protected from infectious diseases because their populations were so isolated that infections could not spread easily, and contact between Europeans and Aboriginals was very limited. In addition, because of the distance from Europe, any smallpox carriers would have either died or recovered by the time their ships reached Australia. Also, from about 1798 many of the immigrants from Europe would have been vaccinated against the disease. Finally, Australia never imported large numbers of slaves and their infectious diseases from Africa as had occurred in the Americas, and bubonic plague did not reach Australia until 1900 [43].

New Zealand was actually more fortunate than Australia. The first European contacts occurred in 1672, but it was not until 1679 that they began having any significant impact. In 1769, the local Maori population was 85–110 000 but it fell to 70 000 by 1840 mainly due to conflict, not disease. The European population was tiny, numbering about 2000, so they presented little or no risk of transmitting disease. By the time Europeans began to arrive in large numbers, between 1850 and 1870, the causes of many infectious diseases and the means of controlling them had been well established. The only significant smallpox epidemic occurred as late as 1913.

From 1788 onwards, populations on the islands of Oceania began to experience European diseases associated with increases in exploration, trade, missionary activity, and labor movements. The large number of small separated islands meant that epidemics might be serious for a distinct population, but could not spread quickly or widely. Following the smallpox epidemic in Sydney in 1788, the disease arrived in some of the nearby islands and spread throughout Oceania during the nineteenth century, ultimately reaching Hawaii in 1853, Papua New Guinea in 1865, and New Guinea in 1870. Tuberculosis

reached Fiji in 1791 and measles began to spread in the area from about 1800 on. In addition to the common European diseases, malaria and dengue began to move throughout the region and, with the arrival of a labor force in the nineteenth century, there were also new importations of infectious diseases, including malaria from Asia and South America.

Infectious diseases in Australia and Oceania played little part in geopolitics – they did not facilitate colonization nor did they bring about the downfall of governments or powers. However, they did have major impacts on the economic development of all countries in the region simply by their presence.

Sub-Saharan Africa

Our hominid predecessors emerged in Africa, interbred with other archaic human species and evolved to become *Homo sapiens*, the species that now inhabits the entire planet. Little is known about the early history of the inhabitants of the continent as, apart from one first century AD document, the “Periplus of the Erythrean Sea,” which describes trade routes down the African coast [44]. There are no written records until about AD 1000 when most of the inhabitants of the interior lived in small, isolated communities that were too small to sustain and spread contagious diseases. They did, however, suffer from both mosquito-transmitted malaria and yellow fever. European diseases reached the African coasts with Portuguese or Arab traders and slavers from the beginning of the sixteenth century and quickly spread inland. They took a disproportionate toll on the indigenous people who had had no opportunity to build up any herd immunity. Although smallpox had been present along African coastal regions from at least the seventh century, the first records of major epidemics are from the Gulf of Guinea in 1680. Thereafter, numerous records of smallpox appear from as far south as Cape Town in 1713. The latter epidemic began when a Dutch ship carrying infected slaves and colonists landed at the Cape and disease quickly spread, killing about a quarter of the European settlers. It had a particularly adverse effect on the Khoikhoi (Khoi or Khoisan people), a genetically distinct population of herdsmen who had inhabited and dominated parts of south-west Africa since the fifth century. Smallpox killed over 90% of the Khoi, who never recovered from their loss, thus allowing settler farmers to take over the territory that they had held for over 1000 years.

Sub-Saharan Africa was to experience other disasters such as cholera and tuberculosis which spread throughout the country after 1900. When the 1918 influenza epidemic arrived in Sierra Leone, it quickly spread and killed an estimated 2 million people.

In some ways, the presence of malaria and yellow fever protected Africa from military invasion because European armies suffered huge losses when they penetrated into an interior so hostile that it permitted little more than the establishment of a few strategically placed forts and garrisons. Parts of West Africa became known as the “white man’s grave” and until about 1900, it was believed that there was something about Africa itself that made it inimical to Europeans. The presence of African diseases prevented or delayed major projects such as the building of roads and railways, leaving some to wonder if, after the ending of the slave trade, Africa was worth the effort of colonizing. It all had been so much easier in the Americas and Australasia. Nevertheless, what has become known as the “scramble for Africa” began followed by the partitioning of Africa among the European powers in 1884–6.

Colonization did have some beneficial effects within Africa. Towards the end of the nineteenth century, herds of cattle were succumbing to a wasting disease called *nagana* (Zulu for “low spirits”), while humans were suffering and dying from a condition known as sleeping sickness or “negro lethargy.” The extremely high fatality associated with sleeping sickness in general meant that small early African hunter-gatherer groups would have had difficulty surviving within the tsetse fly belt that cuts across central Africa. The question arises as to whether these trypanosomal diseases could have played a major role in the history of early humans by serving as an impetus for human migration out of Africa 50000–100000 years ago [10]. Possibly, the combination of trypanosome, tsetse fly, and sleeping sickness was responsible not only for the very slow growth rates of African hunter-gatherer bands, but also for the eventual migration of hominids out of the East African Rift Valley.

British and Scottish colonial scientists and doctors unraveled the mysteries of both diseases, which were found to be caused by protozoan parasites, the trypanosomes [45]. These are extremely active blood parasites whose name is derived from the Greek *trupanon*, or borer. These discoveries led to measures for the control of the diseases and made it safer for Europeans and Africans to keep their cattle over great swathes of Sub-Saharan Africa, thus contributing to the wealth of the continent.

South Asia

The countries of South Asia, present-day India, Bangladesh, Bhutan, Pakistan, the Maldives, Nepal, and Sri Lanka, are separated from the rest of Asia by the Himalayas, and they developed cultures quite distinct from those of the Near East, the Far East, and South-east Asia. Much of what we know about diseases in the past comes from the sixth century BC Ayurvedic texts, the Caraka and Sushruta, which mix spiritual well-being with descriptions of diseases, some of which are difficult to interpret. For the next thousand years or so, trade brought the region in contact with the Arab and European worlds and their diseases, but there are only sporadic references to infectious diseases which probably included cholera, leprosy, typhoid, smallpox, and malaria. Sanskrit medical texts indicate that a disease which may have been smallpox was known in India from about 1500 BC. The first detailed accounts of smallpox in India date from AD 1160. Epidemics of plague occurred in 1443, 1543, and 1573, after which the disease became endemic with occasional epidemics such as that of 1812 that killed half the population of Gujarat.

Cholera is the disease that is most associated with India and the epicenter appears to have been the Ganges delta. In 1600, the British East India Company was established for trade, but after 1857 it was the British government that actually controlled India. Up until British rule in India, *Vibrio cholerae* was restricted to some extent to the Bay of Bengal where the Ganges River empties into the Indian Ocean. However, British trade routes and troop movements changed local cholera outbreaks into epidemics. The first known Indian epidemic occurred in 1503 and in 1817 it killed 4000 people in Calcutta, then spread throughout the subcontinent into the Far East and then to Cuba and Mexico in 1833, Europe in 1835–7, and Africa in 1837. From the nineteenth century onwards, there have been periodic cholera pandemics, nearly all of which originated from the Ganges region where the religious ritual of bathing in that river is thought to have contributed to the spread of the disease.

The European colonization of the Indian subcontinent began in 1498 with the voyages of Vasco da Gama, and later Portuguese traders whose accounts of recognizable diseases appear as more Europeans began to arrive. Because India had already experienced some of the diseases prevalent in Europe, it suffered none of the disastrous epidemics experienced in the Americas and Australasia. India effectively came under British rule from 1765 and inherited a sophisticated health system that it supplemented with the introduction of Western medicine.

Despite its long history of civilization and knowledge of infectious diseases, no particular event in South Asia can be said to have changed the course of world history although diseases that contributed to the outcome of wars that plagued the region throughout its history had significant local consequences. As in Africa they slowed and curtailed the development of roads and railways.

East Asia

East Asia encompasses China, Japan, and Korea. Like South Asia, it is a geographically distinct region with both well-defined epidemiology and etiology of diseases. The Chinese civilization emerged about 4000 BC and from 1765 to 1122 BC experienced a growth in both labor-intensive agriculture and the construction of walled cities. By 221 BC, there had been both a massive growth in China's population and considerable territorial expansion followed by a period during which great dynasties emerged and declined. During the first century BC, China reached as far north as Bengal and by the time of the Tang Dynasty (618–907), there were over 20 cities and a population of about 2 million.

Population growth, the congregation of people in cities, and increasing trade with the outside world created conditions conducive to the spread of infectious diseases; smallpox arrived from the north in 250 BC and from the south in AD 48. Thereafter it became endemic throughout the region. In 1206, Mongol nomads invaded China and established the Yuan dynasty that was replaced in 1368 by the native Ming dynasty, characterized by trade with South-east Asia, South Asia, Africa, and Europe. This period of trading brought new diseases to China and towards the end of the Ming period the pattern of diseases in China resembled that in South Asia and Europe. In 1633, the Ming dynasty came under threat from the Manchu army, descended from non-Chinese Manchurian tribes. The Manchus were so aware of the dangers of smallpox that they used only those soldiers who had recovered from the disease or had been “immunized” against it [46]. This was a successful strategy that ended the Ming dynasty in 1644 and began the Qing dynasty that ruled until 1911. Increased trade and the arrival of Europeans in the seventeenth century did not have the same devastating effects seen in the Americas since the local population had already experienced all the diseases likely to have been carried by foreigners.

From its earliest times, China was in conflict with its neighbor to the east, Japan. It all came to a head with the Sino-Japanese war (1894–5) when the two countries went to war over Korea. The Chinese were decisively defeated and this marked the beginning of Japan as a world power. The Japanese despised the Chinese and this led to the creation of the infamous “Unit 731,” the objective of which was to manufacture biological weapons for use against the Chinese [47]. Between 1940 and 1942, the Japanese bombed over 12 Chinese cities with a variety of agents, including plague-infested fleas: in one attack on Quzhou, 50,000 died and in Ningbo 97% of the population were killed. Altogether, 200–400,000 people perished. The Allied defeat of Japan in 1945 brought these activities to an end.

Humans have inhabited Japan for over 10,000 years but our knowledge of diseases during the early history of Japan is very limited because of the country’s self-imposed isolation. When coupled with distribution of the population within small groups, it rendered Japan relatively free from infectious diseases. Early chronicles dating from about 710–720 BC refer to diseases which might have been malaria, tuberculosis, and leprosy but the whole period 200 BC–AD 495 seems to have been free of any significant impact of any diseases despite population growth over this period. However, in 495 AD smallpox arrived from Korea, but did not spread very far because population movements were limited, largely due to the nature of Japanese terrain. Between 700 and 1050, Japan suffered from a series of 10 devastating “plagues.” These included smallpox in 735–7 (“the great smallpox epidemic”), 790, 812–14, 833, and 853, bubonic plague in 808, influenza between 862 and 1015, and measles in 998 and 1025. The 735–7 great smallpox epidemic alone killed 30–40% of those infected. These plagues had effects similar to those of the Black Death in Europe, including economic stagnation. In addition, Chinese influence declined and Buddhism was adopted. These plagues also allowed the population to build up their herd immunity; between 1050 and 1260, infectious disease had ceased to dominate people’s lives and smallpox had become a disease of childhood. With the expansion of trade routes and the arrival of Europeans in 1543, the only disease passed on to the naive population of Japan was syphilis.

The Japanese economy continued to thrive and with one exception (apart from the venture into biological warfare discussed above), disease played little role in the development of the country or its economy. The exception occurred in the early twentieth century when the Japanese used their knowledge of malaria to persuade the population of Taiwan to abandon their way of life and to become more Japanese [48].

Korea was established in the late third millennium BC by people from northern China and was conquered by the Chinese in 108 BC, by the Mongols in 1231, and became a Japanese protectorate in 1904–5. The first records of smallpox epidemics, via India and China, are from the third century BC. There were epidemics in 552 AD, 585–7, 735–7, and 765, from whence the disease passed to Japan. There were further epidemics in 1418, between 1424 and 1675 and 1680, all with devastating effects, during which kings, princes, and other important leaders died. The population of Korea had not been exposed to European diseases in the same way as the Japanese and in 1707 and between 1752 and 1775, there were epidemics of measles, called “dot eruption disease.” By 1883, smallpox had become a

childhood disease and virtually everyone had scars from the disease or inoculation. By the end of the century, smallpox had been virtually eradicated and the pattern of infectious diseases in Korea closely resembled that which occurred in the Americas. Infectious diseases in Korea, although they had important effects locally and in the neighboring countries, made negligible impact on world history.

Conclusion

Migration, genetics, conflict, and infectious diseases have played significant roles in determining the political maps of the world that have evolved over millennia. Cholera, leprosy, typhoid, typhus, plague, tuberculosis, measles, smallpox, yellow fever, and malaria have all contributed to important historical events such as the decline of the powers of Athens and Rome, the rise of Islam, the end of the feudal system in Europe, the colonization of the Americas, Africa, and Australasia, the end of French colonialism in the Americas and numerous examples of disruption of economic development and subsequent political consequences. In addition, there must have been thousands, if not millions, of minor recorded and unrecorded events, the effects of which have not been evaluated, that might have turned out differently had disease not intervened.

Acknowledgment

We would like to thank Professor Sir Roderick Floud for his careful reading of the original chapter in its first edition. Any errors, however, are our own.

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Chapter 2

Nontraditional infectious diseases surveillance systems

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An official public health surveillance and reporting infrastructure exists in many parts of the world and usually provides timely and reliable reports of infectious disease outbreaks. However, this system misses some events due to reporting failures at various levels and the system may be inadequate or nonexistent in some locations. Nontraditional surveillance systems described in this chapter complement the formal public health system.

One such nontraditional system, ProMED-mail, is a rapid reporting system of emerging infectious diseases in humans, animals, and plants. ProMED-mail focuses on rapid reporting and relies on local sources like newspapers and their websites and local rapporteurs submitting reports of unusual events. An expert in the field puts each report on ProMED-mail into perspective and determines whether the report is credible or not.

Monitoring disease trends and geolocation of acquired diseases among travelers can inform pretravel advice, posttravel management, and preparations for potential introduction of emerging infections. Data from sentinel travelers upon their return to medically sophisticated environments can also benefit local populations in resource-limited countries through the identification of outbreaks that may not have been captured by their domestic surveillance systems. Provider-based surveillance of travelers is increasingly sophisticated. Networks such as GeoSentinel have provided data on cumulative trends in travel-related illness to assess pretravel risk for mass gathering events such as the Beijing Olympic Games, the FIFA World Cup in Brazil or the Rio Olympics. GeoSentinel data have also been used to determine the seasonality of dengue by region of travel and risk of acquiring schistosomiasis by destination, and to identify unusual outbreaks such as sarcocystosis on Tioman Island, Malaysia. Global surveillance of travel-related disease thus represents a powerful tool for the detection of infectious diseases. Such data should encourage clinicians to take a detailed travel history during every patient encounter.

Introduction: informal internet sources for the surveillance of emerging infectious diseases

Traditional public health surveillance depends on a hierarchy of reporting systems. Practitioners, field personnel, laboratories, hospitals, and other healthcare facilities report on selected diseases and outbreaks first through local, state or provincial agencies, who in turn report these events, often in aggregated numerical form, to higher governmental and then regional or international groups. Such reporting is often regulated and mandated by governmental authorities, is the basis of publicly available health statistics, and often informs governmental responses to outbreaks. International agencies such as the World Health Organization (WHO) or the World Organization for Animal Health (Office International des Epizooties; OIE) may then communicate news of significant outbreaks to health agencies in other countries or to the public. These communications often form the basis for international responses. Such reporting systems have many advantages. In parts of the world where the public health infrastructure is well funded and robust, these systems can effectively capture important infectious disease events in a thorough and sensitive manner.

However, formal public health reporting systems are not without disadvantages. Delays at any level (or at several levels) can result in unacceptable lags, as reports must traverse numerous officials prior to reaching national and international attention. Likewise, failure at any level to collect or transmit reports to the next level can result in information never reaching those with the capacity to respond – a break in any link in the chain resulting in failure of the system. Moreover, there are often disincentives to reporting on the presence of diseases or to delay reporting as long as possible. Disease outbreaks can disrupt commerce, discourage tourism or damage the reputation of a locality, region or country. For example, the discovery of bovine spongiform encephalopathy (BSE) in a single cow in the US led to a ban on importation of US beef into Japan that persisted for years [1]. In addition, many official surveillance systems focus on specified “reportable” diseases. As such, they may fail to detect or report newly emerged, undiagnosed or undefined illnesses even if they threaten public health.

A convergence of trends

In the 1970s and 1980s, some authorities believed that infectious diseases had been or were soon to be “conquered.” Adherents to this notion believed that antimicrobials, improved public health measures, vaccines, and general improvements in the human condition would virtually eliminate infectious diseases. Indeed, it was argued that the medical specialty of infectious diseases might become unnecessary, at least in developed countries. This thought was soon challenged, however, by the identification of a multitude of diseases that appeared during this era, not the least of which was HIV infection. By the 1990s, the concept of disease emergence and reemergence had become prominent and the 1992 Institute of Medicine report entitled *Emerging Infections: Microbial Threats to Human Health in the United States* brought these ideas to the forefront [2].

At the same time, the internet was moving from an exclusive tool of the military and academia into the mainstream. With the advent of commercial internet service providers such as America Online, the use of e-mail became common even outside academic institutions. The birth of the World Wide Web meant that individuals around the world without specific technical skills were exchanging more and more information. Moreover, the dissolution of the Soviet Union had revealed the existence of a massive biological warfare program, raising awareness of the threat of the intentional or accidental release of agents that could cause biological harm.

Indeed, it was at a WHO-sponsored meeting in 1993 on the threat of biological weapons that the use of the internet for exchanging information on biological threats was pioneered. Attendees at this meeting began to exchange e-mails regarding outbreaks of diseases potentially related to biological weapons in August 1994. The members began a “listserv” that allowed anyone to send an e-mail to all members of the group. Soon, others heard of this list and asked to join. The originators dubbed this service “ProMED-mail” for the e-mail service of the Program for Monitoring Emerging Diseases.

As ProMED-mail rapidly grew, its founders realized it needed to better regulate the flow of information, and the service began to moderate posts to the lists. A report would flow through a central moderator who would select posts that would be sent to all members of the list and provide commentary on the contents of the reports. Reports included first-hand information from clinicians or laboratories on disease outbreaks as well as media reports of outbreaks. These reports from “informal” sources often preceded official reports of the same outbreaks, and often encouraged official sources to hasten the release of confirmatory reports, leading to an overall improvement in outbreak reporting.

By 1999, ProMED outgrew its unstructured roots and became a part of the International Society for Infectious Diseases. This global organization of infectious disease clinicians provided financial backing for the fledgling organization and created a more formal organizational structure with an advisory board, an editor, associate editors and subject area moderators. Infrastructure was reinforced with support provided by the Oracle Corporation and the Bill and Melinda Gates Foundation.

ProMED-mail today

ProMED is open to all sources of information. Much of the information comes from readers, who may send firsthand information such as a clinician witnessing an unusual syndrome or disease cluster. They may send local news media reports, not just those visible on the web but also local radio or television broadcast reports. Laboratorians may report unusual emerging disease findings from public health, private or academic laboratories. They may also report “rumors” – unverified, often second, or third-hand information. One notable example occurred when a ProMED reader, Steve Cunnion, sent a message describing what a friend had told him regarding a teacher’s chatroom in China. This report of widespread pneumonia in Guangdong formed the basis of ProMED’s report on SARS, which occurred well in advance of most formal and informal reports [3]. Similarly, the first report of a novel coronavirus (later labeled as the MERS-CoV) was first identified by an astute laboratorian in a ProMED report [4].

Currently, ProMED has over 50 staff in 25 countries who communicate via the internet (with face-to-face meetings held every year or two). ProMED’s staff include specialists in many aspects of emerging infectious diseases: virology, parasitology, bacteriology, epidemiology, toxicology, veterinary health, and clinical infectious disease. ProMED staff and volunteers scour hundreds of official and unofficial sites every day for news regarding outbreaks of emerging diseases [5,6]. These include the sites of well-known international organizations like OIE, the Food and Agriculture Organization (FAO), and the WHO, but also many local and regional official health department sites, as well as specialized disease-focused websites, blogs, and mailing lists.

As of July 2015, ProMED has over 75 000 subscribers to its e-mail subscription service. Subscribers represent every country of the world, though more than half are from North America and Western Europe. A number of subscription options are available, including digest forms, animal and plant only, and daily and weekly updates that provide only the titles of reports with links to the full text. The website (<http://promedmail.org>) (Figure 2.1) provides the ability to search using free text and by date range through the entire ProMED-mail archive of over 70 000 reports going back to 1994 and also provides access to a submission system and the regional networks. Many users access ProMED reports via Twitter (@ProMED_mail) and Facebook.

HealthMap

Since 2008, ProMED has had a productive collaboration with HealthMap.org based at Boston Children’s Hospital and Harvard Medical School. This global service includes multilingual web-crawling capacity that automatically finds information on disease outbreaks in publicly available websites, processes the information, and places it on a detailed map of the world. Since its inception, HealthMap has incorporated ProMED reports and, subsequently, GeoSentinel surveillance data into its system.

Figure 2.1 ProMED-mail website allows viewing of posts and provides an interactive map linked to HealthMap, search capacity, subscription and information submission as well as access to regional network websites.

The collaboration began through the development of a specialized map of ProMED reports. Fostered in part by a grant from Google.org, this collaboration has now expanded and includes the following features.

- Provision of automated e-mail alerts of disease information mined by the HealthMap web crawler. These alerts can be tailored by disease, geography, and other features that allow ProMED specialty moderators to keep tabs on areas of particular interest.
- Capacity for ProMED staff to “curate” HealthMap reports, refining the disease name and adding accuracy and precision to the mapping process.
- Inclusion of detailed maps corresponding to areas of disease activity within ProMED reports.
- Organization of ProMED’s vast repository of disease reports (over 70 000 reports going back 16 years) into a structured database; this allows research activities concerning the timing, quality, and accuracy of both informal and official disease reports. This research, in turn, will allow improvements to be made in the detection of disease outbreaks.

Infectious disease surveillance in travelers and migrants

In recent years, clinicians have been faced with the emergence and rapid regional and global spread of Ebola virus, novel influenza strains, SARS, chikungunya virus, multidrug-resistant tuberculosis, and other pathogens. Modern transportation and increased tourism, business travel, and immigration have contributed to dissemination of these high-impact pathogens [7,8].

Human movement has occurred for centuries and will continue, despite the threats posed by infectious agents [9]. A closer look at globally mobile populations that move pathogens across international borders is therefore necessary. Travelers can spread new and reemerging infectious diseases that initially appear in developing countries, and they act as ideal sentinels for the early detection of these diseases. Specialized travel/tropical medicine clinics are ideally situated to detect emerging infections and to track ongoing trends in travel-related illness. Returning travelers seen at a few sentinel sites by such collaborative provider networks as GeoSentinel (www.geosentinel.org) [10,11] provide insight into the transmission of infectious diseases in 249 different countries and territories. Real-time data are captured at the clinical point of service.

GeoSentinel surveillance network

GeoSentinel, established in 1995, is a provider-based surveillance network for travel- and migration-related illness. The GeoSentinel network currently comprises 62 travel/tropical medicine clinics and hospitals, all of which are members of the International Society of Travel Medicine (ISTM). The 62 GeoSentinel sites participate in full sentinel surveillance and are located in 28 countries on six continents (Figure 2.2). These clinics contribute clinic-based sentinel surveillance data on ill returned travelers, immigrants, and refugees using electronic internet-based data entry at the point of care (Figure 2.3). GeoSentinel surveillance data enable patient diagnoses, country of exposure, chronology of travel, and standardized exposure details to be collected for analysis of travel-related morbidity. In addition, such networks can detect disease outbreaks, enhance surveillance, and facilitate rapid communication, response, and dissemination of information among providers and public health partners. As of September 1, 2015, the GeoSentinel dataset contains more than 241 000 patient records, which cover traveler exposures in 249 countries and territories. During the last five years, the database has grown by an average of 23 000 records per year.

An additional 220 ISTM clinics from 42 countries on six continents are GeoSentinel affiliate members. They communicate unusual or alarming cases to GeoSentinel and participate in enhanced surveillance and response. CanTravNet and EuroTravNet are two region-specific networks that are part of GeoSentinel but also conduct analyses of patients from their country or region to provide evidence on outbreaks and infectious disease risk among travelers and migrants [12,13]. Alerts and advisories covering important disease risks and outbreaks in collaboration with the US Centers for Disease Control and Prevention (CDC) and other international organizations are channeled through GeoSentinel sites and affiliate members.

Examples of surveillance response capabilities

Leptospirosis in Borneo A good example of effective detection of outbreaks among travelers was the outbreak report of leptospirosis among Eco-Challenge athletes [14–16]. In September 2000, two US health departments and the GeoSentinel network responded to an increase in cases of febrile illness, characterized by the acute onset of high fever, chills, headache, and myalgias in travelers from more than 20 countries who participated in the Eco-Challenge-Sabah 2000 multisport endurance race, held in Malaysian Borneo. This outbreak was the first recognized multicountry leptospirosis outbreak associated with the increasingly popular activity of adventure travel. These findings emphasize the sentinel role of travelers; studying illnesses in this population can provide insights into the presence and patterns of infectious diseases in places to which they have traveled.

Sarcocystosis in Malaysia In collaboration with TropNet, GeoSentinel identified an outbreak of acute muscular sarcocystosis caused by *Sarcocystis* spp. in 2011 among travelers returning from Tioman Island, Malaysia [17]. There were 68 patients who met the case definition (probable=62; definite, confirmed by muscle biopsy histology or PCR, in 6). Commonly reported symptoms included myalgia, fatigue, fever, and headache. Elevated CPK levels and eosinophilia occurred about five weeks after exposure. The precise source of the outbreak was not identified. However, this outbreak serves as a reminder that a single short exposure in an inopportune location is sufficient to acquire a rare disease such as acute muscular sarcocystosis.

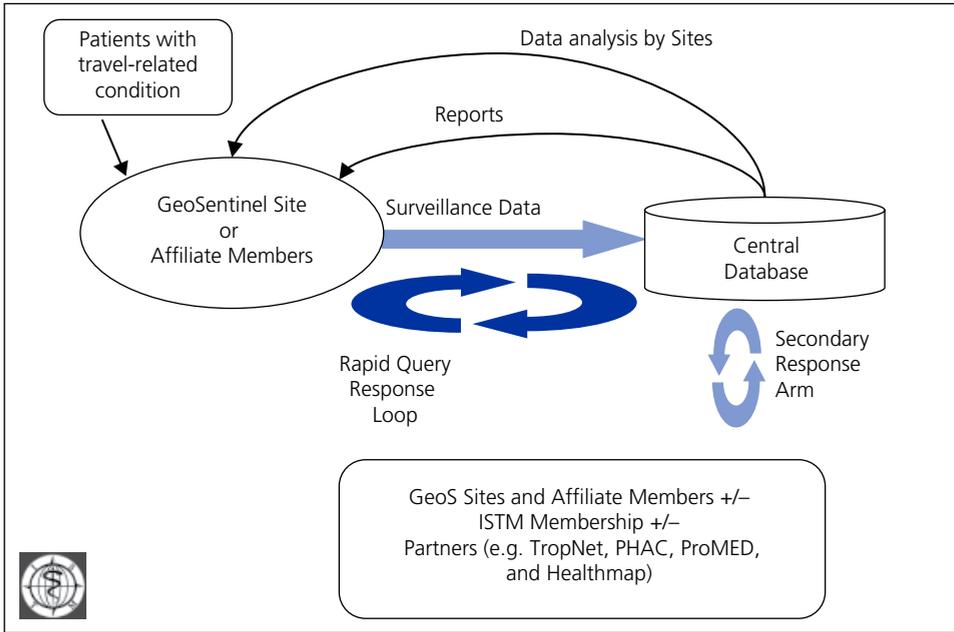


Figure 2.3 GeoSentinel reporting systems.
 PHAC = Public Health Agency of Canada

Surveillance related to mass gathering events

Identifying specific risk information for destination countries can be critical to protect public and individual health during mass gatherings. Ongoing data collection by global health surveillance systems allows country-specific analyses that can provide travelers and their healthcare providers with useful information to prepare for their trips. An early 2008 study of aggregated data from ill travelers to China in the previous decade allowed provision of evidence-based recommendations for the 2008 Beijing Olympics [18]. A similar study was published in 2010 prior to the FIFA World Cup in South Africa [19] and in 2014 before the FIFA World Cup in Brazil [20].

Surveillance and specific travel-associated infections – dengue

A GeoSentinel study from 1997 through 2006 defined, for the first time, seasonality of dengue in returned travelers [21]. Most (68%) of the 522 travelers went to Asia, 15% to Latin America, 9% to the Caribbean, 5% to Africa, and 2% to Oceania. Most infections were acquired in Thailand, India, Indonesia, and Brazil. Infection peaks occurred in South-east Asia in June and September, south-central Asia (i.e. India and Bangladesh) in October, South America in March and August, and the Caribbean in October. These data provide information on relative risk according to season. Detecting dengue cases at atypical times in sentinel travelers can inform the international community of epidemic activity in specific areas. For example, dengue acquired in Côte d’Ivoire and exported to France was identified in GeoSentinel and reported in ProMED [22].

Surveillance of rapidly spreading Zika virus infection

Identification of Zika virus infection in returning travelers evaluated at GeoSentinel sites [23] has aided in confirming active Zika virus transmission in several countries where circulation of the virus had not been recognized, including the first local Zika virus transmission in Costa Rica with exposure in December 2015 [24]. More recently, the acquisition of Zika virus in Vietnam in December 2015 [25] and in Maldives in June 2016 [26] established Zika virus circulation in those countries.

Geolocalization and visualization on the HealthMap platform

The GeoSentinel HealthMap collaboration (Figure 2.4) displays a subset of key GeoSentinel diagnoses from individual patients on a worldwide

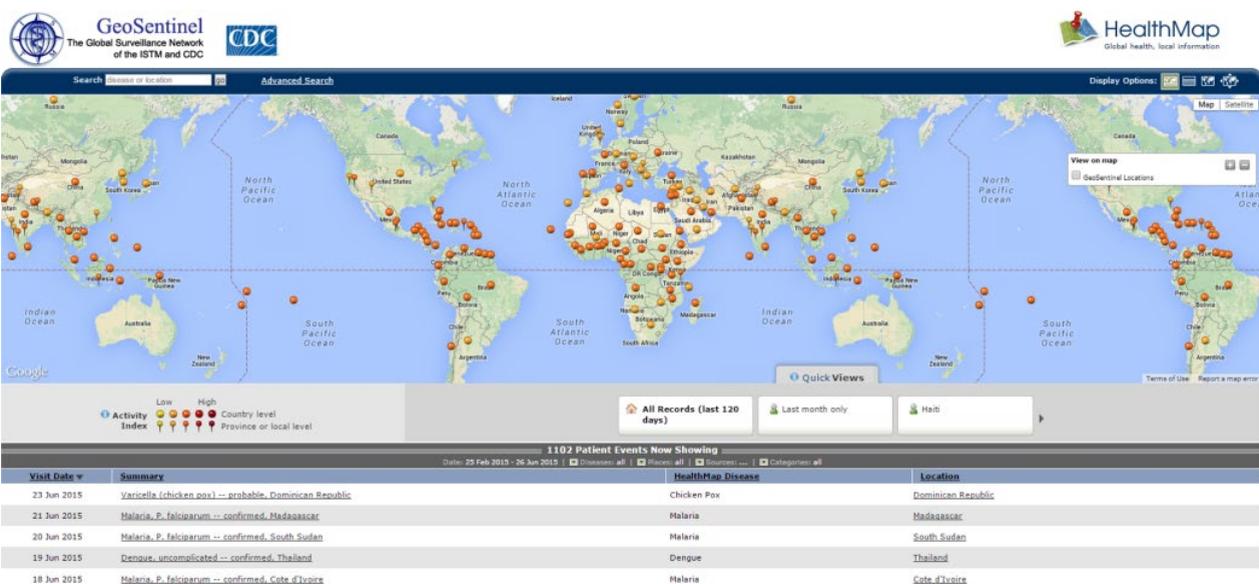


Figure 2.4 Output of significant events is visually geolocated using a GoogleMaps platform. HealthMap heralds a generation of surveillance technology that complements existing travelers' health surveillance systems. Source: Adapted from Brownstein 2008, 2009 [23,24].

Google map in real time as soon as patient records are entered into the system. Event icons display links to relevant web pages in seven languages from HealthMap's proprietary news-crawling software, allowing for detection of diagnosis clusters or suspicious syndromes (e.g. unknown fever) that arise in close proximity [27,28]. Patient icons also contain real-time generation of time-series visualizations of that event in the context of all previous occurrences of that diagnosis in the GeoSentinel database.

Analysis of morbidity and estimating risk by destination GeoSentinel provides a rich database of travel-related morbidity, which has allowed for considerable analysis of destination-specific infectious disease profiles and risk factors [29,30]. When patients present to clinicians after travel to the developing world, travel destinations are associated with the potential for diagnosis of certain diseases. Diagnostic approaches and empiric therapies can be guided by these destination-specific differences. In addition, advice for the prospective traveler can be prioritized and tailored. There are numerous examples of analyses of specific diseases, specific destinations, and specific patient characteristics [31–44].

One health

Students of emerging infectious diseases quickly recognized that the movement of pathogens between species was frequently linked to disease emergence. From its earliest days, ProMED-mail espoused a “one medicine” or “one health” philosophy that recognized the commonality of human and animal diseases. Just as disease outbreaks crossed geographic boundaries, they also have crossed species boundaries. Zoonotic diseases have proven to be the most frequent source of emerging human pathogens. Therefore, veterinary health has always played a major role in reporting on ProMED-mail and many outbreaks of zoonotic diseases have occurred (plague, Ebola, anthrax, tularemia, yellow fever, and rabies, among many others). Moreover, ProMED's founders realized that animal and plant diseases, even if they did not cross over to humans, could affect human health by impacting food supplies. Therefore foot and mouth disease, bluetongue (diseases exclusively of animals), and wheat rust could cause natural disasters and be used as agents of biological warfare.

Regional ProMED networks

Some regions of the world are underserved by communications technology and internet access. These areas often include emerging disease hotspots, such as the Amazon basin of South America, South-east Asia and sub-Saharan Africa. To help address these inequities, to improve cross-border communication within these regions and to improve the flow of emerging disease reports into and out of these regions, ProMED-mail has launched several regional networks. These networks have a degree of independence from the global ProMED list, although ProMED provides the infrastructure, funding, and training for them. A regional top moderator administers the regional network and makes decisions on which posts to carry, based on local interests.

ProMED's first regional network was ProMED-ESP, a Spanish-language network based in Latin America, and ProMED-Port similarly covers Portuguese-speaking Latin America. Other networks include ProMED-MBDS (Mekong Basin Diseases Surveillance) based in South-east Asia and ProMED-RUS which provides Russian-language reports for the independent states of the former Soviet Union. ProMED-EAFR and ProMED-FRA provide reports in English and French respectively covering the African region. The two most recent additions are ProMED-MENA, serving the Middle East and North Africa, and ProMED-SoAs, serving South Asia. Each service has a separately available e-mail list as well as its own website for those interested in those particular areas of the world. As expected, these regional networks have provided enormously rich content that is rebroadcast on the global ProMED-mail service.

Effectiveness of informal-source surveillance

Numerous other programs have begun to use informal-source surveillance, including automated systems like HealthMap and Canada's Global Public Health Information Network (GPHIN), Medisys and others as well as more human-driven systems such as FluTrackers (<http://flutrackers.com>). Moreover, the use of informal sources and the internet for outbreak detection has been widely accepted by the global public health community and codified in the revisions to the International Health Regulations ratified by the World Health Assembly in 2005 that took effect in 2007. Recent work has demonstrated that the time from the beginning of an outbreak until its detection and public reporting has been reduced as informal-source surveillance has blossomed [45].

Mobile technologies

In a traditional healthcare model, information flows between medical professional and patient through well-defined channels and processes. With the growth of readily accessible online health websites, individuals are increasingly accessing this information themselves before consulting a physician. In 2014, 1 in 20 Google searches were health related [46]. The nearly 6 billion health-related Google searches performed every day highlight that there is a large and growing global appetite for health information [47]. How people access information outside traditional healthcare encounters remains loosely structured and largely unregulated; however, modern mobile technologies possess the power and flexibility to alter how individuals can gather and share information on health and infectious diseases around the world.

Since the advent of the modern smartphone, increases in mobile computing power, the global expansion of cellular and Wi-Fi networks, and the emergence of the "Internet of Things" (i.e. an expanding global network of inanimate objects embedded with sensors that gather data, including data on individuals via wearable devices) have pushed smartphone and other mobile devices to the technological center of many people's lives [48]. Mobile devices are now key modalities used for media consumption, with a growing number of applications in other sectors (education, literature, banking, shopping, etc.). While public uptake across some sectors has surged, others such as healthcare have lagged behind. Recently, thousands of fitness and wellness-related mobile health applications have been developed (e.g. via Google Fit, Apple's HealthKit), but relatively few applications have been created pertaining to infectious diseases [49].

Mobile applications for infectious diseases

Several public health initiatives using mobile technology solutions for infectious diseases have been undertaken since the early 2000s but few remain in operation [50]. Many of these applications have been developed around a web-based interface, supplemented with mobile data collection components. Their uses have spanned academic and public health research, public education, continuing medical education for healthcare providers, and general information sharing. Currently, a number of mobile data collection tools exist which, although not specifically designed for infectious diseases, can facilitate the collection of such epidemiological data (e.g. EpiInfo, OpenXData, EpiCollect).

Current examples of mobile applications focusing on infectious diseases vary widely in their target audiences and in the sectors from which they were created. eMocha, a spin-off from the Johns Hopkins Center for Clinical Global Health Education, has created a suite of mobile health applications that are largely targeted to healthcare providers and public health officials [51]. Examples include applications that monitor symptoms among those exposed to pathogens (e.g. contacts of contagious cases) during epidemics, while others are focused on optimizing the clinical and public health management of various infectious diseases.

Although currently few in number, the number of public-facing mobile applications pertaining to infectious diseases is growing. Two distinct classes of such applications have emerged: (i) those created

by medical or public health professionals to provide expert knowledge to the public, and (ii) those that leverage public crowdsourcing as a means to gather infectious disease surveillance data for consumption by the medical and public health community. For example, the CDC recently launched a travelers' health application called TravWell, which provides information to the public about vaccines, preventive antimicrobials, and other important health considerations for travelers to countries around the world [52]. On the other hand, Flu Near You is a crowdsourcing mobile application developed jointly by Boston Children's Hospital, CDC, and the Skoll Global Threats Fund [53]. This application prompts users for weekly updates on their health status, symptoms (if any), onset date, and vaccination status to identify and track influenza-like illnesses across the US. Data are populated within a central server and then displayed to provide users with a weekly snapshot of influenza-like activity in their area. This form of public engagement or "participatory surveillance" could complement other more traditional modalities for timely surveillance of infectious diseases. Since it is estimated that 80% of the world's population will own a smartphone by 2020 [54], mobile technology holds tremendous potential in efficiently engaging vast numbers of people across distant geographies to gather and share infectious disease information in real time [50,55–57].

Conclusion

Timely global surveillance of infectious diseases can facilitate the early detection of outbreaks and strengthen their management, while informing guidelines and strategies to protect the health of travelers. Although the collection of population-based data can be challenging, particularly in resource-limited areas of the world, advances in web and mobile technologies offer considerable promise. Provider-based sentinel systems in returning travelers offer an innovative way to sample disease trends and emerging infections globally. Automated news scanning and data fusion technologies can contribute to early warning systems for disease emergence. Finally, the global rise of smartphone adoption in industrialized and developing regions of the world alike presents new opportunities for infectious disease surveillance through crowdsourcing.

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Chapter 3

Air travel – which infectious disease control measures are worthwhile?

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Air travel is recognized as a major contributor to the global spread of infectious diseases. Since the SARS epidemic in 2002–3, substantial public health resources have been invested in developing strategies for preventing the introduction and spread of infectious disease from one country to another, and between regions within any given country via air travel. Although emerging infectious diseases have received the most attention, several relatively common diseases also have the potential to cause serious illness, including death, and can spread via air travel. Several of the large-scale strategies for preventing disease spread via air travel are resource intensive, require substantial planning and preparation, impose considerable burdens on the travelers, and have been shown to be of questionable benefit. As we anticipate the next emerging infectious disease, or strive to maintain or achieve control of common communicable diseases, the importance of teaching and reinforcing the simplest, least costly, and least disruptive disease control measures cannot be overemphasized. At the individual level, these include consistently practicing good respiratory and hand hygiene, being current on immunizations, avoiding traveling while ill, and avoiding close contact with ill people. On the part of healthcare providers, this includes always inquiring about travel, and integrating that information into health maintenance, differential diagnosis, and treatment.

Introduction

Travel, and air travel in particular, has long been recognized as a major contributor to the global spread of communicable diseases [1,2]. The speed of twenty-first century air travel (a person can travel by air from one place to almost anywhere on earth within a day or two) has allowed people to be efficient transporters of pathogens, including introducing them to areas previously free of the particular pathogen. This includes vector-borne pathogens, such as malaria protozoa, and the dengue, chikungunya, and West Nile viruses, as well as pathogens that are spread person to person [1,2]. This chapter focuses on the person-to-person spread of pathogens.

The spread of diseases via the air transport of people can occur during travel (at the airport or during the flight) or after travel (once the person has arrived at his or her destination). The severe acute respiratory syndrome (SARS) epidemic of 2002–3, along with the emergence of the highly pathogenic avian influenza H5N1 threat in 2003, led to the investment of major public health resources in developing international and national response strategies for preventing the introduction and spread of emerging infectious diseases from one country to another, and between regions in any given country.

The H1N1 influenza pandemic in 2009, the Middle East respiratory syndrome coronavirus (MERS-CoV) that began in 2013, and the largest Ebola virus outbreak in history in western Africa that began in 2014 highlight the ongoing need for continuing and strengthening those efforts.

Emerging infectious diseases, however, are not the only diseases capable of posing public health threats that can be spread via air travel. Air travel also plays a significant role in the international and national spread of communicable diseases that have been around for hundreds or thousands of years [1]. The growing incidence and prevalence of multidrug-resistant tuberculosis (TB) and extensively drug-resistant TB are of particular concern [3]. While evidence from numerous flight-related contact investigations suggests that the risk of in-flight transmission is low, the risk exists, nonetheless [4,5]. Some countries with low incidence of TB disease and robust public health infrastructure spend considerable resources to conduct contact investigations to identify passengers who may have been infected, and to provide appropriate evaluation and treatment, if indicated [5,6]. However, the benefits versus the costs of these air travel-related TB contact investigations remain topics of debate among public health authorities [4].

Safe and effective vaccines are available for many communicable diseases that have potentially serious consequences, including death, such as measles, rubella, pertussis, and polio. Despite the availability of effective vaccines, many of these diseases continue to be endemic in many parts of the world, or were eliminated only to reemerge secondary to the effects of war, political influences or economic strife [1,7,8]. Fears of vaccine side effects and religious or philosophical beliefs have also created pockets of unvaccinated people in countries that otherwise have excellent vaccine coverage [9,10].

Measles

Measles, one of the most contagious diseases known, is still common in many parts of the world, including some countries in Europe, Asia, the Pacific, and Africa. Twenty million measles cases and 146,000 deaths are reported each year [11]. In the United States, despite the elimination of measles in 2000, more than 200 cases were reported in 2011 and more than 600 cases in 2014. Most of these cases were imported from abroad, including from England, France, Germany, India, and the Philippines, by returning, unvaccinated US residents [12]. Measles was eliminated from the rest of the Americas in 2002. However, the Pan American Health Organization states that measles elimination is “facing major challenges, with several ongoing importations of measles in some countries” [13].

Rubella

Rubella, another “old” disease, usually causes only a mild illness in children and adults. However, it can cause devastating outcomes, including stillbirth and a constellation of serious congenital malformations known as congenital rubella syndrome, if a woman is infected during her first trimester of pregnancy [14]. Rubella has been eliminated or nearly eliminated in several countries. The 33,068 rubella cases that were reported to the World Health Organization (WHO) from 161 countries in 2014 represent a 95% decrease from the 670,894 rubella cases reported in 2000. The elimination of rubella in the region of the Americas was announced in April 2015 [15]. Despite tremendous progress, tens of thousands of rubella cases still occur each year, particularly in the western Pacific, South-east Asia, Africa, and the eastern Mediterranean. Large outbreaks of rubella occurred in Poland and Japan in 2013 [14]. The persistent risk of importation by unvaccinated travelers to these areas once again highlights the ongoing importance of ensuring up-to-date immunization status in travelers and among the general public to prevent the importation and secondary spread of rubella.

Enteric diseases

Norovirus is a highly infectious viral gastrointestinal disease transmitted by the oral–fecal route by direct person-to-person contact or indirectly through contaminated food, water or environmental surfaces. Vomitus–oral transmission can also occur, including by aerosolization [16]. While the virus generally causes a mild-to-moderate, self-limiting disease, the infection can cause serious illness in the elderly and very young, usually due to dehydration. Norovirus is the cause of up to 17% of travelers' diarrhea in returning US travelers, and accounts for up to a quarter of all sporadic cases of gastrointestinal illness in the United States. The virus has also caused numerous outbreaks on cruise ships [17] and there is evidence of in-flight transmission [18,19].

Enteric bacterial pathogens cause the majority of travelers' diarrhea and, as with norovirus infection, most infections are short-lived and self-limiting. However, some people may develop persistent infection or postinfectious phenomena, such as irritable bowel syndrome or reactive arthropathy [20,21]. Some bacterial enteric pathogens can cause serious illness and complications, as well as mild or even asymptomatic infection. Potential complications associated with shigellosis include toxic megacolon, intestinal perforation, and the hemolytic uremic syndrome [21]. Typhoid and paratyphoid fevers are systemic diseases with a worldwide estimated incidence of 27 million cases and 210 000 deaths, mostly in the developing world. Most cases in industrialized countries are acquired during travel to endemic areas, and a vaccine is recommended for travel to these areas. Person-to-person transmission is via the fecal–oral or urine–oral routes. A chronic carrier state develops in 2–5% of cases [22].

Although evidence of in-flight transmission of enteric bacterial diseases is lacking, the potential exists because of the modes of transmission, especially given the cramped and limited number of lavatories onboard aircraft.

Travel-specific behaviors for preventing disease

Whether the diseases of concern are emerging infectious diseases or ones that have been around for hundreds of years, they are all amenable to behavioral measures that can prevent infection in the first place or prevent transmission to others. Some of these measures are disease specific, such as being current on immunizations for all routine and appropriate travel-specific vaccine-preventable diseases, avoiding travel to areas where a serious outbreak is occurring, avoiding close contact with ill people while traveling, avoiding contact with animals known or suspected to be reservoirs of the pathogen of concern, and by avoiding ingestion of certain foods or water.

Universal disease control behaviors

Other behavioral measures are universal in preventing the spread of disease, whether the mode of transmission is by the respiratory route, by direct contact with bodily fluids or excretions, by the fecal–oral, vomitus–oral or urine–oral routes, or by contact with contaminated environmental surfaces and other fomites. These universal and common-sense behaviors include not traveling while ill, practicing good respiratory etiquette (covering one's mouth or nose while coughing or sneezing), practicing good hand hygiene (frequent and thorough hand washing or cleansing and avoiding touching one's face or mucous membranes without first washing or cleaning the hands), and avoiding close contact with someone who is ill. Furthermore, they are inexpensive and are not inconvenient to implement. These measures need to be taught, stressed, and reemphasized repeatedly to help ensure they are consistently practiced, not only during travel but also during all activities of daily living.

To promote disease-preventive behaviors, a wide range of methods have been employed, such as placing posters and pamphlets in public locations and healthcare settings, teaching health-promoting behaviors in schools, and providing disease-specific fact sheets and travel-related health information

on local and national public health websites. These disease-preventive measures also need to be taught and stressed in the home and throughout the healthcare system.

Role of healthcare providers and healthcare workers

Healthcare providers (HCPs) play critical roles in preventing the introduction and spread of communicable diseases. All patients, not only those known to have travel plans, should be educated about recommended immunizations and basic health hygiene measures. Education about and reinforcement of disease prevention measures should be advocated whenever patients access the healthcare system, and especially during disease outbreaks or seasonal epidemics. Healthcare providers also need to inform patients who have been diagnosed with a communicable disease when they will no longer be contagious and ensure they understand not to visit public places or travel by public conveyance until they are no longer contagious.

Given the prevalence of international travel, all healthcare providers need to routinely ask about travel, obtain travel histories from all patients, and integrate that information into the differential diagnosis and treatment plan. The consequences of not doing so were tragically illustrated by the death from Ebola disease of a Liberia-born US resident who had traveled to Liberia during the Ebola outbreak, became ill after returning home, was seen at an emergency department, then sent home with a diagnosis of viral infection. The patient had informed someone in the emergency department that he had been in Liberia and exposed to someone with Ebola disease within 21 days of the onset of his illness. Unfortunately, that information was lost in the communication chain and did not reach the person providing the patient's care, and that provider did not ask the patient about travel or potential exposures [23,24].

Another poignant example of the consequences of not asking about travel involved the first case of MERS-CoV in the Republic of Korea in May 2015. That man, an employee of an agriculture products company, had been in the Arabian Peninsula and developed a febrile respiratory illness four days after returning home. It was not until his fourth visit to a healthcare facility that MERS-CoV was suspected and diagnosed. Until then, no one had asked the patient about recent travel, nor had he offered that information. Twenty-seven secondary cases were linked to that first case, many of them from nosocomial spread [25].

Health facility infection control measures

Standard and transmission-based isolation precautions—airborne, droplet, and contact—are well known and established for the hospital setting. Judiciously following procedures for the isolation precautions prescribed for a patient is critical to infection control. The potential consequences of failing to do so were also illustrated when two nurses were infected with the Ebola virus while providing care to the patient mentioned above [23,26]. As of October 2, 2015, 186 cases and 36 deaths from MERS-CoV have been reported in the Republic of Korea. Nosocomial spread has caused the majority of secondary and tertiary cases, reflecting the poor infection control in its public healthcare system [25,27].

Airline responsibilities

The airline industry also has responsibilities and plays important roles in preventing the spread of communicable disease. The International Civil Aviation Organization (ICAO), a specialized agency of the United Nations, works with the 191 member states and aviation organizations to develop international Standards and Recommended Practices (SARPs). The states reference these SARPs when developing their legally enforceable national civil aviation regulations, including those involving communicable diseases [28].

The goal of SARPs related to communicable diseases in air travelers is to promote early identification of travelers with a possible communicable disease of public health importance. This enables in-flight measures for reducing the risk of disease spread to be implemented quickly and to facilitate a timely

and appropriate public health response upon landing. ICAO Document 4444 [29] and Annex 9 to the Chicago Convention, Chapter 8, 8.15 [30] dictate how the pilot in command of an international aircraft is to report a possible communicable disease in a traveler to the appropriate public health authorities. The ICAO Guidelines for States were written to assist them in developing aviation-related plans for any communicable disease that may pose a public health risk. The Aircraft General Declaration describes what signs and symptoms should be considered indications of a possible communicable disease that requires reporting [31].

In the United States, the US 42 Code of Federal Regulations (CFR), Part 71 requires that deaths and certain signs and symptoms suggestive of a communicable disease on international flights arriving in the United States be reported to the Centers for Disease Control and Prevention (CDC). Reporting requirements on interstate flights are stipulated in 42 CFR, Part 70.4. The CDC developed guidelines for airlines to facilitate reporting and on-ground response on flights arriving in the United States to assist the airlines in complying with the federal requirements [32]. The CDC guidelines are consistent with the ICAO SARPs. In-flight infection control guidelines for cabin crew for managing ill travelers during a flight were also developed [33]. The guidelines provide information for cabin crew on general infection control measures, as well as measures targeting respiratory, gastrointestinal, and bloodborne diseases. Examples include separating the ill traveler from other travelers; minimizing the number of crew interacting with the ill person and keeping interactions to a minimum; providing tissues and asking the ill person to cover the mouth when coughing or sneezing, and providing a face mask, if appropriate; and designating one lavatory for someone with diarrhea or vomiting. There is also guidance on targeted clean-up and postflight measures.

Large-scale infectious disease control measures

Several large-scale infectious disease control measures related to air travel were implemented during the SARS epidemic and the A(H1N1) pandemic, and are ongoing for the Ebola disease outbreak in West Africa and the MERS-CoV outbreak in the Middle East and the Republic of Korea. These include entry and exit screening at airports, isolation of ill travelers and quarantine and monitoring of other travelers on the same aircraft, contact tracing of travelers on flights who were potentially exposed to an infected traveler, travel restrictions, and providing information to travelers, airlines, and health authorities. Most of these measures require the expenditure of substantial resources, and involve the collaboration and cooperation of public health and nonpublic health agencies and organizations at the local, regional, national, and international levels.

Some measures place significant burdens on travelers, ranging from missing connecting flights to being held abroad in quarantine for several hours to days. But how effective are these large-scale control measures in preventing the introduction and spread of the targeted diseases?

Evaluation of the effectiveness of infectious disease control measures

Huizer et al evaluated various control measures and determined their relative effectiveness in preventing the transmission of diseases via air travel [34]. They reviewed articles on infectious disease control measures related to air travel that were published in peer-reviewed journals between January 1990 and September 2013. Included in that review were articles that described cases, modeling studies, evidence-based studies, and evaluations of events. From these articles, the authors identified and extracted control measures and the diseases for which they were implemented, and developed a system for scoring each measure. They identified six categories of control measures that involved air travelers.

- 1** Exit and entry screening, including health declarations, medical examination and laboratory testing, and thermal screening
- 2** Providing information to travelers and authorities
- 3** Isolation, quarantine, and health monitoring
- 4** Contact tracing

5 Hygiene measures**6** Travel restrictions

The scoring elements assigned to each control measure included:

- outcomes (extent to which the measures were predicted to prevent (models) or actually prevented disease transmission)
- resources (required funds, supplies, personnel)
- preparations (efforts required to implement the measure in a timely manner)
- passenger inconvenience (burden imposed on the passenger)
- compliance (actions required of passengers).

The authors concluded that the most effective infectious disease control measures were providing information to travelers; isolating ill travelers; monitoring exposed travelers; and hygiene measures (airplane disinfection, air filtering, personal hygiene). Based on their scoring criteria, these measures had scores of 3 or 4 points. Contract tracing, in contrast, had a score of 1. Entry and exit screening, quarantine of fellow travelers, and travel restrictions received the lowest score of minus 4 because of little effect on the outcomes, substantial expenditures or cost in terms of resources, the amount of preparation required, passenger compliance required, and passenger inconvenience [34].

Providing information to passengers Providing information to passengers was determined to be an effective control measure for several reasons. Perhaps foremost is that it is not resource intensive, does not require extensive preparation, and is not inconvenient for passengers. In addition, some studies showed that providing information could affect travel choices, increase compliance with recommended control measures, and promote care-seeking behaviors. However, since an individual's behavior depends on understanding, interest, and choice, providing important information does not guarantee it will be integrated or heeded [34].

Isolation Isolation of ill people to prevent transmission of disease to others is an effective and commonly used control measure in the hospital setting. It may also take place in the home if the person does not require hospitalization, and to a limited degree, it may take place in the setting of an aircraft. Legal enforcement of isolation may be at the local or state/province level or at the federal level, depending on the disease, the country, and the circumstances involved. Isolation may be an effective control measure for preventing disease spread via air travel if the ill person is symptomatic and isolated quickly. Furthermore, it is relatively inexpensive since it primarily involves only the ill person and does not affect other passengers who were on the flight [34].

Health monitoring Health monitoring of people who were exposed to someone with a communicable disease of public health concern is a crucial aspect of quarantine or "semi-quarantine" (some activities allowed outside the home as long as interaction with others or travel by public conveyance is avoided). It ensures that the person receives prompt medical care if illness develops, it prevents exposure to others if the person is contagious before the onset of symptoms, and if the person is allowed to stay at home, the inconvenience of the measure is significantly lessened. It does require some resources in terms of personnel and possibly thermometers for use by the person being monitored, but the benefits compared to the costs and inconvenience outweigh the costs [35].

Hygiene measures The hygiene measures that were evaluated included aircraft disinfection, air filtering, and use of facial masks. Aircraft disinfection and general cleaning are routine practices for preventing disease spread on aircraft [2,36]. Guidelines for special circumstances, such as contamination by respiratory secretions, body excreta or blood, are also available to promote optimal infection control [33]. Wearing of face masks by a person with a respiratory illness may prevent the spread of pathogens from coughing, sneezing or talking. However, the wearing of face masks by non-ill passengers or crew is not recommended. The high-quality air filtration systems used in most modern aircraft are as efficient as those used in hospitals, and more efficient than those used on trains, in office buildings, and in other public places [2].

Entry and exit screening Entry screening of air travelers arriving in China during the A(H1N1) pandemic identified 21.7% (132/608) of cases known to have been imported; however, officials screened

600000 passengers to identify those 132 cases [37]. During the SARS epidemic, among 1.8 million passengers who were screened upon entry to Australia, four cases of SARS were identified (0.0022%), but 25 symptomatic passengers with SARS passed through screening without being identified [38]. The WHO estimated that more than 90% of the public health benefit of entry/exit screening for pandemic influenza A(H1N1) could have been achieved by targeting just eight international airports (exit screening at Mexico's six largest international airports and targeted entry screening at the international airports in Shanghai and Tokyo) [39]. The European Centre for Disease Prevention and Control (ECDC) concluded that entry/exit screening had not proven to be effective in past epidemics, such as SARS and pandemic influenza A(H1N1), and was not an efficient tool for Ebola virus disease [40].

Health declarations Health declarations and thermal screening are tools used in exit and entry screening. In health declarations, passengers are required to report their health status, travel plans, and contact with infected people. Limitations to the usefulness of health declarations include their dependency on the passenger being truthful, their potential to miss cases if the criteria are too restrictive, such as asking about a self-measured fever, or the potential to be too resource intensive if the criteria are too inclusive, such as asking that *any* symptom be reported [34]. The usefulness of thermal screening is also limited by several factors, including variation in accuracy levels of different scanners, the effect of air flow on accuracy, and the effects of room temperature, humidity, time of day, exposure to hot and cold temperature, sunburn, medication, make-up, perspiration, pregnancy, menstruation, and hormonal treatments on body temperature. The body location where the temperature is measured also affects the outcome. During SARS, thermal entry screening of more than 35 million passengers in Canada, China, and Singapore did not detect any cases, nor did exit screening of 7 million cases [34].

Travel restriction Travel restriction was assigned a score of minus 4, based on the predicted outcomes, resources required, inconvenience to travelers, and the need for traveler compliance, and was thus determined not to be an effective control measure. Most of the articles that were evaluated involved mathematical modeling studies that addressed international travel restrictions for pandemic influenza. Those studies concluded that international travel restriction could delay the introduction of pandemic influenza to a new area long enough to allow for preparation for other local control measures, but the travel restrictions would need to be very restrictive, (a 95% reduction in flight volume). Other studies' conclusions were that travel restriction would be most beneficial if used in conjunction with other local control measures, would only work when there are few cases, and would be ultimately unlikely to significantly reduce the global spread [41–43].

Another type of travel restriction is on an individual basis. The United States considers individual travel restriction to be an effective and important tool for preventing disease spread, and has a well-established protocol that includes collaboration with Federal Customs and Border Patrol, airlines, and local and state public health officials. Success of this type of restriction is not dependent on traveler compliance, but rather depends on interagency collaboration [44]. Travel restriction was originally primarily used for infectious TB. From June 2007 to September 2015, approximately 400 people with infectious TB were prevented from traveling while infectious, with an average of 62 people per year (personal communication with Dr Illig, 9/11/15). In response to the evolving Ebola outbreak that began in 2014, a federal decision was made to expand the criteria for imposing travel restrictions to include the need to respond to a public health outbreak or to help enforce a public health order [45]. During 2014, 165 people were placed on travel restriction; 75% of these were healthcare workers returning from West Africa and their families (personal communication with Dr Illig, 9/11/15). Unlike for TB, the duration of those travel restrictions was for only three weeks (the incubation period for Ebola disease) unless disease developed.

Individual travel restriction can be an important control measure for infectious diseases. However, because of the resources needed, the inconvenience to the traveler, and the need for interagency collaboration, implementation of travel restrictions should involve a protocol with clearly defined criteria, not only for imposing the restriction but also for lifting it. Other important factors requiring careful consideration include the characteristics of the specific disease, the circumstances involving that disease, the availability of resources, and the national perspectives and political climate.

Contact investigations (contact tracing) Air travel-related contact tracing was also determined to be of limited effectiveness because it requires substantial cost (personnel), the window for any interventions may be narrow, and it is dependent on the availability of passenger contact information [34]. Flight-related contact investigations that were conducted for SARS had varying outcomes. One study found no evidence of in-flight transmission based on serological testing, but only 36/250 (14.4%) of the passengers identified as sitting within four rows of a confirmed, symptomatic case participated [46]. Another study found one case among 156 passengers (0.64%). Another study found 22 lab-confirmed or probable cases of SARS among 120 travelers (18.3%) who had traveled on a flight with one symptomatic person with lab-confirmed SARS, but at most one case of SARS among travelers who had flown on a flight with four lab-confirmed cases [47].⁴⁷ It is possible that the situation in which there was evidence of transmission to 18.3% of fellow travelers involved a person who was a “super spreader” [48]. A contact investigation involving 268 potential contacts of a person with lab-confirmed Ebola virus disease who had traveled on two flights did not identify any cases among 286 potential contacts [49].

Nonetheless, flight-related contact investigations can be important tools in preventing the spread of disease via air travel, depending on the disease characteristics and the circumstances, as well as the resources and priorities of the country or countries involved.

The United States routinely conducts flight-related contact tracing for measles, and after thorough evaluation, found the protocol to be efficient [50]. Yet other countries may not consider flight-related contact investigations for measles to be worthwhile. The WHO has provided guidelines for flight-related TB contact investigations [51]. However, many countries have their own national policies that, although based on WHO guidelines, may be more or less inclusive and, in part, dependent on their resources and TB incidence [4–6,52].

Quarantine Quarantining people possibly exposed to an infectious disease is an age-old and effective tool for preventing them from spreading the disease to others [35]. While quarantining travelers who were on a plane with a suspected or confirmed case of a disease of concern could theoretically prevent disease spread, the cost of implementing such a quarantine effort, and the inconvenience and cost to travelers would be tremendous. In their review, Huizer et al found that during the A(H1N1) influenza pandemic, 1/151 (0.66%) of identified cases were detected during quarantine of a plane that arrived in Japan, and 120/609 (19.7%) of imported cases identified in China, which represented 2.5% of the 4768 passengers who were quarantined [34].

For controlling the global spread of infectious diseases, the most effective large-scale measures appear to be providing information to travelers, isolating ill travelers, monitoring exposed travelers, and hygiene measures. Individual travel restriction and contact investigations can also be beneficial. Resource-intensive disease control measures, such as entry/exit screening, passenger quarantine, and international travel restriction, remain important potential measures that may be warranted for certain diseases under certain circumstances, but require careful scrutiny and consideration of associated ramifications. Personal measures of respiratory and hand hygiene, although age-old, play critical and pertinent roles in communicable disease control. Perhaps more so than ever as global travel continues to increase in scope as well as in accessibility.

Recommendations

As a global society, we need to repeatedly promote, teach, and emphasize the practice of good respiratory etiquette and good hand hygiene during travel, at home, and in the community. Not traveling while ill and avoiding close contact with others who are ill also need to be emphasized. Healthcare providers need to promote routine and travel-specific immunizations, and ensure that patients and their children are appropriately up to date. They also need to consistently ask patients about intended travel and recent travel, and incorporate that information into their health maintenance counseling, as well as into their differential diagnosis and treatment plan. As we anticipate the next emerging pandemic or epidemic, or strive to maintain or achieve control of common communicable disease, the importance of these simple, least costly, and least disruptive disease control measures cannot be overemphasized.

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Chapter 4

Infectious illnesses on cruise and cargo ships

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General precautions

Maritime ships create a unique environment with specific health concerns. In order to remain healthy at sea, maritime travelers should consult their medical provider before boarding a ship. Travelers with medical conditions should carry sufficient prescription medical supplies and medications in the original labeled containers along with a letter from their provider.

Preventing acute gastroenteritis

Maritime travelers should be reminded to wash hands frequently with soap and water, especially before and after meals and after using the bathroom. They should also avoid eating uncooked or undercooked food and drink only bottled water or beverages if the water source is questionable. Travelers should avoid persons with symptoms of acute gastroenteritis, and should report symptoms of acute gastroenteritis promptly to health staff on board.

Preventing respiratory and vaccine-preventable illness

Influenza season is year round on cruise ships. All travelers should receive the seasonal influenza vaccine at least two weeks prior to boarding and, if possible, receive the vaccine for the hemisphere within which they will be traveling. Maritime travelers should be up to date on all routine vaccinations, including varicella, meningitis, measles, and rubella.

Preventing vectorborne illness

Insect repellants for skin and clothing, covering skin, and staying in air-conditioned areas when possible can aid in preventing vectorborne diseases. Yellow fever vaccine and malaria prophylaxis should also be used when indicated.

Introduction and background

More than 100 disease outbreaks have been reported from ships in the past 30 years [1]. Ships may serve as a source of infection or may facilitate disease transmission; they may also be the vehicle for the international spread of disease. The World Health Organization (WHO) estimates that the average

cruise voyage lasts about seven days, but ranges from several hours to several months [1]. It is estimated that the number of passengers traveling on cruise ships worldwide increased from 13–15 million in 2007 to more than 20 million in 2014 [2]. Travelers from North America were estimated to account for the majority but a decreasing proportion of travelers: approximately 67% in 2007 and 55% in 2014. All continents are visited by cruise ships, and cruise itineraries include shorelines and surrounding areas that may not be part of a typical air or ground travel itinerary. Passenger and crew numbers vary depending on the size of the cruise ship, with a trend toward larger vessels akin to floating cities; it is estimated that, on average, a cruise ship carries about 3000 passengers and 1000 crew [1].

Article 8 of the International Labor Organization Convention [3], which is a legally binding international treaty when ratified by a country's competent authority, requires vessels carrying more than 100 crew members on an international voyage of three days or longer to provide a physician for care of the crew. The revised International Health Regulations (2005) address health requirements for ship operations, including providing standards for ship and port sanitation, vector and rodent control, and disease surveillance, as well as guidance on response to infectious diseases. Safety on board ships and waste and ballast water disposal are regulated by conventions of the International Maritime Organization. However, while individual countries may have disease-reporting requirements related to the shipping industry for vessels entering their ports, there is no international surveillance system [4].

The WHO estimates that the typical cruise traveler is 45–50 years of age and that senior citizens represent about one-third of all passengers. Chronic medical problems are among the most common medical problems reported on cruise ships. Other commonly reported health problems include respiratory tract infections, injuries, motion sickness, and gastrointestinal illness [1].

A comprehensive review of issues related to diseases and outbreaks on passenger ships found that most outbreaks for which a pathogen was determined were due to norovirus, *Legionella* spp., *Salmonella* spp., *Escherichia coli*, *Vibrio* spp., and influenza A and B viruses [5]. Further, the report found that modes of transmission included person to person, waterborne, and foodborne, and that exposures during shore excursions were responsible for some outbreaks [5]. Outbreaks of other diseases of public health concern, such as measles, rubella, varicella, meningococcal disease, hepatitis A, and tuberculosis, among passengers and crew have also been reported [1,6].

Diagnosing and appropriately treating illnesses at sea depend on having the proper equipment, medical personnel, and medications. Although the Cruise Line International Association (CLIA) sets standards of care for its member cruise lines, there is no international agency governing cruise line management. Medical facilities aboard cruise ships vary by cruise line, and some may only be equipped to treat minor nonemergency conditions. Facilities aboard ships that stop in the United States typically adhere to the American College of Emergency Physicians guidelines which outline qualifications for medical personnel on board ships [7].

Influenza

Worldwide, seasonal influenza affects an estimated 5–10% of adults and 20–30% of children, resulting in 250000–500000 deaths each year, according to the WHO [8]. Respiratory illnesses make up an estimated 27% of all recorded illnesses on cruise ships [9] and 16% of medical complaints on cargo ships [10]. Numerous influenza outbreaks have been documented on cruise ships [11–14], military ships [15–17], cargo ships [10] and other vessels, such as sport fishing boats [18]. With regard to influenza, maritime travel creates several unique challenges and issues for consideration.

Yearly influenza epidemics occur in fairly predictable patterns on land in temperate regions, mainly during the winter months, and somewhat less predictably throughout the year in tropical regions. However, at sea, there appears to be no clear seasonality. Large influenza outbreaks have been documented on board ships in the summertime in temperate regions [12,14,19], and on ships that did not visit regions with significant influenza activity [20]. Thus, influenza should be considered to occur year round on ships regardless of itinerary [21]. In addition, influenza outbreaks on ships may be complex, involving multiple strains that may or may not be covered by the currently available influenza vaccine [22].

Passengers and crew on board ships are in close contact for extended periods of time in a semi-closed environment [13], creating suitable conditions for spread of respiratory viruses. Evidence suggests that the crew may serve as reservoirs for influenza on cruise ships and by continuing to work while symptomatic, can sustain an outbreak for multiple voyages as additional new susceptible passengers continue to board [12]. Cruise lines typically recommend that passengers do not board if ill, and present immediately to the ship medical clinic if they become ill; however, passengers may fear that travel plans will be interrupted and be reluctant to report symptoms and comply with isolation [11].

In addition to factors that promote transmission of influenza on ships, there are factors that make it difficult to manage on board. Cruise ship passengers are frequently at increased risk for influenza complications as one-third of passengers are age 65 years or older and co-morbidities are frequent [23]. Although medical personnel on cruise ships typically are able to perform rapid testing for influenza A and B, and are recommended to have a sufficient supply of influenza antivirals available, more advanced care may be limited, requiring medical evacuation of the patient [7]. Testing capabilities, in addition to medical staff and medication, are limited, if not absent, on most cargo ships, although recent research suggests that rapid point-of-care testing may be implementable and useful on these vessels [24].

Vaccination for seasonal influenza at least two weeks prior to boarding, regardless of the time of year, is the primary prevention measure [8,25]. However, this can be challenging in summer months, when vaccine may not be available. If vaccine is not available, clinicians should stress the need for hand and respiratory hygiene and to avoid close contact with others who may be sick [26]. The WHO recommends that, in years in which the northern and southern hemisphere influenza vaccines differ, high-risk travelers should be vaccinated specifically for the hemisphere to which they are traveling at least two weeks prior to travel or, if not available, as soon as they arrive to their destination [27]. Maritime travelers at high risk of influenza complications should discuss the use of antiviral treatment or prophylaxis with their healthcare provider prior to travel [25].

Acute gastroenteritis

Historically, the most common illness acquired while traveling by cruise ship by both passengers and crew is travelers' diarrhea [28]. Countries, political unions, and cities, such as the United States [29], the European Union [30], and Sydney, Australia [31,32], respectively, have implemented programs to facilitate reporting from cruise ships, inspection of ship environments or increased sanitary, engineering or operational preventive actions; however, outbreaks of acute gastroenteritis still occur. Evaluations have found that ship inspection scores are not always predictive of factors leading to outbreaks of acute gastrointestinal illness [33–35]. Most outbreaks of acute gastroenteritis have been linked to norovirus, bacterial agents such as enterotoxigenic *E. coli*, and unknown or unproven agents [33,36], with norovirus as the leading recognized cause [37,38]. For some agents, gastroenteritis outbreaks have been associated with shared bathrooms or the number of persons sharing communal bathrooms, suggesting contamination, perhaps due to vomitus, as a likely source [39]. Outbreaks have also been caused by *Salmonella*, *Shigella*, *Vibrio*, *Staphylococcus aureus* enterotoxin, *Clostridium perfringens*, *Cyclospora cayentanensis*, and hepatitis A and E viruses [25]. It is estimated that postinfectious irritable bowel syndrome may occur in up to 17% of persons who have had travelers' diarrhea [40].

Norovirus is a leading agent of acute gastroenteritis on ships, and most outbreaks have been reported in the United States and Europe [37]. Symptoms include abdominal pain, nausea, vomiting, diarrhea [25], and low-grade fever. Symptoms are debilitating but not usually serious and usually resolve within 48 hours. According to a systematic review by Bert et al, norovirus outbreaks on cruise ships are most often due to contaminated food sources [37], although outbreaks are often associated with other or multiple modes of transmission [41] such as waterborne, environmental contamination, and person-to-person spread. Outbreaks involving the same strain sometimes occurred on subsequent voyages, suggesting the source was embedded and that decontamination efforts had not eliminated the virus from the environment, or infected crew members might have passed infections on to new arriving passengers [36,41]. Norovirus is highly infectious with a low infective dose [42].

Vaccines are not available for the typical agents causing acute gastroenteritis on cruise ships. Preventive measures include frequent handwashing by passengers and crew using soap and water, stringent adherence to food safety measures during food preparation, environmental disinfection, isolation and management of ill people and educating travelers about safe food practices during shore excursions. However, food avoidance measures have not been shown to be consistently effective [40]. Alcohol-based hand sanitizers (at least 60% alcohol) should not be considered an equal alternative to soap and water, but can be applied for immediate use when hands are not visibly soiled between appropriate handwashing. When there is an ill passenger or crew member on a cruise ship with symptoms of acute gastroenteritis, this should be promptly reported to health personnel aboard the ship and ill persons appropriately managed. Ensuring adequate hydration to keep up with fluid losses is the mainstay of treatment for most of the infectious agents causing acute gastroenteritis. Antibiotic treatment has been shown to be effective in reducing the duration and extent of travelers' diarrhea and may be appropriate for some bacterial agents; ciprofloxacin is the recommended treatment (including for self-therapy when appropriate) of travelers' diarrhea, except when illness is acquired in South or South-east Asia, where azithromycin is preferred [40]. Laboratory diagnosis is not likely to be possible, so treatment will be based on clinical diagnosis. Measures to limit transmission should be implemented promptly, including appropriately disinfecting high hand contact surfaces, and known contaminated surfaces using products and procedures approved by the appropriate authority and separating ill persons from well persons, especially among those traveling together.

Vaccine-preventable diseases

Varicella (chickenpox)

While the incidence of varicella on board seagoing vessels is unknown due to the variability in reporting requirements of different countries, varicella is commonly observed on ships and is one of the most frequently reported vaccine-preventable diseases in cruise ships with US ports of call [43].

Varicella is a well-established disease of concern for seagoing vessels. The severity of varicella illness among adults, combined with its ease of spread in the semi-closed ship environment and volume of multinational crew members who lack immunity to varicella, all potentiate its morbidity in a maritime setting [43–45].

Outbreaks of varicella on board seagoing vessels have been reported worldwide, ranging from five to 89 sick persons within two varicella incubation periods based on reports from ships sailing in North American and European waters [43,44]. Outbreaks that span multiple sailings can affect ship operations and expose additional passengers who may be at high risk for varicella complications [46,47].

The majority of reported varicella cases on board seagoing vessels occur in unvaccinated adult crew members from tropical countries (such as India, Indonesia, and the Philippines) where varicella immunity is generally acquired at a later age and varicella infection is common in adolescents and adults [48]. Additionally, both the symptoms and complications of varicella are more severe in adults than in children. On a seagoing vessel, this can result in ill crew members isolated and absent from work duties for days, loss of crucial operational staff, and costly medical evacuations.

Vessels experiencing varicella outbreaks are encouraged to identify close work and social contacts [1] and screen them for susceptibility to varicella [48]. Vessels with smaller crews (<15) should consider all crew members as contacts. All susceptible contacts should be monitored for signs and symptoms of disease and vaccinated with the initial dose of varicella vaccine during the outbreak and a second dose 1–3 months later, depending on their age [48]. All case patients should be isolated until all lesions have crusted over, and should not be roomed with persons lacking proof of immunity to varicella. Case patients older than 12 years of age should be given aciclovir treatment [48].

Varicella is a preventable illness through vaccination. A small number of studies have demonstrated cost-effectiveness by either vaccinating all crew members prior to vessel employment or establishing a preemployment screening program for varicella immunity [49,50].

Measles and rubella

Measles and rubella are reported on ships much less often than varicella. Measles is a highly infectious disease, with up to 90% of susceptible persons developing measles after exposure [51]. Measles transmission has been documented during international travel on ships, planes, and even during short waiting periods in areas such as airport gates [51–53]. Measles is a concern on ships due to the semi-closed environment and variable vaccination coverage of crew members and passengers. Due to the approximately two-week incubation period of measles, travelers on ships may become exposed to measles and develop illness after they disembark the ship, causing outbreaks in port communities [54]. One report documented a cruise ship passenger who caused an outbreak in a hospital after reporting to the hospital emergency department with fever and rash [55]. When evaluating febrile illness, providers should ask about travel, including cruise ship travel. Public health entities should encourage ships to immediately report suspected cases of measles on ships and coordinate communication with local health authorities and ships to encourage enhanced surveillance for measles when a case is identified to prevent outbreaks of measles in port communities imported from ship passengers [55].

On ships, any person reporting fever and maculopapular rash, especially when associated with cough, coryza or conjunctivitis, should be considered a suspect for measles and isolated immediately. If one case of measles is reported on the vessel, cruise ship medical providers should consider notifying everyone on board the ship to encourage early reporting and isolation, as anyone could have been exposed during preboarding or in other common areas of the vessel. Crew members should be vaccinated or screened for measles immunity prior to boarding the vessel, and vaccine should be available on the ship to immunize susceptible contacts if a measles case is identified [52].

Rubella has also been observed on ships, primarily in nonvaccinated crew members. Pregnant women should be screened for rubella immunity prior to boarding a cruise ship, and delay travel if nonimmune [25].

Meningococcal disease

Meningococcal disease progresses rapidly and is potentially life-threatening. It is difficult to diagnose in the early stages when it is most treatable because its clinical symptoms resemble other less life-threatening illnesses, and confirmation of the disease usually requires isolation of *N. meningitidis* from a sterile site, which is usually not possible on a ship [56]. Very few cases of meningococcal disease on ships have been reported in the literature. A case of suspected meningococcal meningitis was reported on an aircraft carrier in a 24-year-old sailor who presented with 4–7 days of symptoms of a common cold, headache, and photophobia and was found to have a petechial rash upon physical exam [57]. The sailor was rapidly isolated and treated with antibiotics, a lumbar puncture was performed, and close contacts on the vessel were given prophylaxis. Additionally, notification was made to the ship's last port of call so a shore-based contact investigation could be performed.

Rapid identification, assessment, and treatment of suspected meningococcal disease are necessary to reduce mortality on ships. Ships without medical providers should be familiar with signs and symptoms of meningococcal disease, be comfortable with isolation of suspected cases and use of droplet precautions, and consult a medical provider ashore. Medical evacuation of the traveler, or a detour to another port of call, may be necessary to get the sick traveler to a higher level of care. The WHO recommends that cargo ships carry adequate supplies of ceftriaxone to treat suspected meningococcal disease cases until intravenous antibiotics can be initiated [58]; these recommendations may vary for other settings. Cruise ships with medical providers should also carry antimicrobial treatment and prophylaxis for meningococcal disease and be comfortable identifying close contacts, including cabin mates, bathroom mates, and childcare center contacts. Close contacts also include persons directly exposed to the traveler's oral secretions, and may include sexual contacts, persons who shared cigarettes with the traveler, meal companions (if they shared food or utensils), and medical staff or other persons who may have performed mouth-to-mouth resuscitation or had other exposure to the traveler's oral

secretions, without use of personal protective equipment [56]. Notifications to health authorities at recent ports of call may also be necessary to conduct a rapid shore-based investigation. Vessel companies may consider vaccinating crews prior to beginning employment on a vessel to reduce the risk of an outbreak or costly medical evacuation [56].

Legionnaires' disease

Legionnaires' disease is a severe pneumonia caused by inhalation of aerosolized water containing gram-negative *Legionella* bacteria. Pontiac fever is a milder infection with similar symptoms to Legionnaires' disease. Cruise ship travel-related outbreaks of Legionnaires' disease are often unrecognized initially and may be detected after reports of clusters of compatible symptoms among cruise ship passengers on repeated trips [57]. A systematic review of travel-associated Legionnaires' disease events found that ship-associated events occurred repeatedly at the same environmental site [58].⁵ Legionnaires' disease transmission on cruise ships has most commonly been associated with hot tubs and whirlpool spas [58,59], including contaminated bath filter stones in spas [58]. Common contributing factors include inadequate disinfection, maintenance, and monitoring, water stagnation, poor temperature control, and poor ventilation [58]; colonization of water distribution systems has been positively correlated with ship age [60].

Symptoms usually start 2–10 days after exposure, with older travelers (≥ 65 years) and those with underlying medical conditions at increased risk for infection. Prompt antibiotic treatment is required and the diagnosis can be made by *Legionella* urine antigen testing. Identifying the pathogen requires culture of respiratory secretions and is important for the interpretation of environmental samples since *Legionella* is common in the environment. Cases of Legionnaires' disease should be quickly reported to allow public health officials to determine if there are links to previously reported clusters and to stop potential clusters and new outbreaks. When cases of Legionnaires' disease are linked to an environmental source, it is important to take samples for laboratory testing and to disinfect the source to prevent continued transmission.

Vectorborne diseases

Maritime travel has an ancient history of vectorborne disease risk, with early practices including quarantining ships in response to plague. In the past century, the introduction of multiple mosquito vectors to previously unaffected regions has occurred through shipborne transportation [61,62]. Although modern reports of transmission of mosquito-transmitted diseases such as malaria, dengue, yellow fever, and chikungunya while at sea are few [63], transmission once in port has been documented numerous times and is considered a significant threat to tourists and crew members [64–71].

Malaria remains a significant disease burden in 97 countries and according to the WHO, the 10000 cases reported yearly in travelers returning from malaria-endemic regions are likely a significant underestimate [72]. Malaria infections among workers on container ships and other commercial vessels have been reported frequently and are considered a significant occupational risk [66–68,70,73]. Similarly, the risk of dengue to travelers is significant, accounting for up to 16% of all febrile illnesses in returning travelers [74]; however, official reports of cases on board ships are scarce [71]. Chikungunya, another disease transmitted by mosquitoes, has now been identified in more than 60 countries, with an expanding scope of endemicity, highlighting the need to be aware of the changing geography of vectorborne disease risk [75].

Although mosquito, tick, and other arthropod behaviors and habitats vary, certain general precautions can be helpful in preventing infection and should be considered while a ship is in port or travelers have disembarked at a port of call. Travelers should be informed that while indoors, they should remain in well-screened or air-conditioned areas [25]. When outdoors, travelers should keep skin covered with clothing, to the degree possible, and treat clothing and gear with products containing 0.5%

permethrin. Bathing or showering within two hours after coming indoors may wash off ticks and other vectors before they attach, or allow detection and removal before transmission. Using repellents that contain 20–30% DEET (N,N-diethyl-m-toluamide) on exposed skin and clothing can provide some protection against ticks and mosquitoes for several hours [76]. Finally, travelers should consult their healthcare provider about whether they need to take antimalarial chemoprophylaxis and be vaccinated for yellow fever or Japanese encephalitis prior to travel and report any travel history and vector contact should they become ill [25].

Ciguatera

Although not an infectious disease, ciguatera fish poisoning is frequently mistaken for one, and is something healthcare providers should be aware of when treating maritime travelers. This illness affects approximately 10000–50000 people each year, and numerous outbreaks on cargo ships have been reported [77–79]. Symptoms develop after ingesting fish containing ciguatoxins, and include nausea, vomiting, diarrhea (onset within 24 hours), and neurological abnormalities (onset within 1–4 days), which can become chronic. The toxin is produced by *Gambierdiscus toxicus*, a one-celled organism that grows on algae in tropical and subtropical waters, which is consumed by reef fish (such as moray eel, barracuda, and red snapper) and concentrated in predatory fish [76]. Crew members on cargo ships are at particular risk due to the fish they purchase or catch for consumption during international travel [77–80].

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Chapter 5

Microbes on the move: prevention, required vaccinations, curtailment, outbreak

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Infectious diseases are mobile and global. The Ebola virus outbreak in 2014–15 posed threats to global health security. In 2016, the rapid spread of Zika virus disease and associated risks of neurological disorders and microcephaly prompted the World Health Organization to declare a Public Health Emergency of International Concern.

This chapter provides a brief overview of the prevention of infection during international travel, the revised International Health Regulations (IHR 2005) with respect to curtailment of infection, and the ECDC approach to outbreak investigation.

Travel is an important factor in the spread of infection. Many disease risks can be mitigated by effective preventive measures such as the use of vaccines, chemoprophylaxis, and personal protection measures against mosquito bites. There are, however, no consensus guidelines worldwide on the global prevention of infectious disease in travelers. Individual travelers are ultimately responsible for their health and well-being while traveling and on their return as well as for the prevention of transmission of communicable disease to others. Yellow fever is the single disease for which proof of vaccination may be required as a condition of entry. Following a change in WHO policy, a single dose of yellow fever vaccine is considered to confer lifetime protection for the vaccinated person. A further mandatory vaccination for Hajj pilgrims is the quadrivalent meningococcal vaccination.

It is difficult to curtail infectious disease as it can rapidly cross borders. The revised IHR were unanimously agreed upon by the World Health Assembly in 2005 as a global legal framework on the use of international law for public health purposes. Compared with the previous regulations, IHR 2005 expand the scope of internationally reportable diseases and events from three diseases (cholera, plague, and yellow fever) to "all events which may constitute public health emergencies of international concern," thus providing criteria for identifying novel epidemic events and specifying conditions for involvement of the international community in outbreak responses.

The investigation of and response to disease outbreaks require coordination of national and international organizations as well as multidisciplinary partnerships. Outbreak investigation, as practiced by the European Centre of Disease Control (ECDC), extends beyond detection, assessment, and response support and includes a large range of activities and proactive work to strengthen public health capacity.

Prevention of disease in travellers

“Viruses and bacteria don’t ask for a green card,” a fact astutely observed in 1993 by the Surgeon General Antonia C. Novello. Human travel is subject to some degree of regulation but who checks the microbial baggage? Most countries have no requirements regarding disease avoidance or vaccination coverage for visitors or travelers.

Protection of travelers and destination populations

Modern travel is swift and easy; it takes 36 hours to travel around the world, much faster than the fanciful 80 days of Jules Verne’s 1873 era. Today, international tourist arrivals exceed 900 million annually and are expected to top 1.5 billion by the year 2020. Who protects the traveler from the global onslaught of microbes encountered during travel that differ so markedly from those of his own home terrain? The destination country may also be affected by the traveler who can introduce a pathogen into a new geographic or ecological niche, such as the historical introduction of measles into the New World by Europeans or the transmission of the chikungunya virus in Italy introduced by a traveler from India to local *Aedes albopictus*. Similarly, it is postulated that the Zika virus was introduced to Brazil by international travelers attending sporting events [1], and this expansion to new geographic areas has had wide-reaching consequences, prompting the World Health Organization (WHO) to declare a Public Health Emergency of International Concern. This emergency situation lasted several months and allowed a coordinated global response and travel advisories. Earlier in 2014–15, the travel-related spread of Ebola virus disease with onward chains of international transmission far from the outbreak epicenter prompted action and restrictions at borders and heightened international health security [2]. Apart from some “obligatory entry requirements” such as yellow fever vaccination (Figure 5.1), general disease preventive measures are largely voluntary.

MODEL INTERNATIONAL CERTIFICATE OF VACCINATION OR PROPHYLAXIS

This is to certify that [name]....., date of birth....., sex....., nationality....., national identification document, if applicable..... whose signature follows..... has on the date indicated been vaccinated or received prophylaxis against: (name of disease or condition)..... in accordance with the International Health Regulations.

Vaccine or prophylaxis	Date	Signature and professional status of supervising clinician	Manufacturer and batch No. of vaccine or prophylaxis	Certificate valid from... until.....	Official stamp of administering centre
1.					
2.					

Figure 5.1 International Certificate of Vaccination and Prophylaxis. Source: World Health Organization 2005.

Ultimately, the traveler is responsible for his own health. He should seek pretravel advice on the risks of infectious disease at the destination, should use precautions to avoid transmitting any infectious disease to others during or after travel, and should report any illness on return, including information on recent travel. Who provides the traveler with all this information? In Europe, individual countries have national guidelines [3]. The US guidelines are formulated by the US Centers for Disease Control and Prevention (CDC). The WHO regularly updates its site on *International Travel and Health* which aims to meet the needs of national health administrations, practicing travel health advisors, tourist agencies, shipping companies, airline operators and all who are called on to give health advice to travelers (www.who.int/ith). A number of travel medicine websites suggest global measures based on country of destination (Box 5.1) and these websites are updated frequently. Concise, up-to-date information is key to the provision of advice on the prevention of disease in travelers.

Box 5.1 A selection of travel medicine websites. For a more extensive listing see www.who.int/ith/links/national_links/en/index.html.

WHO	International Travel and Health	www.who.int/ith
CDC	Centers for Disease Control	www.cdc.gov/travel
NaTHNaC	National Travel Health Network and Centres, United Kingdom	www.travelhealthpro.org.uk

Travel health is an increasingly complex specialty and encompasses travel health advice and recommendations that should be evidence based and rooted in the epidemiology of travel-associated infections and diseases and their global, geographic distribution. Practitioners of preventive travel medicine include general practice health professionals such as general practice doctors and nurses, tropical medicine specialists, specialist “travel clinics,” pharmacists, and occupational medicine professionals [3]. Those seeking pretravel health advice need individualized information on the disease profile at the destination and preventive measures such as vaccinations (routine and travel specific), malaria chemoprophylaxis or stand-by treatment as appropriate, vector bite protection and also competent advice on myriad “minor to major” infectious conditions, including travelers’ diarrhea, water and foodborne infections, droplet or contact infections, sexually transmitted diseases, and rabies. Recent analyses have shown that vaccine-preventable diseases are significant contributors to morbidity and potential mortality in travelers. More research is needed on the uptake, cost-effectiveness, and efficacy of travel medicine preventive measures. An audit is needed of the utility of pretravel recommendations as not all are effective in preventing travel-associated illness [4].

Increasingly, the internet is becoming an important source of information for those seeking travel medicine advice. The importance of this source is likely to increase dramatically in the coming years and it is recognized by the travel medicine community as a major player. Ideally, the travel industry should also play a role in informing potential travelers about possible health risks but this is a gray area and advice is usually confined to information about “obligatory vaccines.” Currently, in terms of international regulations, yellow fever is the single disease with international requirements with the exception of an obligatory quadrivalent meningococcal vaccination for Hajj pilgrims.

Yellow fever

The documented international certificate of vaccination is required by various countries as a condition of entry, particularly if travelers are arriving from infected or potentially infected areas (see www.who.int/ith for this listing). An international certificate is for one individual only and is now valid for the lifetime of the person vaccinated [5] provided that the yellow fever vaccine used has been approved by the WHO. In some circumstances such as immunocompromised individuals or for those who received fractional doses, a booster vaccination dose may be required [6]. The former International Certificate of Vaccination or Revaccination Against Yellow Fever has been revised to the International Certificate

of Vaccination or Prophylaxis and includes documentation not just on yellow fever but on any vaccine or prophylaxis (see Figure 5.1). Currently, no European or North American country requires a yellow fever vaccination certificate as a condition of entry. An historical anecdote explains why the international vaccination book is yellow – apparently in earlier times, ships entering a port would raise a yellow flag to indicate that the crew was free of infectious disease.

Imported disease

Infectious disease is mobile and global. Often, infection in the returned traveler develops only after a certain incubation period. The concept of collective health security is not new and has been applied since the early days of travel. In fourteenth-century Europe, this led to the invention of the practice of “quarantine” (Italian *quaranta giorni* – 40 days), a precaution which was adapted widely in Mediterranean ports (1348 Venice, 1377 Ragusa, 1383 Marseille). In recent years, surveillance networks such as EuroTravNet and GeoSentinel [4,7] have made great progress in elucidating the epidemiology of travel-associated illness and have shown how the profile of acquired infections varies according to the traveler and the geographic areas visited (Figure 5.2). This knowledge can be used as an evidence base for the formulation of geography cum pathogen recommendations.

Curtailement of disease

The revised International Health Regulations have a role in the curtailment of infectious disease. In the wake of the 2003 outbreak of severe acute respiratory syndrome (SARS), preparedness for public health emergencies was propelled into worldwide consciousness. The appearance and rapid international spread of SARS demonstrated to all – including global leaders, ministers of health, prime ministers, and heads of state – how an infectious disease can rapidly cross borders and deliver health threats and economic blows on an unimaginable scale [8]. The IHR (2005) were unanimously agreed upon by the World Health Assembly on May 23, 2005 [9]. This global legal framework constitutes a “major development in the use of international law for public health purposes.” The IHR have allowed rapid responses to publish health infectious disease crises such as the Ebola outbreak in 2014-2015 and the South American Zika emergency in 2016.

New times, new requirements

The revised Regulations reflect a growing understanding that the best way to prevent the global spread of diseases is to detect and contain them while they are still local. WHO member states have obligations to alert the global community about potential disease threats as well as prevent and control the spread of disease inside and beyond their borders. Compared with the previous Regulations, adopted in 1969, IHR 2005 expand the scope of internationally reportable diseases and events, provide criteria for identifying novel epidemic events, and specify conditions for involvement of the international community in outbreak responses. The revision includes the following five substantive changes.

Expanded scope

The previous Regulations applied to only three infectious diseases: cholera, plague, and yellow fever. IHR 2005 reflect shifting concepts about disease control, shaped by recent and impending disease threats and the experiences of the past two decades in detecting and responding to disease outbreaks. The revised Regulations replace the previous disease-specific framework with one built on timely notification of all events that might constitute a public health emergency of international concern, taking into account the context in which an event occurs. The advantage of this approach is its applicability to existing threats as well as to those that are new and unforeseen.

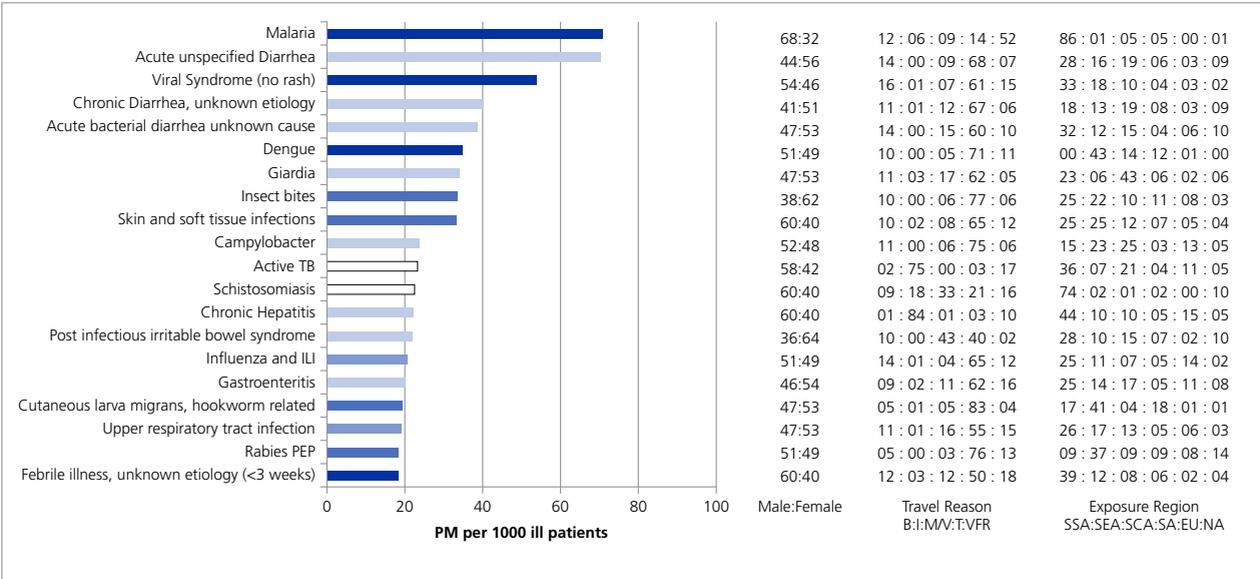


Figure 5.2 Proportionate morbidity of disease according to type of traveler and region of travel. X axis shows the proportionate morbidity (PM) per 1000 ill travelers. Male:female and travel reason ratios are on the right. B:I:M/V:T:VFR = Business:Immigration:Missionary/Volunteer:Tourism:Visiting Friends and Relatives. Exposure areas: SSA, sub-Saharan Africa; SEA, South-east Asia; SCA, South Central Asia; SA, South America; EU, Europe; NA, North Africa. Source: Adapted from Schlagenhauf et al (2015) [4]. Reproduced with permission of Elsevier.

Decision instrument and notification

Expanding the scope of the IHR beyond reporting of three diseases to reporting of any public health emergency of international concern required an algorithm to assist in identification of such events. The resulting decision instrument (Figure 5.3) identifies a limited set of criteria for use by member states for fulfilling the obligation to determine whether an event occurring within their territory might

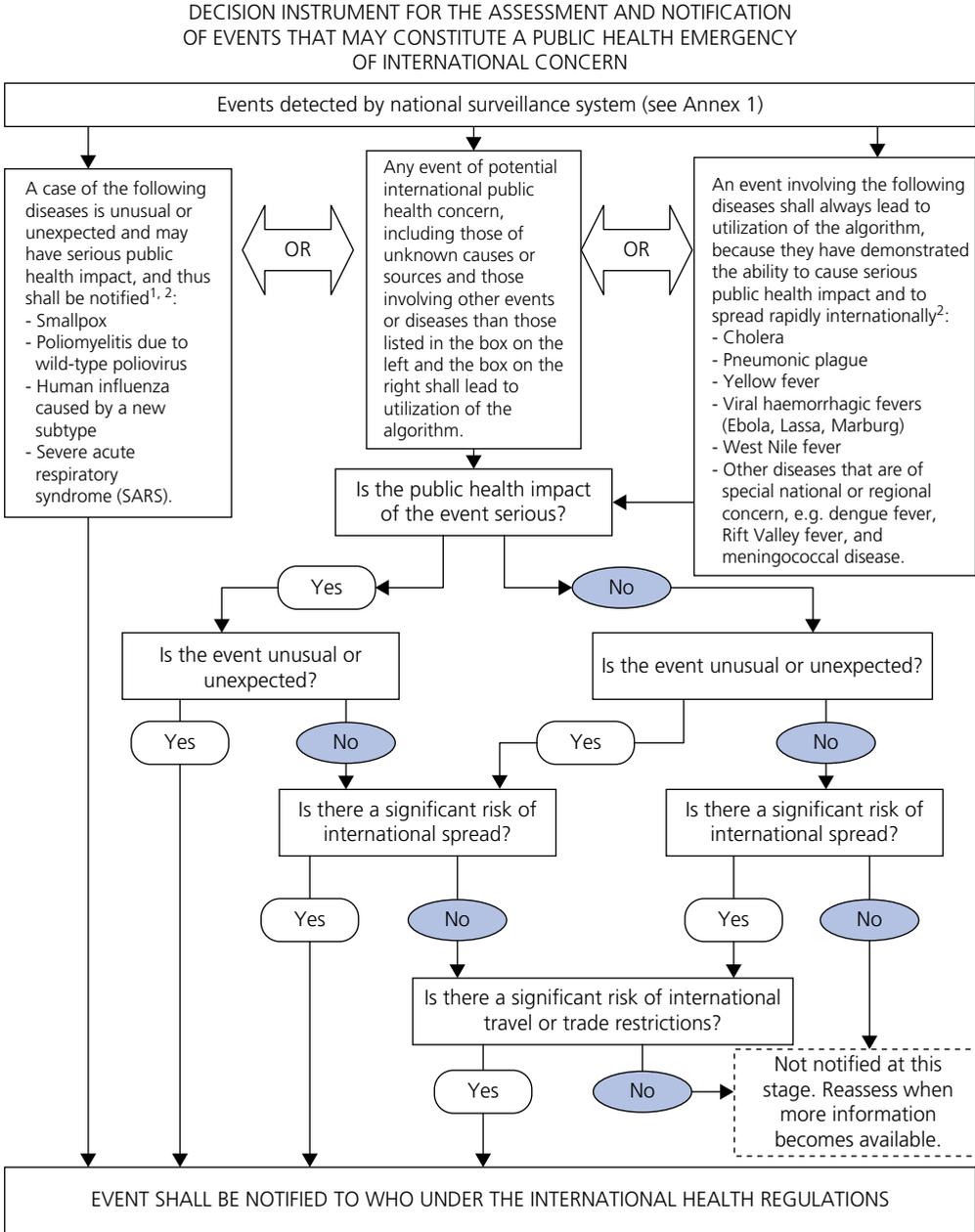


Figure 5.3 Annex 2 – IHR 2005.

constitute a public health emergency of international concern and therefore require formal notification to the WHO within 24 hours of assessment.

The IHR 2005 includes a list of diseases for which a single case must be reported to the WHO immediately, regardless of the context in which the disease occurs. This list includes smallpox, poliomyelitis due to wild-type poliovirus, human influenza caused by a new subtype, or SARS. In addition, an event involving certain other diseases (e.g. cholera, pneumonic plague, yellow fever, viral hemorrhagic fevers) calls for a careful evaluation using the decision instrument to determine whether notification is indicated. After an event is reported, only the Director General of the WHO can determine whether the event formally constitutes a public health emergency of international concern.

Focal and contact points

A third innovation under IHR 2005 is the requirement for member states to designate “national IHR focal points” as the operational link for notification and reporting to the WHO and for the WHO to name corresponding “IHR contact points.” Effective communication between these two organizational entities is central to the rapid management of a possible public health emergency of international concern.

National core surveillance and response capacities

Experiences during the past several years have shown that public health emergencies expose the weaknesses and vulnerabilities of national and subnational public health infrastructure. The fourth change calls for member states to develop, strengthen, and maintain core capacities to:

- detect, assess, notify, and report disease events
- respond promptly and effectively to public health risks and public health emergencies of international concern.

Under IHR 2005, new WHO powers include an information-gathering responsibility that is not limited solely to official state notifications or consultations but covers all available scientific evidence and other relevant information. The WHO can consult nonofficial reports and require countries to collaborate with a request for verification. The WHO is also empowered to recommend and coordinate measures that will help contain the international spread of disease, including public health actions at ports, airports, and land borders, and on means of transportation that involve international travel.

Response to outbreaks

An outbreak of disease calls for an appropriate investigation and response that require a coordination of national and international organizations as well as multidisciplinary partnerships [10]. The following section outlines the approach of the European Centre for Disease Prevention and Control (ECDC) in dealing with disease outbreaks in the European Union (EU), a common market with free movement of people, services, goods, money [11], and also of microbes. Part of the ECDC mission [12] is to participate in the detection, assessment, and investigation of international outbreaks according to the following steps.

Identification of communicable disease public health alerts The process starts by searching for information signals heralding potential EU concern outbreaks. Surveillance systems should be sensitive enough to detect signals indicating outbreaks with epidemic potential efficiently, in order to implement control measures as soon as possible. The ECDC achieves this by analyzing data from indicator-based surveillance systems (at EU level, The European Surveillance System (TESSy: www.ecdc.europa.eu/en/activities/surveillance/Pages/Surveillance_Tessy.aspx) provides a one-stop-shop for case-based reporting from the member states (MS) for the routine surveillance of the 46 diseases listed in Decisions 2002/253/EC and 2003/534/EC plus SARS, West Nile fever and avian influenza [13,14]) and filtering information from event-based surveillance systems (which gather unstructured data from sources of any nature [13], such as MedISys (<http://medusa.jrc.it>)). Unofficial sources (for example, the media) require validation (i.e. confirmation of authenticity)

by cross-checking the information against independent sources. In this context, the newly developed Epidemic Intelligence Information System (EPIS: http://ecdc.europa.eu/en/activities/epidemicintelligence/Pages/EpidemicIntelligence_Tools.aspx), a real-time European web-based communication platform, offers a valuable tool for MS experts to exchange information on outbreak identification, validation, and assessment. Some sources always report validated events, such as the EU Early Warning and Response System (EWRS) [16], the WHO through the International Health Regulations and institutional websites. Moreover, MS communicate validated events having a potential to affect other countries through the EWRS assessed by their public health authorities against established notification criteria [17,18]. The ECDC then gathers all available information to characterize the reported outbreaks by time, place, and persons affected to assess the risk for EU spread. Signals of potential or definite outbreaks with potential public health and EU relevance in terms of severity, spread, and need for further actions generate public health alerts which are evaluated to decide the need for a European-level coordinated response.

Outbreak response and rapid risk assessment Response activities include risk assessment, risk management, and risk communication. In the EU, the MS are responsible for risk management, supported by the coordination of the European Commission (EC) that is also engaged in risk communication. The ECDC mandate covers risk assessment and communication but it can also provide scientific support to the risk management activities. Other stakeholders such as European and international networks, other European agencies, and international organisations (such as the WHO) can be involved.

EU response action plan The EC may then coordinate a plan of action, as was the case with the 2009 influenza A(H1N1) pandemic, creating an *ad hoc* response team with representatives from the affected MS, the ECDC, the EC and, if relevant, other stakeholders. It includes the coordination of an EU-wide outbreak investigation, complementing the investigation being carried out in the affected MS. This usually includes the following stages, several of which may have begun before and can occur simultaneously.

- *Confirm outbreak and diagnosis.*
- *Case definition:* to facilitate common dataset collection and comparable analysis when several EU countries are involved, a common case definition is used (EU case definition where relevant).
- *Case finding:* efforts are made to search for additional cases and for further descriptive and analytical epidemiology in all MS and outside the EU, through indicator and event-based surveillance.
- *Data collection:* a common line listing for cases and key variables at EU level allows for the uncovering of previously unsuspected associations between cases.
- *Descriptive epidemiology:* cases are described by time, place, and person.
- *Generating a hypothesis:* the epidemiological description can provide a hypothesis regarding the infection source.
- *Testing the hypothesis:* different types of analytical studies can be considered (case-control or cohort studies, seroprevalence studies, spatial mapping) to reveal an association between a risk factor and disease. Additional epidemiological, environmental, and microbiological investigations may be required.
- *Control measures (coordinated by EC):* these involve controlling the infection source, if necessary by liaising with other stakeholders (such as the Rapid Alert System for Food and Feed, RASFF – http://ec.europa.eu/food/food/rapidalert/index_en.htm), interrupting transmission or protecting those at risk.

The outbreak team meets regularly to review the investigation and control status, focusing on the protocols and tests in place for patient management, diagnostics and contact tracing, the identification of the population at risk and the measures to prevent new cases in the different MS. The team communicates regularly, exchanging information on the investigation and control measures and sharing updated situation reports and risk assessments. After considering public opinion risks and

preparing media messages, the team decides how information about the event will be made public. Confirmed outbreaks require an active follow-up of all relevant information until fully contained. The documentation of all related activities facilitates information sharing and allows for auditing and evaluation. When considered useful, the lessons learnt at national and EU level can be documented and shared with all involved actors.

Conclusion

Travelers are responsible for their own health during travel but national and international authorities should provide evidence-based prevention guidelines. International health security requires regional and global leadership and a flexible, legal framework so that infectious disease threats can be mitigated.

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Chapter 6

Diagnostic tests and procedures

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This chapter provides guidelines for diagnostic procedures to be performed on admission and the following period until a diagnosis is clear. It is divided according to the focal symptoms from an infection including the central nervous system; ear, nose, and throat; cardiopulmonary; gastrointestinal; hepatobiliary; genitourinary including those that are sexually transmitted; joint and muscle; and cutaneous as well as fever of unknown origin without focal symptoms and patients with eosinophilia. It also includes a section regarding interpreting positive and negative test results.

Understanding diagnostic tests

Diagnostic tests in infectious diseases can be divided into direct and indirect tests. Direct tests identify the organism or part of the organism (antigen) and include culture, polymerase chain reaction (PCR) for nucleic acids, microscopy, and antigen detection. Indirect tests identify the reaction to an infection such as an antibody response or an inflammatory reaction such as raised white cell count, C-reactive protein (CRP) or procalcitonin (PCT).

Direct tests are usually specific for the organism of interest but may lack sensitivity and some, such as culture, have a prolonged turnaround time. All direct tests aiming at finding the microorganism have limits to the lowest number of microorganism or lowest concentration of antigen per volume which can be detected by the test and can therefore produce false-negative results. Indirect tests are often more sensitive than direct tests but tend to be less specific.

Many pathogens are indirectly identified by finding antibodies directed against the organism in the patient's serum. Such an antibody test can be a surrogate screening marker for infection such as antibody tests for HIV and hepatitis C. Every pathogen consists of multiple antigenic sites, called epitopes, and the immune system will develop antibodies and cellular immune recognition directly against many of these epitopes. The antibody test may be polyclonal, i.e. identifying antibodies directed at the organism as a whole, or it may be detecting antibodies against specific parts of the pathogen.

Paired sera 2–3 weeks apart are used to verify a specific infection. If there is a fourfold or more increase in antibody titer (titer=dilution) between the first and second sample, it is generally assumed that the patient has an acute infection with the specific agent. This type of testing rarely affects patient management as results arrive after the patient has recovered. However, such testing can be important for epidemiological studies and in outbreak settings.

Antibody detection can also be used as a presumptive measure for immunity to decide whether vaccination is required or if an exposure has occurred. The absence of detectable antibody following vaccination can reflect primary vaccine failure or waning immunity requiring booster immunization.

Is a result positive or not?

Laboratory tests would ideally provide a definitive diagnosis but, in almost every situation, the clinician must consider the results in the clinical perspective. A result can be falsely negative simply because the number of pathogens in the volume of sample is below the detection threshold of the assay. Similarly, positive growth of bacteria from a clinical sample may reflect colonization rather than true infection. An example is growth of bacteria from a superficial swab of a wound that may not necessarily mean that the bacteria have a role in an invasive infection and the result can be considered false positive.

The terms *sensitivity* and *specificity* are used in the interpretation of laboratory data [1]. Sensitivity is the proportion of patients with a given disease that have a positive test and is expressed as %. Specificity is the proportion of patients without the disease who have a negative test. When test results are continuous, there is a balance between sensitivity and specificity, depending on the cut-off value between a result described as positive or negative. This is best described using the receiver operating characteristic (ROC) curve [2], which describes the balance between sensitivity and specificity depending on different cut-off values.

	Has disease	Doesn't have disease
Test positive	True positive	False positive
Test negative	False negative	True negative

The positive predictive value (PPV) is the proportion of patients with a positive test who have the diagnosis: number of true positives/(number of true positives + number of false positives). PPV predicts the probability that a positive test reflects the underlying condition that you are testing for but is dependent on the prevalence of the condition being similar amongst the population from which it was derived and in which it is applied. PPV is proportional to the prevalence of an infection or condition in the population. Hence, for a given test, the PPV will be much higher if the disease is common than in a low prevalence setting [3–5].

The negative predictive value (NPV) reflects the proportion of patients with a negative test who are correctly diagnosed *not* to have the disease. NPV is indirectly proportional to prevalence and thus in contrast to PPV, when an infection or condition is highly prevalent in the population, the NPV will be lower than in situations of low prevalence.

Validation of diagnostic tests

It is important for diagnostic tests to be validated prior to use. The validation process, which can be performed by the manufacturer or independent researchers, involves applying the new test to a group of patients who have been determined to either have or not have the disease in question based on a reference standard (sometimes called the gold standard). Studies of this kind produce 2×2 tables of true positives, false positives, true negatives, and false negatives. From these tables, it is simple to calculate the sensitivity, specificity, PPV, and NPV. When interpreting these values in a clinical setting, it is important to consider whether the population in whom the test was validated is similar to the population being tested. As with studies of treatments, a positive trial result in one population does not necessarily mean that the results are generalizable to other populations.

CNS infections: meningitis, encephalitis

The key diagnostic tests are lumbar puncture to obtain cerebrospinal fluid (CSF), serological assays, PCR, and computed tomography (CT) and/or magnetic resonance imaging (MRI) scanning of the head and neuroaxis.

Biochemistry/cytology

Cerebrospinal fluid leukocyte count and concentration of protein and glucose lack specificity and sensitivity for the diagnosis of meningitis. A normal cell count is less than 5 cells per microliter, protein less than 50 mg/L and a glucose ratio above 0.5 between blood and CSF.

Cells are differentiated into polymorphs (neutrophils) and mononuclear cells. An elevated polymorph cell count is typical of bacterial infection, whereas mononuclear cells dominate in viral, mycobacterial (or certain other intracellular growing bacteria), and fungal infections. However, it is important to note that there is a large degree of overlap in CSF findings between different etiologies of meningitis and these findings alone can only occasionally determine etiology. Note that lymphoma cells in the CSF will be counted as mononuclear cells.

Microbiology

The gram stain of CSF reveals bacteria in about 50–80% of cases and culture is positive in 80% of cases at best. Antimicrobial therapy prior to lumbar puncture decreases the sensitivity, but culture can identify common pathogens like *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, and *Listeria monocytogenes*. The sensitivity of stains for acid-fast bacteria in *Mycobacterium tuberculosis* meningitis (TBM) is low, as are stains for most fungal meningitides. Direct antigen detection of *C. neoformans* and culture for *Mycobacterium tuberculosis* play an important role. PCR for *M. tuberculosis* is a good “rule in” test, but lacks sensitivity. Viruses can be identified by PCR, by serum antibodies or intrathecal antibody synthesis expressed as a serum/CSF ratio.

Microbiological diagnosis of CNS infections

Microorganism	Culture	16-S-PCR	PCR for specific agents	IgG index for intrathecal antibody synthesis	Agent-specific antibodies (IgM, IgG)
Bacteria	+	+	+	–	–
<i>Mycobacterium tuberculosis</i>	+	–	+	–	Interferon-gamma release assays in blood positive*
Herpes simplex, enterovirus, herpes zoster, EBV	–	–	+	+	–
HIV	–	–	+	–	–
West Nile virus	–	–	+	–	–
Japanese encephalitis	–	–	+	–	–
St Louis encephalitis, tickborne encephalitis (TBE) and other arboviruses	–	–	+	–	–
Nipah and Hendra virus	–	–	+	–	Serum neutralization assay
Chandipura virus	–	–	+	–	–
Rabies	–	–	(+) [†]	(+) [†]	+
<i>Borrelia</i> spp.**	–	–	–	+	–
Syphilis	–	–	+	–	+
Eosinophilic meningoencephalitis ^{††}	–	–	–	–	–
<i>Cryptococcus</i>	+	–	Panfungal PCR	–	Microscopy and antigen-detection

(Continued)

*The interferon-gamma release assays does not differentiate between latent and active tuberculosis. The result is very dependent on the patient’s origin in the developed world. It should not be used in areas highly endemic for tuberculosis, many of which will be positive without active tuberculosis disease.

†Postexposure immunization should be started as soon as possible after exposure. PCR and intrathecal antibody synthesis can only be helpful after CNS symptoms develop.

** In Europe, Lyme borreliosis is caused by *Borrelia burgdorferi* sensu stricto, *B. afzelii*, *B. garinii*, and the recently described species *B. spielmanii*, whereas *B. burgdorferi* dominates in North America. Diagnosis can be difficult and the role of immunoblot using recombinant antigens has not been studied in population-based research. The methods available were reviewed [1].

††Suspected inpatients with CNS symptoms and eosinophilia in peripheral blood often with elevated total IgE. Organisms associated with this entity include the parasites *Angiostrongylus cantonensis*, *Baylisascaris procyonis*, and *Gnathostoma spinigerum* and the dimorphic fungus *Coccidioides immitis*. IgG detection of *Angiostrongylus cantonensis* L3 larvae is available.

Imaging

Magnetic resonance imaging is generally more sensitive compared to CT in patients with encephalitis [6], but is not universally available. The results are generally nonspecific but can be very suggestive in patients with herpes simplex encephalitis and the immunosuppressed host with *Toxoplasma gondii* brain infection. Because of a small risk of cerebral herniation when a lumbar puncture is done when high intracerebral pressure is present (from intracerebral hemorrhage, tumor or cerebral abscess), brain imaging should preferably be performed before lumbar puncture. In low-resource settings where brain imaging is not available, the benefits of lumbar puncture generally outweigh the risks in patients with suspected CNS infection unless they have new onset of seizures or a new unexplained focal neurological deficit.

Ear, nose, and throat

The majority of infections are related to respiratory viruses and Epstein–Barr virus is of particular importance. Streptococcal infection, notably *Streptococcus pyogenes* (group A streptococcus), is important to diagnose as treatment can prevent rheumatic fever.

Basic diagnostics for ear, nose, and throat infections

Microorganism	Diagnostic procedure
Streptococcal infections	Throat swab culture, rapid tests for group A streptococcus [7]
Tuberculosis	Culture and ZN microcopy of biopsy. 16S rRNA PCR. Peripheral blood interferon-gamma release test or Mantoux test
Peritonsillar abscess*	MRI or CT scan of the neck
Necrotizing fasciitis†	MRI or CT scan of the neck
Influenza	Reverse transcriptase PCR or rapid tests (antigen capture)
Epstein–Barr virus	Specific antibody profiling, rapid test of EBV antibodies (monospot, heterophile agglutination test)
HSV I and II	PCR of vesicular fluid. Serology (type specific) will remain positive for life
HIV	Serology, PCR and antigen/antibody rapid tests

*Requires acute ENT evaluation.

†Requires acute surgical evaluation.

Biochemistry/cytology

In viral infections, the CRP is usually only moderately elevated and the differential white blood cell (WBC) count is normal or dominated by a lymphocytosis. Influenza, however, can cause a polymorph leukocytosis. In streptococcal and other bacterial infections, the WBC is usually elevated with a polymorph predominance, and the CRP is more elevated. The CRP response has a lag time of 18–24 hours, which means that in the setting of an acute presentation, the CRP may still be normal or low despite the bacterial etiology. It should be remembered that pertussis (whooping cough) is a bacterial upper respiratory infection due to *Bordetella pertussis* that can cause a peripheral lymphocytosis.

Rapid tests

There are many rapid tests on the market detecting group A streptococcus and EBV (the most common cause of infectious mononucleosis). The sensitivity varies considerably between kits from 62% to 95%, but tests show good specificity [7]. Rapid detection tests of the mononucleosis heterophile antibody are often insensitive in the first week of illness.

Microbiology

Group A streptococcus is readily grown from the oropharynx but other classic upper respiratory pathogens such as *B. pertussis* and the cause of diphtheria, *Corynebacterium diphtheriae*, have a much lower yield from culture. Vincent's angina is an acute necrotizing infection of the pharynx caused by a combination of fusiform bacilli (*Fusiformis fusiformis*, a gram-negative bacillus) and spirochetes.

Imaging

A number of focal, potentially life-threatening bacterial infections of the head and neck can be suspected clinically but are usually confirmed with MRI or CT imaging. These infections, for which the microbiological causes (usually aerobic and anaerobic normal mouth flora) are identified by culture of the pus and/or blood culture, include peritonsillar abscess, lateral pharyngeal abscess, retropharyngeal abscess/fasciitis, and jugular vein septic thrombophlebitis.

Pulmonary infections

Biochemistry/cytology

The CRP is only a rough guideline to differentiate between viral infections or atypical bacteria like *Mycoplasma* and *Chlamydia* and bacterial infections such as *Streptococcus pneumoniae* [8,9]. The CRP response has a lag time of 18–24 hours. An elevated peripheral WBC count with increased polymorphs is characteristic of pyogenic bacterial infections.

Microbiology and rapid tests

Microbiology and rapid tests in pulmonary infections [10]

Microorganism	Culture*	16-S-PCR	PCR for specific agent	Agent-specific antibodies (IgM, IgG) obtained with at least 2 weeks interval	Microscopy	Other tests
Viruses	-	-	+	+	-	
<i>Mycoplasma</i> and chlamydiae	-	-	+	+	-	
<i>Chlamydophila psittaci</i>	-	-	+	+	-	
<i>Streptococcus pneumoniae</i> and other bacterial infections	+	+	+	-	-	
Fungal infections [†]	+	-	-	-	-	
<i>Pneumocystis jiroveci</i> **	-	-	+		+	
<i>Mycobacterium tuberculosis</i>	+	-	+ ^{††}	-	+	TST or interferon-gamma release assays [§]
Melioidosis [11]	+	+	-	-	Specific direct immunofluorescence	Haemagglutination assay

*Culture of expectorate or, if negative, after BAL.
[†]Silver stain or Gomori-methenamine silver stain or direct fluorescent stain of BAL or expectorate.
^{**}Detection of galactomanan for *Aspergillus*. *Candida manan* is under evaluation, but seems promising with invasive candidiasis.
^{††}Gene Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) rapid PCR has been introduced in many countries as a first-line test for open pulmonary TB. The Xpert MTB/RIF has high sensitivity, even in smear-negative HIV-coinfected persons, a rapid turnaround time of 1–2 hours, and provides information on rifampin resistance of the *M. tuberculosis* if present [12].
[§]Interferon-gamma release assays have a sensitivity in many studies around 70%. Thus a negative interferon-gamma release assay does not rule out tuberculosis.

Interferon-gamma release assays and tuberculin skin tests will be negative in immunocompromised patients, for instance HIV infected with a low CD4 T-cell count. In severe TB, these tests can also be negative despite disseminated tuberculosis – so-called anergy.

Eosinophilia and pneumonia – see under Eosinophilia and elevated IgE below.

Imaging

A plain chest X-ray will show an infiltrate in most cases of pneumonia if symptoms have persisted for more than two days. CT or MRI are usually not needed in uncomplicated pneumonia but if symptoms persist despite treatment, CT or MRI is helpful to diagnose empyema and/or lung abscess.

Cardiac infections

Endocarditis is usually a clinical diagnosis based on fever and presence of a murmur. Continuously positive blood culture is needed [13]. A normal procalcitonin and C-reactive protein does not exclude endocarditis [14].

Microbiology

Diagnosis of infections causing endocarditis, myocarditis, and pericarditis

Microorganism	Culture*	16-S-PCR	PCR for specific agents	Agent-specific antibodies (IgM, IgG) obtained with at least 2 weeks interval	Microscopy	Other tests
Bacterial infections	+	+	+	–	–	
Virus	–	–	+	+	–	
<i>Mycoplasma</i> and chlamydiae	–	–	+	+	–	
Q-fever (<i>Coxiella burnetii</i>)	–	+	+	+	–	
Fungal infections [†]	+	–	–	–	–	
<i>Mycobacterium tuberculosis</i>	+	–	+ ^{**}	–	+	TST or interferon-gamma release assays
Chagas disease, <i>Trypanosoma cruzi</i>	–	–	+ ^{††}	+	–	

*Culture of blood or pericardial aspirates.
[†]Detection of galactomanan in *Aspergillus* infections.
^{**}Specific PCR, for instance using the Gene Xpert system.
^{††}Chagas disease is a cause of cardiomyopathy in South and Central America. PCR can be performed on blood or biopsy material [15].
[‡]PCR

Imaging

Transthoracic echocardiography (TTE) and/or transesophageal echocardiography (TEE) should always be performed in suspected endocarditis, myocarditis, and pericarditis. Positron emission tomography (PET) may provide additional information on extracardial foci of infection, but do not replace TTE and TEE in the acute phase.

Gastrointestinal infections

Biochemistry/cytology

Elevated WBC count is generally found in bacterial infections of the gastrointestinal tract, especially when there is invasive disease. The toxin-associated *Clostridium difficile* colitis can also be linked with an elevated WBC.

Microbiology

Microscopy for cysts from protozoa like *Giardia*, helminth eggs like *Ascaris*, and routine culture will identify common bacterial pathogens such as *Salmonella* spp., *Campylobacter*, *Yersinia*, and *Shigella*. PCR and immunofluorescence are far more sensitive than microscopy for enteric protozoan parasites like *Giardia* and cryptosporidia [16]. Immunofluorescence assays are commercially available for *Giardia* and cryptosporidia and have the same sensitivity as PCR [16]. Especially in immunocompromised patients with diarrhea and negative microscopy for enteric protozoans, PCR or immunofluorescence should be performed.

Vibrio cholerae and pathogenic *E. coli* like enterotoxin producing *Escherichia coli* (ETEC) and verotoxin producing *Escherichia coli* (VTEC) require specific media. In outbreak situations, a rapid dipstick test for *V. cholerae* can be useful [17].

Microbiological diagnosis of gastrointestinal infections

Microorganism	Culture	Agent-specific culture	PCR for specific agent	Microscopy	Other specific diagnostic tests
<i>Salmonella</i> , <i>Shigella</i> spp., <i>Campylobacter</i> , <i>Yersinia</i>	+	-	-	-	-
<i>Vibrio cholerae</i>	-	+	+	-	Rapid dipstick tests [9]
<i>Clostridium difficile</i> (Cd)	+	+	-	-	Toxin detection in feces
ETEC, VTEC	-	+	-	-	PCR for O27 and other Cd Toxin detection in culture supernatants
Viruses	+	-	+	-	Rapid tests for rotavirus
<i>Giardia intestinalis</i>	-	-	+*	+	Immunofluorescence of fecal smear with labeled specific antibodies
<i>Cryptosporidium</i> spp., <i>Cyclospora cayetanensis</i> †	-	-	+*	+	Immunofluorescence of fecal smear with labeled <i>Cryptosporidium</i> -specific antibodies
<i>Entamoeba histolytica</i> and <i>E. dispar</i>	-	-	+*	+	Staining of feces preserved in formalin, SAF or polyvinyl alcohol
Presumed nonpathogenic intestinal protozoan parasites like <i>Blastocystis hominis</i> , <i>Dientamoeba fragilis</i>	-	-	+	(+)	Staining of feces preserved in formalin, SAF or polyvinyl alcohol
<i>Microsporidia</i> spp.	-	-	+**	+††	Electron microscopy has been used, also PCR

Microorganism	Culture	Agent-specific culture	PCR for specific agent	Microscopy	Other specific diagnostic tests
<i>Schistosoma mansoni</i>	–	–	–	+ [§]	<i>Schistosoma</i> antibodies are more sensitive than microscopy in patients with a low worm load. Egg detection in feces and urine
Other intestinal helminths	–	–	–	+	See section on Eosinophilia and elevated IgE
<i>Helicobacter pylori</i>	–	–	+ ^{§§}	–	Urea breath test, rapid antigen detection tests under evaluation [18]. <i>Helicobacter</i> -specific antibodies cannot be used to confirm eradication
<i>Tropheryma whipplei</i>	–	–	+ ^{§§}	–	
<i>Mycobacterium tuberculosis</i>	–	+	+	–	TST or interferon-gamma release assays may be false negative

*PCR is much more sensitive compared to microscopy for the diagnosis of intestinal parasites [16].
† Modified Ziehl–Neelsen staining.
** PCR on corneal scrapings and intestinal biopsies.
†† Polychrome staining.
§ Microscopy of feces concentrated a.m. Kato or microscopy of biopsies from the rectal mucosa.
§§ PCR on biopsy material.

Imaging

Imaging is not specific for most intestinal infections, but is helpful if the diagnosis is not clear or inflammatory bowel diseases such as Crohn disease, ulcerative colitis or diverticulitis are considered. Imaging can confuse ileocecal tuberculosis with Crohn disease and amebiasis with ulcerative colitis. Pancolitis with colon wall thickening is common in *C. difficile* toxin disease. PET may be helpful, showing increased metabolic activity in areas with inflammation.

Hepatobiliary infections

Biochemistry/cytology

The liver enzymes alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (the latter being less specific for the liver) will be elevated in viral hepatitis and certain bacterial infections like leptospirosis and reflect a parenchymal destruction of hepatocytes.

Parasitic infection like liver flukes and echinococcosis may sometimes result in elevated eosinophil count and elevated total IgE, but not always.

Microbiology

Microbiology diagnosis of hepatobiliary infections

Microorganism	Culture	16-S-PCR	PCR for specific agent	Agent-specific antibodies (IgM, IgG) obtained with at least 2 weeks interval	Microscopy	Other tests
Hepatitis A	–	–	+	+	–	
Hepatitis B	–	–	+	+	–	
Hepatitis C, E	–	–	+	+	–	
CMV, EBV	–	–	+	+	–	
Bacterial liver abscess	+	+	+	–	–	Imaging with CT or MRI will show a hypodense lesion without a wall
Leptospirosis	–	–	+	+	–	
<i>Mycobacterium tuberculosis</i>	+	–	+	–	+	TST or interferon-gamma release assays may be false negative
Amebic liver abscess (<i>Entamoeba histolytica</i>)	–	–	+	+	–	Imaging with CT or MRI will show a hypodense lesion without a wall
<i>Fasciola hepatica</i> , <i>F. gigantum</i> , <i>Opistorchis</i> spp., <i>Clonochis sinensis</i>	–	–	–	+*	+†	Imaging with CT or MRI will show hypodense lesions often multiple, some of which may be subcapsular
<i>Echinococcus granulosus</i>	–	–	–	+	+	Imaging with CT or MRI will show hypodense lesions and a dense, fibrous capsule often with calcifications [19]
<i>Echinococcus multilocularis</i>	–	–	–	+**	+	Imaging with CT or MRI will show an invasive solid process without a clear capsule
<i>Leishmania</i> spp.	–	–	+††	+	+††	

*Antibody assays are available for fascioliasis.

†Eggs can be detected in feces.

**Serology is cross-reactive between *E. granulosus* and *E. multilocularis* and the diagnosis rests on a combination of serology and imaging, and has recently been reviewed.

††PCR and microscopy of bone marrow aspirate.

Imaging

Computed tomography or MRI is generally not of any value in acute hepatitis. Ultrasound, CT or MRI are essential in the diagnosis and staging of echinococcosis and diagnosis of the liver flukes, liver abscess, and cholecystitis.

Upper and lower urinary tract infections

Biochemistry/cytology

C-reactive protein and WBC will usually be elevated in upper urinary tract infections (pyelonephritis), but may be normal in uncomplicated cystitis. A rapid urine dipstick test for leukocytes, blood, protein, nitrite, and leukocyte esterase will often be positive in both lower and upper urinary tract infections. Dipstick tests, urine culture for bacteria, and clinical symptoms should be considered together for a diagnosis of lower or upper urinary tract infection [20].

Microbiology and rapid tests

A urinary sample for culture is essential before antibiotic treatment is started.

Microbiology diagnosis of genitourinary tract infections

Microorganism	Culture	16-S-PCR	PCR for specific agent	Agent-specific antibodies (IgM, IgG) obtained with at least 2 weeks interval	Microscopy	Other tests
Bacterial infections	+*	-	-	-	+	
<i>Mycobacterium tuberculosis</i>	+	-	+	-	+	TST or interferon-gamma release assays
<i>Schistosoma haematobium</i>	-	-	-	+	+	Biopsy of bladder wall and urine sediment may show <i>Schistosoma</i> eggs with a terminal spine

*In patients with fever and a suspected urinary tract infection, blood samples for culture should be obtained before antibiotic treatment is started.

Imaging

Ultrasound, CT or MRI are usually not needed in lower urinary tract infection, but if symptoms persist despite treatment, imaging is helpful to diagnose a renal stone, hydronephrosis, perirenal abscess and strictures seen in long-standing schistosomiasis, brucellosis, and tuberculosis.

Sexually transmitted diseases and other genital infections

Acute venereal diseases are usually a clinical diagnosis based on the history, physical examination, and tests for specific agents.

Biochemistry

Biochemistry will seldom be of great help.

Microbiology and rapid tests

Microbiology diagnosis of sexually transmitted diseases and other genital infections

Microorganism	Culture	16-S-PCR	PCR for specific agent	Agent-specific antibodies (IgM, IgG) obtained with at least 2 weeks interval	Microscopy	Other tests
<i>Neisseria gonorrhoeae</i>	+	–	+	–	+*	
<i>Chlamydia trachomatis</i> † including lymphogranuloma venereum**	+	–	+	–	–	–
<i>Mycoplasma genitalium</i> †	–	–	+††	–	–	
Syphilis [21,22]	–	–	+	+	+	Serial tests often necessary
Chancroid (<i>Haemophilus ducreyi</i>)	+	?	+	–	–	
Granuloma inguinale (<i>Calymmatobacterium granulomatis</i>)	(+) [§]	?	+	–	+	Painful chancre
Herpes genitalis	–	–	+	(+) ^{§§}	–	
<i>Gardnerella vaginalis</i>	+	?	–	–	–	–
Scabies	–	–	–	–	+	
<i>Mycobacterium tuberculosis</i>	+	–	+	–	+	TST or interferon-gamma release assays

*Less sensitive than culture and PCR.

†Sample by urinary tract scrapings.

**Lymphogranuloma venereum is caused by *Chlamydia trachomatis* serovars L1, L2, and L3 and can be differentiated from other chlamydiae by PCR [23,24].

††PCR only increases diagnostic sensitivity in primary syphilis, not in secondary or tertiary syphilis.

§Not routinely available.

§§Many people will have antibodies against herpes from a previous infection, and the diagnosis relies on clinical findings and PCR.

Joint, muscle, skin, and soft tissue infections

Some infections like streptococcal skin infections (erysipelas) are a clinical diagnosis but the deeper joint, muscle, and soft tissue infections need biopsies or aspirates for culture and/or 16-S-PCR for diagnosis. Necrotizing fasciitis is an acute surgical emergency necessitating surgical debridement [25].

Biochemistry/cytology

C-reactive protein or PCT and WBC will usually be elevated in bacterial infections like septic arthritis, streptococcal skin infections, and necrotizing fasciitis. Long-standing osteomyelitis will often be followed by a normocytic, normochromic anemia.

Microbiology

Culture should be obtained from blood before treatment is started. Culture from wounds will usually show bacteria which contaminate the wound, which in most cases are not representative of the bacteria causing invasive infection.

Culture should be obtained from relevant samples by taking biopsies (osteomyelitis), aspirating abscesses and joint fluid for culture and/or PCR (16-S-PCR).

Microbiology diagnosis of joint, muscle, skin, and soft tissue infections

Microorganism	Culture	16-S-PCR	PCR for specific agent	Microscopy	Other tests
Bacterial infections (septic arthritis, osteomyelitis, myositis)	+	+	-	-	
Necrotizing fasciitis*	+	+	-	-	
<i>Mycobacterium tuberculosis</i>	+	-	+	+	TST or interferon-gamma release assays
<i>Trichinella</i> spp.	-	-	+ [†]	+	Serology available

*Necrotizing fasciitis is most commonly caused by invasive group A streptococcus (iGAS), but almost all bacteria have been reported to cause necrotizing fasciitis, including *E. coli* and *Vibrio vulnificus* especially seen after wounds in maritime environments.

[†]From muscle biopsy.

Imaging

X-ray or CT imaging is needed if necrotizing fasciitis is suspected and air in soft tissues is an important indicator of this condition. Osteomyelitis may show on plain X-rays, but rarely before four weeks after the infection started. MRI is more sensitive, CT less sensitive. PET scans are helpful to identify multiple foci.

Rash

A rash is a nonspecific symptom which can be seen in many viral, fungal, some bacterial infections and noninfection-related conditions such as autoimmune disorders and hypersensitivity reactions to drugs.

A rash is a diffuse reddening (erythema) of the skin and can be divided into macular (nonelevation of the affected areas), papular (elevation of the affected areas), vesicular (small clear vesicles) or pustular (vesicles containing pus). A rash with bleeding in the skin is a purpura or ecchymosis. If the manifestation of bleeding is pinpoint, it is referred to as a petechia. Acute febrile illnesses with petechiae and purpurae include meningococemia and spotted fever group rickettsioses such as African tick bite fever and Rocky Mountain spotted fever.

Biochemistry

C-reactive protein and WBC will usually be only slightly elevated or normal in uncomplicated viral infections. Total IgE and eosinophil count are elevated in invasive helminth infections like filariasis and onchocerciasis. Coagulation parameters and thrombocytes may be abnormal in hemorrhagic fevers including dengue virus, malaria, and septicemia.

Microbiology

Microbiology diagnosis of patients with a rash

Microorganism	Culture	16-S-PCR	PCR for specific agent	Microscopy	Specific antibodies either IgM or paired samples for increase in IgG titer	Other tests
Streptococcal group A infections (scarlet fever)	+*	+	-	-	+	
Bacterial infections with an erythematous rash†	(+)	(+)	(+)	-	+	
Viral infections with an erythematous rash**	-	-	(-)	-	+	
Viral infections with a vesicular rash††	-	-	+	-	(+)	
Viral infections with a haemorrhagic rash (purpura)§	-	-	+	-	+	Patients suspected of hemorrhagic fever should be isolated
Rickettsial infections with a hemorrhagic rash (purpura)§§	-	+	+	-	+	
<i>Mycobacterium leprae</i>	-	+	+¶	+¶¶	-	
Fungal infections with rash***	-	-	+	+	-	

*Throat swab.

† *Bartonella quintana*, *B. henselae*, *B. bacilliformis*, *Borrelia recurrentis*, *Borrelia burgdorferi*, *Chlamydia psittaci*, *Francisella tularensis*, *Mycoplasma pneumoniae*, *Leptospira* spp., *Listeria monocytogenes*, *Salmonella typhi*, *Spirillum minus*.

** Adenovirus, EBV, CMV, enterovirus (coxsackie, echo), dengue fever, HIV, human herpes virus 6, measles, parvovirus B19, rubella.

†† Herpes simplex, monkey pox, varicella zoster, vaccinia.

§ Ebola, Marburg, yellow fever, Crimean Congo hemorrhagic fever.

§§ Rickettsial spotted fever (SF) group (Rocky Mountain SF, Mediterranean SF, rickettsial pox, endemic typhus, murine typhus, scrub typhus).

¶ Not routinely available.

¶¶ Microscopy of biopsies from peripheral nerves or nasal scrapings.

*** *Candida* spp., *Cryptococcus* spp., *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, mucormycosis.

Imaging

Imaging is only indicated if systemic, deep infections are suspected.

Fever without focal symptoms

Patients commonly present with a fever but no symptoms or signs to guide the clinician towards a cause and this is called undifferentiated fever. Only if the fever persists for three weeks or more and the patient has undergone basic investigations which have ruled out common infections is the patient said to have classic fever of unknown origin (FUO). Other categories of FUO are HIV associated, hospital acquired, and neutropenic. As a general rule, around one-third of patients with FUO will have a final diagnosis of infection. Around one-third will have a noninfectious cause such as malignancy or connective tissue disease and in around one-third no cause will be found.

Initial tests on admission

The approach to a patient with an undifferentiated febrile illness starts with a thorough history, including travel and exposure risks. Fever unrelated to infection, such as from autoimmune disorders, malignancies, endocrinology disorders, and drug reactions, should be considered when planning diagnostic investigations [20].

Biochemistry/cytology

Hemoglobin, WBC plus differential count, liver parameters, serum electrolytes, BUN, creatinine, CRP, and ESR should be performed. Thrombocytopenia may indicate hemorrhagic fevers including dengue, malaria, leptospirosis or disseminated intravascular coagulation as part of bacterial septicemia.

Screening for autoimmune diseases by antinuclear antibodies, ANA, ANCA, and rheumatoid factor should take place.

Microbiology

Microscopy and culture from blood, urine, throat, sputum, wounds, sores, pustules or vesicles.

HIV testing.

Imaging

Chest X-ray as a minimum, ultrasound±CT or MRI of thorax and abdomen to rule out intraabdominal abscess, pleural effusions, enlarged glands in the mediastinum or abdomen. PET scan may be useful to visualize inflammatory foci and small malignancies.

Other

- Electrocardiogram.
- Consider TTE or TEE.

Continued testing

It is important to reexamine the patient on a daily basis as new clinical signs can emerge. Biochemistry should be repeated on a daily basis and blood cultures should be taken every 1–2 days or if there is a rigor or rapid rise in temperature.

Specific cultures and serological studies are indicated based on particular aspects of the clinical circumstances in patients with undifferentiated febrile illnesses.

Specific cultures and serological studies in particular clinical circumstances

Circumstance	Organism
Exposure to cats, especially kittens with fleas	<i>Bartonella henselae</i> (cat scratch disease)
Exposure to fresh water (river rafting)	Leptospirosis
Exposure to rodents	Leptospirosis, visceral leishmaniasis
Exposure to rabbits	Tularemia
Ingestion of unpasteurized dairy products	Brucellosis, salmonellosis
Exposure to ticks	Rickettsiosis, e.g. African tick bite fever, Rocky Mountain spotted fever, Crimean-Congo Hemorrhagic Fever (CCHF), Mediterranean spotted fever, babesiosis. See the chapter(s) on the parts of the world where the patient traveled
Travel to central valley of California, Mexico or parts of Central America	Coccidioidomycosis

Zika virus infection

Detection of Zika virus RNA

Real-time reverse transcription-polymerase chain reaction (rRT-PCR) testing should be performed on serum collected during the first two weeks after symptom onset.

For asymptomatic pregnant women who have traveled to areas with active ZIKV transmission, rRT-PCR testing is recommended on serum and urine within two weeks of the date of last possible exposure.

Real-time reverse transcription-polymerase chain reaction testing is also indicated for pregnant women who present for care ≥2 weeks after exposure and are found to be IgM positive. In areas with active ZIKV transmission, asymptomatic pregnant women should undergo IgM testing as part of

routine obstetric care in the first and second trimesters. Repeat rRT-PCR testing is included as a subsequent test for women who are IgM positive.

Zika virus-specific IgM and neutralizing antibodies typically develop towards the end of the first week of illness. IgM levels are variable but generally are positive, starting near day four post onset of symptoms and continuing for 12 weeks.

Therefore, if rRT-PCR is negative on serum and urine, serum IgM antibody testing for Zika, dengue, and chikungunya virus infections should be performed. In addition, serum samples collected ≥ 14 days after symptom onset, with no earlier samples collected, should be tested for anti-Zika virus, anti-dengue virus, and anti-chikungunya virus IgM antibodies.

Zika IgM-ELISA

The Zika IgM antibody capture enzyme-linked immunosorbent assay is used for the qualitative detection of Zika virus IgM antibodies in serum or cerebrospinal fluid. However, due to cross-reaction with other flaviviruses and possible nonspecific reactivity, results may be difficult to interpret. Consequently, presumed positive, equivocal, or inconclusive tests must be forwarded for confirmation by plaque-reduction neutralization testing. Plaque-reduction neutralization testing is performed in specialized reference laboratories to confirm presumed positive, equivocal or inconclusive IgM results (www.cdc.gov/zika/hc-providers/types-of-tests.html).

Malaria

Travel to malaria-endemic area: remember that *Plasmodium vivax* and *P. ovale* can relapse later, usually within 12 months after return, and malaria can be transmitted by *Anopheles* mosquitoes carried on an airplane or via blood transfusion.

Microscopy of Giemsa-stained thick blood films is the gold standard and can detect down to 5 parasites per microliter of blood [26]. Rapid diagnostic tests (RDTs) are increasingly being used and show good sensitivity and specificity down to a parasite density of 200 parasites per microliter at least for *P. falciparum* and *P. vivax* infections. Rapid diagnostic tests are validated by the WHO [27]. They are antigen capture assays and usually combine a *P. falciparum*-specific antigen like the HRP2 (histidine rich protein 2) with capture of a panmalaria antigen like aldolase or LDH.

However, it seems that the sensitivity to plasmodia other than falciparum is lower and it is important to remember that the RDTs may be false negative.

Eosinophilia and elevated IgE

Eosinophilia and/or increased total IgE is a common finding in systemic, helminth infections, i.e. infections with roundworms (nematodes), tapeworms (cestodes), and flukes (trematodes). Eosinophilia and IgE can be normal in chronic infections with low activity.

Biochemistry

C-reactive protein may or may not be slightly to moderately elevated, depending on the particular microorganism.

Microbiology

Diagnosis rests on a history of exposure in a relevant geographical area, symptoms and detection by microscopy, PCR or specific antibodies as shown below.

Key symptoms and method of diagnostics for helminths

Helminth	Disease	Key symptoms	Diagnosis
<p>Cestodes, tapeworms <i>Diphyllobothrium latum</i> <i>Echinococcus granulosus</i></p>		<p>Diarrhea, anemia Cysts in liver or other organs</p>	<p><i>Microscopy</i>: eggs in feces <i>Antibodies</i>: in blood <i>Microscopy</i>: cysts material <i>Eosinophilia</i> and elevated <i>total IgE</i> may be seen in active, expanding cysts <i>Imaging</i>: cysts in affected organs <i>Antibodies</i>: blood. Cross-reactivity with <i>E. granulosus</i> <i>Microscopy</i> of cyst material <i>Eosinophilia</i> and elevated <i>total IgE</i> may be seen in active, expanding cysts <i>Imaging</i>: expanding mass often in the liver <i>Microscopy</i>: eggs in feces <i>Microscopy</i>: eggs in feces <i>Microscopy</i>: eggs in feces but cannot be distinguished from <i>T. saginata</i> <i>Antibodies</i>: used in cysticercosis, cross-reactivity with other helminths <i>Eosinophilia</i> and elevated <i>total IgE</i> may be seen but not always <i>Imaging</i>: cysts in the brain and other organs</p>
<p><i>Echinococcus multilocularis</i></p>		<p>Expanding, semi-solid liver tumor without fibrous capsule</p>	
<p><i>Hymenolepis nana</i> <i>Taenia saginata</i> <i>Taenia solium</i></p>	<p>Cysticercosis</p>	<p>Diarrhea, often asymptomatic Diarrhea, often asymptomatic Can give cysticercosis with multiple small cysts in muscles and brain by ingestion of eggs. Common cause of epilepsy in poor countries. Subcutaneous nodules</p>	
<p>Trematodes (flukes) <i>Clonorchis sinensis</i></p>		<p>Biliary cirrhosis, often asymptomatic</p>	<p><i>Microscopy</i>: eggs in feces <i>Imaging</i>: hypodense lesions in the liver</p>

<i>Fasciola hepatica</i>	Biliary cirrhosis	<p><i>Microscopy</i>: eggs in feces</p> <p><i>Antibodies</i>: tests have been developed</p> <p><i>Eosinophilia</i> and elevated <i>total IgE</i> may be seen but not always</p> <p><i>Imaging</i>: hypodense lesions in the liver</p> <p><i>Microscopy</i>: eggs in feces. Eggs are very similar to <i>F. hepatica</i></p> <p><i>Imaging</i>: hypodense lesions in the liver</p> <p><i>Microscopy</i>: eggs in feces</p> <p><i>Antibodies</i>: tests have been developed</p> <p><i>Imaging</i>: hypodense lesions in the liver</p> <p><i>Microscopy</i>: eggs in sputum</p> <p><i>Antibodies</i>: tests have been developed</p> <p><i>Imaging</i>: lesions in the lungs which may resemble tuberculosis</p> <p><i>Microscopy</i>: eggs seen in urine, bladder and rectal biopsy. <i>S. mansoni</i> eggs found in feces in heavy infections. (Urine collected at midday for <i>S. haematobium</i> and <i>S. japonicum</i>, consider filter enrichment.)</p> <p>Advanced cases might require biopsies (rectal for all species and bladder for <i>S. japonicum</i> and <i>S. haematobium</i>).</p> <p><i>Antibodies</i>: more sensitive compared to microscopy</p> <p><i>Eosinophilia</i> and elevated <i>total IgE</i> may be seen but not always</p> <p><i>Imaging</i>: fibrotic scarring in the bladder and upper urinary tract</p>
<i>Fasciolopsis buski</i>	Diarrhea, intestinal wall abscess, intestinal hemorrhaging	
<i>Opisthorchis felineus</i>	Biliary cirrhosis, often asymptomatic	
<i>Paragonimus westermani</i> , <i>P. africanus</i>	Lung lesions with fibrosis and hemoptysis. May be located in other organs including the brain	
<i>Schistosoma haematobium</i>	Liver cirrhosis can be seen in all <i>Schistosoma</i> infections.	Schistosomiasis
<i>S. japonicum</i>		Bilharzia
<i>S. mansoni</i>	<i>Haematobium</i> gives hematuria, scarring of the bladder and urinary tract, abdominal cramps. <i>Mansoni</i> gives diarrhea, abdominal cramps, and rectal cancer. <i>Japonicum</i> more likely to give liver fibrosis	
<i>S. intercalatum</i>		
<i>S. mekongi</i>		
Nematodes (roundworms) <i>Ascaris lumbricoides</i>	Often nonpathogen. May give eosinophilic pneumonia in heavy infections. Intestinal obstruction	

(Continued)

Helminth	Disease	Key symptoms	Diagnosis
<i>Enterobius vermicularis</i> <i>Strongyloides stercoralis</i>	Pinworm	Pruritus ani Often nonpathogen. Diarrhea. May give rash, urticaria, pruritus, and overwhelming infection in immunocompromised. Can remain silent for years	<i>Microscopy</i> : Scotch tape test <i>Microscopy</i> : larvae found in feces <i>Antibodies</i> : blood
<i>Trichuris trichiura</i> <i>Trichinella spiralis</i> native a.o.	Whipworm Trichinellosis	Diarrhea, rectal prolapse, malabsorption Fever, muscle pain, myocarditis, rash. Diarrhea in the acute stage	<i>Microscopy</i> : eggs in feces <i>Microscopy</i> : muscle biopsy <i>Antibodies</i> : blood, preferred method in humans <i>Eosinophilia</i> and elevated <i>total IgE</i> often but not always and depend on the time after infection <i>Microscopy</i> : eggs in feces
<i>Ancylostoma duodenale</i> <i>Necator americanus</i>	Hookworms	Penetrate skin and may give a rash at the site of invasion. Diarrhea, anemia, malabsorption	
<i>Wuchereria bancrofti</i> <i>Brugia malayi</i> and <i>B. timori</i>	Filariasis Elephantiasis	Fever, lymphadenopathy, after many years of repeated infections elephantiasis may develop	<i>Microscopy</i> : microfilaria, thick blood film Giemsa stained. ICT for rapid and early antigen detection, direct detection (Giemsa) of microfilariae in blood. Caveat daytime/nocturnal patterns, concentration technique, skin snips <i>PCR</i> <i>Antibodies</i> : extensive cross-reactivity between filarial species. <i>Eosinophilia</i> and elevated <i>total IgE</i> almost always elevated to very high levels

<i>Loa loa</i>	Rash, anterior and posterior uveitis. Moving edema "Calabar swellings"	Microscopy: microfilaria, thick blood film Giemsa stained Antibodies: extensive cross-reactivity between filarial species <i>Eosinophilia</i> and elevated <i>total IgE</i> almost always elevated to very high levels Microscopy: microfilaria found in skin snips Antibodies: extensive cross-reactivity between filarial species <i>Eosinophilia</i> and elevated <i>total IgE</i> almost always elevated Long worm protruding from wound often at the lower extremities <i>Eosinophilia</i> and elevated <i>total IgE</i> almost always elevated Antibodies: extensive cross-reactivity between filarial species <i>Eosinophilia</i> and elevated <i>total IgE</i> almost always elevated to very high levels in visceral larvae migrans but not in cutaneous larva migrans
<i>Onchocerca volvulus</i>	African river blindness, onchocerciasis Anterior uveitis, subcutaneous, painless nodules. fever, lymphangitis	
<i>Dracunculus medinensis</i>	Guinea worm Long worm protruding from wound often at the lower extremities. Superinfection	
<i>Toxocara canis, T. cati</i>	Cutaneous and visceral larva migrans Creeping eruption Moving eruption, intense itching, sometimes multiorgan, systemic infection	

Imaging

Magnetic resonance imaging and CT scan are of value in infections with liver flukes and echinococcosis.

Diagnostics in areas with limited resources

Computed tomography scan and MRI are often unavailable outside tertiary academic teaching hospitals. When available, they may be employed in the diagnostic work-up of infection and are particularly useful in assessment of occult infection in the immunocompromised host with HIV.

Ultrasound is cheaper and more commonly available outside specialist centers. In rural areas, the diagnostic armamentarium may be limited to basic microscopy±basic biochemistry such as tests on cerebrospinal fluid.

Interferon-gamma release assays such as QuantiFERON-in-tube are rarely used to diagnose active tuberculosis due to high background prevalence of latent tuberculosis infection. The same is true for the tuberculin skin test (TST) in adults, although the TST is employed in the assessment of children who are contacts of tuberculosis patients.

The result of a paucity of diagnostic tests in resource-limited settings is an increase in the use of syndromic management and empirical antimicrobial regimens for clinically diagnosed infections. Switches in treatment are commonly dictated not by new information from sensitivity results but rather by lack of improvement in the clinical condition.

Basic diagnostics of pulmonary infections

Fiberoptic bronchoscopy, bronchiolar lavage, and transbronchial biopsy are only available in specialist centers. Chest X-ray is the standard. Gene Xpert MTB/RIF rapid PCR has been introduced in many countries as a first-line test for open pulmonary TB. The Xpert MTB/RIF has high sensitivity, even in smear-negative HIV-coinfected persons, a rapid turnaround time of two hours, and provides information on rifampin resistance of *M. tuberculosis* if present.

Basic diagnostics of gastrointestinal symptoms

Empirical/syndromic treatment of diarrhea with antibiotics is common in resource-limited countries.

Basic diagnostics of sexually transmitted infections

The majority of countries with limited resources employ a syndromic approach to management of sexually transmitted infection and therefore do not use diagnostic tests, but rather treat individual syndromes.

Basic diagnostics of patients with adenopathy

Fine needle aspiration or biopsy should be performed on all suspicious lymph nodes, particularly those that are asymmetrical and >1.5cm. Specimens should be sent for tuberculosis microscopy, culture (±histology), PCR, and cytology. If a diagnosis is not forthcoming, the node should be excised whenever possible and sent for the above tests.

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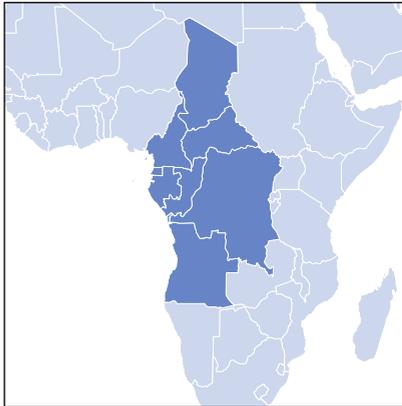
Chapter 7

Central Africa

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Angola
Cameroon
Central African Republic (CAR)
Chad
Republic of Congo (Congo-Brazzaville)
Democratic Republic of Congo (DRC)
Republic of Equatorial Guinea
Gabon
Sao Tomé and Príncipe

The pattern of infectious diseases in Central Africa is determined by its geoclimatic conditions and socioeconomic factors. The climate in most parts is tropical, i.e. hot and humid. The region is dominated by the Congo River and its tributaries. The area is covered mostly by savannah or primary and secondary tropical rainforest. Healthcare systems in some parts of Central Africa are disrupted. There are many diseases on which no data on prevalence and incidence are available. Prevalence data on these diseases can only be derived from single case reports or by analogy with other areas in Africa.

Sao Tomé and Príncipe is an island nation in the Gulf of Guinea with a different disease spectrum, but tropical disease like malaria, dengue, schistosomiasis, lymphatic filariasis from *Wuchereria bancrofti*, and geohelminth infections do occur. No human cases of yellow fever have been reported. Ciguatera fish poisoning is endemic.

Dominating the picture: HIV and tuberculosis

The burden of the HIV and tuberculosis co-epidemics is high in the Central African region. According to WHO and UNAIDS 2012 and summarized by Janssen et al (not counting Angola in the Central African region) in 2014, HIV-1 prevalence varies between 1.1% in the DRC and 6.2% in Equatorial Guinea in the age group of 15–49 year olds, with an ART coverage between 38% of those eligible in the DRC and 67% in Gabon [1]. Regarding tuberculosis, the reported incidence per 100 000 population varies between 139 in Equatorial Guinea and 428 in Gabon. TB case detection rates were estimated to range from 48% in Cameroon to 71% in Gabon; treatment success rates for TB were estimated as 51% in Gabon and 80% in Cameroon. The rates of notified TB patients tested varied from 17% in the DRC to an officially reported 100% in Gabon. HIV-TB co-infection rate estimates vary between 15% and 40%; however, all data need to be considered with caution, given the patchy data collection and the varying methodology applied to analyze them. Little is known about ART resistance so far, and few data have been collected systematically regarding TB drug resistance [1]. What is clear, however, is that there is a considerable problem of MDR-TB in the region which remains largely unaddressed in several countries [2].

CNS infections: meningitis, encephalitis

Acute CNS infections with less than four weeks of symptoms

	Frequently found disease	Rare diseases
Meningitis	Meningococcal meningitis* Meningitis by gram-positive bacilli** Enterovirus meningitis Meningitis by other gram-negative bacilli	Tuberculous meningitis† Eosinophilic meningitis in schistosomiasis Neurosyphilis Listeriosis Leptospirosis
Encephalitis	Cerebral malaria†† Herpes simplex and enterovirus encephalitis§§	Trypanosomiasis§ Rabies‡ Ebola and Marburg fever West Nile virus¶¶ Loiasis*** Neurocysticercosis
Myelitis	Spinal tuberculosis Tropical spastic paraparesis†	HIV myelopathy Schistosomiasis

* High incidence in countries in the “meningitis belt”; however, epidemics were also reported from a string of countries along the Rift Valley and Great Lakes regions, extending as far south as Mozambique and from here west to Angola and Namibia in southern Africa.

† Tuberculous meningitis more often chronic (initially light symptoms and late diagnosis).

** Especially in children: *Haemophilus influenzae*, *Streptococcus pneumoniae*.

†† Patients from malaria endemic areas may have asymptomatic parasitemia plus meningitis by other microorganisms. In cerebral malaria, neck stiffness and photophobia are usually absent. When in doubt, perform lumbar puncture.

§ *Gambiense* human African trypanosomiasis is a chronic disease with progression over months, even years, to the final CNS stage of complete lethargy, coma, and death. *Rhodesiense* human African trypanosomiasis is an acute disease with involvement of the CNS within days to weeks after the infective tsetse fly bite. In most parts of Central Africa, *T. brucei gambiense* prevails [3].

(Continued)

^{§§}In malaria-endemic areas, the diagnosis of *P. falciparum* malaria is one of exclusion, because up to 70% of children in the community may have parasitemia and yet be asymptomatic. However, in resource-poor countries, exclusion of viral encephalitis is problematic and practically no information is available on prevalence and manifestation of the neurotropic viruses in Central Africa.

[§]Rabies is a major public health problem, mainly because of poor management of dog bites [4].

^{¶¶}Serological evidence of human exposure to WNV has been reported in the CAR, Cameroon, Gabon, and the DRC.

^{***}Antifilarial drugs can induce an encephalopathy in patients with very high Loa loa microfilaremias. Exceptionally, loa loa can provoke encephalitis in the absence of treatment.

[#]Konzo can be a differential diagnosis: an epidemic paralytic disease occurring in outbreaks in remote rural areas of low-income African countries, associated with several weeks of almost exclusive consumption of insufficiently processed “bitter” (high cyanide content) cassava.

Chronic CNS infections with more than four weeks of symptoms in immunocompetent and immunocompromised patients

The most common chronic CNS infection is tuberculous meningitis, usually with gradual onset of fever, headache, altered consciousness, and cranial nerve palsies. Tuberculomas can give rise to focal neurological defects. Neurosyphilis should be considered in any patients with elevated spinal fluid WBC count.

West African trypanosomiasis (WAT) is a chronic disease with progression over months, even years, to the final CNS stage of complete lethargy, coma, and death - see footnote § in the table under Acute CNS infections with less than four weeks of symptoms. Neurocysticercosis is common and is an important cause of epilepsy in the region [5]. Neurobrucellosis is to be expected in areas with livestock breeding only.

HIV-1 is another common neuroinfection in the region. Neurocognitive disorders are common in HIV patients. All HIV-related CNS infections can be seen [6], in particular cryptococcal meningitis [7], CMV, and histoplasmosis. JC is a neurotropic virus and may cause progressive multifocal leukoencephalopathy (PML). Infections with *Nocardia*, *Candida* and *Aspergillus* species may be seen in immunocompromised patients but data are not available from the region. Infection with *Toxoplasma gondii* is probably common in the region, and should be considered in HIV-positive patients with CNS symptoms, especially if focal lesions are found on CNS scans. Encephalitis caused by the free-living ameba *Acanthamoeba* spp. and *Balamuthia mandrillaris* is probably found in immunocompromised patients, but has never been described from the region. Occasionally, immune reconstitution inflammatory syndrome (IRIS) may occur in the brain, when antiretroviral therapy is started.

Besides HIV-1, HIV-2 is also endemic in Central Africa. High prevalences have been reported in Equatorial Guinea. Longitudinal studies suggest that the rate of progression to advanced HIV-related disease and mortality is far lower for HIV-2 than for HIV-1. Dual infection with HIV-1 and HIV-2 is possible.

In patients with a gradually appearing, symmetrical paraparesis of the lower limbs with signs of pyramidal tract involvement, sometimes also with bladder disorders, HTLV-1 infection has to be considered. In some parts of Central Africa, up to 1–5% of the general population is infected [8]. Other subtypes have been described in that region, for example HTLV-3 [9].

Ear, nose, throat, and upper respiratory tract infections

Acute and chronic infections

Acute and chronic suppurative otitis is highly prevalent in the area, affecting mainly children. Predominant bacterial agents in chronic discharging ears are gram-negative bacteria including *Pseudomonas aeruginosa*. Otomycosis is a differential diagnosis.

Streptococcal throat infection is common, and patients may develop rheumatic fever. Group A streptococci as well as other beta-hemolytic streptococci account for a considerable morbidity and mortality. Other causes of pharyngitis include Vincent's angina and EBV. Diphtheria should be suspected in a patient if a creamy adherent membrane is present over part of the tonsil (no data from Central Africa).

Tuberculosis can affect nose, nasopharynx, oropharynx, middle ear, mastoid bone, larynx, deep neck spaces, and salivary glands – usually associated with pulmonary tuberculosis.

Rare diseases include rhinoscleroma, a slowly developing granulomatous process in the nose caused by *Klebsiella rhinoscleromatis*. Rhinosporidiosis is another granulomatous disease caused by *Rhinosporidium seeberi* (Mesomycetozoea = unicellular parasites). Rhinoentomophthoromycosis (conidiobolomycosis) is a rare grossly disfiguring infection of the facial soft tissues, usually spreading from an endonasal lesion and caused by different fungi (*Conidiobolus* spp. and *Basidiobolus ranarum*) [10]. Leprosy may affect the larynx and chronic nasal discharge, sometimes bloodstained, occurs in lepromatous leprosy. Nasal destruction is seen in yaws and leprosy (and in lupus vulgaris).

Ear, nose, and throat infections in immunocompromised host

Ear, nose, and throat diseases in HIV patients include cervical lymphadenopathy, otitis media, oral candidiasis, and adenotonsillar diseases. The bacteriology of sinusitis in HIV infection often indicates opportunistic organisms not responsive to standard medical therapy, such as CMV, *Aspergillus*, and atypical mycobacteria. Tuberculosis must always be considered. In immunosuppressed patients, rare diseases have to be considered.

Sickle cell disease is a common inherited blood disorder in Central Africa. When bone is involved, infarction and osteomyelitis can be seen in the maxillofacial bone and skull base.

Children with protein-energy malnutrition may develop gangrenous stomatitis (cancrum oris, noma).

Cardiopulmonary infections

Acute infections with less than four weeks of symptoms

Pulmonary infection with less than four weeks of symptoms

	Frequently found disease	Rare diseases
Pneumonia	<i>Streptococcus pneumoniae</i> * <i>Haemophilus influenzae</i> † <i>Staphylococcus aureus</i> †† Tuberculosis Viruses (rhino, adeno)	<i>Mycoplasma</i> , <i>Chlamydia</i> , <i>Legionella</i> Q-fever** Histoplasmosis, blastomycosis
Lung abscess	Gram-positive bacteria	Amebiasis§
Cough with eosinophilia	Schistosomiasis (Katayama syndrome) Ascariasis (Löffler's syndrome)	Paragonimiasis

* Most frequent; patients with hypogammaglobulinemia, asplenia, nephrotic syndrome, and sickle cell anemia are at special risk.

† Responsible for 3–5% of episodes of pneumonia.

** Important differential diagnosis in febrile patients in general [11].

†† Causing 1–2% of pneumonias.

§ Liver abscess rupturing through diaphragm.

Endocarditis, myocarditis, pericarditis with less than four weeks of symptoms

	Frequently found disease	Rare diseases
Endocarditis	Subacute and acute bacterial endocarditis by <i>S. aureus</i> and streptococci spp.	Q-fever (<i>Coxiella burnetii</i>) <i>Bartonella quintana</i> infection <i>Tropheryma whipplei</i> infection
Myocarditis	Acute virus myocarditis Bacterial myocarditis (e.g. leptospirosis) Malaria*	Trypanosomiasis <i>Trichinella</i> infection
Pericarditis	Viral pericarditis [†] Pyogenic pericarditis ^{††} Tuberculosis	Amebic pericarditis**

* Mostly in addition to other organ complications.

[†] Fever, pericardial pain, but no evidence of systemic pyogenic infection.

** By rupture of left-sided liver abscess through diaphragm.

^{††} Often in the course of bronchopneumonia or osteomyelitis, *S. pneumoniae*, *S. aureus*.

Chronic infections with more than four weeks of symptoms

Pneumonia with more than four weeks of symptoms Tuberculosis should always be considered in patients with cough and fever for more than four weeks. *Nocardia*, histoplasmosis, and blastomycosis are primarily infections in immunocompromised patients. Paragonimiasis is a differential diagnosis to tuberculosis and the main symptoms are cough and blood-flecked sputum. The radiological pictures show nodular infiltration, and sometimes pleural fluid and/or cavities. Paragonimiasis is to be suspected in patients with pulmonary findings similar to TB but with negative TB diagnostics. Pulmonary melioidosis has been described in rare cases in Central Africa and can be a differential diagnosis [12].

Endocarditis and pericarditis with more than four weeks of symptoms Rheumatic heart disease (differential diagnosis: Libman–Sacks endocarditis in patients with SLE), tuberculosis, Q-fever, and other rickettsial infection like *Bartonella quintana* should be considered. Tuberculous pericarditis may directly spread from the tracheobroncheal tree or thoracic lymph nodes.

Infections in the immunocompromised host

Pneumonia in the immunocompromised host Lung infections due to bacteria, including tuberculosis, are also found in the immunocompromised host. Reports from Central Africa have suggested that *Pneumocystis jiroveci* pneumonia (PJP) is a less important cause of morbidity than in the developed world. However, more recent studies have shown high seroprevalence rates of *P. jiroveci* in healthy individuals with HIV as well as high rates of clinical disease in African children. This suggests that PJP may be more common in Central Africa than was previously recognized [13,14]. CMV, adenovirus, and HSV are common viral causes and fungi such as *Candida* spp., *Aspergillus*, *Nocardia*, and *Actinomyces*, as well as gram-positive rod bacteria, should be considered.

Endocarditis, myocarditis, pericarditis in the immunocompromised host Myocarditis may be caused by HIV infection, *Cryptococcus*, *Toxoplasma gondii*, and *Mycobacterium avium intracellulare* (MAI). Tuberculosis is a common cause of pericarditis.

Gastrointestinal infections

Gastrointestinal infections with less than four weeks of symptoms

	Frequently found disease	Rare diseases
Diarrhea	Salmonellosis Shigellosis <i>Campylobacter</i> infection Giardiasis ETEC infection Noro- and rotavirus infection <i>Clostridium difficile</i>	Amebic colitis* Cholera† <i>E. coli</i> O157** Cryptosporidiosis Cyclosporiasis Strongyloidiasis Ebola virus disease

*Typically with bloody diarrhea; diagnosis can be made when hematophagous trophozoites are found in stool.

†Cholera is endemic in Central Africa. Outbreaks as well as sporadic cases can be expected and notification is unreliable if existent at all [15]. Notified outbreaks are published in the WHO Weekly Epidemiological Record (www.who.int/wer/en/index.html).

**Single cases have been reported [16].

†† Common gastrointestinal manifestations include diarrhea (70%), nausea and vomiting (60%), and abdominal pain (45%). The diarrhea and nausea and vomiting frequently produce profound, life-threatening hypovolemia and electrolyte imbalances [17].

Chronic gastrointestinal infections with more than four weeks of symptoms

Infections with *Giardia intestinalis* and *Cryptosporidium* spp. may cause long-lasting, fluctuating gastrointestinal symptoms. Other intestinal parasites include hookworm infections, *Ascaris lumbricoides*, and *Trichuris trichiura*. Infection with *Strongyloides stercoralis* is common but sometimes asymptomatic. It may, however, cause unspecific intestinal symptoms and severe disease in immunocompromised patients (for example, in HTLV-1 infection). Schistosomiasis from *S. mansoni* and rarely *S. intercalatum* is another common cause of chronic gastrointestinal symptoms. Enterocolitis caused by *Entamoeba histolytica* may present both as an acute dysentery and more prolonged infection in the colon, mimicking inflammatory colitis.

Tuberculosis should always be considered in patients with long-lasting gastrointestinal symptoms. It is assumed that Whipple disease is found in Central Africa – some data are available from Gabon [18]. Enteritis necroticans is a segmental necrotizing infection of the jejunum and ileum caused by *Clostridium perfringens* type C. It affects primarily children with severe protein malnutrition. There are, however, no data from Central Africa.

Diarrhea in the immunocompromised host

Giardia lamblia, cryptosporidia, *Cyclospora cayatanensis*, *Cystoisospora belli*, and *Microsporidium* spp. should be considered. Other opportunistic infections include tuberculosis, intestinal cytomegalovirus infection, and *Mycobacterium avium intracellulare* infection.

Infections of liver, spleen, peritoneum

Acute infections of liver, spleen, peritoneum with less than four weeks of symptoms

	Frequently found disease	Rare diseases
Jaundice	Malaria* Hepatitis A	Hepatitis C Hepatitis E

(Continued)

	Frequently found disease	Rare diseases
	Hepatitis B [†] EBV, CMV infection Hepatitis E ^{††}	Rickettsiosis Leptospirosis** Syphilis II Relapsing fever Visceral leishmaniasis [§] Fitz-Hugh–Curtis syndrome ^{§§} Ebola and Marburg fever Yellow fever CCHF and Lassa ^{††} Trypanosomiasis
Space-occupying lesion in liver Splenomegaly	Bacterial liver abscess Malaria Typhoid fever Bacterial endocarditis Viral hepatitis EBV, CMV	Amebic liver abscess Trypanosomiasis Kala azar Relapsing fever Dengue Brucellosis Tuberculosis

* Slight hemolytic jaundice is frequent. Elevation of liver enzymes >3× of the upper normal limit and marked jaundice may result from direct damage of hepatocytes and is indicative of severe malaria.

[†] Predominantly genotypes A and E.

** Not much data available, but aphorism holds true also for Central Africa: “Wherever leptospire and leptospirosis is searched for, they are invariably discovered” [19].

^{††} CCHF virus was isolated in 1956 from a febrile patient in Belgian Congo. Outbreaks have been described in the DRC, otherwise there are only few data [20]. Lassa fever cases have been described in Orientale Province in DRC.

[§] To be expected in the northern part of Central Africa, e.g. Cameroon.

^{§§} Perihepatitis is seen in Fitz-Hugh–Curtis syndrome, which is a subgroup of pelvic inflammatory syndrome usually caused by gonorrhoea (acute gonococcal perihepatitis) or *Chlamydia* infection.

Chronic infections of liver, spleen, peritoneum with more than four weeks of symptoms

	Frequently found disease	Rare diseases
Jaundice	Chronic viral hepatitis Schistosomiasis*	Brucellosis Q-fever hepatitis Toxocariasis Hepatic tuberculosis [†] Leprosy** Histoplasmosis Porocephalosis ^{††}
Space-occupying lesion in liver		Tuberculosis Melioidosis
Ascites Splenomegaly [§]	Tuberculous peritonitis Hepatosplenic schistosomiasis Hyperreactive malaria syndrome	Schistosomiasis <i>mansoni</i> Tuberculosis Brucellosis

* Hepatic schistosomiasis is most often due to *S. mansoni*. The pathological effects of *S. intercalatum*, occurring in several foci in Central Africa, are mostly limited to mild intestinal disease.

†TB may occur as miliary, nodular, and solitary abscess forms.

**Granulomatous hepatitis may be seen in patients with lepromatous leprosy.

††Porocephalosis is a rare parasitic infection caused by the pentastomid *Armillifer armillatus* and described primarily from Cameroon.

§Abnormal immunological reaction to *Plasmodium* infection, huge splenomegaly >10cm below costal margin, serum IgM more than 2× standard deviation (2SD) above the local mean, high titer of malarial antibodies, and response to antimalarial drugs are the cornerstones of the diagnosis. Splenic lymphoma with villous lymphocytes co-exists with this condition and it should always be considered in the differential diagnosis of unresponsive or poorly responsive cases of hyperreactive malarial splenomegaly.

Infections of liver, spleen, peritoneum in immunocompromised host

Infections in the immunocompromised host are no different from the immunocompetent host.

Genitourinary infections

Acute genitourinary infections with less than four weeks of symptoms

Cystitis, pyelonephritis, and nephritis with less than four weeks of symptoms Uropathogenic *E. coli* is the most common cause of infection in patients with normal urinary tract anatomy.

Acute and chronic sexually transmitted diseases with less than four weeks of symptoms

	Frequent diseases	Rare diseases
Urethritis and discharge	Gonorrhea Chlamydial urethritis Trichomoniasis	<i>Mycoplasma urethritis</i>
Genital ulcers	Syphilis Ulcer molle Genital herpes	Lymphogranuloma inguinale Donovanosis*

*The painless genital ulcers can easily be mistaken for syphilis.

Chronic genitourinary infections with more than four weeks of symptoms

Cystitis, pyelonephritis, and nephritis with more than four weeks of symptoms In patients from Central Africa with chronic genitourinary infections, tuberculosis and *Schistosoma haematobium* infection must be considered. *Schistosoma haematobium* may cause hematuria and hemospermia.

Hydrocele can occur in Bancroftian filariasis. Testicular enlargement may occur in mumps, filariasis, Kaposi sarcoma and during erythema nodosum leprosum. Chronic epididymoorchitis is seen in TB and syphilis.

Cystitis, pyelonephritis, and nephritis infections in the immunocompromised host

Infections in the immunocompromised host are similar to those in the immunocompetent host.

Patients with sickle cell disease are at increased risk for urinary tract infection.

Urinary tract infections in HIV-positive patients are more frequent than in uninfected patients. Necrotizing fasciitis of the genitalia (Fournier's gangrene) may develop. Impairment of kidney function

is usually caused by HIV-associated nephropathy, caused by direct infection of the renal cells with the HIV-1 virus or by changes in the release of cytokines during HIV infection.

Sexually transmitted diseases in the immunocompromised host

Sexually transmitted disease courses in the immunocompromised host are no different from those in the immunocompetent host.

Infections of joints, muscle, and soft tissue

Acute infections of bone, joints, and muscle with less than four weeks of symptoms

	Frequently found disease	Rare diseases
Osteoarthritis	Septic arthritis Gonococcal arthritis Rheumatic fever Chikungunya, dengue, Zika virus*	Brucellosis [§] <i>Histoplasma duboisii</i> infection Leprosy
Osteomyelitis	Acute hematogenous osteomyelitis [†]	
Myositis**	Pyomyositis ^{††} Other bacterial myositis Group A streptococcal necrotizing myositis Acute rhabdomyolysis ^{§§}	Trichinosis Gas gangrene (clostridial myonecrosis)

*Viral arthritis is typical in chikungunya and can mimic seronegative rheumatoid arthritis. Dengue affects tendons, muscles, joints, and bones. Polyarthralgia in dengue fever is known, but arthritis is rare. The same is true for Zika virus infection [21].

[†]Most often *S. aureus*, rarely streptococci and enterobacteriaceae, in sickle cell anemia very often salmonella.

**Myositis is defined as inflammation of a muscle, especially a voluntary muscle, and characterized by pain, tenderness, swelling, and/or weakness.

^{††}Pyomyositis is defined as an acute intramuscular bacterial infection which is neither secondary to a contiguous infection of the soft tissue or bone nor due to penetrating trauma. Infections result from hematogenous spread and are usually due to *S. aureus*.

[§]*Brucella abortus* is endemic from Sudan to Cameroon.

^{§§}Seen in leptospirosis, pneumococcal sepsis, echovirus infections, and malaria (but also e.g. in snake bite and other noninfectious conditions).

Chronic infections of bone, joints, and muscle with more than four weeks of symptoms and in the immunocompromised host

Tuberculosis should always be considered; additionally, consider mycobacteria other than tuberculosis (MOTT) in the immunocompromised patient. Leprosy, brucellosis, actinomycosis, and nocardiosis are rare causes of arthritis and osteomyelitis.

Patients with hemoglobinopathies like sickle cell disease and thalassemia have a high risk of osteomyelitis due to episodes of microthrombosis, osteonecrosis, and secondary infections. In the immunocompromised host, HIV-associated arthritis should be considered. Rare causes – mainly in immunocompromised patients – are infections with *Histoplasma duboisii*, *Cryptococcus neoformans*, and microsporidia.

Infections of skin and soft tissues

Skin infections

	Frequently found disease	Rare diseases
Maculopapular	Dengue, EBV, CMV, acute HIV infection, syphilis	Rickettsiosis Relapsing fever
Papular, vesicular		Monkey pox* Tanapox†
Papular and petechia		Leptospirosis
Papillomatous		Yaws**
Chancre, erythematous		Trypanosomiasis
Hematoma	Meningococcal sepsis	Viral hemorrhagic fevers
Ulcer††	Buruli ulcer Tropical ulcer	Cutaneous diphtheria Syphilitic gumma
Subcutaneous nodules	Onchocerciasis§	Buruli mycobacteria§§
Migratory subcutaneous swellings, eye worm	Loiasis¶	
Itching	Filarial infection, incl. <i>M. perstans</i>	
Multiple manifestations		Leprosy¶¶

* Recently reemerging in the DRC [22].

† Endemic to equatorial Africa. It begins with a febrile prodrome that is soon followed by the eruption of one or more large, superficial nodules, typically on the extremities.

** Still an issue in Central Africa, particularly in the pygmy population of south-western CAR and in the DRC.

†† Always consider Marjolin's ulcer as a differential diagnosis, an aggressive ulcerating squamous cell carcinoma presenting in an area of previously traumatized, chronically inflamed or scarred skin.

§ Uneven distribution in Central Africa. In Angola, onchocerciasis is distributed in discrete foci. In Cameroon and DRC, onchocerciasis is a country-wide public health problem. In Chad, the onchocerciasis focus is located in the southern part of the country. In the DRC, onchocerciasis is distributed in foci in the south of the country. Onchocerciasis is endemic on Bioko Island, which is situated off the coast of Cameroon and Gabon. In Gabon, there are only a few villages where onchocerciasis remains a problem.

§§ Buruli ulcer may initially present as a subcutaneous nodule – rarely diagnosed in this stage.

¶ Loiasis is quite frequently imported by travellers from Central Africa [23].

¶¶ Leprosy cases in Central Africa: www.who.int/lep/situation/africa/en/index.html.

Soft tissue infections

Cellulitis and subcutaneous tissue infections including necrotizing fasciitis are frequently encountered. A subcutaneous mycosis frequently seen is chromoblastomycosis, characterized by vegetative and verrucal lesions which occur predominantly on the lower limbs. Mycetomas are chronic, inflammatory swellings with numerous sinuses, caused by molds or bacteria (in Africa predominantly eumycetomas, often caused by *Madurella mycetomatis*). Entomophthoromycosis is a slowly progressing infection of the subcutaneous tissue or paranasal sinuses caused by *Conidiobolus coronatus* leading to grotesque deformation of the face. The distribution of sporotrichosis in Central Africa is not well known, but single cases have been reported.

Skin infections in immunocompromised host

Skin infections that particularly affect HIV patients include herpes simplex, zoster, molluscum contagiosum, dermatophytosis, unusual forms of scabies, cryptococcosis, histoplasmosis, and staphylococcal folliculitis (DD papular pruritic eruption). Bacillary angiomatosis is only rarely reported.

Lymphadenopathy

Acute lymphadenopathy with less than four weeks of symptoms

	Frequently found disease	Rare diseases
Localized	Regional lymphadenitis HIV infection Mycobacterial adenitis	Lymphatic filariasis Lymphogranuloma inguinale, chancroid, granuloma inguinale Rubella Trypanosomiasis* Leprosy† Plague**
Generalized	HIV infection CMV and EBV infection Measles Toxoplasmosis	Brucellosis Histoplasmosis Secondary syphilis Tuberculosis Rickettsiosis

*Typically, enlargement of posterior cervical lymph nodes (Winterbottom's sign).
†As part of reactional state in erythema nodosum leprosum.
**Bubonic plague – plague lately reported in the DRC, outbreaks in Ituri subregion.

Chronic lymphadenopathy

Tuberculosis, filariasis, and brucellosis should be considered. Kala azar patients present signs of parasitic invasion of the reticuloendothelial system, such as enlarged spleen and liver, but also enlarged lymph nodes (more frequent in Africa than in India).

Fever without focal symptoms

Acute fever with less than four weeks of symptoms

Frequently found disease	Rare diseases	Very rare diseases
Malaria Typhoid fever Sepsis Unspecific viral infection, dengue, chikungunya, Zika virus infections Endocarditis	Amebic liver abscess* Rickettsiosis† CMV, EBV, acute HIV	Relapsing fever Trypanosomiasis Viral hemorrhagic fever**

*Rarely without pain in the upper abdomen.
†Rickettsioses (also called typhus) in Central Africa mainly from spotted fever group, predominantly *R. africae* [24]. Disease occurs in rural settings and in international travelers returning from safari, hunting, camping, etc. Symptoms include fever but also eschars, maculopapular or vesicular rash and lymphadenopathy. Few data concerning other rickettsial diseases. In Cameroon, human monocytotropic ehrlichiosis (HME), caused by *Ehrlichia chaffeensis*, has been described [25].
** May begin with monosymptomatic fever.

Chronic fever with more than four weeks of symptoms in immunocompetent and immunocompromised patients

The differential diagnosis of prolonged pyrexia is long: malaria, tuberculosis, enteric fever, visceral leishmaniasis, pneumonia, urinary tract infection, abscesses, infective endocarditis, secondary syphilis, and trypanosomiasis. Noninfectious causes should be considered, especially malignancies and autoimmune diseases.

Eosinophilia

	Frequently found disease	Rare diseases
Asymptomatic	Intestinal worms Schistosomiasis Filariasis	
With fever	Katayama syndrome	Acute <i>Fasciola hepatica</i> infection* Trichinosis
With subcutaneous swellings	Loiasis	Paragonimiasis
With abdominal pain	Intestinal worms (<i>Ascaris lumbricoides</i> , <i>Necator americanus</i> , <i>Trichuris trichiura</i>) Toxocariasis (<i>Toxocara canis</i> , <i>T. cati</i>)	
With elevated transaminases	Toxocariasis (<i>Toxocara canis</i> , <i>T. cati</i>) Strongyloidiasis	Fascioliasis*
With pulmonary infiltrate	Loeffler's syndrome Katayama syndrome	Paragonimiasis

*Practically no data from Central Africa, maybe to be expected in northern areas with livestock breeding.

Children

Diarrhea (19%), pneumonia (18%), malaria (16%), other infections (9%), and AIDS (4%) are estimated to be the most important killers of children in Central Africa [26]. All of these diseases may lead to delays in child development which may, in turn, result in increased susceptibility to childhood diseases. Malnutrition, commonly found in young children, can additionally aggravate these conditions.

The childhood vaccination program in the region is not achieving complete coverage, especially for measles, mumps, and rubella (MMR). Outbreaks of measles have been reported from the DRC as well as most other countries in the region. This means that rubella and mumps may be prevalent and a risk to nonimmunized travelers. The countries in the region are working towards a third diphtheria-tetanus-pertussis vaccination (DT3) but low coverage <90% and suboptimal data completeness are reported from some countries in the region (www.who.int/immunization/GIN).

Antibiotic resistance

In Central Africa, resistance of common pathogens to antibiotics is alarmingly widespread. Though data are limited and of mixed quality since blood cultures are rarely done, they do allow us to sketch the current situation [27,28].

Methicillin-resistant *Staphylococcus aureus* (MRSA) is found frequently [29–31]. In Cameroon, MRSA was found in 21% of the samples; Panton Valentine leukocidin genes were highly prevalent [32]. Data on *Streptococcus pneumoniae* are limited; while resistance to penicillin appears to be rare, resistance to

chloramphenicol and sulfamethoxazole/trimethoprim exceeds 50%. In *Shigella* and *Salmonella*, high resistance rates to ampicillin, chloramphenicol, streptomycin, sulphonamides, trimethoprim, and tetracycline were noted. Other enterobacteriaceae appear to be increasingly resistant to commonly used antibiotics like amoxicillin/clavulanic acid and first-generation cephalosporins [33]. High rates of antimicrobial resistance were reported in uropathogens like *E. coli* and *Klebsiella* spp. in Bukavu/Congo [34]. Reports on antibiotic resistance of *Vibrio cholerae* 01 El Tor from Chad and Cameroon show nearly no resistance while in the DRC and Angola, multidrug resistance to first-line drugs like ampicillin, tetracycline, doxycycline, sulfamethoxazole/trimethoprim, nalidixic acid, and chloramphenicol was highly prevalent during the reported outbreaks.

Drug resistance in *Mycobacterium tuberculosis* is common. A study from 2007 found that the primary resistance rate reached 43.5%; the multidrug resistance rate (MDR-TB) notified as resistant to both rifampicine and isoniazide was 5.3% [35]. XDR strains have been reported from Central Africa.

Demographic data

Basic economic and demographic data

Country	GNI per capita (USD)*	Life expectancy at birth (both sexes)†	School enrollment, primary (% gross)
Angola	7000	52	n.d.
Cameroon	2770	57	111
Central African Republic	600	51	95
Chad	2010	52	95
Democratic Republic of Congo	740	52	111
Republic of Congo	4600	59	109
Equatorial Guinea	23.470	56	91
Gabon	17.230	64	n.d.
São Tomé and Príncipe	2950	67	118

FNI, gross national income.

*World Bank figures, 2013. GNI per capita based on purchasing power parity (PPP). PPP GNI is gross national income (GNI) converted to international dollars using purchasing power parity rates. An international dollar has the same purchasing power over GNI as a US dollar has in the United States. GNI is the sum of value added by all resident producers plus any product taxes (less subsidies) not included in the valuation of output plus net receipts of primary income (compensation of employees and property income) from abroad.

†WHO figures, 2013.

Distribution of causes of death in 0–4 year olds, 2013 (in %) in selected countries

	Congo	Angola
HIV/AIDS	5.6	1.2
Diarrheal diseases	5.2	14.6
Pertussis	2.2	0.6
Tetanus	0.3	1.2
Measles	0	0.4
Meningitis/encephalitis	1.1	3.6
Malaria	21.8	12.6

Source: World Health Organization. The global burden of disease: 2014 update.

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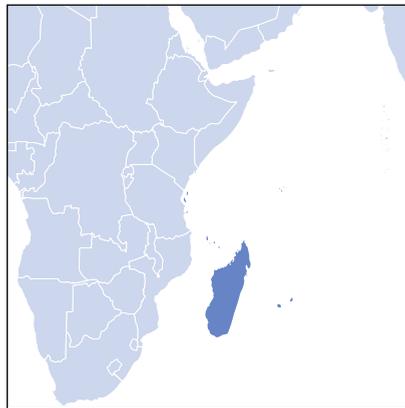
Chapter 8

East Africa: Madagascar and Indian Ocean Islands

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Comoros
Madagascar
Maldives
Mauritius
Réunion (Fr.)
Seychelles

In Reunion, Mauritius, Maldives, and Seychelles, improved socio-sanitation conditions over the past years have dramatically decreased the incidence of tropical disease levels comparable with those observed in developed countries. Malaria, schistosomiasis, and lymphatic filariasis have been eradicated, as well as cysticercosis with the exception of Reunion. Amebiasis, typhoid fever, and leprosy have become rare. However, because of the geographical proximity of Madagascar and Comoros where the diseases are endemic, there is a risk of reintroduction of vectorborne infections. Epidemics of dengue and chikungunya were recently observed over all the islands. Tuberculosis remains a public health concern in the whole area. Data collected by the GeoSentinel surveillance network for 1415 ill travelers returning from Indian Ocean Islands during 1997–2010 showed that *Plasmodium falciparum* malaria (from Comoros and Madagascar), acute nonparasitic diarrhea (notably from Madagascar and Maldives), intestinal helminthes, protozoans and shistosomiasis from Madagascar were the most frequent diagnoses. Arboviral infections (dengue and chikungunya) showed a sustained increase and peaked in 2006. Respiratory and skin infections were less frequently reported [1].

CNS infections: meningitis, encephalitis

Acute infections with less than four weeks of symptoms

Besides cosmopolitan infections, local infections like Toscana virus infection, West Nile encephalitis, rabies, and typhus should be considered.

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Enteroviruses, herpes virus, varicella zoster virus <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> [2,3], <i>Neisseria meningitidis</i>	Rabies virus (Madagascar only) [4], West Nile virus (Madagascar) [5] Neurosyphilis <i>Listeria</i> , <i>Mycobacterium tuberculosis</i> , <i>Angiostrongylus cantonensis</i> [6,7]	Influenza <i>Klebsiella pneumoniae</i>

Infection with symptoms for more than four weeks and in the immunocompromised host

Consider noninfectious causes like lymphoma.

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
HIV, <i>Mycobacterium tuberculosis</i>	<i>Mycobacterium tuberculosis</i> <i>Cryptococcus</i> spp., <i>Candida</i> spp., <i>Aspergillus</i> spp., <i>Rhodotorula</i> , <i>Nocardia</i> , <i>Toxoplasma</i>

Ear, nose, and throat infections

Ear, nose, and throat infections with less than four weeks symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Rhinovirus, corona virus, VRS, myxovirus, herpes virus, adenovirus, enterovirus (tonsillitis, rhinitis, otitis) Epstein–Barr virus (tonsillitis), coxsackievirus (conjunctivitis) [8,9] <i>Streptococcus</i> (tonsillitis, otitis), <i>Haemophilus B catarrhalis</i> (otitis)	<i>Mycobacterium tuberculosis</i> (tonsillitis, otitis)	Diphtheria (tonsillitis)

Ear, nose, and throat with symptoms for more than four weeks and in the immunocompromised host

Consider also noninfectious causes like cancer.

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Tuberculosis, syphilis (tonsillitis)	<i>Candida</i> spp.

Cardiopulmonary infections

Pneumonia with less than four weeks symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Influenza [10] <i>Streptococcus pneumoniae</i> , <i>Mycoplasma pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Staphylococcus aureus</i> , <i>Chlamydia pneumoniae</i> [11–14]	<i>Legionella pneumophila</i>	Diphtheria, <i>Klebsiella pneumoniae</i> , <i>Yersinia pestis</i> [15]

Endocarditis with less than four weeks symptoms

Frequently found microorganisms	Rare microorganisms and conditions
<i>Staphylococcus</i> and <i>Streptococcus</i> spp.	<i>Neisseria gonorrhoeae</i>

Pulmonary symptoms for more than four weeks and in the immunocompromised host

Consider also noninfectious causes like lung cancer, autoimmune lung fibrosis, and Wegener granulomatosis.

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
COPD Tuberculosis [16], <i>Aspergillus</i>	CMV <i>Aspergillus</i> , <i>Candida</i> , <i>Pneumocystis jirovecii</i>

Endocarditis for more than four weeks and in the immunocompromised host

Consider also noninfectious causes like sarcoidosis.

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Staphylococcus</i> and <i>Streptococcus</i> spp., <i>Enterococcus</i>	<i>Aspergillus</i> , <i>Candida</i>

Gastrointestinal infections

Gastrointestinal infections with less than four weeks symptoms

Consider also noninfectious causes like inflammatory bowel disease and intestinal malignancies like colon cancer.

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Adenovirus, norovirus and calicivirus, rotavirus, hepatitis A virus <i>Escherichia coli</i> , <i>Salmonella</i> spp., <i>Campylobacter</i> , <i>Shigella</i> <i>Giardia intestinalis</i> , <i>Trichomonas intestinalis</i>	<i>Cryptosporidium</i> spp.	Tuberculosis <i>Cyclospora cayetanensis</i> Mb. Whipple

Diarrhea is often associated with infections with bacteria, viruses, and parasites. Repeated negative bacterial cultures and microscopy for parasites should lead to the consideration that the symptoms may not be caused by an infection. Inflammatory bowel disease like colitis and Mb Chron are differential diagnoses and malabsorption and celiac disease must also be considered.

Gastrointestinal infections with symptoms for more than four weeks and in the immunocompromised host

Consider noninfectious causes like inflammatory bowel disease, intestinal malignancies like colon cancer, malabsorption, and celiac disease.

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Hepatitis A Tuberculosis <i>Giardia intestinalis</i> , <i>Entamoeba histolytica</i> , cryptosporidia, <i>Trichomonas intestinalis</i> , helminths (<i>Ascaris lumbricoides</i> , <i>Trichuris trichura</i> , <i>Hymenolepis nana</i> , <i>Strongyloides stercorali</i> (Madagascar, Comoros) [17,18], <i>Schistosoma mansoni</i> (Madagascar)	Herpes virus, CMV <i>Isospora</i> , <i>Microsporidium</i> <i>Candida</i>

Infections of liver, spleen, peritoneum

Acute infections of liver, spleen, peritoneum with less than four weeks of symptoms

	Frequently found disease	Rare diseases
Jaundice	Hepatitis A Hepatitis B EBV, CMV infection	Hepatitis C Hepatitis E [19] Rickettsiosis Leptospirosis Syphilis II Crimean Congo hemorrhagic fever*
Space-occupying lesion in liver Splnomegaly	Bacterial liver abscess Typhoid fever Bacterial endocarditis Viral hepatitis EBV, CMV	Amebic liver abscess Visceral leishmaniasis Relapsing fever Brucellosis Tuberculosis

* Has not been described.

Chronic infections of liver, spleen, peritoneum with more than four weeks of symptoms

	Frequently found disease	Rare diseases
Jaundice	Chronic viral hepatitis Schistosomiasis*	Toxocariasis Hepatic tuberculosis [†] Leprosy (Madagascar, Comoros) Histoplasmosis
Space-occupying lesion in liver Ascites Splnomegaly	Tuberculous peritonitis Hepatosplenic schistosomiasis	Tuberculosis Schistosomiasis* Tuberculosis Brucellosis

*Hepatic schistosomiasis is most often due to *S. mansoni* and only present in Madagascar.
[†]Hepatic TB may occur as miliary, nodular, and solitary abscess forms.

Infections of liver, spleen, peritoneum in immunocompromised host

Infections in the immunocompromised host are no different from those in the immunocompetent host.

Genitourinary infections

Cystitis, pyelonephritis, and nephritis with less than four weeks symptom

Consider also noninfectious causes, especially malignancies like renal cell carcinoma.

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>E. coli</i> , <i>Klebsiella pneumoniae</i> , <i>Staphylococcus saprophyticus</i> , <i>Proteus mirabilis</i>	<i>Pseudomonas aeruginosa</i> , <i>Enterococcus faecalis</i>	Tuberculosis

Sexually transmitted infections with less than four weeks symptoms

Frequently found microorganisms	Rare microorganisms and conditions
<i>Chlamydia</i> spp., <i>Neisseria gonorrhoeae</i> , <i>Gardnerella vaginalis</i> , syphilis <i>Trichomonas vaginalis</i>	Lymphogranuloma venereum, Ducey's disease <i>Entamoeba dispar</i> and <i>E. histolytica</i> (Madagascar, Comoros)

Cystitis, pyelonephritis, and nephritis with symptoms for more than four weeks and in the immunocompromised host

Consider also noninfectious causes, especially malignancies like renal cell carcinoma.

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Tuberculosis, <i>Schistosoma haematobium</i> (Madagascar) [20]	<i>Candida</i>

Sexually transmitted infections with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than four weeks	Microorganisms in the immunocompromised host
HIV Herpes virus Papilloma virus Hepatitis B virus Syphilis <i>Neisseria gonorrhoeae</i>	Syphilis Lymphogranuloma venereum <i>Candida</i>

Joint, muscle, and soft tissue infections

Joint, muscle, and soft tissue infections with less than four weeks symptoms

Frequently found microorganisms
<i>Staphylococcus aureus</i> <i>Streptococcus pneumoniae</i>

Joint, muscle, and soft tissue infections with more than four weeks symptoms and in the immunocompromised host

Microorganisms with symptoms for more than four weeks	Microorganisms in the immunocompromised host
Tuberculosis	<i>Candida</i> , dermatophytes

Skin infections

Skin infections with less than four weeks symptoms

Frequently found microorganisms	Rare microorganisms and conditions
Erysipelas, <i>Streptococcus pneumoniae</i> <i>Staphylococcus aureus</i> <i>Borrelia</i> spp. <i>Dermatomycesis</i>	Lice, scabies

We have not listed a rash due to viral infections as this is not considered an infection limited to the skin.

Skin infections with more than four weeks symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Syphilis, tuberculosis, leprosy (Madagascar, Comoros) Scabies	<i>Candida</i> Dermatophytes

Adenopathy

Adenopathy of less than 4 weeks duration

Frequently found microorganisms
Epstein–Barr virus, cytomegalovirus, parvovirus B19, HIV <i>Toxoplasma gondii</i>

Adenopathy of more than four weeks duration and in the immunocompromised host

If the diagnosis is not made within a few days, biopsies should be performed to exclude malignancies like lymphoma and carcinomas.

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Rubella, <i>Toxoplasma gondii</i> Tuberculosis	Adenovirus, HIV, CMV

Fever without focal symptoms

Fever for less than four weeks without focal symptoms

Frequently found microorganisms	Rare microorganisms and conditions
Dengue, chikungunya (La Reunion, Madagascar, Comoros, Mayotte, Seychelles) [21–29]	Rift Valley fever virus, Crimean Congo fever (Madagascar), HIV, influenza [30]
<i>Salmonella typhi</i> (Mauritius), leptospirosis (Seychelles, La Reunion, Mayotte, Maurice, Comoros, Madagascar) [31–34]	Tuberculosis
Malaria (Madagascar, Comoros), <i>P. falciparum</i> predominant [33–35]	<i>Schistosoma mansoni</i> and <i>haematobium</i> (Madagascar only)

Fever for more than four weeks without focal symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks
Tuberculosis HIV

Non-infectious causes should be considered from the beginning, including malignancies like lymphoma and autoimmune diseases.

Eosinophilia and elevated IgE

Eosinophilia and elevated IgE for less than four weeks

Frequently found microorganisms	Rare microorganisms and conditions
<i>Ascaris lumbricoides</i> , <i>Trichuris trichura</i> , <i>Hymenolepis nana</i> (Madagascar, Comoros)	Filaria (<i>Wuchereria bancrofti</i>)

Eosinophilia and elevated IgE for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks

Strongyloides stercoralis (Comoros, Madagascar)
Schistosoma mansoni and haematobium (Madagascar)
 Cysticercosis (Madagascar, Reunion, Comoros)
 Visceral larva migrans
 Angiostrongylus (La Reunion, Madagascar, Comoros)

Antibiotic resistance

Escherichia coli shows high resistance rates against ampicillin, co-trimoxazole, nalidixic acid, and ciprofloxacin in Mauritius [38,39]. Methicillin-resistant *Staphylococcus aureus* is still rare in the area. A low prevalence of multidrug-resistant tuberculosis was observed in Madagascar and Reunion [40,41]. In Madagascar and Comoros, *P. falciparum* exhibits a high level of resistance to antimalarials, including artemisinin derivatives and atovaquone-proguanil [42–45].

Vaccine-preventable diseases in children

According to the WHO (www.who.int/immunization_monitoring/data/en/), the childhood vaccination program includes vaccination against tuberculosis, diphtheria, tetanus, poliomyelitis (oral polio vaccine), pertussis, measles, and hepatitis B in all islands. Vaccination against *Haemophilus influenzae* infection is provided in all islands with the exception of Maldives. Vaccination against mumps and rubella is provided in Mauritius, Reunion, Seychelles, and Maldives. Of interest, rare cases of diphtheria are reported from Madagascar and Mauritius only. Cases of measles, rubella, and pertussis are reported from the entire region with local variations. Tetanus is mainly reported from Madagascar, Comoros, and Mauritius.

Basic economic and demographic data

Basic demographics*	GNI† per capita (USD)	Life expectancy at birth (total, years)	School enrollment, primary (% net)
Comoros	750	65	55
Madagascar	410	61	98
Mauritius	6400	72	95
Seychelles	10290	73	99

*World Bank
 †Gross National Income

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Chapter 9

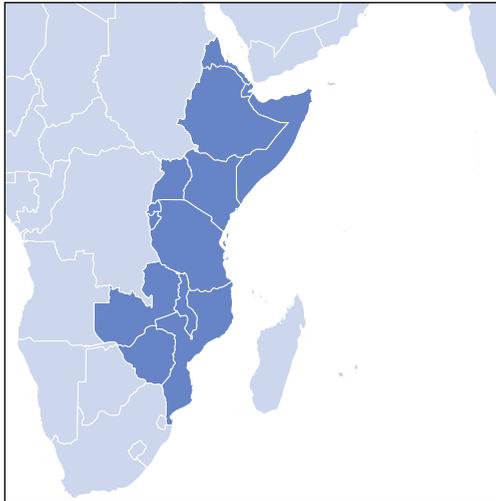
Eastern Africa

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Eritrea
Djibouti
Somalia
Ethiopia
Kenya
Uganda
Rwanda
Burundi
Tanzania
Malawi
Mozambique
Zambia
Zimbabwe

Travelers in East Africa are potentially exposed to malaria, HIV, tuberculosis, and many other infectious diseases. Exposure determines the risk – from travelers’ diarrhea and vectorborne diseases to extremely rare infections. Patients with a history of stay or visit to Eastern Africa and presenting with an acute febrile illness may have acquired an infection specific for the region or common worldwide (e.g. EBV, influenza).

Parasites

Malaria occurs throughout the region – except for highland areas in Eritrea, Ethiopia, Kenya, and Tanzania – with varied transmission patterns. *P. falciparum* is the predominant species, with widespread chloroquine resistance. There is emerging drug resistance of *P. vivax* to chloroquine in Ethiopia [1,2]. At present, there are no confirmed reports of artemisinin resistance in Africa.

Malaria transmission in Eastern Africa

Country	Malaria endemic areas	Major <i>Plasmodium</i> species
Burundi	All	<i>P. falciparum</i> 100%
Eritrea	All areas at altitudes <2200m, no malaria in Asmara	<i>P. falciparum</i> 60%, <i>P. vivax</i> 39%
Ethiopia	All areas at altitudes <2500m, no malaria in Addis Ababa	<i>P. falciparum</i> 64%, <i>P. vivax</i> 36%
Kenya	All areas at altitudes <2500m, no malaria in Nairobi	<i>P. falciparum</i> 100%
Malawi	All	<i>P. falciparum</i> 100%
Mozambique	All	<i>P. falciparum</i> 100%
Rwanda	All	<i>P. falciparum</i> 100%
Somalia	All	<i>P. falciparum</i> 100%
Tanzania	All areas at altitudes <1800m	<i>P. falciparum</i> 100%
Uganda	All	<i>P. falciparum</i> 100%
Zambia	All	<i>P. falciparum</i> 100%
Zimbabwe	All	<i>P. falciparum</i> 100%

Source: Adapted from World Malaria Report 2015. Available at: www.who.int/malaria/publications/world-malaria-report-2015/wmr2015-profiles.pdf (accessed 12 October 2016).

Virus

Human immunodeficiency virus (HIV) prevalence rates show a north–south distribution, ranging from 0.6% in Eritrea to 15% in Zimbabwe [3].

The epidemiology of dengue and chikungunya in Africa is far from clear, but the wide geographical distribution of their primary vectors (*Aedes aegypti* and *A. albopictus*), rapid human population growth, unplanned urbanization, and increased international travel make their transmission likely (see Arthropod-borne virus infections below). Zika virus is present but the endemicity unclear. Dengue epidemics are infrequently reported in Eastern Africa, and both viruses are increasingly recognized to significantly contribute to the number of “fever” patients presenting to local health facilities (see Arthropod-borne virus infections below) [4,5]. Rift Valley fever is endemic in Mozambique, Zimbabwe, and Zambia but outbreaks may occur in all countries of East Africa, usually after periods of increased rain (see Arthropod-borne virus infections below). Yellow fever may occur from Ethiopia to Tanzania, but the risk is low. Eritrea, Malawi, Mozambique, Zambia, and Zimbabwe are free of yellow fever.

Bacteria

Tuberculosis continues to be a major health issue throughout East Africa. Mozambique, Ethiopia, Zimbabwe, Uganda, Kenya, and Tanzania are listed among the 22 high-burden countries with the highest estimated tuberculosis incidence rates reported by the WHO [6]. Currently, the estimated percentage of multidrug-resistant tuberculosis (MDR-TB) among all tuberculosis cases in the region ranges from 0.3% (Zambia) to 5.2% (Somalia) [7], and cases of extensively drug-resistant tuberculosis (XDR-TB) have been reported from Ethiopia, Djibouti, Kenya, Tanzania, Mozambique, and Zimbabwe [8]. The classic sub-Saharan “meningitis belt,” with its infamous epidemics of meningococcal disease, ranges from Senegal to Eritrea and extends south through the Rift Valley to the Great Lakes region as far as Mozambique. Epidemic waves can last 2–3 years, typically occur in the dry season (December to June), and subside during the intervening rainy seasons.

CNS infections: meningitis, encephalitis, and other infections with neurological symptoms

Acute CNS infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Adenoviruses	CMV	Chikungunya
Enteroviruses (coxsackie, echo)	HHV 6 & 7	Trypanosomiasis
HSV 1 & 2	HIV	Filoviruses (Ebola, Marburg)
Varicella zoster	Influenza viruses	West Nile fever
<i>Haemophilus influenzae</i>	Measles	Polyomavirus (JC & SV-40)
Meningococci	Mumps	Poliomyelitis
Pneumococci	Parainfluenza viruses	Rabies
Staphylococci	EBV	LCMV
Streptococci	<i>Chlamydia pneumoniae</i>	Rift Valley fever
Malaria – <i>P. falciparum</i>	<i>Mycoplasma pneumoniae</i>	Sindbis virus
	Listeriosis	Angiostrongyloidiasis
		Primary amebic meningoencephalitis

CNS infections with more than four weeks symptoms and in the immunocompromised host

Microorganisms with more than 4 weeks symptoms	Microorganisms in the immunocompromised host
HIV	Tuberculosis
Brucellosis	Toxoplasmosis
Syphilis	Cryptococcosis
Tuberculosis	
Toxoplasmosis	
Trypanosomiasis*	
Angiostrongyloidiasis*	
Cysticercosis*	

* Rare infection.

Ear, nose, and throat infections

Ear, nose, and throat infections with less than four weeks symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Adenoviruses	Diphtheria	Filoviruses (Ebola, Marburg)
EBV	<i>Neisseria gonorrhoeae</i>	(initially pharyngitis)
Enteroviruses	Necrotizing fasciitis	
CMV	Peritonsillar abscess	
Coronaviruses	(<i>Fusobacterium necrophorum</i>)	

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Human Metapneumovirus HSV 1 & 2 Measles Parainfluenza viruses Rhinoviruses <i>Bordetella pertussis</i> <i>Haemophilus influenzae</i> <i>Moraxella catarrhalis</i> <i>Mycoplasma pneumoniae</i> Staphylococci Streptococci	Vincent angina (<i>Fusobacterium nucleatum</i> , <i>Treponema vincentii</i>)	

Ear, nose, and throat infections with more than four weeks symptoms and in the immunocompromised host

Microorganisms with more than 4 weeks symptoms	Microorganisms in the immunocompromised host
Syphilis Tuberculosis Rhinoscleroma (<i>Klebsiella rhinoscleromatis</i>)* Lingulosis*	Tuberculosis Candidiasis Mucormycosis* Rhinosporidiosis* (<i>Rhinosporidium seeberi</i>)
*Rare infection.	

Cardiopulmonary infections

Pulmonary infections with less than four weeks symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Adenoviruses Influenza viruses Parainfluenza viruses RSV <i>Chlamydia pneumoniae</i> <i>Klebsiella pneumoniae</i> <i>Legionella</i> <i>Moraxella catarrhalis</i> <i>Mycoplasma pneumoniae</i> <i>Bordetella pertussis</i> <i>Staphylococcus aureus</i>	Q-fever Pulmonary symptoms due to parasitic migration: Ascariasis – Löffler's syndrome Hookworm (<i>N. americanus</i>) Strongyloidiasis Toxocariasis Tropical pulmonary eosinophilia (Filariasis) Schistosomiasis, Katayama fever	Anthrax Meliodosis Plague Psittacosis Relapsing fever, borreliosis Rickettsiosis Acute bronchopulmonary aspergillosis (ABPA) <i>Aspergillus</i> spp. Blastomycosis Histoplasmosis
(Continued)		

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Staphylococci coag. neg. <i>Streptococcus pneumoniae</i>		(<i>H.capsulatum</i> var <i>gati</i> & var <i>duboisii</i> – African histoplasmosis)

Middle East respiratory syndrome coronavirus (MERS-CoV) was identified as the cause of severe respiratory disease in humans on the Arabian Peninsula in 2012. Widespread circulation of MERS-CoV among dromedaries has been identified as a possible source for human infections. Although to date no human cases have been reported from Africa, serological evidence suggests the circulation of the virus among dromedaries across broad areas of Africa (Tunisia, Egypt, Sudan, Ethiopia) [9]. It may be speculated that the disease is currently underdiagnosed in humans having close contact with dromedaries in Africa.

Endocarditis with less than four weeks symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Streptococci <i>Staphylococcus aureus</i> Staphylococci coag. neg.	Q-fever HACEK group bacteria <i>Bartonella</i> spp. Enterococci <i>Neisseria gonorrhoeae</i> Salmonellosis <i>Pseudomonas aeruginosa</i> Rickettsiosis Tuberculosis	Rat-bite fever Histoplasmosis Propionebacterium

Myocarditis with less than four weeks symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Adenoviruses Enteroviruses (coxsackie) Echoviruses	CMV Influenza viruses Mumps Parvovirus B19 Relapsing fever Rickettsiosis Staphylococci Streptococci Tuberculosis	Chikungunya Dengue EBV HSV Varicella zoster virus Brucellosis <i>Campylobacter</i> spp. Diphtheria Legionellosis <i>Neisseria meningitidis</i> Q-fever Rickettsiosis Trichinellosis Trypanosomiasis

Pulmonary infections with more than four weeks symptoms and in the immunocompromised host

Microorganisms with more than 4 weeks symptoms	Microorganisms in the immunocompromised host
Atypical mycobacteria Meliodosis*	Atypical mycobacteria Meliodosis*
Pertussis Tuberculosis Paragonimiasis* Pentostomiasis* Dirofilariasis*	Nocardiosis <i>Rhodococcus equi</i> Tuberculosis <i>Pneumocystis jiroveci</i> <i>Aspergillus</i> spp. Blastomycosis <i>Candida</i> spp. Histoplasmosis (<i>H.capsulatum</i> var <i>gati</i> & var <i>duboisii</i> – African histoplasmosis)
*Rare infection.	

Endocarditis with more than four weeks symptoms and in the immunocompromised host

Microorganisms with more than 4 weeks symptoms	Microorganisms in the immunocompromised host
Brucellosis Q-fever	Bartonellosis Tuberculosis Aspergillosis Blastomycosis <i>Candida</i> spp. Cryptococcosis Histoplasmosis

Consider also systemic lupus erythematoses (Libman–Sacks endocarditis).

Myocarditis with more than four weeks symptoms and in the immunocompromised host

Brucellosis and tuberculosis should be considered. Aspergillosis, blastomycosis, candidiasis, cryptococcosis, and histoplasmosis are other rare possibilities.

Gastrointestinal infections

Gastrointestinal infections with less than four weeks symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Adenoviruses	Cholera	Atypical mycobacteria
Astroviruses	<i>Vibrio parahaemolyticus</i>	Enteritis necroticans
Caliciviruses (noroviruses)	<i>Yersinia</i> spp.	(pigbel, <i>C. difficile</i> type C)
Rotaviruses	Cryptosporidiosis	<i>Isospora</i>
Sapoviruses	<i>Balantidium coli</i>	<i>Sarcocystis</i> spp.
<i>Campylobacter</i> spp.		<i>Trichinella</i>
<i>Salmonella</i> spp.		
Typhoid fever		
Shigellosis		
Enteropathogenic <i>E. coli</i>		
<i>Giardia intestinalis</i>		
<i>Entamoeba histolytica</i>		

In gastroenteritis with a very short incubation period (hours), toxins should be considered (staphylococci, *Bacillus cereus*, and *Clostridium*).

- *Travelers’ diarrhea*: in a large prospective cohort study, a two-week-incidence of travelers’ diarrhea of 29.1% has been reported from the East African [10]. The spectrum of pathogens includes bacteria (pathogenic *E. coli*, *Salmonella*, *Shigella*, *Campylobacter*, etc.) viruses, and protozoa (*Amoeba*, *Giardia*, etc.).
- *Cholera*: the risk for travelers to affected areas is estimated to be less than 1 in 500 000 (0.001–0.01% per month of stay) [11].

Gastrointestinal infections with more than four weeks symptoms and in the immunocompromised host

Microorganisms with more than 4 weeks symptoms	Microorganisms in the immunocompromised host
Tuberculosis	Bartonellosis
<i>Entamoeba histolytica</i>	Tuberculosis
<i>Balantidium coli</i>	Cryptosporidiosis
Ascariasis	Cyclosporiasis
Cyclosporiasis	Isosporiasis
Strongyloidiasis	<i>Microsporidia</i> spp.
Trichinellosis*	Strongyloidiasis
Trichuriasis	Candidiasis
Schistosomiasis	Blastomycosis
Taeniasis*	Histoplasmosis

* Rare infection.

Consider also tropical enteropathy/sprue, postinfective irritable bowel syndrome, and inflammatory bowel disease.

Infections of liver, spleen, peritoneum

Acute infections of liver, spleen, and peritoneum with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
CMV	Coxsackieviruses	Yellow fever
EBV	HSV	Bartonellosis
Hepatitis A	Mumps	Blastomycosis
Hepatitis E	Leishmaniasis, visceral	Histoplasmosis
Leptospirosis	(<i>L. donovani</i> , <i>L. infantum</i>)	
Q-fever	Relapsing fever	
Rickettsiosis	Rickettsiosis	
Typhoid fever	<i>Salmonella</i> spp.	
Amebic liver abscess	<i>Shigella</i>	
	Syphilis	
	<i>Yersinia</i> spp.	

- *Hepatitis A*: acute viral hepatitis A should be considered in any unvaccinated patient presenting with fever and jaundice.
- *Leptospirosis*: infections are caused by exposure to contaminated water. Symptoms include high fever, headache, chills, intense myalgia, conjunctival suffusion, jaundice, and gastrointestinal symptoms. Liver failure, kidney failure, and pulmonary hemorrhage as well as aseptic meningitis can manifest in severe cases. Leptospirosis should be suspected in adventure travelers (especially water sports).

Chronic infections of liver, spleen, and peritoneum with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with more than 4 weeks symptoms	Microorganisms in the immunocompromised host
Hepatitis B (±delta agent)	Atypical mycobacteriosis
Hepatitis C	Melioidosis*
Brucellosis	Tuberculosis
Tuberculosis	Strongyloidiasis
Amebic liver abscess	Candidiasis
Leishmaniasis, visceral*	Blastomycosis
<i>Capillaria hepatica</i> *	Histoplasmosis
<i>Echinococcus granulosus</i> *	Leishmaniasis, visceral
Fascioliasis*	(<i>L. donovani</i> , <i>L. infantum</i>)
Schistosomiasis	Cryptosporidiosis
Toxocariasis, visceral larva migrans	

* Rare infection, consider malignancy.

Genitourinary infections

Cystitis, pyelonephritis, and nephritis with less than four weeks symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Enterococci <i>Enterobacter</i> spp. <i>Escherichia coli</i> <i>Klebsiella pneumoniae</i> Leptospirosis Mycoplasma – nongonococcal urethritis (NGU) <i>Proteus</i> spp. Relapsing fever, borreliosis Rickettsiosis <i>Shigella</i> (HUS) Staphylococci <i>Ureaplasma urealyticum</i> (NGU)	Hanta Ascariasis (GN) Strongyloidiasis (GN) Lymphatic filariasis (GN) Onchocerciasis (GN) Loiasis (GN)	Polyomaviruses (BK, JC) (in immunocompromised)

Sexually transmitted infections with less than four weeks symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
HSV 2 Gonorrhea – <i>N. gonorrhoeae</i>	–	–

Cystitis, pyelonephritis, and nephritis with more than four weeks symptoms and in the immunocompromised host

Microorganisms with more than 4 weeks symptoms	Microorganisms in the immunocompromised host
Tuberculosis Schistosomiasis – <i>Schistosoma haematobium</i>	Tuberculosis Candidiasis

Consider also para/postinfectious glomerulonephritis/nephrotic syndrome.

Sexually transmitted infections with more than four weeks symptoms and in the immunocompromised host

Microorganisms with more than 4 weeks symptoms	Microorganisms in the immunocompromised host
Papillomaviruses Chancroid – <i>Haemophilus ducreyi</i> Donovanosis (granuloma inguinale) – <i>Calymatobacterium granulomatis</i> Gonorrhoea – <i>Neisseria gonorrhoeae</i> Lymphogranuloma venereum (<i>C. trachomatis</i> serovar L1-L3) Syphilis venereal Trichomoniasis Ectoparasites (e.g. lice, scabies)	The same microorganisms are seen as in the immunocompetent host

Joint and muscle infections

Joint and muscle infections with less than four weeks symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Adenoviruses	<i>Clostridium perfringens</i> (gas gangrene)	Hepatitis B & C
CMV	Leptospirosis	HSV 2
Chikungunya	<i>Neisseria gonorrhoeae</i>	Parvovirus B19
Dengue	Nonclostridial myonecrosis	Varicella zoster
EBV	Anaerobic streptococcal	West Nile virus
Enteroviruses (Coxsackie, echo)	myositis (e.g. GAS, peptostreptococci, streptococci)	Yellow fever
HIV	Synergistic nonclostridial myonecrosis (polymicrobial infection)	Rat-bite fever (spirillosis, streptobacillosis)
Influenza viruses	Vascular gangrene (often polymicrobial infection)	Trichinellosis
O'nyong nyong	Relapsing fever, borreliosis	<i>Entamoeba histolytica</i>
Parainfluenza viruses	Rickettsiosis	
Sindbis virus	<i>Salmonella</i> spp.	
	Staphylococci (tropical pyomyositis)	
	Streptococci	

Consider also reactive arthritis:

- poststreptococcal reactive arthritis/rheumatic fever arthritis
- Reiter's syndrome (*Chlamydia trachomatis*)
- *Shigella*, *Yersinia*, *Salmonella* spp., etc.

Joint and muscle infections with more than four weeks symptoms and in the immunocompromised host

Microorganisms with more than 4 weeks symptoms	Microorganisms in the immunocompromised host
Chikungunya	Melioidosis*
Brucellosis	Tuberculosis
Tuberculosis	<i>Aspergillus</i> spp.
Melioidosis	<i>Candida</i> spp.
Syphilis endemic (yaws)	Cryptococcosis
Cysticercosis*	Histoplasmosis
Echinococcosis*	
Trichinellosis*	

* Rare infection, consider rheumatological diseases.

Skin infections

Skin infections with less than four weeks symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
HSV 1 & 2	Hand, foot & mouth disease	Monkey pox
Varicella zoster	(Coxsackie A & enterovirus 71)	Orf virus
Staphylococci		Tanapox
Streptococci	Tungiasis	Anthrax
Cutaneous larva migrans		Diphtheria, cutaneous
Myiasis (<i>Cordylobia antropophaga</i>)		erysipelothrix
		<i>Neisseria gonorrhoeae</i> , disseminated

Skin infections with more than four weeks symptoms and in the immunocompromised host

Microorganisms with more than 4 weeks symptoms	Microorganisms in the immunocompromised host
Molluscum contagiosum	Melioidosis*
Papillomaviruses	Tuberculosis, cutaneous
Leprosy*	Strongyloidiasis
Melioidosis*	Blastomycosis
<i>Mycobacterium ulcerans</i> (Buruli ulcer)*	Cryptococcosis
Necrotizing ulcer of skin (tropical ulcer)	Entomophthoromycosis
Noma*	(subcut. Basidiobolus) *
Syphilis, endemic	Mycetoma – Madura foot*
Syphilis, venereal	Sporotrichosis
Tuberculosis, cutaneous	Scabies
Cutaneous amebiasis*	

Microorganisms with more than 4 weeks symptoms	Microorganisms in the immunocompromised host
Leishmaniasis, cutaneous* (<i>L. tropica</i> , <i>L. aethiopica</i> , <i>L. major</i>)	
Trypanosomiasis*	
Cysticercosis*	
Dracunculiasis*	
Gnathostomiasis*	
Loiasis*	
Lymphatic filariasis*	
Mansonelliasis (<i>M. perstans</i>) *	
Onchocerciasis*	
Schistosomiasis (cercarial dermatitis)	
Strongyloidiasis	
Pityriasis versicolor	
Tinea/ringworm	
Mycetoma – Madura foot*	
Scabies	
* Rare infection.	

Adenopathy

Adenopathy of less than four weeks duration

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Adenoviruses	Diphtheria	Crimean-Congo HF
CMV	Leptospirosis	Filoviruses (Ebola, Marburg)
Enteroviruses (Coxsackie)	Relapsing fever, borreliosis	Rift Valley fever
Dengue	Rickettsiosis	HTLV-1
EBV	Syphilis	Anthrax
HHV 6 & 7	Typhoid fever	Bartonellosis
HIV	Toxoplasmosis	Brucellosis
HSV 1 & 2		Chancroid – <i>Haemophilus ducreyi</i>
Measles		Lymphogranuloma venereum
Mumps		Plague
Parvovirus B19		Rat-bite fever (spirillosis, streptobacillosis)
Rhinoviruses		
Rubella		
Varicella zoster		

Adenopathy of more than four weeks duration and in the immunocompromised host

Microorganisms with more than 4 weeks symptoms	Microorganisms in the immunocompromised host
Atypical mycobacteria	Atypical mycobacteria
Bartonellosis	Bartonellosis
Brucellosis	Melioidosis*
Melioidosis*	Nocardiosis
Tuberculosis	<i>Rhodococcus equi</i>
Toxoplasmosis	Tuberculosis
Trypanosomiasis*	Toxoplasmosis
Loiasis*	Blastomycosis
Lymphatic filariasis (<i>Wuchereria bancrofti</i>) *	Histoplasmosis
Mansonelliasis (<i>M. perstans</i>) *	Sporotrichosis
Sporotrichosis	

* Rare infection – consider malignancy.

African trypanosomiasis (African sleeping sickness) is transmitted by the tsetse fly and caused by the protozoa *Trypanosoma brucei*. East African trypanosomiasis is caused by *Trypanosoma brucei rhodesiense* and shows more acute and severe symptoms than the West African variant caused by *Trypanosoma brucei gambiense*. In the first stage of the disease, generalized swelling of lymph nodes (characteristically along the back of the neck – Winterbottom’s sign) and fever are seen. The second stage (meningoencephalitic stage), which gave rise to the term “sleeping sickness,” begins when the parasite invades the central nervous system (usually some weeks after infection). The presence of an inoculation chancre (a painful, circumscribed, indurated papule, 2–5 cm in diameter), which develops 5–15 days after the bite (disappearing after 23 weeks), facilitates the diagnosis. Trypanosomiasis in travelers has been reported from Tanzania, Botswana, Rwanda, Kenya, Malawi, Uganda, and Zambia.

Fever without focal symptoms

Fever less than four weeks without focal symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Malaria	Hanta	Crimean-Congo HF
CMV	Sindbis	Bunyamwera virus
Chikungunya	O’nyong nyong	Bwamba virus
Dengue	Rift Valley fever	Filoviruses (Ebola, Marburg)
EBV		Lujo hemorrhagic fever
Hepatitis A		Orungo virus
Hepatitis B		Wesselsbron virus
Hepatitis C		Yellow fever
HIV		Zika virus
Influenza		Antrax
Measles		Bartonellosis, <i>Bartonella quintana</i> – trench fever
Varicella zoster		

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Adenoviruses		Melioidosis
Relapsing fever, borreliosis		Plague
Rickettsiosis		Psittacosis
African tick bite fever		Rat-bite fever (spirillois, streptobacillosis)
Rickettsial pox		
Typhus epidemic/louse borne <i>Rickettsia prowazekii</i>		
Typhus endemic/murine/tick borne (<i>Rickettsia typhi</i>)		
Typhoid fever		
Schistosomiasis, Katayama fever		

African tick bite fever (ATBF), caused by *Rickettsia africae*, appears to be the most important “spotted fever” in East Africa [12]. Transmitted by *Amblyomma* ticks, safari tourists, backpackers, hunters, sports competitors, and foreign aid workers are particularly at risk. The average incubation period is one week. Eschars (often multiple) are observed in 95% of patients [13], and 4–9% of first-time Norwegian travelers to rural subequatorial Africa had specific antibodies to *R. africae* [14,15].

Louseborne relapsing fever (LBRF) caused by *Borrelia recurrentis* is found in East African countries and is especially prevalent in Ethiopia [16]. The repeated episodes of fever, interrupted by periods of relative well-being, are often misdiagnosed as malaria.

Arthropod-borne virus infections: dengue fever, caused by a flavivirus, is transmitted by day-biting *Aedes* mosquitoes, and characterized by abrupt onset of fever, retroorbital headache, myalgia (“break-bone” fever), a discrete uniform rash, and arthralgia. Five percent of imported dengue fever cases in Europe are infected in Africa [17,18].

Among the arboviruses endemic in East Africa, the togaviruses *chikungunya*, *O'nyong nyong*, and *Sindbis* can cause fever with pronounced arthralgia. The characteristic polyarthralgic complaints of chikungunya may persist for days, weeks, months, or in some cases even years. *Zika virus* and *Wesselsbron virus* are members of the Flaviviridae virus family. Common symptoms include mild headaches, maculopapular rash, fever, malaise, conjunctivitis, and arthralgia. *Bunyamwera virus* is an Orthobunyavirus belonging to the Bunyaviridae family that contains the La Crosse virus, the causative virus of La Crosse encephalitis. It causes a mild febrile illness sometimes with conjunctivitis, rash, and mild CNS symptoms. *Orungo virus* belongs to the orbivirus family and has been described from Uganda, where it causes a mild febrile illness. *Bwamba fever virus*, transmitted by *Anopheles funestus*, is from the genus Orthobunyavirus and causes a mild febrile illness. Bwamba fever is believed to be endemic in East Africa, especially Kenya, Tanzania, and Uganda.

Viral hemorrhagic fevers: The overall travel-related risk of contracting a viral hemorrhagic fever is conservatively estimated at <1 in 1 million travel episodes to endemic African countries. Febrile patients returning from East Africa are at least 1000 times more likely to have malaria [19].

Ebola and Marburg virus: cases and outbreak clusters of viral hemorrhagic fevers (HF) due to filoviruses are rare events, but have occurred in Eastern Africa (Ebola: Uganda; Marburg: Kenya, Uganda). They are associated with very high case fatality rates. Current evidence suspects fruit bats to be the animal reservoir for Ebola and Marburg viruses. Index cases are often infected by handling corpses of primates. Nosocomial spread usually results from reuse of needles and syringes and direct contact to infected blood, body secretions or tissues. Travelers should be informed that visits to bat-infested caves have a risk for infection, as documented by two cases of Marburg HF in a Dutch and an American tourist returning from Uganda in 2008 [20,21]. *Lujo virus* (belonging to the

Arenavirus family) and *Ilesha virus* (belonging to the Orthobunyavirus family) are other rare HF viruses. Only one outbreak of Lujo virus has occurred so far, in Zambia with a case fatality rate of 80% [22].

Rift Valley fever (RVF) is a mosquito-borne viral zoonosis transmitted by mosquitoes or by contact with the blood or tissue of infected animals and possibly from the ingestion of raw milk. RVF is distributed throughout East Africa in single cases, and epidemic outbreaks have been reported. Most human cases are relatively mild, but RVF-associated encephalitis, retinitis (leading to blindness) or the hemorrhagic form has been reported [23].

Crimean Congo hemorrhagic fever (CCHF) is transmitted by ticks and occurs in Ethiopia, Kenya, Tanzania, Uganda, and Madagascar [24].

Fever for more than four weeks without focal symptoms and in the immunocompromised host

Microorganisms with more than 4 weeks symptoms	Microorganisms in the immunocompromised host
Atypical mycobacteriosis	Atypical mycobacteriosis
Brucellosis	Bartonellosis
Infective endocarditis	Melioidosis*
Melioidosis*	Nocardiosis
Pyogenic intraabdominal abscess	<i>Rhodococcus equi</i>
Q-fever	Tuberculosis
Relapsing fever, borreliosis	Leishmaniasis, visceral (<i>L. donovani</i> , <i>L. infantum</i>)
Syphilis	Toxoplasmosis
Tuberculosis	Strongyloidiasis
Amebic liver abscess	<i>Strongyloides</i> hyperinfection syndrome
Leishmaniasis, visceral (<i>L. donovani</i> , <i>L. infantum</i>) *	Blastomycosis
Strongyloidiasis	Cryptococcosis
Toxoplasmosis	Histoplasmosis
Trypanosomiasis*	
Toxocariasis, visceral larva migrans	

* Rare infection.

Eosinophilia and elevated IgE

Eosinophilia and elevated IgE for less than four weeks

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Acariasis	Hymenolepiasis	–
Cercarial dermatitis (swimmer’s itch, avian <i>Schistosoma</i> spp.)		
Cutaneous larva migrans		
<i>Strongyloides</i>		
Myiasis (<i>Cordylobia antropophaga</i>)		

Eosinophilia and elevated IgE for more than four weeks and in the immunocompromised host

Microorganisms with more than 4 weeks symptoms	Microorganisms in the immunocompromised host
Angiostrongyloidiasis*	Strongyloidiasis
Cysticercosis*	Scabies
Diphyllobotriasis*	+ the organisms listed under the
Dirofilariasis*	immunocompetent host with symptoms both
	less and more than 4 weeks
<i>Echinococcus granulosus</i> *	
Fascioliasis*	
Gnathostomiasis*	
Hookworm (<i>Necator americanus</i>)	
Loiasis*	
Lymphatic filariasis*	
<i>Mansonella</i> *	
<i>Onchocerca</i> *	
<i>Paragonimus</i> spp. *	
Schistosomiasis	
Strongyloidiasis	
Taeniasis (<i>T. saginata</i> , <i>T. solium</i>)*	
Toxocariasis, visceral larva migrans	
Trichinellosis*	
Trichostrongylus*	
Trichuriasis	
Scabies	
* Rare infection.	

Acute schistosomiasis (Katayama fever): schistosomiasis is present throughout East Africa. The most prevalent species are *S. haematobium* and *S. mansoni*. *S. intercalatum* is only reported from Uganda [25]. In its second phase, fever, eosinophilia, urticaria, and possibly pulmonary symptoms appear as “Katayama fever.” Parasite ova are absent from urine and stool during the prepatent period (~1–3 months), with serology being the diagnostic method of choice.

Antibiotic resistance

Uncontrolled over-the-counter sale as well as uncritical usage of antibiotics in humans and livestock leads to an increase in antimicrobial resistance which is widespread in most African countries. Few appropriate laboratory facilities provide very scarce data on antibiotic resistance in East Africa.

Streptococcus pneumoniae: isolates collected in Kenya, Uganda, and Tanzania remain susceptible to the most commonly used antibiotics with the exception of trimethoprim/sulfamethoxazole, and have exhibited no resistance to penicillin [26]. The prevalence of resistance to cefotaxime, erythromycin, and amoxicillin is low (0–1.5%). Worries about chloramphenicol resistance in meningitis cases appear to be unfounded as a decrease from 9% in 2004 to 2% in 2008 was observed [26].

Typhoid fever: multidrug-resistant (MDR) *Salmonella typhi* strains (resistant to ampicillin, trimethoprim, chloramphenicol, streptomycin, sulfonamides, and tetracyclines) and *S. typhi* strains with decreased ciprofloxacin susceptibility have emerged in the East African region. During a prolonged outbreak in western Uganda, the percentage of MDR strains of *S. typhi* rapidly increased from 5% in 2009 to 83% in 2011, and rates of resistance to nalidixic acid increased from 0% in 2009 to 6% in 2011, and reached 87.5% in 2012 [27]. *Salmonella typhi* strains with combined MDR and decreased ciprofloxacin susceptibility have been reported in Kenya, Uganda, Malawi, and Mozambique [28]. Currently, third-generation cephalosporins such as ceftriaxone or cefotaxime as well as the macrolide antibiotic azithromycin provide alternatives to cover these strains. Extended-spectrum beta-lactamase (ESBL)-*S. typhi* strains have not yet been reported from Eastern Africa.

Shigella: extensive outbreaks and epidemics of MDR *Shigella dysenteriae* have been reported over the last four decades in Eastern Africa. The isolates have been resistant to ampicillin, chloramphenicol, tetracyclines, trimethoprim, and nalidixic acid. Third-generation cephalosporins such as ceftriaxone or cefotaxime as well as the newer fluoroquinolones and pivmecillinam provide alternatives.

Campylobacter: multidrug resistance, including to macrolides and fluoroquinolones, has increasingly been reported, but limited data are available from East Africa. Susceptibility testing, if available, should guide antimicrobial treatment.

Nosocomial resistance situation: the scarce microbiological resistance data from East African hospitals show a worrisome picture. Two recent studies on surgical site infections in Uganda and Tanzania show high proportions of methicillin-resistant *Staphylococcus aureus* (MRSA) (37.5–44%) and even higher proportions of ESBL-producing enterobacteriaceae (92.3% of *E. coli* and 69% of *Klebsiella pneumoniae* isolates) [28–30]. Data on the prevalence of carbapenem resistance in East Africa are very limited. However, a recent study on the prevalence of carbapenemase genes among 227 MDR gram-negative bacteria (MDR-GNB) isolated from clinical specimens in a tertiary hospital in Tanzania identified 80 (35%) to be positive for one or more carbapenemase genes. Most carbapenemase genes were detected in *K. pneumoniae* (n=24; 11%), followed by *P. aeruginosa* (n=23; 10%), and *E. coli* (n=19; 8%) [31].

Vaccine-preventable diseases in children

Immunization coverage among one year olds in the Eastern African region

	Measles (%)	Diphtheria Tetanus Polio (DTP3)	Hepatitis B (HepB3)
Burundi	98	96	96
Comoros	82	83	83
Djibouti	82	82	82
Eritrea	96	94	94
Ethiopia	62	72	72
Kenya	93	76	83
Madagascar	63	74	74
Malawi	88	89	89
Mauritius	99	98	98
Mozambique	85	78	78

	Measles (%)	Diphtheria Tetanus Polio (DTP3)	Hepatitis B (HepB3)
Rwanda	97	98	98
Seychelles	97	98	99
Somalia	46	42	34
Tanzania	99	91	91
Uganda	82	78	78
Zambia	80	79	79
Zimbabwe	93	95	95
WHO-African region (total)	74	75	76

Data obtained from <http://data.unicef.org/resources/immunization-summary-a-statistical-reference-containing-data-through-2013> and www.cdc.gov/mmwr/preview/mmwrhtml/mm6346a4.htm.

Basic economic and demographic data

	GNI per capita (USD)	Life expectancy at birth (total, years)	School enrollment, primary (% net)*
Burundi	260	54	137
Djibouti	1030	61	68
Erithrea	490	62	42
Ethiopia	470	63	87
Kenya	1160	61	112
Madagascar	440	64	145
Malawi	270	55	141
Mozambique	610	50	105
Rwanda	630	63	134
Somalia	150	55	29
Tanzania	630	61	93
Uganda	550	59	110
Zambia	1810	57	115
Zimbabwe	860	58	97

GNI, gross national income.
 *School enrollment can exceed 100% due to the inclusion of over-aged and under-aged students because of early or late school entrance and grade repetition.
 Source: World Bank data: <http://data.worldbank.org/country>.

Cause of death in children under five expressed as % of the total number of deaths

Causes of death in children underfive (%)	Regional average –WHO African region	Burundi Eritrea Ethiopia Kenya Madagascar Malawi Mozambique Rwanda Tanzania Uganda Zambia Zimbabwe											
		Burundi	Eritrea	Ethiopia	Kenya	Madagascar	Malawi	Mozambique	Rwanda	Tanzania	Uganda	Zambia	Zimbabwe
Neonatal causes	26.2	23.3	27.4	30.2	24.2	25.6	21.7	29.0	21.7	26.9	23.6	22.9	28.1
Pneumonia	21.1	22.8	18.6	22.3	19.9	20.7	22.6	21.2	23.2	21.1	21.1	21.8	14.7
Diarrheal diseases	16.6	18.2	15.6	17.3	16.5	16.9	18.1	16.5	18.5	16.8	17.2	17.5	12.1
Malaria	17.5	8.4	13.6	6.1	13.6	20.1	14.1	18.9	4.6	22.7	23.1	19.4	0.2
HIV/AIDS	6.8	8.0	6.2	3.8	14.6	1.3	14.0	12.9	5.0	9.3	7.7	16.1	40.6
Measles	4.3	3.0	2.5	4.2	3.2	5.0	0.3	0.3	1.6	1.3	3.0	1.2	2.9
Injuries	1.9	1.8	3.0	1.7	2.7	2.4	1.7	1.0	1.8	2.0	2.2	1.0	1.2
Others	5.6	14.6	13.0	14.3	5.3	8.0	7.6	0.1	23.7	0.0	2.1	0.1	0.3

Source: Adapted from WHO information obtained from www.afro.who.int/en/countries.html.

Top ten causes of deaths all ages expressed as % of the total number of deaths

Top ten causes of deaths all ages (%)	Burundi Eritrea Ethiopia Kenya Madagascar Malawi Mozambique Rwanda Tanzania Uganda Zambia Zimbabwe											
	Burundi	Eritrea	Ethiopia	Kenya	Madagascar	Malawi	Mozambique	Rwanda	Tanzania	Uganda	Zambia	Zimbabwe
Lower respiratory tract infections	12	16	12	10	14	12	7	13	12	11	12	4
Diarrheal diseases	8	6	6	7	9	8	8	10	6	8	7	2
HIV/AIDS	22	16	12	38	3	34	28	18	29	25	43	67
Perinatal conditions	6	6	8	4	7	3	5	7	4	4	4	2
Malaria	4	6	3	5	11	8	9	2	10	11	9	NS
Tuberculosis	3	5	4	5	4	2	3	4	18	4	3	3
Cerebrovascular diseases	3	4	3	4	5	3	2	3	3	3	2	2
Ischemic heart disease	3	3	3	4	4	3	2	3	3	3	2	2
Road traffic accidents	2	2	NS	2	3	1	ND	2	2	NS	1	NS
Measles	NS	3	4	NS	5	NS	3	2	NS	2	1	1

Source: Adapted from WHO information obtained from www.afro.who.int/en/countries.html.
NS, not stated.

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Chapter 10

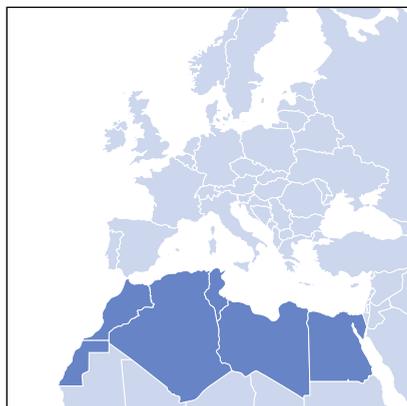
North Africa

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Algeria
Egypt
Libya
Morocco
Sudan
Tunisia
Western Sahara

Two regions should be individualized in the North African area. In the region of the Maghreb (Morocco, Algeria, Tunisia, and Libya) and Egypt due to climatic and socioeconomic conditions, the traveler is at risk of acquiring a number of infections common to other geographic areas. However, he is also at risk of acquiring more exotic infections including Mediterranean spotted fever, typhus, rabies, intestinal parasitosis, visceral and cutaneous leishmaniasis, and hydatidosis. Schistosomiasis is present in Egypt. *Plasmodium vivax* is present in limited areas including Elfeyoum in Egypt, the area of Janet and Ghardaia in the south of Algeria, and the area of Khourigba in Morocco, and a few places in Libya in the valleys and isolated oases in the south west (Fezzan).

By contrast, in Sudan, the traveler is at risk of tropical diseases overrepresented in Africa as a whole, including *P. falciparum* malaria, dengue, chikungunya, and yellow fever. Schistosomiasis is also a public health concern in Sudan.

North Africa as a whole is a high-risk area for travelers' diarrhea, and other fecal-oral acquired infections such as hepatitis A and less commonly typhoid fever. HIV and tuberculosis dominate the spectrum of communicable diseases in the area.

CNS infections: meningitis, encephalitis

Acute infections with less than four weeks of symptoms

Besides cosmopolitan infections [1–3], local infections like Toscana virus infection [4], West Nile encephalitis [5], rabies, and typhus should be considered. Among enteroviruses [6], Coxsackievirus is frequently responsible for meningitis [7]. *Brucella* is frequent in breeding areas and may be responsible for meningitis [8]. *Leptospira* is frequent in North Africa, but rarely responsible for meningitis.

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Enteroviruses, Coxsackievirus, herpes virus, varicella zoster virus, Toscana virus <i>Neisseria meningitidis</i> , <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i>	Rabies virus, West Nile virus Neurosyphilis <i>Listeria</i> , <i>Mycobacterium tuberculosis</i> , <i>Brucella</i> , <i>Leptospira</i> , <i>Rickettsia prowazekii</i> , <i>Rickettsia conorii</i>	Influenza <i>Brucella</i> , <i>Klebsiella pneumoniae</i> , <i>Tropheryma whipplei</i> , <i>Rickettsia typhi</i> [9] <i>Naegleria</i> and other free-living ameba

Infection with symptoms for more than four weeks and in the immunocompromised host

Consider also noninfectious causes such as lymphoma.

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
HIV, <i>Mycobacterium tuberculosis</i> [10,11], neuroborreliosis	<i>Mycobacterium tuberculosis</i> <i>Cryptococcus</i> spp., <i>Candida</i> spp., <i>Aspergillus</i> spp., <i>Rhodotorula</i> , <i>Nocardia</i> , <i>Toxoplasma</i>

Ear, nose, and throat infections

Ear, nose, and throat infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Rhinovirus, coronavirus, VRS, myxovirus, herpes virus, adenovirus, enterovirus (tonsillitis, rhinitis, otitis), Epstein-Barr virus (tonsillitis) <i>Streptococcus</i> (tonsillitis, otitis), <i>Haemophilus B catarrhalis</i> (otitis)	Vincent's angina <i>Mycobacterium tuberculosis</i> (tonsillitis, otitis)	Diphtheria (tonsillitis)

Ear, nose, and throat with symptoms for more than four weeks and in the immunocompromised host

Consider also noninfectious causes like cancer.

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Tuberculosis, syphilis (tonsillitis)	<i>Candida</i> spp.

Cardiopulmonary infections

Pneumonia with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Influenza <i>Streptococcus pneumoniae</i> , <i>Mycoplasma pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Staphylococcus aureus</i> , <i>Chlamydia pneumoniae</i> [12], <i>Coxiella burnetii</i>	<i>Legionella pneumophila</i> , <i>Chlamydia psittaci</i>	Diphtheria, <i>Klebsiella pneumoniae</i>

Endocarditis with less than four weeks of symptoms [13,14]

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Staphylococcus</i> and <i>Streptococcus</i> spp. <i>Bartonella</i> spp. [15]	<i>Neisseria gonorrhoeae</i> , <i>Coxiella burnetii</i> , HACEK group <i>Brucella</i>	<i>Candida</i> spp.

Pulmonary symptoms for more than four weeks and in the immunocompromised host

Consider also noninfectious causes like lung cancer, autoimmune lung fibrosis, and Wegener's granulomatosis.

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
COPD Tuberculosis <i>Brucella</i> <i>Aspergillus</i>	CMV <i>Coxiella</i> <i>Aspergillus</i> , <i>Candida</i> , <i>Pneumocystis</i>

Endocarditis for more than four weeks and in the immunocompromised host

Consider also noninfectious causes like sarcoidosis.

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Staphylococcus</i> and <i>Streptococcus</i> spp., <i>Enterococcus</i> , <i>Coxiella burnetii</i> , <i>Bartonella quintana</i> , <i>Brucella</i>	<i>Aspergillus</i> , <i>Candida</i>

Gastrointestinal infections

Gastrointestinal infections with less than four weeks of symptoms

Consider also noninfectious causes like inflammatory bowel disease and intestinal malignancies like colon cancer.

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Adenovirus, norovirus and calicivirus, rotavirus, hepatitis A virus [16] <i>Escherichia coli</i> , <i>Salmonella typhi</i> and <i>non-typhi</i> [17], <i>Campylobacter</i> , <i>Shigella</i> <i>Giardia intestinalis</i> , <i>Trichomonas intestinalis</i> , <i>Entamoeba histolytica</i> [18]	Whipple's disease <i>Helicobacter pylori</i> <i>Cryptosporidium</i> spp.	Tuberculosis, Whipple <i>Cyclospora caytanensis</i> [19]

Diarrhea is often associated with infections with bacteria, viruses, and parasites. Repeated negative bacterial cultures and microscopy for parasites should lead to the consideration that the symptoms may not be caused by an infection. Inflammatory bowel disease like colitis and Mb Chron are differential diagnosis and malabsorption and celiac disease must also be considered.

North Africa is one of the destinations from where travelers' diarrhea is very frequently reported.

Gastrointestinal infections with symptoms for more than four weeks and in the immunocompromised host

Consider also noninfectious causes like inflammatory bowel disease and intestinal malignancies like colon cancer, malabsorption, and celiac disease.

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Hepatitis A Whipple, tuberculosis <i>Giardia intestinalis</i> , <i>Entamoeba histolytica</i> , <i>Cryptosporidium</i> , <i>Trichomonas intestinalis</i> , helminths (<i>Ascaris lumbricoides</i> , <i>Trichuris trichiura</i> , <i>Hymenolepis nana</i> , <i>Strongyloides stercoralis</i> , <i>Echinococcus granulosus</i> , <i>Schistosoma mansoni</i> (Sudan and Egypt only) [18]	Herpes virus, CMV <i>Isospora</i> , <i>Microsporidium</i> <i>Candida</i>

Infections of liver, spleen, and peritoneum

Acute infections of liver, spleen, and peritoneum with less than four weeks of symptoms

	Frequently found disease	Rare diseases
Jaundice	Hepatitis A, B, C, E EBV, CMV infection Leptospirosis	Rickettsiosis Syphilis II CCHF*
Space-occupying lesion in liver Splenomegaly	Bacterial liver abscess Typhoid fever Visceral leishmaniasis (in children) Bacterial endocarditis Viral hepatitis EBV, CMV Brucellosis Tuberculosis	Amebic liver abscess Visceral leishmaniasis (in adults) Relapsing fever

*Has not been described.

Chronic infections of liver, spleen, and peritoneum with more than four weeks of symptoms

	Frequently found disease	Rare diseases
Jaundice	Chronic viral hepatitis Schistosomiasis*	Brucellosis Q-fever hepatitis Toxocariasis Hepatic tuberculosis† Leprosy† Histoplasmosis
Space-occupying lesion in liver Ascites Splenomegaly	Tuberculous peritonitis Hepatosplenic schistosomiasis Brucellosis	Tuberculosis Schistosomiasis* Tuberculosis

*Hepatic schistosomiasis is most often due to *S. mansoni* and only present in Sudan and Egypt.
†Hepatic TB may occur as miliary, nodular, and solitary abscess forms.

Infections of liver, spleen, and peritoneum in the immunocompromised host

Infections in the immunocompromised host are no different from those in the immunocompetent host.

Genitourinary infections

Cystitis, pyelonephritis, and nephritis with less than four weeks of symptoms

Consider also noninfectious causes, especially malignancies like renal cell carcinoma.

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>E. coli</i> , <i>Klebsiella pneumoniae</i> , <i>Staphylococcus saprophyticus</i> , <i>Proteus mirabilis</i>	<i>Pseudomonas aeruginosa</i> , <i>Enterococcus faecalis</i> ,	Tuberculosis

Sexually transmitted infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Chlamydia</i> spp., <i>Neisseria gonorrhoeae</i> , <i>Gardnerella vaginalis</i> , syphilis <i>Trichomonas vaginalis</i>	Lymphogranuloma venereum, Ducrey's disease <i>Entamoeba dispar</i> and <i>E. histolytica</i>	

Cystitis, pyelonephritis, and nephritis with symptoms for more than four weeks and in the immunocompromised host

Consider also noninfectious causes, especially malignancies like renal cell carcinoma.

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Tuberculosis, <i>Schistosoma haematobium</i> [20]	<i>Candida</i>

Sexually transmitted infections with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
HIV Herpes virus Papilloma virus Hepatitis B virus Syphilis <i>Neisseria gonorrhoeae</i>	Syphilis <i>Candida</i>

Joint, muscle, and soft tissue infections

Joint, muscle, and soft tissue infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Staphylococcus aureus</i> <i>Streptococcus</i> (not <i>pneumoniae</i>)		Lice, scabies

Joint, muscle, and soft tissue infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Tuberculosis	<i>Candida</i> , dermatophytes, <i>Cryptococcus</i> , atypical mycobacteria

Skin infections

Skin infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Erysipelas, <i>Streptococcus</i> (not <i>pneumoniae</i>) <i>Staphylococcus aureus</i> <i>Borrelia</i> spp. Dermatomycosis		Anthrax

We have not listed a rash due to viral infections as this is not considered an infection limited to the skin.

Skin infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Syphilis, tuberculosis [21], leprosy <i>Leishmania</i> [22] Blastomycosis Scabies	<i>Candida</i> Dermatophytes [23]

Adenopathy

Adenopathy of less than four weeks duration

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Epstein–Barr virus, cytomegalovirus, parvovirus B19, HIV <i>Toxoplasma gondii</i>	Tularemia, <i>Bartonella</i>	Ehrlichia Anthrax <i>Yersinia pestis</i> [24]

Adenopathy of more than four weeks duration and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Rubella, <i>Toxoplasma gondii</i> Tuberculosis	Adenovirus, HIV, CMV

If the diagnosis is not made within a few days, biopsies should be performed to exclude malignancies like lymphoma and carcinomas.

Fever without focal symptoms

Fever less than four weeks without focal symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Dengue (Sudan only) [25], chikungunya (Sudan only) [26], yellow fever (Sudan only) [26] <i>Salmonella typhi</i> , Mediterranean spotted fever (<i>Rickettsia coronii</i>) [28–30], <i>Rickettsia</i> spp. [31–41], <i>Brucella</i> , <i>Streptococcus</i> (endocarditis) Malaria (Sudan only) [42], amebiasis	Rift Valley fever virus [27], West Nile virus, HIV Tuberculosis, <i>Coxiella burnetii</i> <i>Schistosoma</i>	<i>Mycobacterium</i> (atypical) <i>Leishmania</i> (visceral)

NB: *Schistosoma haematobium* is present in the whole region, while *Schistosoma mansoni* is only present in Sudan and Egypt.

Fever for more than four weeks without focal symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Coxiella burnetii</i> [43], tuberculosis, <i>Bartonella quintana</i> [44]	Leishmaniasis (visceral), tuberculosis, <i>Mycobacterium</i> (atypical)

Noninfectious causes should be considered from the beginning, including malignancies like lymphoma and autoimmune diseases.

Eosinophilia and elevated IgE

Eosinophilia and elevated IgE less than four weeks

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Ascaris lumbricoides</i> , <i>Trichuris trichiura</i> , <i>Hymenolepis nana</i>	<i>Toxocara</i> , <i>Fasciola</i>	Myiasis [45], filariasis, <i>Trichinella</i>

Eosinophilia and elevated IgE for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Strongyloides stercoralis</i> , <i>Echinococcus granulosus</i> , <i>Schistosoma mansoni</i> and <i>S. haematobium</i> , <i>Dracunculus medinensis</i> (Sudan only)	

NB: *Schistosoma haematobium* is present in the whole region, while *Schistosoma mansoni* is only present in Sudan and Egypt.

Basic diagnostics in patients with eosinophilia and elevated IgE

Microorganism	Diagnostics
<i>Ascaris</i> spp. <i>Toxocara</i> spp.	Fecal microscopy Serology

Antibiotic resistance

Multidrug-resistant *Salmonella enterica* has been isolated in Algeria [46]. *Shigella dysenteriae* and enteropathogenic *Escherichia coli* show high resistance rates against ampicillin, chloramphenicol, tetracyclines, co-trimoxazole, nalidixic acid, sulphonamide, and neomycin in Sudan [47]. High degrees of penicillin resistance are observed in *Streptococcus pneumoniae* in North African countries, as well as dual resistance to penicillin and erythromycin [48,49]. Methicillin-resistant *Staphylococcus aureus* has been isolated in travelers returning from North Africa [50]. A high prevalence of multidrug-resistant tuberculosis was also described in Egypt [51]. In Sudan, *P. falciparum* exhibits a high level of resistance to antimalarials, leading the country to adopt artesunate+ sulphadoxine/pyrimethamine combination as the first-line drug [52].

Vaccine-preventable diseases in children

According to the WHO (www.who.int/immunization_monitoring/data/en/), the childhood vaccination program includes vaccination against tuberculosis, diphtheria, tetanus, poliomyelitis (oral polio vaccine), pertussis, measles, and hepatitis B in all North African countries. Vaccination against *Haemophilus influenzae* infection is provided in Algeria, Morocco Sudan, and Libya. Vaccination against mumps is provided in Morocco, Egypt, and Libya, and vaccination against rubella in Morocco, Tunisia, Egypt, and Sudan. Finally, vaccination against meningitis A and C is provided in Egypt and against meningitis A, C, Y, and W135 in Libya. Of interest, cases of diphtheria and poliomyelitis are reported from Sudan only. Cases of tetanus, measles, rubella, and pertussis are reported from the entire North African area with local variations (WHO).

Basic economic and demographic data

Basic demographics	GNI per capita (USD)	Life expectancy at birth (total, years)	School enrollment, primary (% net)
Algeria	4260	72	95
Egypt	1800	70	96
Libyan Arab Jamahiriya	11 590	74	NA
Morocco	2580	71	89
Sudan	1130	58	41
Tunisia	3290	74	95
Western Sahara	NA	NA	NA

GNI, gross national income; NA, not available.

Causes of death in children underfive. Regional average*

	%
Neonatal causes	26
Pneumonia	21
Diarrheal diseases	17
Malaria	17

(Continued)

	%
HIV/AIDS	7
Measles	4
Injuries	2
Others	6

*WHO regional average, 2006 data.

Most common causes of deaths all ages* in three countries selected for a low (Sudan), middle (Morocco), and high (Libya) regional GNI per capita

	%		
	Sudan	Morocco	Libya
Ischemic and hypertensive heart disease	8	24	28
HIV/AIDS	6	NS	NS
Lower respiratory infections	NS	6	5
Cerebrovascular disease	5	7	8
Malaria	6	NS	NS
Perinatal conditions	5	7	4
Tuberculosis	5	NS	NS
Diarrhea	6	4	2
Measles	5	NS	NS
War	4	NS	NS
Road traffic accidents	3	4	4
Cirrhosis of the liver	NS	3	2
Chronic obstructive lung disease	NS	2	2
Nephritis and nephrosis	NS	3	3

*WHO 2002.
NS, not stated.

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Chapter 11

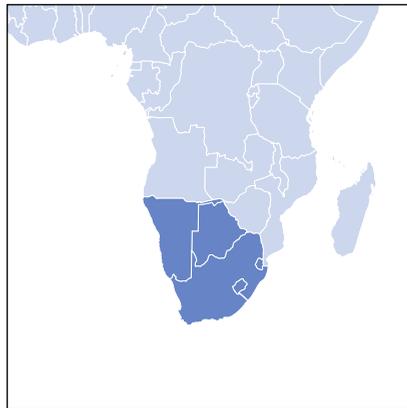
Southern Africa

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Botswana
Lesotho
Namibia
South Africa
Swaziland

Southern Africa's burden of disease is dominated by the collision of two epidemics; HIV and tuberculosis. Malaria completes the triumvirate of major clinical infectious diseases, with endemic areas in all countries except Lesotho. The traveler to southern Africa is at risk of acquiring a number of infections either common to other geographic areas or those that are overrepresented in Africa as a whole. These infections include vector-borne diseases such as African tick bite fever, the most common cause of febrile syndrome in the returning traveler from South Africa, mosquito-borne West Nile virus and Sindbis, and water-related infections such as schistosomiasis and leptospirosis. Southern Africa is an intermediate risk area for travelers' diarrhea, and other fecal-oral acquired infections such as hepatitis A and, less commonly, typhoid fever, are important causes of morbidity in visiting travelers. Increasingly, infections acquired in southern Africa such as tuberculosis and common bacterial infections come with the added complication of multidrug resistance.

Acute infections within four weeks of exposure

Three infections dominate the infectious diseases landscape of southern Africa; HIV, malaria, and tuberculosis. As the incubation period of tuberculosis even for primary infection is rarely less than weeks, it will not be discussed further in this section.

Worldwide, southern Africa is the region most seriously affected by HIV. South Africa is home to the largest population of people living with HIV [1], and its seroprevalence rate amongst antenatal women is 29.5% [2]. This is eclipsed by Swaziland’s antenatal seroprevalence rate of 42% in 2008, which has steadily increased since 1992 [1]. Overall, each country in southern Africa has adult seroprevalence rates exceeding 15% [2]. HIV seroconversion illness is clinically apparent in 40–90% of new HIV infections, with symptoms occurring within days or weeks of infection which generally last <14 days [3]. Although clinical features are often nonspecific, fever is the most common symptom. A maculopapular rash is evident in 40–80% of patients and mucocutaneous ulceration and aseptic meningitis are frequently seen [4]. HIV seroconversion illness should be considered in any traveler returning from southern Africa with fever and nonspecific symptoms. Furthermore, pretravel advice should incorporate strong messaging around safe sex practices, with particular reference to condom use.

Southern Africa has low rates of malaria transmission compared to other endemic regions in Africa and transmission is commonly seasonal. The summer months of September to May see the highest rates of transmission, which does not occur uniformly throughout each country but is found in distinct geographic areas (Table 11.1). Of the five countries in southern Africa, Lesotho, whose lowest point is 1400 metres, is the only country where malaria transmission does not occur. Chloroquine resistance is widespread and the drug is no longer used for malaria prophylaxis, or for treatment of *P. falciparum*. Mefloquine, atovaquone-proguanil or doxycycline are recommended for chemoprophylaxis.

Table 11.1 Malaria transmission in southern Africa.

Country	Malaria endemic areas	Malaria type	Seasonal transmission [5]
Botswana	North of 22°S in the northern provinces of Central, Chobe, Ghanzi, Ngamiland and Okavango Delta area	<i>P. falciparum</i>	September to May in northern provinces and Okavango Delta
Lesotho	None	NA	NA
Namibia	Northern Namibia bordering Angola – Kunene, Ohangwena, Okavango, Omaheke, Omusati, Oshana, Oshikoto, Otjozondjupa provinces and the Caprivi Strip	<i>P. falciparum</i>	Year round along the Kuene river, Caprivi and Kavango regions. September to May in other areas
Swaziland	Low-altitude areas bordering Mozambique in the east, and South Africa in the north and south	<i>P. falciparum</i>	Seasonal risk September to May (Big Bend, Mhlume, Simunye, and Tshanen)
South Africa	Mpumalanga Province (areas below 1500 m) bordering Mozambique, and bordering on and including the Kruger National Park), north-eastern Limpopo Province and the far north of KwaZulu-Natal Province bordering on Mozambique	<i>P. falciparum</i> >90% <i>P. ovale</i> and <i>P. vivax</i> reported rarely	Seasonal risk September–May

Source: Adapted from information from the CDC Malaria Map Application available at www.nicd.ac.za/?page=south_africa_malaria_risk_map&id=256 (accessed 13 October 2016).

In addition to HIV and malaria, patients presenting with acute febrile illness from southern Africa within four weeks of exposure may have acquired an infection that is either particular to the African continent or tropical climes or is common worldwide, for example influenza and other upper respiratory tract viral infections. The latter will not be discussed further in this chapter.

Fever and rash

- *African tick bite fever* (ATBF) is a common cause of fever in travelers returning to their home country from South Africa [6], and travel to southern Africa is a recognized risk factor for acquiring *Rickettsia africae*, the causative organism [7]. Risk factors for exposure to the *Amblyomma* ticks which transmit *R. africae* in southern Africa include male sex, traveling for tourism, and travel during the summer months [7]. Interestingly, travel during winter was found to be a risk factor in multivariate analysis for those restricting their travel to South Africa [6]. ATBF should be suspected in any traveler returning with the classic triad of fever, eschar, and maculopapular rash, although in up to 45% of patients, the rash may be vesicular [8], and rash may be absent in a percentage of travelers with ATBF. Spotted Mediterranean fever rickettsiosis may also be acquired in southern Africa from *Rhipicephalus* spp. ticks (brown dog tick), which carry *R. conorii*. This infection presents with similar clinical features, although clinically disease may be more severe. Diagnosis is primarily made on clinical features and risk exposure. Complications of bleeding and multisystem disease may occur in a small percentage of persons. Treatment is with doxycycline.
- *Acute schistosomiasis*, also known as Katayama fever, is endemic in southern Africa and follows swimming in inland waterways. Penetration of water-borne cercariae through the skin may lead to cercarial dermatitis hours after exposure: an itchy, localized rash, which resolves within hours. Katayama fever, an acute hypersensitivity reaction to circulating schistosomules, may occur 2–8 weeks after infection. It is characterized by fever, urticaria, and eosinophilia ± wheeze. *Schistosoma* ova are commonly absent from urine or stool at this stage and serological tests can take one to three months to become positive. Treatment is with prednisone.
- *Typhoid fever* may become evident in a febrile patient with or without bowel disturbance. Rose spots are generally rare, especially in dark-skinned patients. Leukopenia is characteristic and blood cultures should be sent with early instigation of antibiotic therapy.
- *Meningococcal meningitis or septicemia* occurs sporadically throughout southern Africa, but is more common in the winter months.
- *Viral exanthems* such as measles and rubella are common in southern Africa and may be acquired by nonimmune travelers.
- *West Nile fever* due to infection with the mosquito-transmitted West Nile virus (WNV) is endemic in southern Africa. Although 80% of cases are asymptomatic, abrupt onset of high fever (often >39°C), headache, myalgia, and gastrointestinal symptoms occur in approximately 20%. A transient nonitchy maculopapular rash may occur, commonly affecting the trunk and extremities. West Nile neuroinvasive disease will occur in <1% of infected individuals and carries a mortality of up to 30% [9].
- *Sindbis, Zika and chikungunya*, have a predilection for causing arthritis, but may also be characterized by rash in addition to fever. Sindbis is more commonly reported than chikungunya in southern Africa, having a wider geographic distribution. Both are mosquito borne and cause an abrupt onset of fever with polyarticular small joint arthralgia and chills. A maculopapular rash involving trunk, limbs, face, palms, and soles may occur early in the illness. Mild leukopenia with relative leukocytosis may be present. Treatment is supportive. Zika and dengue transmission has not been reported in the subregion.
- *Strongyloidiasis* has a tropical and subtropical distribution and a prepatent period of 17–28 days. Patients may present with pruritus at the site of larval entry or pulmonary symptoms related to larval migration. If autoinfection ensues, signs of established infection such as larva currens may occur. Hyperinfection in immunocompromised patients may develop.

- *Viral hemorrhagic fevers* can present with a morbilliform rash, in particular Congo-Crimean hemorrhagic fever (CCHF), which is endemic in a number of areas throughout southern Africa, and the newly identified Lujo virus, a novel arenavirus that was the focus of an outbreak in a Johannesburg Hospital, South Africa, in 2008. The index patient was from Lusaka, Zambia [10].

Fever and jaundice

- *Hepatitis A*, manifesting 2–6 weeks after infection with the picornavirus, is commonly asymptomatic in children, but up to 70% of adults will experience jaundice. Fulminant hepatitis is rare and treatment is supportive. Vaccination for travelers to the region is recommended to prevent this infection.
- *Leptospirosis* caused by the spirochete *Leptospira* is a zoonosis transmitted by rats. Exposure to rat excreta in infected water increases the risk of acquisition in travelers undertaking water sports such as white water rafting. Leptospirosis also occurs in urban areas where rats co-habit. It classically runs a biphasic course with initial bacteremia followed by an immune phase associated with antibody production and immune complex deposition. Abrupt onset of fever with nonspecific symptoms occurs. Conjunctival suffusion without purulent discharge and intense myalgia are common. Headache, retroorbital pain, and aseptic meningitis may occur. Weil’s disease describes the severe form of leptospirosis accompanied by hepatic (jaundice) and renal failure, carrying a mortality rate of up to 15%.
- *Hepatitis E* is far less common than its counterpart hepatitis A virus, yet can cause higher rates of severe disease.

Relapsing fever

- *Tickborne relapsing fever (TBRF)* is endemic to the southern Africa region, transmitted by members of the *Ornithodoros* soft tick species. *Borrelia duttonii* is the predominant cause of the abrupt febrile illness with nonspecific symptoms that last several days, followed by a crisis and cessation of fever. If untreated, the fever recurs on average seven days later. Multiple relapses can occur, which tend to be milder as time progresses [11].

Diarrhea and fever

- *Travelers’ diarrhea (TD)*. Southern Africa is classified as an intermediate risk region for acquiring TD; 8–20% of travelers experience TD associated with a stay of ≥2weeks abroad [12]. A suggestion that South Africa is a low-risk country in contrast to its neighbors was not supported by a 2010 study [6]. The most common cause of TD is enterotoxigenic *E. coli*. Early treatment rather than prophylactic antibiotics is recommended for travelers to the region.
- *Amebiasis* caused by the protozoan *Entamoeba histolytica* has a clinical spectrum from asymptomatic to dysentery to fulminant colitis. Metronidazole or tinidazole is the treatment of choice.
- *Cholera* epidemics have been reported from time to time in southern Africa including the spillover of the Zimbabwean cholera epidemic of 2009 to southern African countries. South Africa and Botswana were particularly affected. Sporadic cases and small clusters continue to occur, but the risk of acquiring cholera in the region is low.

CNS infections: meningitis, encephalitis, and other infections with neurological symptoms

Acute infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
<i>Plasmodium falciparum</i> <i>Streptococcus pneumoniae</i>	<i>Listeria monocytogenes</i> <i>Haemophilus influenzae</i>	Influenza Measles

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
<i>Neisseria meningitidis</i>	<i>Treponema pallidum</i>	West Nile virus
Enteroviruses	<i>Leptospirosis</i> spp.	<i>Brucella</i>
Herpes virus (type I)	SFG rickettsioses	Rabies
HIV		<i>Plasmodium vivax</i> malaria

Meningitis and encephalitis with symptoms for more than four weeks and in the immunocompromised host

Consider also noninfectious causes like lymphoma.

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Tuberculosis	<i>Cryptococcus</i> spp.
Neurocysticercosis	Tuberculosis
<i>Cryptococcus</i> spp.	<i>Toxoplasma gondii</i>
HIV	Cytomegalovirus
	HIV
	<i>Nocardia</i>
	JC virus
	<i>Aspergillus</i>
	Varicella zoster virus
	Epstein–Barr virus, EBV-driven primary CNS lymphoma

Basic diagnostics of CNS infections

Computed tomography and MRI are not commonly available in southern Africa outside tertiary hospitals. When available, they may be employed in the diagnostic work-up and are particularly useful in the diagnosis of space-occupying masses in the immunocompromised host. Similarly, PCR is only offered in specialist laboratories. Interferon-gamma release assays such as QuantiFERON are not used to diagnose active tuberculosis due to high background prevalence of latent tuberculosis infection. The same is true for tuberculin skin tests in adults, although the latter are more commonly employed in suspected pediatric cases. Often, no investigations are available or are limited to cell counts and biochemistry on spinal fluid. There is an increased reliance on history and examination findings.

Ear, nose, and throat infections

Ear, nose, and throat infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Streptococcal throat infection	Peritonsillar abscess*	<i>Haemophilus influenzae</i> type B (incidence reduced by vaccination program)

(Continued)

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Viral infections : influenza A and B, parainfluenza, rhinovirus Epstein–Barr virus Herpes virus (type I and II)	Tuberculosis Necrotizing fasciitis* Lemierre’s syndrome* Vincent’s angina	<i>Neisseria gonorrhoeae</i> Diphtheria
*Require acute ENT evaluation.		

Ear, nose, and throat with symptoms for more than four weeks and in the immunocompromised host

Consider also noninfectious causes like vasculitis and lymphoma.

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Tuberculosis <i>Pseudallescheria boydii</i>	<i>Candida</i> Herpes virus Human herpes virus 8 (Kaposi’s sarcoma) <i>Pseudomonas aeruginosa</i> Epstein–Barr virus, EBV-driven non-Hodgkin’s lymphoma Cancrum oris

Cardiopulmonary infections

Pneumonia with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Streptococcus pneumoniae</i> <i>Legionella pneumophila</i> <i>Mycoplasma pneumoniae</i> <i>Chlamydia pneumoniae</i> Respiratory viruses <i>Haemophilus influenzae</i>	<i>Staphylococcus aureus</i> Influenza Aerobic gram-negative bacilli (e.g. <i>Klebsiella pneumoniae</i>) Löefflers syndrome (e.g. <i>Ascaris lumbricoides</i> migration)	<i>Chlamydia psittaci</i> Histoplasmosis Diphtheria

Endocarditis with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Nonhemolytic streptococci <i>Staphylococcus aureus</i>	<i>Bartonella</i> spp. <i>Coxiella burnetii</i>	<i>Pseudomonas aeruginosa</i> <i>Brucella</i>
Enterococci	HACEK group	
Coagulase-negative staphylococci (<i>S. epidermidis</i>)	Nutritionally variant streptococci (<i>Abiotrophia/Granulicatella</i> spp.) <i>Streptococcus pneumoniae</i> <i>Neisseria gonorrhoeae</i>	

Pulmonary symptoms for more than four weeks and in the immunocompromised host

In addition to opportunistic pathogens such as *P. jiroveci*, the most common organisms associated with pulmonary infection in HIV-infected patients are *Streptococcus pneumoniae* and *Haemophilus influenzae*. Consider also noninfectious causes like lung cancer, autoimmune lung fibrosis, and Wegener's granulomatosis.

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Tuberculosis <i>Cryptococcus</i> spp. <i>Aspergillus</i> <i>Nocardia</i> COPD	<i>Mycobacterium tuberculosis</i> <i>Pneumocystis jiroveci</i> <i>Cryptococcus</i> spp. CMV Nontuberculous Mycobacteria <i>Aspergillus</i> , <i>Candida</i> , other deep fungal infections <i>Rhodococcus equi</i> Lymphoid interstitial pneumonitis <i>Pseudomonas aeruginosa</i>

Endocarditis for more than four weeks and in the immunocompromised host

As infective endocarditis is a recognized cause of pyrexia of unknown origin, all the organisms listed above may cause a clinical illness that lasts for >4 weeks. In the immunocompromised host, *Aspergillus* must be considered, and very rarely, tuberculosis in high-prevalence countries of southern Africa.

Basic diagnostics of pulmonary infections

Fiberoptic bronchoscopy, bronchiolar lavage, and transbronchial biopsy are only available in specialist centers and CT is not routinely used for diagnosis of pneumonia in southern Africa. A number of southern African countries have rolled out Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) as part of their national tuberculosis programs. Xpert MTB/RIF has high sensitivity, even in smear-negative HIV-coinfected persons, a rapid turnaround time of 1–2 hours, and provides information on rifampin resistance of the *M. tuberculosis* if present.

Basic diagnostics of endocarditis

High index of suspicion in any patient with fever, murmur±extracardiac embolic phenomena such as Roth spots, Osler's nodes, etc. Echocardiography is limited to specialist centers in southern Africa so more reliance is made on clinical diagnosis and use of criteria such as the Duke criteria.

Gastrointestinal infections

Gastrointestinal infections with less than four weeks of symptoms (a)

Consider also noninfectious causes like inflammatory bowel disease and intestinal malignancies like colon cancer.

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Salmonella</i> (non-typhi) <i>Shigella</i> <i>Campylobacter</i> Enterotoxigenic <i>E. coli</i> <i>Staphylococcus aureus</i> toxin <i>Giardia intestinalis</i> <i>Entamoeba histolytica</i> <i>Ascaris lumbricoides</i> <i>Enterobius vermicularis</i> (pinworm)	<i>Salmonella typhi</i> <i>Bacillus cereus</i> toxin <i>Anisakis</i> spp.	Whipple's disease and conditions

Gastrointestinal infections with symptoms for more than four weeks and in the immunocompromised host

Consider also noninfectious causes like inflammatory bowel disease and intestinal malignancies like colon cancer, malabsorption, and celiac disease.

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Ascaris lumbricoides</i> Hookworm spp. <i>Schistosoma mansoni</i> Taeniasis (<i>solium</i> and <i>saginata</i>) <i>Strongyloides stercoralis</i> <i>Trichuris trichiura</i> Fascioliasis (<i>F. hepatica</i>) Visceral toxocariasis (visceral) Tuberculosis HIV	<i>Candida</i> <i>Cryptosporidium</i> <i>Isospora belli</i> Microsporidiosis <i>Salmonella</i> (non-typhi) Cytomegalovirus Tuberculosis Nontuberculous mycobacteria Histoplasmosis Herpes virus type 1 AIDS cholangiopathy Human herpes virus 8 (Kaposi's sarcoma) Lymphoma

Basic diagnostics of gastrointestinal symptoms

Empirical/syndromic treatment of diarrhea with antibiotics is common in southern Africa, which may eliminate the chance of making an etiological diagnosis. Endoscopy and intestinal biopsy are restricted to specialist centers, yet play a vital role in management of HIV patients with gastrointestinal symptoms when available.

Genitourinary infections

Cystitis, pyelonephritis, and nephritis with less than four weeks symptoms

Consider also noninfectious causes, especially malignancies like renal cell carcinoma.

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>E. coli</i> <i>Klebsiella pneumoniae</i> <i>Proteus</i> spp. Tuberculosis HIV-associated nephropathy	<i>Enterococcus</i> spp. <i>Pseudomonas aeruginosa</i> <i>Staphylococcus aureus</i> Perirenal abscess Leptospirosis	

Sexually transmitted infections with less than four weeks symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Primary syphilis Herpes simplex type II <i>Neisseria gonorrhoeae</i> Chancroid <i>Chlamydia</i> spp. <i>Trichomonas</i>	Lymphgranuloma venereum Granuloma inguinale	Tuberculosis

Cystitis, pyelonephritis, and nephritis with symptoms for more than four weeks and in the immunocompromised host

Consider also noninfectious causes, especially malignancies like renal cell carcinoma.

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Bacterial infections in patients with long-term catheters and renal stones <i>Schistosoma haematobium</i> Tuberculosis HIV-associated nephropathy	Tuberculosis <i>Candida</i> Human herpes virus 8 (Kaposi's sarcoma) <i>Pneumocystis jiroveci</i> (extrapulmonary)

Sexually transmitted infections with symptoms for more than four weeks and in the immunocompromised host

Syphilis and genital warts due to human papilloma virus may both persist for >4 weeks. Stigmatization in relation to any sexually transmitted infection that causes penile deformity may lead to delayed presentation in patients with penile edema secondary to lymphogranuloma venereum or tuberculosis.

Basic diagnostics of sexually transmitted infections

The majority of southern African countries take a syndromic approach to management of sexually transmitted infection and therefore do not employ diagnostic tests, but rather treat individual syndromes.

Joint, muscle, and soft tissue infections

Joint, muscle, and soft tissue infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Staphylococcus aureus</i> (including tropical pyomyositis) <i>Neisseria gonorrhoeae</i>	Reiter's syndrome Necrotizing fasciitis Group G streptococci Viral arthritis (parvovirus, rubella, hepatitis B, enteroviruses) Tuberculosis <i>Salmonella</i> (non-typhi) <i>Neisseria meningitidis</i> Sindbis and chikungunya	<i>Streptococcus pneumoniae</i> Fournier's gangrene (perineum and urogenital)

Joint, muscle, and soft tissue infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms associated with symptoms for >4 weeks include tuberculosis, HIV and *Brucella*. In the immunocompromised host, *Candida* and cryptococcal spp. are important causes.

Skin infections

Skin infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Staphylococcus aureus</i> and group A beta-hemolytic streptococci (impetigo, boils, etc.) Ringworm (<i>Tinea</i> spp.)	Hydradenitis suppurativa <i>Streptococcus pneumoniae</i>	Gnathostomiasis*

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Herpes viruses (VZV and HSV) Spotted fever group rickettsioses (ATBF and Mediterranean spotted fever) Scabies Helminths (acute schistosomiasis, hookworm-associated cutaneous larva migrans, strongyloidiasis) Tinea versicolor (<i>Malassezia furfur</i>)	<i>Bacillus anthracis</i>	
*Reported cases after ingestion of raw bream in the Okavango Delta.		

We have not listed a rash due to viral infections as this is not considered an infection limited to the skin.

Skin infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Syphilis Tuberculosis Sporotrichosis <i>Mycobacterium leprae</i> <i>Mycetoma</i> (actinomycosis, <i>Nocardia</i>) Human herpes virus (endemic Kaposi's sarcoma)	Human herpes virus (Kaposi's sarcoma) Deep fungal infection (histoplasmosis, emmonsiosis, blastomycosis, sporotrichosis, and cryptococcosis) Tuberculosis <i>Bartonella</i> (bacillary angiomatosis) <i>Candida</i>

Adenopathy

Adenopathy of less than four weeks duration

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
HIV Local suppurative disease (staphylococci, streptococci) Infectious mononucleosis (EBV, CMV, and <i>Toxoplasma gondii</i>)	<i>Bartonella</i> (cat scratch disease) never seen here – thought to be very rare Parvovirus B19	<i>Brucella</i>

Adenopathy of more than four weeks duration and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
HIV Tuberculosis Syphilis	HIV Tuberculosis Human herpes virus (Kaposi’s sarcoma, multicentric Castleman’s disease) Epstein–Barr virus (non-Hodgkin’s lymphoma) Deep fungal infection (histoplasmosis, sporotrichosis, blastomycosis) Nontuberculous mycobacteria

Basic diagnostics of patients with adenopathy

Fine needle aspiration or Trucut biopsy should be performed on all suspicious lymph nodes, particularly those that are asymmetrical, >1.5 cm or matted. Specimens should be sent for tuberculosis microscopy, culture (±histology), and cytology. Xpert MTB/RIF has good sensitivity for tuberculous adenopathy, enabling a diagnosis within 1–2 hours [14].¹⁴ If a diagnosis is not forthcoming, the node should be excised whenever possible and sent for the above tests.

Fever without focal symptoms

Fever less than four weeks without focal symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Malaria HIV Tuberculosis Endocarditis Pyogenic abscess Infectious mononucleosis (EBV, CMV, toxoplasmosis)	<i>Brucella</i>	

Fever for more than four weeks without focal symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Tuberculosis HIV	Tuberculosis Epstein-Barr virus, EBV-associated lymphoma Cryptococcal spp. and other disseminated deep fungal infections

Noninfectious causes should be considered from the beginning, including malignancies like lymphoma and autoimmune diseases.

Eosinophilia and elevated IgE

Eosinophilia and elevated IgE for less than four weeks

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Ascaris</i> spp. Hookworm spp. <i>Schistosoma</i> spp. Taeniasis (<i>solium</i> and <i>saginata</i>) <i>Strongyloides stercoralis</i> <i>Trichuris trichiura</i> Toxocariasis	Fascioliasis (<i>F. hepatica</i>)	

Eosinophilia and elevated IgE for more than four weeks and in the immunocompromised host

All of the above helminth infections can present with symptoms for >4 weeks. *Strongyloides stercoralis* hyperinfection syndrome must be considered in the immunocompromised host.

Antibiotic resistance

Antimicrobial resistance surveillance is lacking in sub-Saharan Africa except national surveillance system in South Africa. National surveillance data are available from The Group for Enteric, Respiratory and Meningeal Surveillance, South Africa (GERMS-SA) program. GERMS-SA is a program with 25 enhanced surveillance sites using specific case definitions and standardized testing methods.

Methicillin-resistant *Staphylococcus aureus*

Methicillin-resistant *Staphylococcus aureus* is currently one of the most commonly identified resistant pathogens, documented in approximately 40% of public sector, hospitalized patients in blood isolates from sentinel sites laboratory surveillance, 2012 data [15]. In the enhanced surveillance data, risk factors for MRSA infections were HIV, a low CD4 T-cell count, previously hospitalized patients, and antimicrobial use [16]. In the past decade, community-associated MRSA (CA-MRSA) without healthcare-associated risk factors has emerged in South Africa [17].

Resistance in *Streptococcus pneumoniae*

High-level resistance to beta-lactams and multidrug resistance in *S. pneumoniae* are an ongoing global concern [18]. However, due to vaccination there is a changing dynamic of pneumococcal diseases in countries where it was introduced. Rates of invasive pneumococcal disease among children in South Africa fell substantially by 2012 due to the introduction of a 7-valent pneumococcal conjugate vaccine (PCV) in 2009. PCV affected antimicrobial resistance due to a decline in the proportion of penicillin-nonsusceptible PCV7 serotypes, from 70% of isolates in 2009 to 47% in 2012 ($P < 0.001$) [19]. Penicillin-nonsusceptible isolates have a prevalence of 29% in invasive pneumococci, in all provinces

of South Africa, being common in children less than five years of age [19]. The rate of disease caused by ceftriaxone-nonsusceptible isolates declined, as did the rate of invasive disease caused by multidrug-resistant isolates [20].

Multidrug-resistant gram-negative bacteria

Multidrug-resistant gram-negative bacteria are generally resistant to more than two classes of antimicrobial agents. However, some strains may also be resistant to the carbapenems, leaving colistin as the only agent available for treatment [21]. The spread of carbapenem-nonsusceptible Enterobacteriaceae poses a threat to healthcare and patient safety globally. Distribution of the most common carbapenemase genes NDMs, OXAs, and VIMs in South African healthcare facilities necessitates structured antibiotic resistance surveillance [22]. National surveillance of *Salmonella* typhi isolates from invasive sites showed resistance to ampicillin (37%), chloramphenicol (38%), and ciprofloxacin (10%) among 60 isolates [24]. Fluoroquinolones (FQ) are used for treatment of invasive diarrheal disease in patients with *Salmonella*, which occurs more frequently in HIV-infected persons [23]. In South Africa, FQ resistance is at the low levels in all *Salmonella* invasive and noninvasive isolates (4.5%) [24]. In contrast to other Enterobacteriaceae, extended-spectrum beta-lactamases (ESBLs) were detected in 3.4% of all *Salmonella* isolates [24]. Amongst Enterobacteriaceae, the highest prevalence of ESBLs is in *Klebsiella pneumoniae* (68%) [25]. FQ use has been shown to be the only independent risk factor for FQ resistance in *Escherichia coli* strains causing urinary tract infections [26,27]. FQ resistance rates of 23% have been reported from private healthcare facilities, 5% of which were ESBLs [26,27]. The latest survey of urinary tract infections in private and public healthcare facilities from one South African province showed that susceptibilities to FQ and cephalosporins were 94% and 90%, respectively [28].

Vaccine-preventable diseases in children

The childhood vaccination program will vary to some extent in southern African countries. While the basic Expanded Program for Immunization (EPI) is fairly uniform across the region, a number of new vaccines have been introduced in the past few years in South Africa as part of the EPI schedule.

Vaccine coverage is variable, both across the region and within countries, and has a major impact on occurrence of disease and outbreaks; for example, measles outbreaks have been reported quite widely in South Africa and Zimbabwe. A number of childhood vaccines are registered and available in some of the countries but usage is, for the most part, restricted to the private sector because of resource limitations.

Additional vaccines to those listed in the EPI program, which are available and registered for use in children, include meningococcal vaccine, seasonal influenza vaccine, human papilloma virus, and varicella zoster. Vaccines for special indications include rabies vaccine for postexposure prophylaxis.

Expanded Program For Immunisation (EPI) (SA) schedule as of 1 March 2014.

Age	Vaccine needed
At birth	OPV (0): oral polio vaccine BCG (0): Bacillus Calmette–Guérin vaccine
6 weeks	OPV (1): oral polio vaccine RV (1): rotavirus vaccine DTaP-IPV/Hib (1): diphtheria, tetanus, acellular pertussis/inactivated polio vaccine and <i>Haemophilus influenzae</i> type b Heb B (1): hepatitis vaccine PCV (1): pneumococcal conjugated vaccine

Age	Vaccine needed
10 weeks	DTaP-IPV/Hib (2): diphtheria, tetanus, acellular pertussis/inactivated polio vaccine and <i>Haemophilus influenzae</i> type b Heb B (2): hepatitis vaccine
14 weeks	RV (2): rotavirus vaccine DTaP-IPV/Hib (3): diphtheria, tetanus, acellular pertussis/inactivated polio vaccine and <i>Haemophilus influenzae</i> type b Heb B (3): hepatitis vaccine PCV (2): pneumococcal conjugated vaccine
9 months	Measles vaccine (1) PCV (3): pneumococcal conjugated vaccine
18 months	DTaP-IPV/Hib (4): diphtheria, tetanus, acellular pertussis/inactivated polio vaccine and <i>Haemophilus influenzae</i> type b Measles vaccine (2)
6 years	Td vaccine: tetanus and reduced amount of diphtheria vaccine
9 years	HPV: human papilloma vaccine, bivalent vaccine for girls only. Two doses six months apart
12 years	Td vaccine: tetanus and reduced amount of diphtheria vaccine

Basic economic and demographic data*

Basic demographics	GNI per capita, 2009 (USD)	Life expectancy at birth (total, years)	School enrollment, primary (% net)
Botswana	6260	51	84
Lesotho	1020	43	72
Namibia	4310	53	87
South Africa	5770	50	86
Swaziland	2350	46	87

*World Development Indicators database, revised 9 July 2010. <http://siteresources.worldbank.org/DATASTATISTICS/Resources/GNIPC.pdf>
GNI, gross national income.

Cause of death in children under five expressed as % of the total number of deaths*

	Botswana	Lesotho	Namibia	South Africa	Swaziland	Regional average
Neonatal causes	40	33	39	35	27	26
Pneumonia	1	5	3	1	12	21
Diarrheal diseases	1	4	3	1	10	17
Malaria	0	0	0	0	0	17
HIV/AIDS	54	56	53	57	47	7
Measles	0	0	0	0	0	4
Injuries	3	2	3	5	4	2
Others	0	0	0	1	1	6

*WHO regional average, 2000–2003. Available at: www.who.int/whosis/mort/profiles/en/#

Top ten causes of deaths all ages in 2002, expressed as % of the total*

	Botswana	Lesotho	Namibia	South Africa	Swaziland
HIV/AIDS	80	63	51	52	64
IHD/hypertensive heart disease	2	3	4	4	2
Cerebrovascular disease	2	3	4	5	2
Lower respiratory tract infection	1	4	2	4	5
Tuberculosis	1	2	4	2	4
Measles	1	3	NS	2	NS
COPD	NS	2	NS	NS	1
Perinatal conditions	1	1	4	1	2
Violence	2	3	2	NS	NS
Road traffic accidents	NS	NS	2	3	1
Diabetes	1	1	NS	2	NS

*World Health Organization 2006. Available at: www.who.int/whosis/mort/profiles/en/#P
IHD, ischemic heart disease; NS, not stated.

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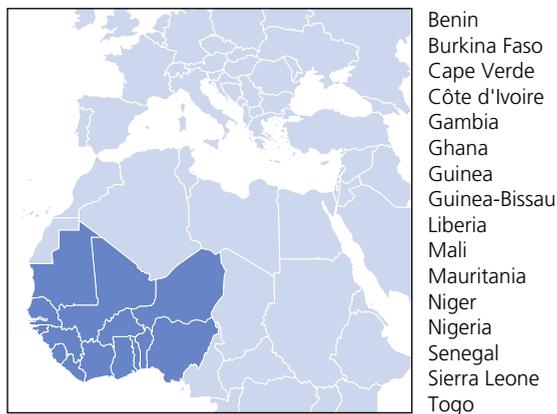
Chapter 12

West Africa

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The majority of West Africa is composed of plains lying less than 300 meters above sea level. The south towards the Atlantic coast is wet with abundant rainfall and the northern part semi-arid, known as the Sahel. Like many parts of sub-Saharan Africa, adequate healthcare infrastructures are lacking and basic epidemiological data for many diseases are not available.

Viral hemorrhagic fever

West Africa experienced the largest ever recorded outbreak of Ebola virus disease (EVD) in 2014–15 with more than 20000 cases, mainly in Guinea, Sierra Leone, and Liberia.

Viral hemorrhagic fever needs rapid exclusion in any traveler returning with fever from an endemic region within 21 days, and travelers with fever from these countries should be rapidly assessed and isolated if suspicion of EVD or any other hemorrhagic fever is maintained.

Symptoms include fever, headache, myalgia, pharyngitis, diarrhea, vomiting, retrosternal pain, purpuric rash, and bleeding.

West Africa has also experienced outbreaks of yellow fever, and Lassa fever is endemic in Sierra Leone and probably other West African countries. There is serological evidence of Crimean Congo

hemorrhagic fever (CCHF) in West Africa and the tick vector is present, but no human cases have so far been reported. Dengue virus is endemic in West Africa and chikungunya is probably present based on data from sero-surveys. Nothing is known about hantavirus or Zika in West Africa.

Malaria

Malaria is endemic throughout much of West Africa, and shows high transmission rates, particularly in the forested regions. Any traveler from West Africa with fever should be investigated for malaria without delay.

Malaria parasite rates are not uniform in the region, with some areas having endemic and perennial transmission while others have epidemic and strongly seasonal transmission. Transmission peaks during the rainy season, which falls roughly between April and August with a second peak between October and November. *P. falciparum* malaria may mimic other infections (gastroenteritis, respiratory tract infections, hemorrhagic fever or nonspecific viral infections). Chloroquine resistance is widespread and chloroquine should not be used for either treatment or prophylaxis of *falciparum* malaria in Africa. Artemisinin combination therapies (ACTs) are the drug of choice for both uncomplicated and complicated malaria.

Five *Plasmodium* parasite species cause malarial disease in humans (*falciparum*, *vivax*, *malariae*, *ovale*, and *knowlesi*). *P. falciparum* accounts for the vast majority of cases. The majority of deaths occur among children under the age of five, who die mostly from severe malaria including severe malarial anemia or cerebral malaria [1,2].

Malaria infections are complex and have very variable clinical phenotypes, ranging from mild febrile illness to life-threatening malaria. The clinical presentation is influenced by hemoglobin polymorphisms like sickle cell disease and thalassemia [3].

Pregnancy-associated malaria

Pregnancy-associated malaria (PAM) is an overwhelming public health problem in sub-Saharan Africa where 32 million pregnant women are estimated to be infected each year [4]. The epidemiology and clinical presentation of PAM depend on the intensity of malaria transmission [5,6]. Disease control strategies in this group have focused on intermittent preventive treatment (IPTp) using sulfadoxine-pyrimethamine (SP) in the second and the third trimester, use of insecticide-treated nets (ITNs) provided at antenatal booking, and effective case management of malarial illness and anemia.

CNS infections: meningitis, encephalitis

Acute CNS infections with less than four weeks of symptoms

	Frequently found disease	Rare diseases
Meningitis	Meningococcal meningitis* Meningitis from gram-positive bacilli† Enterovirus meningitis Meningitis from other gram-negative bacilli	Tuberculous meningitis Eosinophilic meningitis in schistosomiasis Neurosypphilis Listeriosis Leptospirosis

(Continued)

	Frequently found disease	Rare diseases
Encephalitis	Cerebral malaria** Herpes simplex and enterovirus encephalitis [§]	Trypanosomiasis ^{††} Rabies Ebola and Marburg virus ^{††} West Nile virus [‡] Neurocysticercosis
Myelitis	Spinal tuberculosis Tropical spastic paraparesis ^{¶¶}	HIV myelopathy Schistosomiasis Brucellosis

* High incidence in countries in the ‘meningitis belt.’
[†]In children: *Haemophilus influenzae*, *Streptococcus pneumoniae*.
^{**}Asymptomatic malaria parasitemia may be found in patients with bacterial meningitis by other microorganisms. Neck stiffness and photophobia are usually absent in cerebral malaria. Lumbar puncture essential.
^{††}African trypanosomiasis caused by *T. gambiense* is a chronic encephalitis with progression over months to the final CNS stage of complete lethargy, coma, and death. *T. rhodesiense* is an acute disease with involvement of the CNS within days to weeks after the infective tsetse fly bite [7].
[§]May co-exist with asymptomatic malaria parasitemia.
^{§§}CNS symptoms in patients with Ebola virus disease are probably caused by dehydration, electrolyte disturbances, and acidosis.
[‡]Epidemiology largely unknown in the region.
^{¶¶}An epidemic paralytic disease occurring in outbreaks in remote rural areas of low-income African countries, associated with several weeks of almost exclusive consumption of insufficiently processed “bitter” (high cyanide content) cassava.

Chronic CNS infections with more than four weeks of symptoms in immunocompetent and immunocompromised patients

The most common chronic CNS infection is tuberculous meningitis, usually with gradual onset of fever, headache, altered consciousness, and cranial nerve palsies. Tuberculomas can give rise to focal neurological defects. Neurosyphilis should be considered in any patients with elevated spinal fluid WBC count. Both TB and syphilis are common in HIV patients and HIV in itself is a neurotropic virus.

West African trypanosomiasis (WAT) caused by *T. gambiense* is a chronic disease with progression over months to the final CNS stage of complete lethargy, coma, and death. Neurocysticercosis is common and is an important cause of epilepsy in the region [8].

Neurocognitive disorders are common in HIV patients. All HIV-related CNS infections can be seen [9], in particular cryptococcal meningitis, CMV, and histoplasmosis. JC is a neurotropic virus and may cause progressive multifocal leukoencephalopathy (PML). Infections with *Nocardia*, *Candida*, and *Aspergillus* species may be seen in immunocompromised patients. Infection with *Toxoplasma gondii* is probably common in the region, and should be considered in HIV-positive patients with CNS symptoms, especially if focal lesions are found on CNS scans.

High prevalences of HIV-2 have been reported in Guinea-Bissau. Longitudinal studies suggest that the rate of progression to advanced HIV-related disease and mortality is far lower for HIV-2 than for HIV-1. Dual infection with HIV-1 and HIV-2 is possible. HTLV-1 infection has to be considered in patients with paraparesis and other HTLV types may exist but data are limited [10].

Ear, nose, throat, and upper respiratory tract infections

Acute and chronic infections

Acute and chronic suppurative otitis is highly prevalent in West Africa, affecting mainly children. Predominant bacterial agents in chronic discharging ears are gram-negative bacteria, including *Pseudomonas aeruginosa*. Otitomycosis is a differential diagnosis.

Streptococcal throat infection is common, and patients may develop rheumatic fever. Other causes of pharyngitis include Vincent's angina and EBV. Diphtheria should be suspected if a creamy adherent membrane is present over part of the tonsil (no data from West Africa).

Rhinoscleroma is a slowly developing granulomatous process in the nose caused by *Klebsiella rhinoscleromatis*. Rhinosporidiosis is another granulomatous disease caused by *Rhinosporidium seeberi*. Leprosy may affect the larynx and chronic nasal discharge, sometimes bloodstained, occurs in lepromatous leprosy. Nasal destruction is seen in yaws and leprosy (and in lupus vulgaris).

Ear, nose, and throat infections in the immunocompromised host

Ear, nose, and throat diseases in HIV patients include cervical lymphadenopathy, otitis media, oral candidiasis, and tonsillar diseases. The bacteriology of sinusitis in HIV infection often identifies opportunistic organisms not responsive to standard medical therapy, such as CMV, *Aspergillus*, and atypical mycobacteria. Tuberculosis must always be considered.

Sickle cell disease is a common inherited blood disorder in Central Africa. When bone is involved, infarction and osteomyelitis can be seen in the maxillofacial bone and skull base or other bones.

Children with protein-energy malnutrition may develop gangrenous stomatitis (cancrum oris, noma).

Cardiopulmonary infections

Pulmonary infection with less than four weeks of symptoms

	Frequently found disease	Rare diseases
Pneumonia	<i>Streptococcus pneumoniae</i> * <i>Haemophilus influenzae</i> † <i>Staphylococcus aureus</i> †† Tuberculosis Viruses (rhino, adeno)	<i>Mycoplasma</i> , <i>Chlamydia</i> , <i>Legionella</i> Q-fever** Histoplasmosis, blastomycosis
Lung abscess	Gram-positive bacteria	Amebiasis
Cough with eosinophilia	Schistosomiasis (Katayama syndrome) Ascariasis (Löffler's syndrome) Paragonimiasis	

* Most frequent; patients with hypogammaglobulinemia, asplenia, nephrotic syndrome, sickle cell anemia are at special risk.

† Responsible for 3–5% of episodes of pneumonia.

** Important differential diagnosis in febrile patients in general [11].

†† Causing 1–2% of pneumonias.

Endocarditis, myocarditis, pericarditis with less than four weeks of symptoms

	Frequently found disease	Rare diseases
Endocarditis	Subacute and acute bacterial endocarditis by <i>S. aureus</i> and streptococci spp.	Q-fever (<i>Coxiella burnetii</i>) <i>Bartonella quintana</i> <i>Tropheryma whipplei</i> infection
Myocarditis	Acute virus myocarditis Bacterial myocarditis (e.g. leptospirosis) Malaria*	Trypanosomiasis <i>Trichinella</i> infection
Pericarditis	Viral pericarditis† Pyogenic pericarditis†† Tuberculosis	Amebic pericarditis**

* Mostly in addition to other organ complications.
 † Fever, pericardial pain, but no evidence of systemic pyogenic infection.
 ** By rupture of left-sided liver abscess through diaphragm.
 †† Often in the course of bronchopneumonia or osteomyelitis, *S. pneumoniae*, *S. aureus*.

Pneumonia with more than four weeks of symptoms

HIV should always be considered in patients with fever for more than four weeks. Tuberculosis should always be considered in patients with cough and fever for more than four weeks. *Nocardia*, histoplasmosis, *Pneumocystis*, and blastomycosis are primarily infections in immunocompromised patients. Paragonimiasis is a differential diagnosis to tuberculosis and the main symptoms are cough and blood-flecked sputum. Melioidosis has not been described from West Africa but cases have been found in Central Africa.

Endocarditis and pericarditis with more than four weeks of symptoms

Rheumatic heart disease, tuberculosis, Q-fever, and other rickettsial infections like *Bartonella quintana* should be considered. Tuberculous pericarditis may directly spread from the tracheobronchial tree or thoracic lymph nodes.

Pneumonia in the immunocompromised host

Lung infections as in the immunocompetent host due to bacteria including tuberculosis are also found in the immunocompromised host. Reports from West Africa have suggested that *Pneumocystis pneumonia* (PJP) is a less important cause of morbidity than in the developed world.

Cytomegalovirus, adenovirus, and HSV are common viral causes and fungi such as *Candida* spp., *Aspergillus*, *Nocardia*, and *Actinomyces*, as well as gram-positive rod bacteria, should be considered.

Endocarditis, myocarditis, pericarditis in the immunocompromised host

Myocarditis may be caused by HIV infection, *Cryptococcus*, *Toxoplasma gondii*, and *Mycobacterium avium intracellulare* (MAI). Tuberculosis is a common cause of pericarditis.

Gastrointestinal infections

Gastrointestinal infections with less than four weeks of symptoms

	Frequently found disease	Rare diseases
Diarrhea	Salmonellosis Shigellosis <i>Campylobacter</i> infection Giardiasis ETEC infection Norovirus and rotavirus infection <i>Clostridium difficile</i>	Amebic colitis* Cholera† <i>E. coli</i> O157** Cryptosporidiosis Cyclosporiasis Strongyloidiasis Ebola virus disease††

*Typically with bloody diarrhea; diagnosis can be made when hematophagous trophozoites are found in stool.

†Cholera is endemic in West Africa [5]. Notified outbreaks are published in the WHO Weekly Epidemiological Record (www.who.int/wer/en/index.html). Reported in ProMED (www.promedmail.org) as “acute watery diarrhea.”

**Single cases have been reported from Central Africa [6].

††Common gastrointestinal manifestations include diarrhea 70%, nausea and vomiting 60%, and abdominal pain 45% [7].

Chronic gastrointestinal infections with more than four weeks of symptoms

Infections with *Giardia intestinalis* and *Cryptosporidium* spp. may cause long-lasting, fluctuating gastrointestinal symptoms. Other intestinal parasites include hookworm infections, *Ascaris lumbricoides*, and *Trichuris trichiura*. Infection with *Strongyloides stercoralis* is common but sometimes asymptomatic. It may, however, cause unspecific intestinal symptoms in immunocompromised patients (HIV-infected patients). Schistosomiasis from *S. mansoni* may cause chronic gastrointestinal symptoms. Enterocolitis caused by *Entamoeba histolytica* may present both as an acute dysentery and more prolonged infection in the colon, mimicking inflammatory colitis.

Tuberculosis should always be considered in patients with long-lasting gastrointestinal symptoms. It is assumed that Whipple's disease is found in West Africa, but it has never been documented.

Diarrhea in the immunocompromised host

Giardia lamblia, cryptosporidia, *Cyclospora cayetanensis*, *Isospora belli*, and *Microsporidium* spp. should be considered. Other opportunistic infections include tuberculosis, intestinal cytomegalovirus infection, and *Mycobacteria avium intracellulare* infection.

Infections of liver, spleen, peritoneum

Acute infections of liver, spleen, peritoneum with less than four weeks of symptoms

	Frequently found disease	Rare diseases
Jaundice	Malaria* Hepatitis A Hepatitis B†	Hepatitis C Hepatitis E Rickettsiosis

(Continued)

	Frequently found disease	Rare diseases
	EBV, CMV infection Hepatitis E ^{§§}	Leptospirosis** Syphilis II Relapsing fever (<i>Borrelia recurrentis</i>) Visceral leishmaniasis ^{††} Gonococcal perihepatitis Ebola and Marburg fever Yellow fever CCHF and Lassa [§] Trypanosomiasis
Space-occupying lesion in liver Splenomegaly	Bacterial liver abscess Malaria Typhoid fever Bacterial endocarditis Viral hepatitis EBV, CMV	Amebic liver abscess Trypanosomiasis Visceral leishmaniasis Relapsing fever Dengue Brucellosis Tuberculosis
<p>* Slight hemolytic jaundice is frequent. [†] Predominantly genotypes A and E. ^{**} Not much data available, but leptospirosis is found worldwide [8]. ^{††} Rare in West Africa [§] CCHF is probably present but data are scarce. Lassa fever is common in eastern Sierra Leone. ^{§§} Not reported but probably present.</p>		

Chronic infections of liver, spleen, peritoneum with more than four weeks of symptoms

	Frequently found disease	Rare diseases
Jaundice	Chronic viral hepatitis Schistosomiasis*	Brucellosis Q-fever hepatitis Toxocariasis Hepatic tuberculosis [†] Leprosy** Histoplasmosis
Space-occupying lesion in liver	Amebic liver abscess	Tuberculosis Melioidosis
Ascites Splenomegaly	Tuberculous peritonitis Hepatosplenic schistosomiasis Hyperreactive malaria syndrome ^{††d}	<i>Schistosoma mansoni</i> Tuberculosis Brucellosis
<p>* Hepatic schistosomiasis is most often due to <i>S. mansoni</i>. [†] Hepatic TB may occur as miliary, nodular, and solitary abscess forms. ^{**} Granulomatous hepatitis may be seen in patients with lepromatous leprosy. ^{††} Abnormal immunological reaction to <i>Plasmodium</i> infection, huge splenomegaly >10 cm below costal margin, and response to antimalarial drugs are the cornerstones of the diagnosis.</p>		

Infections of liver, spleen, peritoneum in the immunocompromised host

Infections in the immunocompromised host are no different from the immunocompetent host.

Genitourinary infections

Cystitis, pyelonephritis, and nephritis with less than four weeks of symptoms

Uropathogenic *E. coli* are the most common cause of infection in patients with normal urinary tract anatomy.

Acute and chronic sexually transmitted diseases with less than four weeks of symptoms

	Frequent diseases	Rare diseases
Urethritis and discharge	Gonorrhea	Mycoplasma urethritis
Genital ulcers	Chlamydial urethritis	Granuloma inguinale (<i>Klebsiella granulomatis</i>)*
	Trichomoniasis	
	Syphilis	
	Ulcus molle (chancroid caused by <i>Haemophilus ducreyi</i>)	
	Genital herpes	Lymphogranuloma inguinale (<i>Chlamydia trachomatis</i>)

*The painless genital ulcers can easily be mistaken for syphilis.

Cystitis, pyelonephritis, and nephritis with more than four weeks of symptoms

In patients from West Africa with chronic genitourinary infections, tuberculosis and *Schistosoma haematobium* infection must be considered. *S. haematobium* may cause hematuria and hemospermia [9].

Hydrocele can occur in Bancroftian filariasis. Testicular enlargement may occur in mumps, filariasis, and erythema nodosum leprosum. Chronic epididymoorchitis is seen in TB and syphilis.

Cystitis, pyelonephritis, and nephritis infections in the immunocompromised host

Infections in the immunocompromised host are similar to those in the immunocompetent host.

Patients with sickle cell disease are at increased risk for urinary tract infection.

Urinary tract infections in HIV-positive patients are more frequent than in uninfected patients. Necrotizing fasciitis of the genitalia (Fournier's gangrene) may develop. Impairment of kidney function is usually caused by HIV-associated nephropathy, arising from direct infection of the renal cells with the HIV-1 virus or changes in the release of cytokines during HIV infection.

Sexually transmitted diseases in the immunocompromised host

Sexually transmitted disease causes in the immunocompromised host are no different from those in the immunocompetent host.

Infections of bone, joints, and muscles

Acute infections of bone, joints, and muscles with less than four weeks of symptoms

	Frequently found disease	Rare diseases
Osteoarthritis	Septic arthritis Gonococcal arthritis Rheumatic fever Chikungunya, dengue, Zika virus*	Brucellosis <i>Histoplasma duboisii</i> infection Leprosy
Osteomyelitis	Acute hematogenous osteomyelitis†	
Myositis ^c	Pyomyositis** Other bacterial myositis Group A streptococcal necrotizing myositis Acute rhabdomyolysis††	Trichinosis Gas gangrene (<i>Clostridium perfringens</i>)

*Viral arthritis is typical in chikungunya and can mimic seronegative rheumatoid arthritis. Dengue affects tendons, muscles, joints, and bones. Polyarthralgia in dengue fever is rare.
 †Most often *S. aureus*, rarely streptococci and Enterobacteriaceae; in sickle cell disease often salmonella.
 **Pyomyositis is defined as an acute intramuscular bacterial infection which is neither secondary to a contiguous infection of the soft tissue or bone nor due to penetrating trauma. Infections result from hematogenous spread and are usually due to *S. aureus*.
 ††Seen in leptospirosis, pneumococcal sepsis, echovirus infections, and malaria. Snake bite is a differential diagnosis.

Chronic infections of bone, joints, and muscles more than four weeks of symptoms and in the immunocompromised host

Tuberculosis should always be considered; additionally, consider mycobacteria other than tuberculosis (MOTT) in the immunocompromised patient. Leprosy, brucellosis, actinomycosis, and nocardiosis are rare causes of arthritis and osteomyelitis.

Patients with hemoglobinopathies like sickle cell disease and thalassemia have a high risk of osteomyelitis due to episodes of microthrombosis, osteonecrosis, and secondary infections.

In the immunocompromised host, HIV-associated arthritis should be considered. Rare causes, mainly in immunocompromised patients, are infections with *Histoplasma duboisii*, *Cryptococcus neoformans*, and microsporidia.

Infections of skin and soft tissues

Skin infections

	Frequently found disease	Rare diseases
Maculopapular	Dengue, EBV, CMV, acute HIV infection, syphilis	Rickettsiosis Relapsing fever
Papular, vesicular	Varicella, herpes simplex, molluscum contagiosum	
Papular and petechia	Meningococcal sepsis	Leptospirosis
Papillomatous		Yaws [10]
Chancre, erythematous		Trypanosomiasis

	Frequently found disease	Rare diseases
Hematoma	Meningococcal sepsis	Viral hemorrhagic fevers
Ulcer	Buruli ulcer	Cutaneous leishmaniasis*
	Tropical ulcer	Cutaneous diphtheria
Subcutaneous nodules†	Cysticercosis	Syphilitic gumma
	Onchocerciasis**	
Itching	Filariasis	
	Onchocerciasis	
	Scabies	
	Lice	
Multiple manifestations		Leprosy

*A new subspecies of Leishmania, *Leishmania enriettii*, has been isolated from patients from Ghana with cutaneous leishmaniasis [11].

†Buruli ulcer may initially present as a subcutaneous nodule – rarely diagnosed in this stage.

**Onchocerciasis is widespread in West Africa. Since the WHO-sponsored Onchocerciasis Control Program ceased to operate, the infection is returning.

Soft tissue infections

Cellulitis and subcutaneous tissue infections including necrotizing fasciitis are frequently encountered.

Subcutaneous mycosis frequently seen: chromoblastomycosis characterized by vegetative and verrucal lesions which occur predominantly on the lower limbs; mycetomas are chronic, inflammatory swellings with numerous sinuses, caused by molds or bacteria (in Africa predominantly eumycetomas, often caused by *Madurella mycetomatis*); entomophthoromycosis is slowly progressing infection of the subcutaneous tissue or paranasal sinuses caused by *Conidiobolus coronatus*, leading to grotesque deformation of the face. The distribution of sporotrichosis in West Africa is not well known, but single cases have been reported.

Skin infections in the immunocompromised host

Skin infections that particularly affect HIV patients include herpes simplex, zoster, molluscum contagiosum, dermatophytosis, unusual forms of scabies, cryptococcosis, histoplasmosis, and staphylococcal folliculitis (papular pruritic eruption). Bacillary angiomatosis is only rarely reported. Leprosy should always be kept in mind, especially in patients with neuropathy.

Lymphadenopathy

Acute lymphadenopathy with less than four weeks of symptoms

	Frequently found disease	Rare diseases
Localized	Mycobacterial adenitis Rickettsia	Lymphatic filariasis Lymphogranuloma inguinale, chancroid, granuloma inguinale Rubella Trypanosomiasis*

(Continued)

	Frequently found disease	Rare diseases
Generalized	HIV infection CMV and EBV infection Measles Toxoplasmosis	Leprosy [†] Plague Brucellosis Histoplasmosis Secondary syphilis Tuberculosis Rickettsiosis including Q-fever

*Typically enlargement of posterior cervical lymph nodes (Winterbottom's sign).
[†]As part of reactional state in erythema nodosum leprosum.

Chronic lymphadenopathy

Tuberculosis, filariasis, and brucellosis should be considered. Kala azar (visceral leishmaniasis) patients present signs of parasitic invasion of the reticuloendothelial system, such as enlarged spleen and liver, but enlarged lymph nodes are rare.

HIV tests are mandatory in patients with chronic enlarged lymph nodes and biopsy is needed to rule out lymphoma and obtain a sample for culture and susceptibility tests in tuberculosis.

Fever without focal symptoms

Acute fever with less than four weeks of symptoms

Frequently found disease	Rare diseases	Very rare diseases
Malaria Typhoid fever Sepsis Unspecific viral infection, influenza, dengue, chikungunya, Zika virus infections Endocarditis	Amebic liver abscess* Rickettsiosis [†] CMV, EBV, acute HIV	Relapsing fever Trypanosomiasis Viral hemorrhagic fever**

*Rarely without pain in the upper abdomen.
[†]Rickettsioses (tick typhus) in West Africa mainly from spotted fever group, predominantly *R. africae* [12]. Symptoms include fever but also eschars, maculopapular or vesicular rash, and lymphadenopathy. No data concerning ehrlichiosis exist from West Africa [12].
 ** May begin with monosymptomatic fever. In the recent outbreak in West Africa, hemorrhagic symptoms were seen only in a minority of patients.

Chronic fever more than four weeks of symptoms in immunocompetent and immunocompromised patients

The differential diagnosis of prolonged pyrexia is long: HIV, malaria, tuberculosis, enteric fever, visceral leishmaniasis, pneumonia, urinary tract infection, abscesses, infective endocarditis, secondary syphilis, trypanosomiasis, and brucellosis. Noninfectious causes should be considered, especially malignancies and autoimmune diseases.

Eosinophilia

	Frequently found disease	Rare diseases
Asymptomatic	Intestinal worms <i>Strongyloides stercoralis</i> Schistosomiasis Filariasis	
With fever	Katayama syndrome	Acute <i>Fasciola hepatica</i> infection Trichinellosis
With subcutaneous swellings	Loiasis Onchocerciasis Cysticercosis	Paragonimiasis
With abdominal pain	Intestinal worms (<i>Ascaris lumbricoides</i> , <i>Necator americanus</i> , <i>Trichuris trichiura</i>) Toxocariasis (<i>Toxocara canis</i> and <i>T. cati</i>)	
With elevated transaminases	Toxocariasis (<i>Toxocara canis</i> and <i>T. cati</i>)	Fascioliasis
With pulmonary infiltrate	<i>Strongyloides stercoralis</i> Loöffler's syndrome Katayama fever	Paragonimiasis

Antibiotic resistance

Data are very limited on antibiotic resistance patterns from West Africa. ESBL is common [13]. Resistance rates across West Africa are variable: for *S. pneumoniae* resistance rates to penicillin, amoxicillin and erythromycin are very low and vary between none in Cote d'Ivoire to 3% in Nigeria [14]. Importantly, bacteremias due to *S. pneumoniae* remain sensitive to penicillin. Rates of macrolide resistance are similar (<4%). However, high-level resistance has been found to co-trimoxazole (17% Cote d'Ivoire, 83% Nigeria), which poses a major problem for its use in many treatment protocols for empiric therapy of both upper and lower respiratory infections. Beta-lactamase production by *H. influenzae* is variable (5% Cote d'Ivoire, 26% Senegal). *Gonococcus* resistance has been well documented, with a dramatic increase in both West and Central African penicillinase-producing strains, for example 73% of organisms in Abidjan and 65% of strains resistant to tetracycline [15]. Enteric organisms still appear to remain sensitive to ciprofloxacin and this is still recommended as first-line treatment, in contrast to Asian strains.

Children

Infections causing the greatest mortality in children under five years of age include pneumonia (21%), diarrheal disease (17%), malaria (17%), HIV/AIDS (7%), and measles (4%). These are linked directly to socioeconomic status but for pneumonia and measles, appropriate vaccine coverage would significantly reduce mortality and morbidity. Education and distribution of insecticide-treated bednets has been shown to significantly reduce deaths from malaria. The Extended Program of Immunization (EPI) cover in the region is variable (84–98% in Ghana, 39–50% in Nigeria). Rates vary within countries and with vaccine, for example there is greater uptake for BCG than MMR (WHO statistics).

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Chapter 13

East Asia

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Mongolia
South Korea
North Korea

The geography of infectious diseases in East Asia is diverse due to significant variations in climate (subtropical, temperate, and subarctic) as well as marked differences in environment, population density, and cultures. Socioeconomic changes have led to significant improvements in healthcare in Japan, South Korea, and China's major cities. Rural China and Mongolia continue to experience inequity in access to healthcare and public health measures, thus impacting the type and incidence of infectious diseases that occur in these areas.

Acute infections within four weeks of exposure

China is the world's most populous country with over 1.3 billion persons. Although the public health system has been improved by substantial investments from all levels of government, infectious diseases still remain a major population health issue and are influenced by rapid urbanization and climate change. At present, the migrant population searching for better employment opportunities in urban areas exceeds 221 million in China. Gonorrhoea, hepatitis, TB, malaria, and measles are the most frequently found microorganisms and diseases among migrant population from rural areas to big cities. The prevalence of human immunodeficiency virus (HIV) and TB is high within the Chinese mainland, and co-infection is increasing – 22.8% of AIDS patients are infected with TB [1].

Infectious Diseases: A Geographic Guide, Second Edition. Edited by Eskild Petersen, Lin H. Chen, and Patricia Schlagenhaupt-Lawlor.

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An increase of vector/rodent-borne diseases such as dengue fever, malaria, and hemorrhagic fever with renal syndrome is observed in some regions of China, which may be due to the warmer climates and inadequate facilities in cities. The prevalence of malaria is increasing in central parts of China (most cases are *vivax* malaria), but the region of southern China still maintains the highest incidence [2], and *Plasmodium falciparum* is only found in southern China in Yunnan and Hainan. China also accounts for 90% of the reported global cases of hemorrhagic fever with renal syndrome [3]. Although reported cases of Japanese encephalitis have decreased from 10308 in 1996 to 2541 in 2010 [4], Shaanxi, Chongqing, Sichuan, Guizhou, Henan, and Yunnan provinces have the highest prevalence in China (JE incidence >1/100000) [5].

Zoonoses such as avian influenza, rapidly reemerging brucellosis (6448 new cases in 2003 to 38151 in 2011) and high level of rabies (approximately 2000 annual cases) are also a significant public health problem. In 2013, 136 people were infected with avian influenza H7N9, and more than one-third of these patients died [6]. A wide range of infectious diseases such as syphilis, neonatal tetanus, schistosomiasis, Crimean-Congo hemorrhagic fever, tick-borne encephalitis, clonorchiasis, and other food- and soil-borne helminthiasis associated with poverty or lifestyle are found in different regions.

Vaccine-preventable infections such as hepatitis A and B, typhoid, rabies, measles, and influenza are common in China. In 2014, 114890 new cases of hepatitis and 25477 influenza patients were reported [7].

Japan's healthcare infrastructure is well developed yet still faces potential threats from emerging infections such as avian influenza, HIV, tuberculosis, severe fever with thrombocytopenia syndrome (SFTS), and dengue. Dietary preferences for raw or undercooked fish and seafood can lead to food-borne helminthiasis such as anisakiasis, diphyllorthisiasis, angiostrongyliasis, larva migrans, and paragonimiasis. Three rickettsial diseases are endemic: Japanese spotted fever, scrub typhus (the most common), and Q-fever [8]. Japanese encephalitis is also endemic but has a very low prevalence following preventive measures including pediatric vaccinations. Malaria has been controlled since 1961. In recent years further cases of SFTS have been reported with a mortality of 27% [9]. An autochthonous dengue case was identified in August 2014, after 70 years of absence [10]. Then cases presumably contracted at the same park in Tokyo accumulated, finally giving a total of 160 domestically acquired dengue cases. Fortunately, there were no fatalities, and dengue fever was not seen in 2015.

South Korea's medical system has also significantly improved with fewer communicable diseases reported. There is risk, however, for food- and water-borne outbreaks due to changes in dietary habits and increasing levels of travel. A significant number of vaccine-preventable illnesses occur (in 2007 more than 20000 cases of chickenpox; 118% increase in mumps) [11]. Since 1986, *vivax* malaria has reemerged in the demilitarized zone and is currently limited to rural areas in northern Kyonggi and Kangwon provinces believed to originate from North Korea. Measles importation and limited transmission to local areas still occur in South Korea, and measles incidence was 0.93 cases/1000000 people during 2008–13 [12]. The incidence of TB is 86 per 100000 person, and 2.7% are MDR-TB [13].

Data for infectious diseases in North Korea are limited but similar organisms present in South Korea and along the Chinese border are expected. Outbreaks of communicable diseases may be influenced by factors such as malnutrition and poverty. As with South Korea, *P. vivax* malaria reemerged in 1986 and is found in the southern part of the country towards the demilitarized zone.

Historically, Mongolia has had a nomadic or semi-nomadic population with a close association with livestock. Recently, the rural population has been moving into the capital city, Ulaan-Baatar. Respiratory and diarrheal diseases are common, as is brucellosis [14]. Sexually transmitted infections (40.3%), viral hepatitis (23.7%), and tuberculosis (9.6%) are the most commonly reported infections [8], and an increase of syphilis has been observed (71 per 100000 in 2001 to 152 per 100000 in 2011) [15]. Other important but less common diseases are echinococcosis, plague, tularemia, anthrax, and rabies [11].

The following tables outline many of the infectious diseases in East Asia. It is important to keep in mind the changing nature of this region and the impact this may have on infectious disease patterns.

CNS infections: meningitis, encephalitis, and other infections with neurological symptoms

Acute infections with less than four weeks of symptoms

Frequently found microorganisms	Less common microorganisms and disease
Enteroviruses*	<i>Treponema pallidum</i>
<i>Streptococcus pneumoniae</i>	<i>Brucella</i> spp.†
<i>Streptococcus agalactiae</i> **	<i>Listeria monocytogenes</i>
<i>Haemophilus influenzae</i> type b††	Rabies§
<i>Neisseria meningitidis</i> §§	Influenza viruses
Japanese encephalitis virus¶	Tick-borne encephalitis¶¶
Herpes simplex I and II	<i>Angiostrongylus cantonensis</i> #
<i>Mycobacterium tuberculosis</i>	Cerebral malaria##

*Leading cause of aseptic meningitis. Outbreaks of acute encephalitis due to EV-71 in China.
†High incidence in Mongolia, sporadic cases in South Korea and Japan.
**Most common type of bacterial meningitis in neonates.
††Most common childhood meningitis in Mongolia [16].
§Japan considered rabies-free; 2500 cases reported by China CDC in 2007.
§§Rare in Japan.
¶Highly endemic in China. Low annual incidence in Japan and South Korea but high reported prevalence of JEV-positive pigs. Not endemic in Mongolia.
¶¶Northeast China, Japan (Hokkaido). First reported case in US traveler 2007 in Tianjin, China [17]; the first case was found in Japan in 1993, followed by the second case in 2016.
#Associated with ingestion of raw fish and snails in China, south Japan, and Korea. Outbreak in Beijing in 2006.
##*P. falciparum* is endemic in Yunnan and Hainan, China.

CNS infections with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
HIV	<i>Nocardia</i>
<i>Mycobacterium tuberculosis</i>	Polyoma virus*
<i>Cysticercus cellulosae</i>	<i>Cryptococcus</i> spp.
	<i>Toxoplasma gondii</i>

*Include JC virus and BK virus.

Ear, nose, and throat infections

Ear, nose, and throat infections with less than four weeks of symptoms

Frequently found microorganisms	Less common microorganisms and conditions
Enterovirus (Coxsackievirus, echovirus, EV-71)	Peritonsillar abscess
Rhinovirus	Necrotizing fasciitis
Adenovirus, coronavirus	<i>Mycobacterium tuberculosis</i>
Influenza A and B, parainfluenza	<i>Staphylococcus aureus</i>
Respiratory syncytial virus	<i>Corynebacterium diphtheriae</i>
Measles virus	<i>Neisseria gonorrhoeae</i>
Rubella virus [†]	<i>Chlamydia trachomatis</i>
Epstein–Barr virus	<i>Legionella</i> spp.
Varicella zoster virus	Cytomegalovirus
<i>Haemophilus influenzae</i> type b*	HIV
<i>Moraxella catarrhalis</i>	
<i>Mycoplasma pneumoniae</i>	
<i>Chlamydia</i> spp.	
Streptococcal spp.	
Herpes simplex I and II	

[†]Rubella not included in all regions of China's national vaccination program with epidemics every 6–8 years.
*More common in China, Mongolia, and North Korea due to lack of vaccination against *H. influenzae* type b.

Ear, nose, and throat with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i>	<i>Candida</i> spp.
Epstein–Barr virus	<i>Aspergillus</i> spp.
Cytomegalovirus	Herpes simplex I and II
	Cytomegalovirus
	Human herpes virus 8*

*Associated with Kaposi's sarcoma.

Cardiopulmonary infections

Pneumonia with less than four weeks of symptoms

Frequently found microorganisms	Less common microorganisms and diseases
<i>Streptococcus pneumoniae</i>	<i>Legionella</i> spp.
<i>Klebsiella pneumoniae</i>	<i>Burkholderia pseudomallei</i> *

Frequently found microorganisms	Less common microorganisms and diseases
<i>Haemophilus influenzae</i> <i>Moraxella catarrhalis</i> <i>Mycoplasma pneumoniae</i> <i>Staphylococcus aureus</i> <i>Chlamydia pneumoniae</i> Influenza, parainfluenza, Respiratory syncytial virus (RSV)	<i>Staphylococcus aureus</i> <i>Orientia tsutsugamushi</i> [†] (scrub typhus) <i>Leptospira interrogans</i> ** <i>Paragonimus westermanii</i> ^{††} <i>Gnathostoma spinigerum</i> [§] <i>Bacillus anthracis</i> (anthrax) RSV <i>Mycobacterium tuberculosis</i> <i>Yersinia pestis</i> (pneumonic plague) ^{§§} Dengue hemorrhagic fever [¶] Nontuberculous mycobacteria (<i>Mycobacterium kansasii</i>) ^{¶¶} <i>Salmonella</i> spp. [#] <i>Acinetobacter baumannii</i> * SARS-corona virus <i>Coxiella</i> spp. ^{##}
<p>Southern China (Hainan, Fujian, Guangdong, Taiwan). [†]Caused by bite of infected chigger mites in China, Korea, and Japan. **Increased incidence in China; decreasing in Korea and Japan. ^{††}Food-borne trematode, endemic in southern Japan, Korea, and central China. [§]Japan, Korea, and China. ^{§§}Mongolia and China (Qinghai Province, Xinjiang, and Yunnan). [¶]Rare cases reported in south China [18]. ^{¶¶}Korea. [#]China. ^{##}Less than 10 indigenous cases reported in Japan.</p>	

Endocarditis with less than four weeks of symptoms

Frequently found microorganisms	Less common microorganisms and disease
<i>Staphylococcus aureus</i> <i>Streptococcus viridians</i> and <i>S. bovis</i> Coagulase-negative staphylococci (<i>S. epidermidis</i>) <i>Streptococcus pneumoniae</i> <i>Enterococcus</i>	<i>Neisseria gonorrhoeae</i> <i>Bartonella quintana</i> <i>Coxiella burnetii</i> <i>Brucella</i> <i>Propionibacterium acnes</i> <i>Haemophilus</i> spp., <i>Actinobacillus</i> <i>actinomycetemcomitans</i> , <i>Cardiobacterium</i> <i>hominis</i> , <i>Eikenella corrodens</i> , and <i>Kingella</i> spp. (HACEK group) <i>Pseudomonas aeruginosa</i> <i>Candida</i> spp.

Pulmonary symptoms for more than four weeks and in the immunocompromised host

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms and diseases in the immunocompromised host
<i>S. pneumoniae</i> <i>M. catarrhalis</i> (sinuses) <i>H. influenzae</i>	<i>Pneumocystis jiroveci</i> Cytomegalovirus Deep mycoses (<i>Candida</i> , <i>Cryptococcus</i> , mucormycosis, <i>Aspergillus</i> , <i>Nocardia</i> , actinomycosis)
<i>S. aureus</i> <i>M. tuberculosis</i> <i>M. kansasii</i> , <i>Mycobacterium avium</i> complex <i>P. aeruginosa</i> <i>Aspergillus</i> spp. <i>Histoplasma capsulatum</i> * <i>Cryptococcus</i> spp.† <i>Echinococcus granulosus</i> and <i>E. multilocularis</i>	<i>Histoplasma capsulatum</i> * <i>M. tuberculosis</i> Nontuberculous mycobacteria <i>Rhodococcus equi</i> <i>P. aeruginosa</i> <i>Nocardia</i> spp.
*South-east China (Hainan, Fujian, Guangdong, Taiwan). †71% of clinical strains in China (1985–2006) were from patients with no apparent risk factors [19].	

Endocarditis for more than four weeks and in the immunocompromised host

The causative organisms can be any of those listed in the endocarditis table above. This may occur most commonly in cases of subacute endocarditis as progressive symptoms may develop over weeks to months.

Gastrointestinal infections

Gastrointestinal infections with less than four weeks of symptoms

Frequently found microorganisms and diseases	Less common microorganisms, conditions, and diseases
Norovirus and calicivirus Rotavirus Enterotoxigenic <i>Escherichia coli</i> * Shiga toxin-producing <i>E. coli</i> <i>Shigella</i> spp.** <i>Salmonella</i> , non-typhi†† <i>Vibrio parahaemolyticus</i> <i>Salmonella typhi</i> and <i>S. paratyphi</i> §§ <i>Campylobacter</i> spp. <i>Bacillus cereus</i> toxin#	<i>Entamoeba histolytica</i> <i>Giardia intestinalis</i> * <i>Cryptosporidium</i> spp. <i>Diphyllobothrium</i> spp.† <i>Anisakis</i> <i>M. tuberculosis</i> <i>Streptococcus suis</i> § <i>Vibrio cholerae</i> ¶ <i>V. parahaemolyticus</i> ¶¶ <i>Fasciolopsis buskii</i> (giant intestinal fluke)## <i>Strongyloides stercoralis</i> <i>Taenia saginata</i>

Frequently found microorganisms and diseases	Less common microorganisms, conditions, and diseases
<p><i>Enterobius vermicularis</i>, other helminths Hookworm (<i>Ancylostoma duodenale</i>, <i>Necator americanus</i>) <i>Taenia solium</i></p>	
<p>*Rare in Japan. †Cestode acquired by ingesting raw or undercooked fish, more common in Japan. **<i>Shigella flexneri</i> is a common bacterial pathogen in Mongolia. ††Common in Mongolia during summer months. §Outbreak in Sichuan, China (2005) with 215 reported cases. §§More common in China; infrequent in Mongolia, Japan. ¶Endemic in China, Korea. Outbreak in Selenge Province, Mongolia, 1996. ¶¶Sporadic cases, common source outbreaks in Japan. #Commonly associated with improperly stored cooked rice. ##China.</p>	

Gastrointestinal infections with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<p><i>A. lumbricoides</i> <i>Trichuris trichiura</i> Hookworm spp. (<i>N. americanus</i> and <i>A. duodenale</i>)* <i>Helicobacter pylori</i>† <i>T. solium</i> and <i>T. saginata</i> <i>S. stercoralis</i> <i>M. tuberculosis</i> <i>Tropheryma whipplei</i> (Whipple's disease) <i>Giardia intestinalis</i> <i>Fasciolopsis buskii</i> (giant intestinal fluke)**</p>	<p><i>Candida</i> spp. Herpes simplex I <i>Cryptosporidium parvum</i> and <i>hominis</i> Cytomegalovirus <i>M. tuberculosis</i> <i>Isospora belli</i> <i>Microsporidium</i> spp. <i>E. histolytica</i> <i>Strongyloides stercoralis</i> <i>Cyclospora cayatanensis</i>††</p>
<p>*39 million reported cases in China in 2006; associated with poverty and tropical/subtropical climates. †Decreased prevalence with improved socioeconomic conditions; associated with gastric carcinoma and peptic ulcer disease. **China. ††Endemic in China; rare cases reported in Japan.</p>	

Infections of liver, spleen, and peritoneum

Acute infections of liver and biliary tract with less than four weeks of symptoms

Frequently found microorganisms and disease	Less common microorganisms and diseases
Hepatitis A	Hepatitis D
Hepatitis B*	Hepatitis E
Hepatitis C	Amebic liver abscess
Epstein–Barr virus	Dengue virus [†]
Cytomegalovirus	<i>Leptospira</i>
<i>Clonorchis sinensis</i> **	Herpes simplex virus
<i>Brucella</i> ^{††}	Crimean-Congo hemorrhagic fever [§]

High incidence in Mongolia; decreasing in China and Korea with vaccination programs.
[†]Southern China.
^{**}Estimated 30 million persons infected worldwide, mostly in China; more than 2 million cases in Korea from 1974 to 1982; decreasing in Japan; associated with cholangiocarcinoma.
^{††}1000–1500 cases reported per year in Mongolia.
[§]Xinjiang, China.

Chronic infections of the liver and biliary tract

Frequently found microorganisms	Less common microorganisms and diseases
Chronic hepatitis B or C	<i>Brucella</i> spp.
<i>Schistosoma japonicum</i> *	<i>C. burnetii</i> (Q-fever)
<i>Clonorchis sinensis</i>	<i>Echinococcus granulosus</i> and <i>multilocularis</i> [†]
<i>Toxocara canis</i> and <i>cati</i>	

*Common in Yangtze River basin; decreased by 90% in past 50 years; still endemic in 110 counties (up to 1% prevalence) [20].
[†]China, Mongolia, and northern Japan, and *E. granulosus* occurs only very rarely in Japan.

Infections of liver and biliary tract in the immunocompromised host

Similar microorganisms can be found in both immunocompetent and immunocompromised individuals.

Genitourinary infections

Cystitis, pyelonephritis, and nephritis with less than four weeks of symptoms

Frequently found microorganisms	Less common microorganisms and diseases
<i>E. coli</i>	Hantavirus (hemorrhagic fever with renal syndrome)*
<i>Klebsiella pneumoniae</i>	<i>Enterococcus</i> spp.
<i>S. aureus</i>	<i>Ureaplasma</i>
<i>P. aeruginosa</i>	<i>Mycoplasma</i>
<i>Proteus</i> spp.	<i>M. tuberculosis</i>

Frequently found microorganisms	Less common microorganisms and diseases
<i>S. saprophyticus</i> [†]	<i>L. interrogans</i> Adenovirus
*20 000–50 000 reported cases per year in China; 1 000 cases per year in South Korea; no reports of this disease in Japan recently; not found in Mongolia.	
[†] In Japan, cystitis due to <i>S. saprophyticus</i> occurs often, especially among sexually active women.	

Sexually transmitted infections with less than four weeks of symptoms

Frequently found microorganisms and disease	Less common microorganisms and diseases
<i>C. trachomatis</i> <i>N. gonorrhoeae</i> Primary syphilis* <i>Mycoplasma spp.</i> Human papillomavirus <i>Trichomonas vaginalis</i> Molluscum contagiosum	<i>Haemophilus ducreyi</i> Lymphogranuloma venereum <i>E. histolytica</i> <i>Pediculosis pubis</i> Scabies
*Syphilis was nearly eliminated in China (1950s); 10-fold increase in last decade with 278 215 reported cases and 9 480 reported cases with congenital syphilis (2008). Most commonly reported communicable disease in Shanghai (2008) [21]; increasing in Mongolia (2008) [14].	

Cystitis, pyelonephritis, and nephritis with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Proteus spp.</i> <i>Enterobacter spp.</i> <i>P. aeruginosa</i> <i>Mycoplasma spp.</i> <i>M. tuberculosis</i>	<i>Candida spp.</i> <i>M. tuberculosis</i> <i>Corynebacterium spp.</i>

Sexually transmitted infections with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Human papilloma virus <i>T. pallidum</i> HIV*	Human papilloma virus Molluscum contagiosum HIV
*Low prevalence in Mongolia (820 HIV positive, 2009) but at increased risk due to changes in travel, lower age population, and increased sexually transmitted infections. Estimated 740 000 HIV positive in China (2009) with 70–80% in Yunnan, Guangxi, Henan, Sichuan, Xinjiang, and Guangdong; almost 13 000 HIV positive in South Korea 2008 (UNAIDS); around 1 500 cases of HIV infection are newly reported each year in Japan. No report available for North Korea.	

Joint, muscle, and soft tissue infections

Joint, muscle, and soft tissue infections with less than four weeks of symptoms

Frequently found microorganisms and diseases	Less common microorganisms and diseases
<i>Staphylococcus aureus</i> <i>Streptococcus pneumoniae</i> , <i>Streptococcus</i> spp. Parvovirus B19 Rubella	Cysticercosis* <i>Trichinella spiralis</i> <i>N. gonorrhoeae</i> <i>H. influenzae</i> Human <i>Sarcocystis</i> <i>Salmonella</i> spp. <i>Brucella</i> <i>Clostridium tetani</i> (tetanus)†
*China and Mongolia. †More common in rural China, mostly neonatal tetanus.	

Joint, muscle, and soft tissue infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms and disease with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Borreliosis (Lyme disease)* <i>M. tuberculosis</i> <i>Brucella</i>	<i>Candida</i> spp.
*Endemic in China and Mongolia.	

Skin infections

Skin infections with less than four weeks of symptoms

Frequently found microorganisms	Less common microorganisms and diseases
<i>Staphylococcus aureus</i> Group A streptococcus <i>Tinea</i> spp. Scabies Herpes viruses <i>Candida</i> spp. <i>S. pneumoniae</i>	Cutaneous anthrax <i>Borrelia</i> spp. <i>Spirillum minus</i> and <i>Actinobacillus muris</i> (ratbite fever)* Cutaneous leishmaniasis† <i>Mycobacterium ulcerans</i> <i>O. tsutsugamushi</i> (scrub typhus)** <i>Sparganium mansonii</i> (sparganosis)†† Cutaneous larva migrans§ <i>Rickettsia heilongjiangensis</i> (Far Eastern spotted fever)§§

Frequently found microorganisms	Less common microorganisms and diseases
	<i>Rickettsia japonica</i> (Japanese spotted fever) [§] <i>Rickettsia siberica</i> (North Asian tick typhus) <i>Rickettsia typhi</i> (murine typhus)
<p>*There are cases but very rare in Japan. [†]Xinjiang Uygur Autonomous Region, China. ^{**}Seasonal autumn outbreaks in north China, Korea; summer in south China; summer and autumn in Japan. [§]Southern China. ^{§§}North-east China. [¶]241 reported cases in Japan (2014). ^{¶¶}North China and Mongolia.</p>	

Skin infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms and diseases in the immunocompromised host
<i>T. pallidum</i> <i>M. tuberculosis</i> Human herpes virus 8 (Kaposi's sarcoma) <i>Mycobacterium leprae</i> * <i>Wuchereria bancrofti</i> (lymphatic filariasis) [†]	<i>Candida</i> spp. Human herpes virus 8 (Kaposi's sarcoma) Nontuberculous mycobacteria Deep fungal infections <i>M. tuberculosis</i>
<p>*Approximately 10 cases reported per year in Japan, recently, three or less indigenous cases are reported annually in Japan. [†]Lymphatic filariasis has recently been eliminated in China; South Korea close to elimination [11].</p>	

Adenopathy

Adenopathy of less than four weeks

Frequently found microorganisms	Less common microorganisms and diseases
Epstein-Barr virus Cytomegalovirus Parvovirus B19 HIV <i>Toxoplasma gondii</i> Suppurative staphylococcal or streptococcal infections	<i>Francisella tularensis</i> (tularemia) <i>B. quintana</i> <i>Ehrlichia</i> * <i>Babesia</i> [†]
<p>*China. [†]Korea.</p>	

Adenopathy of more than four weeks duration and in the immunocompromised host

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms and diseases in the immunocompromised host
<i>Toxoplasma gondii</i> <i>M. tuberculosis</i> HIV	Cytomegalovirus Epstein–Barr virus HIV <i>M. tuberculosis</i> Nontuberculous mycobacteria Deep fungal infections

Fever without focal symptoms

Fever less than four weeks without focal symptoms

Frequently found microorganisms	Less common microorganisms and diseases
Endocarditis Epstein–Barr virus Cytomegalovirus <i>Toxoplasma gondii</i> HIV Parvovirus B19	<i>Brucella</i> <i>M. tuberculosis</i> <i>C. burnetii</i> Dengue virus* <i>Plasmodium</i> spp.† <i>F. tularensis</i> (tularemia) <i>Babesia</i> <i>Ehrlichia</i> <i>O. tsutsugamushi</i> and other rickettsiae <i>R. japonica</i> ** <i>S. typhi</i> and <i>S. paratyphi</i> Bunyavirus††

*Southern China.
 †Southern China, Korea.
 **Western Japan, Korea.
 ††China [22] (severe fever with thrombocytopenia syndrome).

Fever for more than four weeks without focal symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Toxoplasma gondii</i> <i>M. tuberculosis</i> HIV	Cytomegalovirus Epstein–Barr virus <i>M. tuberculosis</i>

Eosinophilia and elevated IgE

Eosinophilia and elevated IgE for less than four weeks

Frequently found microorganisms	Less common microorganisms and diseases
<i>Ascaris lumbricoides</i> and <i>suum</i>	<i>S. japonicum</i>
Hookworm spp. (<i>N. americanus</i> and <i>A. duodenale</i>)	<i>Gnathostoma spinigerum</i> *
<i>T. solium</i> and <i>T. saginata</i>	<i>Strongyloides stercoralis</i>
<i>Toxocara</i> spp.	<i>Angiostrongylus cantonensis</i>
<i>Trichuris trichiura</i>	<i>Anisakis</i> spp.
<i>Clonorchis sinensis</i>	<i>Paragonimus</i> spp.

*Korea, Japan, and China.

Eosinophilia and elevated IgE for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Ascaris lumbricoides</i> and <i>suum</i>	<i>Ascaris lumbricoides</i> and <i>suum</i>
Hookworm spp. (<i>N. americanus</i> and <i>A. duodenale</i>)	Hookworm spp. (<i>N. americanus</i> and <i>A. duodenale</i>)
<i>T. solium</i> and <i>T. saginata</i>	<i>T. solium</i> and <i>T. saginata</i>
<i>Toxocara</i> spp.	<i>Toxocara</i> spp.
<i>Trichuris trichiura</i>	<i>Trichuris trichiura</i>
<i>Clonorchis sinensis</i>	<i>Clonorchis sinensis</i>
<i>Schistosoma japonicum</i>	<i>Schistosoma japonicum</i>
<i>Gnathostoma spinigerum</i>	<i>Gnathostoma spinigerum</i>
<i>Strongyloides stercoralis</i>	<i>Strongyloides stercoralis</i>
<i>Anisakis</i>	<i>Anisakis</i>
<i>Paragonimus</i> spp.	<i>Paragonimus</i> spp.
	<i>Angiostrongylus cantonensis</i>

Antibiotic resistance

Resistance in pneumococci

Based on the revised CLSI, fully resistant nonmeningeal pneumococci are only reported in China (2.2%) and Korea (0.3%), but 60–83.3% of meningeal pneumococcal isolates are resistant to penicillin. China is the leader of macrolide resistance (96.4%), followed by South Korea (77.7%), and Japan (61.1%). The prevalence rate of MDR pneumococcal isolates is also highest in China (83.3%), and the most common pattern of MDR is resistance to cefuroxime, erythromycin, clindamycin, and co-trimoxazole. Only 0–6.5% isolates are resistant to fluoroquinolones (levofloxacin, moxifloxacin, gatifloxacin) in north-east Asia, and moxifloxacin is the most effective drug for pneumococci [23].

Salmonella

The resistance in *Salmonella* is increasing in China, and the rate of all *Salmonella* isolates resistant to ciprofloxacin is 11.1%; 30–40% of *Salmonella* spp. are intermediately resistant [24]. In a multicenter surveillance study from China, *S. enteritidis* (31.4%) and *S. typhimurium* (27.3%) were the most prevalent serotypes among nontyphoidal *Salmonella* (NTS), and a high prevalence of resistance for nalidixic acid (67.8%), sulfamethoxazole (50.4%), tetracycline (42.7%), ampicillin (41.4%), and streptomycin (39.6%) is observed; 23% of nalidixic acid-resistant *Salmonella* isolates are resistant to ciprofloxacin [25].

Enterobacteriaceae and *E.coli*

In China, the ESBL-positive rates of *E. coli* and *K. pneumoniae* are 68.2% and 43.7%, and MDR is 79% and 57.1% respectively [11]. ESBL (+) *E. coli* strains are much more likely to be found in ICU or urinary surgery wards [26], and the resistance to ciprofloxacin (74%), gentamicin (69.5%), and levofloxacin (63%) is higher. The resistance of *P. aeruginosa* to fluoroquinolones, imipenem, and polymyxin is 25%, 29%, and <10% respectively [24]. In Japan, among the three most common ESBL-producing organisms (*Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*), *P. mirabilis* often shows the highest percentages of antibiotic resistance (even up to 50%) [27]. In addition, quinolone-resistant *E. coli* is also rapidly expanding, found in 12–30% of isolates from complicated cystitis cases according to a study in 2008 [28]. Carbapenem-resistant Enterobacteriaceae (CRE) are increasing in Asia. In China, 1.4% of Enterobacteriaceae isolates are resistant to imipenem (higher than the average rate of 0.7%), and Japan shows the lowest rate (0.2%). The resistance rate of *E. coli* to imipenem (0.2%) is lowest among all the Enterobacteriaceae genera (0.8%) [29].

Resistance in TB

According to the WHO, in 2013, 300 000 cases of MDR were identified, and more than half the cases were in India, China and the Russian Federation. In the latest report from the WHO (2015) [30], 5.7% of new cases and 26% retreatment cases from China were MDR, and the rate of successful treatment is only about 42%. Among the MDR isolates, 8.3% of new cases and 8% previously treated cases have XDR-TB [31]. In Mongolia, MDR was found in 7.5%, with respectively 27.5% and 1.4% of patients with and without prior history of treatment [32]. The prevalence of MDR-TB/XDR-TB is relatively lower in other north-east Asia countries [33]. In Japan, MDR tuberculosis was found in 0.81% of newly registered tuberculosis cases in 2009, and the cure rate was around 50–60% [34].

Malaria

The prevalence of malaria is low in north-east Asia; in China and South Korea, only 2921 cases and 638 cases was reported in 2014 respectively [35]. *P. falciparum* is the main species that is resistant to anti-malarial drugs. In Hainan, a province of south China, the resistance rates of chloroquine, piperaquine, pyronaridine, and artesunate detected *in vitro* were 71.9%, 40.6%, 12.5%, and 0%, respectively [36].

Methicillin-resistant *Staphylococcus aureus*

In the region, MRSA is highly prevalent in hospitals, but the incidence of CA-MRSA infection was much lower. In China, 76.9% of nosocomial-acquired *S. aureus* isolates are MRSA [37], while a more recent study shows that the rate of MRSA decreased from 73.6% in 2008 to 45% in 2012 [38]. In Japan and Korea, MRSA accounted for 8–34.8% of community *S. aureus* isolates. However, the prevalence rate of HA-MRSA is reported to be 56.8–77.6% [39,40]. An increase of vancomycin-intermediate *S. aureus* (VISA) and heterogeneous VISA (hVISA) has been observed in the last decade. Rates of hVISA in China, Korea, and Japan are 11.1–22.1%, 0.7–33.7%, and 0.6–6.5% respectively [41,42]. Vancomycin-resistant *S. aureus* has been reported in Korea [43].

Influenza

Adamantane-derived drugs have been used for influenza treatment for many years, but nearly all the H1N1, H1N1pdm-2009 and H3N2 are resistant. In the Chinese mainland, all H3N2 have been resistant to adamantane-derived drugs since 2003 and the percentage of adamantane-resistant H1N1 had increased to 98.7% in 2007 [44]. All the influenza B isolates in China [45] and the majority of H1N1pdm-2009 are susceptible to oseltamivir [46], although the NA amino acid substitution H275Y has been observed (in China and Japan) [47]. For seasonal influenza A, resistance is increasing. In a study in Japanese children, 18% of isolates were resistant to influenza A. Another research in Guangdong, China, demonstrated that resistance was higher than 95% to influenza A(H1N1) in 2009 [46].

Vaccine-preventable diseases in children

All countries in the region have pediatric vaccination programs. However, only Japan and Mongolia include *H. influenzae* type b vaccine in their routine vaccine program, and invasive pediatric cases such as meningitis and bacteremia are on the dramatic decrease, giving a 98% decrease rate in Japan [48]. Vaccines against *S. pneumoniae* are also generally unavailable, but the pneumococcal 13-valent conjugate vaccine became routine in 2013 in Japan, leading to a 56–61% decrease in invasive pneumococcal disease cases among children since then [48]. Japanese encephalitis vaccine is an important part of childhood immunizations in China, Japan, and South Korea and has greatly affected the incidence rate of this potentially fatal disease. Many north-east Asian countries are hyperendemic for hepatitis B, with the majority of transmissions at birth. The hepatitis B vaccine series is included in pediatric vaccination schedules in China, South Korea, North Korea, Mongolia and just recently, in Japan, too. Since 2008, hepatitis A vaccination has also been included in national routine immunization in China.

Varicella, human papilloma virus, influenza, and meningococcal vaccines also vary between country programs but are generally not included, except for meningococcal A or meningococcal A and C in China and meningococcal ACWY in Mongolia. All countries give a dose of BCG at birth to reduce the risk of meningeal or miliary tuberculosis and all give at least one measles vaccine dose. Mumps vaccine is not offered in North Korea.

Although the programs have been implemented, problems still occur. Surveillance in China shows an increased incidence rate of mumps i (22.5 per 100 000 in 2009 versus 33.9 per 100 000 in 2011), with children aged 5–6 years having the highest incidence rate [49]. Such resurgence is also observed in Korea [50]. In China, although the annual incidence of measles, in cases per 100 000 population, decreased from 9.95 in 2008 to 0.46 in 2012, it then rose to more than 1.96 in 2013 [51], and 40% are aged 8 months to 6 years. In recent years, outbreaks of measles are still reported in China [52–54] and Korea [55] but the “elimination” of measles was verified in March 2015 by WPRO-WHO [56]. In addition, Chinese researchers estimated the infection rate of pertussis was 7000–9395/100 000 persons [57], and a resurgence in South Korea has been reported [58]. Major outbreaks of influenza occur seasonally.

In order to decrease the burden of disease caused by vaccine-preventable illnesses, there is a significant need for strengthening of infectious diseases surveillance and better access to pediatric immunizations within many parts of this region.

Basic economic and demographic data*

	GNI per capita (USD)	Life expectancy at birth (total, years)	School enrollment, primary (% net)
China	2940	73	NA
Japan	38 210	83	99
Korea (North)	NA	67	NA

(Continued)

	GNI per capita (USD)	Life expectancy at birth (total, years)	School enrollment, primary (% net)
Korea (South)	21 530	79	98
Mongolia	1680	67	89

*World Bank.
GNI, gross national income; NA, not available.

Causes of death in children under five. Regional average*

	%
Neonatal causes	47
Pneumonia	14
Diarrheal diseases	12
Malaria	0
HIV/AIDS	0
Measles	1
Injuries	7
Others	18

*WHO regional average, 2000–2003 data.

Most common causes of deaths in all ages* in Mongolia, China, and Japan

	%		
	Mongolia	China	Japan
Cerebrovascular disease	13	18	14
Chronic obstructive lung disease	NS	14	NS
Tuberculosis	5	3	NS
Lower respiratory infections	4	3	9
Diarrheal diseases	4	NS	NS
Perinatal conditions	5	3	NS
Ischemic and hypertensive heart disease	9	8	10
Road traffic accidents	6	NS	NS
Self-inflicted injuries	NS	3	3
All cancers	12	13	21
Urogenital diseases	NS	NS	2

*WHO 2006.
NS, not stated, i.e. not included in the 10 most common causes of death.

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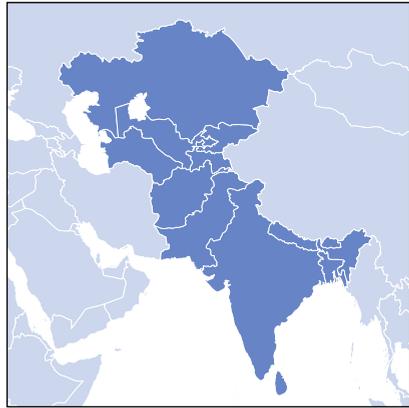
Chapter 14

South Central Asia

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Afghanistan
Bangladesh
Bhutan
India
Kazakhstan
Kyrgyzstan
Nepal
Pakistan
Sri Lanka
Tajikistan
Turkmenistan
Uzbekistan

The South Central Asian region varies vastly in geography (from sea level to Mt Everest), climate, language, and culture. All are developing countries with gross national income (GNI) varying from USD690 (Afghanistan) to 11 550 (Kazakhstan) per capita. Life expectancy ranges from 61 in Afghanistan to 74 in Sri Lanka and Iran. Infectious diseases account for the vast majority of mortality and morbidity in this region.

Important regional infections within four weeks of exposure

Diarrhea

Diarrhea is a leading illness in the region among the local population and among travelers [1,2], with bacterial etiology predominating. *Campylobacter* leads the etiology of travelers' diarrhea (TD) (Nepal data) and with enterotoxigenic *E. coli* (ETEC) and *Shigella* makes up the top three bacterial pathogens throughout the region [3–5]. Prevalent nonbacterial etiology includes *Giardia*, rotavirus, *Cryptosporidium*,

astrovirus, adenovirus, and norovirus [3–8]. *Cyclospora* is a seasonal pathogen during monsoons (Nepal) and cholera is notable in local populations [9] and in outbreaks [10].

Respiratory illness

Circulating measles in the region poses a threat to the traveler, with outbreaks among the local population reported in Pakistan, Kazakhstan, and Afghanistan [11,12] and cases among travelers in the last five years [13]. Pneumococcal disease including penicillin-resistant disease is common; predominant pneumococcal serotypes are serotype 1 in Nepal, serotype 14 in Bangladesh and India, and serotype 19F in Sri Lanka and Pakistan [14].

The 2015 influenza season was particularly severe in India, with a predominance of AH1N1 and over 800 fatalities despite its circulating in India since first introduced by a traveler from the USA in 2009 [15]. H1N1 predominated during 2015 in Nepal and Bangladesh whereas Kazakhstan, Uzbekistan, and Pakistan saw more H3N2 predominating in late 2014 and a prevalence of influenza B in early 2015 [16].

Fever without rash

Febrile illness in the region is predominantly attributed to enteric fever (*S. typhi* and *paratyphi*), dengue [17], rickettsial disease (see Fever with rash), leptospirosis (including outbreaks after flooding [18]), and malaria, particularly *Plasmodium vivax* and *falciparum* (India, Bangladesh, Pakistan, and Afghanistan) [19].

Viral and emerging febrile diseases account for a portion of fevers: chikungunya and West Nile virus (WNV) in Nepal [20,21]; hantavirus in Afghanistan [22]; Crimean Congo hemorrhagic fever (CCHF) endemic in Afghanistan and Pakistan and emerging in India [23–25]; Nipah virus in Bangladesh and India; malaria imported into Sri Lanka [26]. These illnesses demonstrate the evolution of vector-borne disease in the region reflective of environmental changes [27,28] and travel. Cross-over to travelers to the region is likely to increase [29,30].

Fever with rash (or typhus-like illness)

For fever with rash, measles, rubella, and rickettsial diseases are common. Rickettsial disease is predominantly murine typhus (*Rickettsia typhi*), scrub typhus (*Orientia tsutsugamushi*), Indian tick typhus (*R. conorii*), and Siberian tick typhus (*R. sibirica*) [31]. Unidentified and emerging rickettsiae are suspected as laboratory facilities are limited in the region and identified only by outside analysis, as was a case of *R. honei* reported in Nepal [30]. Notably, Kazakhstan experienced increased rickettsioses incidence and a fourfold increase in the rubella incidence in 2014 [32].

Zika virus

There were notable mosquito-borne Zika virus infections in Bangladesh and India prior to 2015 but no documented cases or transmission since 2016. There are no reports of recent Zika infections in the region but due to the presence of the vectors (*Aedes aegypti* and *Aedes albopictus*) in the region, notably in India, Bangladesh, and Nepal, active transmission of chikungunya and dengue is significant. Nepal began testing for Zika in early 2016 with no cases noted to date.

Hepatitis

The Indian subcontinent is endemic for enterically transmitted hepatitis A and E, with epidemics [33] and cases documented among foreign travelers [34,35].

CNS infections: meningitis and encephalitis

Acute infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
<p>Bacterial: <i>Streptococcus pneumoniae</i>, <i>Haemophilus influenzae</i>, <i>Neisseria meningitidis</i>, <i>Listeria monocytogenes</i>, group B streptococcus</p> <p>Viral: Japanese encephalitis, enterovirus 71 [36], dengue, WNV, chikungunya/Nipah/Hendra (Henipa)*, measles, mumps, herpes simplex virus, adenovirus, rabies virus, varicella zoster virus, influenza (including H1N1), malaria</p> <p>Focal lesions: streptococcal spp. (<i>viridans</i>), <i>Staphylococcus aureus</i>, anaerobes, esp. <i>Bacteroides</i>, <i>M. tuberculosis</i>, neurocysticercosis (<i>Taenia solium</i>), <i>Echinococcus granulosus</i>[§]</p>	<p><i>E.coli</i>, <i>Klebsiella</i> and <i>Pseudomonas aeruginosa</i></p> <p>Tick-borne encephalitis[§] (including Kyasanur Forest virus[†]), Langatrubella, Chandipura virus, rickettsias (<i>Orientia tsutsugamushi</i>, <i>R. typhi</i>, <i>R. conorii</i>), leptospirosis, parainfluenza, poliovirus, echovirus, enterovirus 67</p>	<p>Bagaza virus [37] <i>Acanthamoeba</i>[§] <i>Naegleria fowleri</i>[§] <i>Angiostrongylus cantonensis</i> <i>Blastomyces dermatitidis</i> Acute hemorrhagic leukoencephalitis (Hurst's disease) with <i>P. vivax</i>** Anthrax [38] Nocardia <i>Borrelia burgdorferi</i>^{††}</p>
<p>*Outbreaks in Bangladesh and West Bengal [39]. †Tropical India [40]. **Case report from India [41]. ††Kazakhstan [42]. §Kazakhstan [43,44].</p>		

Meningitis and encephalitis with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than four weeks	Microorganisms in the immunocompromised host
<p><i>M. tuberculosis</i> (TB), neurocysticercosis (<i>T. solium</i>), Nocardia, Epstein-Barr virus, <i>Yersinia</i>*, <i>Brucella</i></p>	<p>TB, Nocardia, <i>Treponema pallidum</i>, <i>Toxoplasma gondii</i></p> <p>Fungal: <i>Aspergillus</i>, <i>Cryptococcus neoformans</i>, Zygomycetes, <i>Histoplasma capsulatum</i>, <i>Cladosporium</i>, <i>Madurella mycetomatis</i></p> <p>Viral: JC virus causing progressive multifocal leukoencephalopathy, cytomegalovirus</p> <p>Free-living amoeba: <i>Acanthamoeba</i> and <i>Balamuthia</i>[†]</p>
<p>*Kazakhstan. †India [45].</p>	

Ear, nose, and throat infections

Ear, nose, and throat infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Bacterial: <i>Streptococcus pyogenes</i> , <i>Neisseria gonorrhoeae</i> , <i>H. influenzae</i> , <i>M. catarrhalis</i> , <i>Chlamydia pneumoniae</i> Viral: EBV, CMV, adenovirus, Coxsackie	Bacterial: <i>Aranobacterium haemolyticum</i> , Group A, C & G streptococci, Actinomyces, Fusariosis, peritonsillar abscess*, <i>Staph. aureus</i> , mixed anaerobic or gram-negative bacteria, Ludwig’s angina Viral: parotitis (mumps), HSV	Diphtheria Retropharyngeal abscess Tularemia† Helminths: <i>Dirofilaria</i> ** Fungi: <i>Pseudallescheria boydii</i>
*Require acute ENT evaluation. †Kazakhstan [46]. **India [47].		

Ear, nose, and throat with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Chronic suppurative otitis media, <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>Proteus</i> anaerobes <i>M. tuberculosis</i> (esp. pharyngeal) Nose: <i>M. leprae</i> , <i>Blastomyces dermatitidis</i>	<i>M. tuberculosis</i> , <i>M. avium intracellulare</i> complex <i>Aspergillus flavus</i> , <i>A. fumigatus</i> , Mucormycetes (esp. <i>Rhizopus arrhizus</i>) [48], <i>Penicillium marneffei</i> *
*India and Kazakhstan [49].	

Cardiopulmonary infections

Pneumonia with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Streptococcus pneumoniae</i> , <i>Staphylococcus aureus</i> , <i>Mycoplasma pneumoniae</i> , <i>H. influenzae</i> , <i>Moraxella</i> spp.* <i>Legionella</i> Hospital acquired: <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter</i> , <i>Klebsiella pneumoniae</i> , <i>E. coli</i> spp.† Viral: influenza including H1N1, parainfluenza, respiratory syncytial virus (RSV)	Streptococcus Group A,C & G <i>Burkholderia pseudomallei</i>	Diphtheria <i>Yersinia pestis</i>
* [50]. †Region notable for prevalence of multidrug-resistant pathogens including extended-spectrum beta-lactamase and carbapenemases (see Antibiotic resistance).		

Endocarditis/myocarditis with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<p><i>Streptococcus pyogenes</i> (myocarditis/rheumatic heart disease)</p> <p><i>Streptococcus viridans</i> and other streptococci spp.</p> <p>Group C & G coagulase-negative staphylococci</p> <p><i>Staphylococcus aureus</i> (including MRSA), gram-negative (<i>E. coli</i>, <i>Klebsiella</i>, <i>Enterobacter</i>), <i>Enterococcus faecalis</i></p>	<p>Gram-negative bacilli – HACEK group</p> <p><i>Salmonella typhi</i>, <i>S. paratyphi</i>, <i>Bartonella henselae</i>, <i>Bartonella quintana</i>,</p> <p>Leptospirosis (myocarditis), <i>Coxiella burnetii</i></p> <p>Viral: dengue [51], Coxsackie B, hepatitis E [52]</p>	<p>Fungal: <i>Aspergillus</i>, zygomycetes, <i>Candida</i> spp., <i>Scedosporium apiospermum</i>, <i>Kodameae ohmeri</i> [53]</p> <p>Rat-bite fever (<i>Streptobacillus moniliformis</i> and <i>Spirillum minus</i>)</p> <p>Atypical mycobacterium (<i>M. abscessus</i>), <i>Brucella</i>, <i>Chryseobacterium meningosepticum</i> [54]</p>

Pulmonary symptoms for more than four weeks and in the immunocompromised host

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<p><i>M. tuberculosis</i>, <i>Histoplasma capsulatum</i>, <i>Aspergillus</i></p>	<p><i>Streptococcus pneumoniae</i>, <i>Pneumocystis jiroveci</i>, <i>Nocardia</i>, <i>Aspergillus</i>, <i>Histoplasma capsulatum</i>, <i>Cryptococcus neoformans</i>, <i>Blastomyces dermatitidis</i> (rare), CMV, VZV</p>

Endocarditis for more than four weeks and in the immunocompromised host

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<p>Coagulase-negative staphylococci, nonhemolytic streptococci</p>	<p>Fungal: <i>Aspergillus</i>, zygomycetes, <i>Candida</i> spp., <i>Scedosporium apiospermum</i>, <i>Kodameae ohmeri</i></p>

Gastrointestinal infections

Gastrointestinal infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Acute diarrhea: <i>Campylobacter</i> , <i>Shigella</i> , enterotoxigenic <i>E. coli</i> , <i>Salmonella</i> (non-typhi), <i>Staphylococcus aureus</i> toxin causing food poisoning, <i>Vibrio cholerae</i> *, <i>Aeromonas</i>	<i>Yersinia enterocolitica</i> , <i>Clostridium difficile</i> , <i>C. botulinum</i> [55] <i>E. histolytica</i> , cryptosporidia spp. <i>Dientamoeba fragilis</i>	<i>Tropheryma whipplei</i>
Acute parasitic diarrhea: <i>Giardia intestinalis</i> , <i>Cyclospora cayatenensis</i>		
Viral: rotavirus, norovirus, enterically transmitted hepatitis: hepatitis E, hepatitis A <i>Helicobacter pylori</i>		

*Common in local diarrheal patients and throughout the region post disasters.

Gastrointestinal infections with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Protozoa: <i>Giardia</i> , <i>Cyclospora cayatenensis</i> , <i>E. histolytica</i> , <i>D. fragilis</i> , <i>M. tuberculosis</i>	<i>Isospora belli</i> , microsporidia, <i>Cryptosporidium</i> , <i>Cyclospora</i> , <i>Strongyloides stercoralis</i> , <i>M. tuberculosis</i> , MAC
Helminths (nematodes): <i>Ancylostoma duodenale</i> , <i>Ascaris lumbricoides</i> , <i>Enterobius vermicularis</i> , <i>Trichuris trichiura</i> , <i>Strongyloides stercoralis</i>	
Cestodes: <i>D. latum</i> , <i>Taenia saginata</i> , <i>T. solium</i> , <i>Hymenolepis nana</i> , <i>Echinococcus</i> (hydatid cyst in liver), visceral leishmaniasis, <i>Opisthorchis felineus</i> *	

*Kazakhstan [56,57]

Genitourinary infections

Cystitis, pyelonephritis, and nephritis with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>E. coli</i> , <i>Staphylococcus aureus</i> , <i>Klebsiella pneumoniae</i> , <i>Proteus</i> , <i>Pseudomonas aeruginosa</i> (hospital-acquired), <i>Staphylococcus saprophyticus</i>	<i>M. tuberculosis</i>	<i>Candida</i> , <i>Aspergillus</i> , myiasis [58]

Sexually transmitted infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions
HSV-2, <i>Chlamydia trachomatis</i> , <i>Trichomonas vaginalis</i> , <i>Neisseria gonorrhoeae</i> *, syphilis	<i>Lymphogranuloma venereum</i>
*Quinolone resistance and penicillinase-producing organisms predominate, with ceftriaxone resistance emerging [59,60].	

Cystitis, pyelonephritis, and nephritis with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Chronic UTI with same organism as acute infection* <i>M. tuberculosis</i> <i>Candida albicans</i>	<i>E.coli</i> , <i>Staph. aureus</i> , <i>Enterococcus</i> , <i>Pseudomonas</i> , <i>Klebsiella pneumoniae</i> <i>Candida albicans</i> , mucormycosis <i>M. tuberculosis</i>
*Including ESBL-producing organisms [61].	

Sexually transmitted infections with symptoms for more than four weeks and in the immunocompromised host [62]

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Bacterial: syphilis Viral: HPV, HSV, HBV, HIV Molluscum contagiosum	HSV, syphilis, HIV, chancroid (<i>H. ducreyi</i>), scabies

Joint, muscle, and soft tissue infections

Joint, muscle, and soft tissue infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Bacterial: <i>Staphylococcus aureus</i> , Group A beta-hemolytic streptococcus, <i>E. coli</i> , <i>Neisseria gonorrhoeae</i> Viral: chikungunya	Necrotizing fasciitis, <i>Acinetobacter baumannii</i> , Group B, C & G beta-hemolytic streptococci, <i>Burkholderia pseudomallei</i>	Fournier's gangrene (perineum and urogenital; polymicrobial), <i>Aspergillus fumigatus</i> , <i>Clostridium perfringens</i> , <i>C. tetani</i> , <i>Sporotrichum schenckii</i>

Joint, muscle, and soft tissue infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>M. tuberculosis</i> , <i>Brucella melitensis</i> ,* <i>Br. abortus</i> ,* <i>Br. suis</i> ,* <i>Br. ovis</i> ,* <i>Yersinia pseudotuberculosis</i> ,* <i>Chlamydia trachomatis</i> ,* <i>Leptospira</i> ,* <i>Borrelia burgdorferi</i> ,* <i>Chlamydomphila psittaci</i> † Rat-bite fever (esp. <i>Streptobacillus moniliformis</i> and <i>Spirillum minus</i>) Viral: chikungunya virus	Actinomycotic mycetoma (<i>Actinomadura</i> , <i>Streptomyces</i> , and <i>Nocardia</i> spp.), Eumycetoma, <i>Salmonella typhi</i> , ecthyma gangrenosum (<i>Pseudomonas aeruginosa</i>), <i>Candida</i> spp.

Especially Kazakhstan [63].
 † Especially Kyrgyzstan.

Skin infections

Skin infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Staph. aureus</i> , <i>Streptococcus pyogenes</i>	Parasitic: <i>Leishmania</i> , esp. <i>L. donovani</i> * Fungal: <i>Pityriasis alba</i> , Tinea (<i>Trichophyton violaceum</i> , <i>T. mentagrophytes</i> , <i>Microsporum canis</i>), <i>Apophysomyces</i> [48] Infestations: Scabies, lice	Rickettsial spp., yaws (<i>T. pallidum</i> subsp. <i>pertenue</i>)

* Especially India, Pakistan, Afghanistan, and Kazakhstan, including reports among soldiers returning from Afganistan [64,65].

Skin infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>M. tuberculosis</i> (lupus vulgaris, scrofuloderma, and tuberculosis verrucosa Curtis) <i>Mycobacterium leprae</i> * Cutaneous leishmaniasis Pityriasis versicolor	Candidiasis Herpes simplex, dermatophytosis of the skin, Molluscum contagiosum, genital warts, HSV, <i>Demodex folliculorum</i> , <i>Sarcoptes scabiei</i> , mycoses (<i>Trichophyton</i> , <i>Microsporium</i> , <i>Epidermophyton</i>), <i>Treponema pallidum</i> [66]

Adenopathy

Adenopathy of less than four weeks duration

Common	Rare	Very rare
Tonsillopharyngitis and suppurative infections (oral streptococci, <i>Strep. pyogenes</i>) Infectious mononucleosis (EBV, CMV) and HIV Reactive lymphadenitis	Kawasaki disease Rubella Lymphatic filariasis	<i>Strongyloides stercoralis</i> <i>Yersinia pestis</i> Leprosy

Adenopathy of more than four weeks duration and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Rare microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Mycobacteria (TB, MAC and others) EBV, CMV	<i>Nocardia</i> , Actinomyces Brucellosis Leprosy Rosai-Dorfman disease	TB, suppurative lymphadenitis Reactive lymphadenopathy HIV, EBV, CMV <i>Cryptococcus histoplasmosis</i> , <i>P. marneffeii</i> [49]

Fever without focal symptoms

Fever less than four weeks without focal symptoms

Frequently found microorganisms and conditions	Rare microorganisms and conditions	Very rare microorganisms
Salmonellosis*	<i>Coxiella burnetii</i>	Rat-bite fever (<i>Streptobacillus moniliformis</i> and <i>Spirillum minus</i>)
Viral: dengue, JE, WNV, chikungunya, acute HIV, infectious mononucleosis (EBV, CMV)	Tularemia	Viral: hantaviruses, sandfly fever virus [22], Chandipura virus, tetanus (<i>C. tetani</i>), Kyasanur Forest disease*
Rickettsiosis (<i>R. typhi</i> , <i>Orientia tsutsugamushi</i> , <i>R. conorii</i> , <i>R. sibirica</i> **)	Ehrlichia	
<i>Mycoplasma pneumoniae</i>	Plague	
Leptospirosis	Babesiosis	
Malaria (<i>P. falciparum</i> , <i>P. vivax</i> , <i>P. malariae</i>)		
Bacterial endocarditis	Parvovirus B19, CCHF [63,67]	
Abdominal abscess (pyogenic/amebic)	<i>Trichinella</i>	
Viral hepatitis (hepatitis A, B, E)		

* Including *S. paratyphi* outbreak among travelers to Nepal [68].
 † Karnataka, Tamil Nadu, and Kerala [69].
 ** *B. burgdorferi*, *B. miyamotoi*, *E. muris*, *A. phagocytophillum* detected in *Ixodes persulcatus* ticks in Almaty and the East Kazakhstan region of Kazakhstan [43].

Fever for more than four weeks without focal symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>M. tuberculosis</i>	Tuberculosis, MAC
Toxoplasmosis	CMV, adenovirus
Brucellosis (<i>B. melitensis</i> , <i>B. abortus</i> , <i>B. suis</i>)	Histoplasmosis, cryptococcosis, <i>Aspergillus</i>
<i>Opisthorchis felineus</i>	
<i>Opisthorchis viverrini</i>	
Malaria (<i>P. vivax</i> , <i>P. ovale</i> , <i>P. malariae</i>)	
<i>Chlamydomphila psittaci</i> *	
<i>Toxoplasma gondii</i> *	
<i>Borrelia burgdorferi</i> *	
<i>Borrelia miyamotoi</i> *	

* Kazakhstan [42,70].

Eosinophilia and elevated IgE

Eosinophilia and elevated IgE for less than four weeks

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Intestinal nematodes: <i>Ascaris lumbricoides</i> and <i>suum</i> , hookworm (<i>Necator</i> spp.)	Nematodes: <i>Toxocara</i> spp., <i>Trichinella spiralis</i> <i>Angiostrongylus cantonensis</i> and <i>costaricensis</i>	<i>Gnathostoma spinigerum</i> (eosinophilic meningitis) Phaeohyphomycosis <i>Diphyllobothrium latum</i>
Tissue nematodes: <i>Wuchereria bancrofti</i> , <i>Brugia malayi</i> : lymphatic filariasis and tropical pulmonary eosinophilia	HIV Aspergillosis (allergic bronchopulmonary aspergillosis)	Trematodes: <i>Fasciolopsis buski</i> , <i>Clonorchis sinensis</i> , <i>Ophisthorcis</i> spp., <i>Fasciola hepatica</i>
Cestodes: <i>Echinococcus</i> , cysticercosis (<i>Taenia</i> spp.), <i>Paragonimus westermani</i>	Trematodes: <i>S. haematobium</i> and <i>S. mansoni</i>	

Eosinophilia and elevated IgE for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Strongyloides stercoralis</i> <i>Ascaris lumbricoides</i> and <i>A. suum</i> , <i>Toxocara</i> spp. (visceral larva migrans)	<i>Toxocara</i> spp. Protozoa: <i>Dientamoeba fragilis</i> , <i>Isospora belli</i> , <i>Cryptosporidium parvum</i> , sarcocystis
Filariasis <i>M. tuberculosis</i>	<i>Strongyloides stercoralis</i> <i>Cryptococcus neoformans</i> , <i>Pneumocystis jirovecii</i> <i>M. tuberculosis</i>

Antibiotic resistance

Antibiotic resistance (AR) for the region continues to rise and remains one of the highest in the world.

Multidrug-resistant gram-negative bacilli

Several recent data demonstrate the significant rate of AR, especially ESBL- and carbapenemase-producing enterobacteria in the region [71,72]. There is continued spread of novel carbapenemase New Delhi metallo-beta-lactamase (NDM-1) that originated in India in 2008 [73] throughout the region and among travelers returning from India [74,75]. *Klebsiella pneumoniae* resistance to

carbapenems is widespread [76]. Resistance to third-generation cephalosporins, including ESBL-producing organisms, is seen in Afghanistan [77], Bangladesh [78], Pakistan, Kazakhstan [79], and Bhutan.

Enteric fever: *Salmonella typhi* and *paratyphi*

Very high nalidixic acid resistance (NAR) among salmonellae and reduced susceptibility to ciprofloxacin should be assumed for much of the region (India, Nepal [80], Pakistan [81], Bangladesh [82], Uzbekistan [83], Kazakhstan [84], and Tajikistan [85]) and is associated with treatment failures among travelers [86]. Emerging resistance to azithromycin in India, Pakistan, and Nepal [80,87] and ceftriaxone is concerning [81,82,88]. Among returned travelers with enteric fever, increased minimum inhibitory concentrations (MICs) for azithromycin were highest in regions where ciprofloxacin MICs were also increased. By region, South Asia has the second highest rates, where over 20% of isolates had increased MICs to both drugs [89].

Diarrheal pathogens, especially travelers' diarrhea

The region is among the highest for association of acute diarrheal illness among travelers [2]. Azithromycin resistance continues to emerge among diarrheal pathogens, especially among *Shigella* (30% and 38% reduced susceptibility in Bangladesh and Nepal respectively) [34,90], though this remains a drug of choice for TD. Quinolone resistance is nearly complete for *Campylobacter* in Nepal (97% NAR and ciprofloxacin resistance) and India [91], and is rising in Bangladesh and Pakistan [9]. The majority of *Shigella* and ETEC also demonstrate reduced susceptibility to the quinolones (Nepal data among travelers: 82% and 79% NAR and cipro R for *Shigella*; 100% and 26% respectively for ETEC). A study of colonization by ESBL-producing Enterobacteriaceae among returned travelers showed the highest occurrence for travelers to South Asia who developed TD and took antibiotics at 46% [92].

Multidrug-resistant tuberculosis

Countries in the region notable for high MDR tuberculosis include Bangladesh, India, Kazakhstan, Kyrgyzstan, Pakistan, Tajikistan, and Uzbekistan with % TB cases with MDR-TB ranging from 1.4% and 29% (new and retreatment cases in Bangladesh) to 26% and 55% (new and retreatment cases in Kyrgyzstan).

Streptococcus pneumoniae resistant to penicillin

Penicillin-resistant *Strep. pneumoniae* continues to rise with 48% reported in Nepal (National Data 2012) and Pakistan 14% (2013). Sri Lanka reported the highest nonsusceptibility of 90% to penicillin and 50% to cefotaxime [14]. Susceptibility of isolates in Kazakhstan ranged from 59% to penicillin to 81% to cefuroxime [93,94].

Drug-resistant malaria

Artemisinin resistance extends from Myanmar to border areas of Bangladesh [95,96] but remains minimal in India. Resistance to the antifolate component of the artesunate plus sulphadoxine-pyrimethamine regimen is notable in Afghanistan [97].

Methicillin-resistant *Staphylococcus aureus*

Methicillin-resistant *Staph. aureus* is well established in the region [77,98]. *Staph. aureus* resistance to clindamycin and reduced susceptibility to vancomycin are reported from Nepal and India [99–101].

Vaccine-preventable diseases in children

In 2013, an estimated 21.8 million infants worldwide were not reached with routine immunization services, of whom nearly half live in three countries: India, Nigeria, and Pakistan. Vaccine-preventable diseases account for a significant number of childhood illnesses and deaths in the region. Measles incidence has increased in Kazakhstan despite a national vaccination campaign peaking in 2014; the majority of cases have been adults [12]. Otherwise measles cases and deaths have been steadily declining [102], although cases continue to occur, mainly in India but also in Pakistan [103], Nepal, Afghanistan, Sri Lanka, and Bangladesh. A two-dose measles immunization program has been started in all countries but coverage remains poor for the second dose in India and Afghanistan, at 40%, and 60% in Pakistan.

Pakistan and Afghanistan are the only two polio endemic countries in the region with ongoing wild poliovirus transmission. In 2014, 85% of the global total of 359 cases of paralytic poliomyelitis due to wild poliovirus were reported from Pakistan, with 28 cases from Afghanistan, primarily as a result of cross-border importation. Diphtheria continues to be reported in outbreaks from India [104]. Most of the countries in the region are endemic for enteric fever (predominantly *S. typhi* in the unimmunized population) and Hepatitis A, with outbreaks occurring from time to time, but vaccination programs have not been introduced. The WHO cites pediatric immunization coverage at >95% in Bhutan, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Sri Lanka, and Uzbekistan, and approaching 90% for most vaccines in Bangladesh and Nepal whereas coverage hovers around 70% for Afghanistan, India and Pakistan [105]. JE vaccine has been introduced in endemic areas of Nepal, India, and Sri Lanka but Nepal saw a very significant rise in JE cases in 2014 and the first case of JE in a traveler [29]. Significant increases were noted for diphtheria, mumps, and pertussis in Nepal in 2014. Rabies is endemic in the region and most deaths from rabies occur in Asia. In travelers, an average of 3.7 cases were documented each year during 2004–2012 [31]. Preexposure immunization is recommended for selected travelers [106–108].

Based on an evaluation of pneumococcal subtypes in the South Asian Association for Regional Cooperation (SAARC) countries, PCV-10 is suitable for India, Nepal, Bangladesh, and Sri Lanka whereas PCV-13 may be more suitable for Pakistan [14].

Basic economic and demographic data*

	GNI per capita (USD)	Life expectancy at birth (total years)	School enrollment, primary (% net)
Afghanistan	690	61	104
Bangladesh	1010	70	114
Bhutan	2330	68	112
India	1570	66	113
Iran	5780	74	106
Kazakhstan	11 550	70	106
Kyrgyzstan	1210	70	106
Nepal	730	68	135
Pakistan	1360	66	93
Sri Lanka	3170	74	98
Tajikistan	990	67	100
Turkmenistan	6880	65	NA
Uzbekistan	1880	68	93

*World Bank figures.

GNI, gross national income; NA, not available.

Most common causes of deaths in all ages* in the countries of the region (%)

	Afghanistan	India	Nepal	Tajikistan	Bangladesh	Kazakhstan	Pakistan	Turkmenistan	Bhutan	Sri Lanka	Uzbekistan
Ischemic heart disease	8.1	12.4	9.2	21.4	5.7	32.5	8.4	33	8.2	23.6	34.2
COPD	NS	10.8	9.2	2.8	7.6	3.1	4.6	2.9	7.3	4.4	2
Stroke	6.2	9	8.2	13.3	5.5	16.8	6.3	12.3	5.5	11	15.9
Diarrheal diseases	6.4	6	3.3	3.7	NS	NS	4.8	NS	NS	NS	NS
LRTI	11.6	4.9	7	8.4	7.8	2.1	7.8	4.2	6.5	5.3	4.1
Preterm birth complications	5.2	3.9	2.5	4.4	2.9	NS	5.8	2.1	2.4	NS	1.9
Tuberculosis	4.4	2.7	3	NS	7.9	NS	4.6	NS	NS	NS	NS
Diabetes	NS	NS	2.8	NS	3.1	NS	3	1.7	3.2	7.4	2.2
Self-harm	NS	2.6	3	NS	NS	2.5	NS	2.2	2.5	4.5	NS
Road injury	2.6	2.4	2.7	2.6	NS	2.1	NS	1.9	NS	2	1.7

* WHO 2012: www.who.int/gho/countries/en/.

COPD, chronic obstructive pulmonary disease; LRTI, lower respiratory tract infection; NS, not stated, i.e. not included in the 10 most common causes of death.

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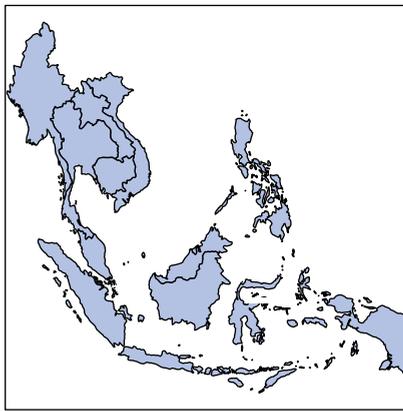
Chapter 15

South-east Asia

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Brunei Darussalam
Cambodia
Indonesia
Lao PDR
Malaysia
Myanmar (Burma)
Philippines
Singapore
Thailand
Timor-Leste
Vietnam

South-east Asia is the most densely populated area of the world and a global hotspot for the emergence of new infectious diseases and drug resistance. The emergence and spread of artemisinin-resistant malaria and multidrug-resistant TB and the widespread use of often poor-quality anti-infective drugs emanating from this region all pose serious global risks. Socioeconomic factors, tropical climate with vegetation ranging from paddy fields over scrublands to tropical jungle, as well as abundant domestic animal reservoirs (pigs, poultry) allow for a wide range of infectious diseases. Unfortunately, epidemiological data on many of these infectious diseases remain limited, and their prevalence and incidence are often uncertain.

Important regional infections within four weeks of exposure

Malaria

Ruling out malaria remains essential in the work-up of a febrile traveler. Malaria transmission in South-east Asia (SEA) is usually low unstable and seasonal, except for lowland areas of Papua New Guinea where higher and more stable transmission occurs. Malaria is therefore not a common

Infectious Diseases: A Geographic Guide, Second Edition. Edited by Eskild Petersen, Lin H. Chen, and Patricia Schlagenhauf-Lawlor.

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infectious disease acquired in SEA. The prevalences of *P. falciparum* and *P. vivax* are similar and malaria is largely found in forest and forest-fringe areas and some coastal areas. *Falciparum* malaria is often multidrug resistant. Occasional infections with the dangerous monkey malaria *P. knowlesi* may also occur.

Key symptoms: Fever, shivering, abdominal/bone/joint pain. Acute onset.

Typhus-like illness

Many infections present with flu-like symptoms, fever, variable skin rash, and nonspecific symptoms (myalgia, arthralgia, etc.), often accompanied by disorientation, confusion, and other CNS symptoms. Patients usually present with approximately 3–6 days of fever. The following diseases need to be considered.

Dengue fever is the most likely infection to be acquired by a traveler to SEA. Transmitted by the day-biting mosquitoes *Aedes aegypti* and *A. albopictus*, which are prevalent in urban areas, it usually causes an acute flu-like illness affecting all age groups, but seldom causes death. The incubation phase of 3–8 days is followed by a sudden onset of fever, headache, muscle/joint pains, and variable CNS symptoms. A rash may develop within a few days of onset. Serious complications (shock syndrome, hemorrhage, hepatitis, myocarditis, encephalitis) are uncommon.

Key symptoms: Acute systemic muscle and/or bone pain with high fever, petechial hemorrhages, usually lack of respiratory symptoms.

Chikungunya virus is an arbovirus also transmitted by *Aedes aegypti* and *A. albopictus*, with monkeys as reservoirs. Outbreaks reported from SEA are sometimes associated with severe illness and symptoms. A prolonged arthralgia-dominated disease follows the initial acute febrile phase of 2–5 days, and disabling arthralgia can persist for weeks or months. Currently, chikungunya is of concern in Sri Lanka, Cambodia, Laos, and eastern Thailand.

Key symptoms: Arthralgic pain with fever. Lack of other symptoms. Acute onset.

Scrub typhus and murine typhus are the two major rickettsial diseases in SEA. Scrub typhus is a rural but increasingly urban disease with a seasonal pattern, caused by *Orientia tsutsugamushi* and transmitted by *Leptotrombidium* mites. It is often associated with an eschar at the mite bite site. Murine typhus is a more urban disease following no seasonality, caused by *Rickettsia typhi* and transmitted by fleas depositing feces on the human skin, followed by self-inoculation through scratching (no eschar). Both diseases begin with a flu-like illness after a 3–10-day incubation period, and can develop serious complications if untreated. Rickettsial diseases are among the leading causes of fever throughout SEA, major contributors to CNS infections in Laos and associated with a high rate of abortion and adverse pregnancy outcomes.

Key symptoms: Fever, myalgia, sometimes skin rash. Scrub typhus often with lymphadenopathy, approximately half of cases with an eschar, history of rural activity. Murine typhus with urban activity, lymphadenopathy is rare. Both diseases with potentially severe complications if misdiagnosed/untreated.

Leptospirosis is a biphasic infection with a 4–14-day incubation period. It begins with flu-like symptoms occasionally with subconjunctival hemorrhages, meningitis, jaundice, and renal failure. Leptospirosis is often misdiagnosed as it may present with a wide range of symptoms.

Key symptoms: Acute onset with myalgia and jaundice. Exposure to contaminated environmental water.

Typhoid fever (*Salmonella typhi* serovar *typhi*) is a subacute febrile illness with sweating and gastrointestinal symptoms (abdominal discomfort, diarrhea or constipation), sometimes accompanied by faint roseola and depressed sensorium. Complications around the third week include intestinal hemorrhage (bleeding into Peyer's patches), perforation of the distal ileum with septicemia/peritonitis and metastatic abscesses (rarely CNS, endocarditis, osteitis, etc.). Currently, typhoid is of general concern in India, Nepal, Bangladesh, Myanmar, Cambodia, Laos, and Indonesia.

Key symptoms: Slowly worsening fever with abdominal symptoms.

Melioidosis (*Burkholderia pseudomallei*) is an important serious systemic abscess-forming infection, which is prevalent in many parts of SEA and particularly infects patients with diabetes, renal failure,

cirrhosis or thalassemia, or receiving immunosuppression. It is transmitted via contact to contaminated soil and environmental water and can present either as an acute form (incubation approximately 1–3 weeks) or manifest after a latent period for up to 62 years.

Key symptoms: Acute fever with foci, usually in lungs, liver, spleen, prostate, joints or skin.

CNS infections

The most common causes of CNS infections in SEA include viral meningoencephalitis (enterovirus and flavivirus groups) and bacterial meningitis caused by *Rickettsia* spp., *O. tsutsugamushi* and *Leptospira*, as well as *Streptococcus pneumoniae*, *Haemophilus influenzae B*, *Neisseria meningitidis*, and *Mycobacterium tuberculosis*. *Streptococcus suis* occurs mainly in Vietnam.

Rare causes include the following.

- *Angiostrongylus cantonensis* – ingestion of undercooked snails or slugs can result in eosinophilic meningoencephalitis.
- *Gnathostoma* spp. – humans become infected through ingestion of raw or undercooked paratenic hosts (fish, frogs, eels, pigs, and birds).
- *Zoonotic paramyxoviruses* (*Nipah*, *Hendra*) – rare causes of epidemic (often severe) encephalitis and aseptic meningitis associated with exposure to flying foxes or fruit bats or fruit contaminated by them. Reports are limited to Malaysia, Bangladesh, Singapore, and northern Australia.
- *Rabies* (*Lyssavirus*, *Rhabdoviridae*) – rabies causing a uniformly fatal encephalitis in humans remains an important disease in SEA, usually acquired from dog bite. Pre- and postexposure prophylaxis and vaccination are recommended.

Hepatitis

Hepatitis A is widespread throughout SEA. Chronic hepatitis B prevalence (HBsAg positivity) is high in SEA; about 70–90% of the population becomes HBV infected before the age of 40, and up to 20% of people are HBV carriers (HBsAg positivity). Hepatitis C prevalence varies among East Asian countries, ranging from about 0.5% in Singapore and Hong Kong, approximately 2–3% in China, 6% in Vietnam and Thailand, and over 10% in Myanmar. Hepatitis E is acquired from contaminated drinking water and fecooral transmission throughout the region and is probably predominantly acquired from pigs. Special caution applies to pregnant women, as during the third trimester of pregnancy, hepatitis E can be severe with a case fatality rate reaching 20%.

Parasitic disease

Trematodes Schistosomiasis (*S. mekongi* and *S. japonicum*) occurs in the Philippines and one small area of Laos and Cambodia. Liver flukes (*Fasciola hepatica*) are common throughout SEA but *Clonorchis* spp. are more limited to Laos, Cambodia, Thailand, and Vietnam although prevalences are high in some areas (e.g. Southern Laos). Lung flukes (*Paragonimus westermanii* – associated with freshwater crabs) may cause hemoptysis and are an important differential diagnosis to TB.

Cestodes Due to the widespread presence of domestic pigs, taeniasis is common in Laos and adjoining countries (*T. solium* and *T. saginata*). Neurocysticercosis should be considered in cases of CNS symptoms in returning travelers.

Nematodes The intestinal helminths *Necator americanus*, *Ancylostoma duodenale* (hookworms), *Ascaris lumbricoides* (roundworms), *Trichuris trichiura* (whipworm), and *Strongyloides stercoralis* are all common. *Enterobius vermicularis* (threadworm) is common in young children.

While hookworm is prevalent in SEA, disease burden is low, but roundworm infestation is common. Disseminated strongyloidiasis may occur many years after exposure in immunocompromised patients.

Gnathostomiasis – *Gnathostoma* spp. are hosted in dogs and cats, and transmitted to humans by ingestion of larvae-containing meat. Although they can invade any organ system (eye, lung, GI tract, etc.), the most important are CNS complications due to larval migration leading to radiculomyelitis, encephalitis, and subarachnoid hemorrhage.

Influenza (H1N1) and avian influenza (H5N1)

South-east Asia is a hotspot for pandemic influenza. It was the epicenter for H5N1 and was significantly affected by H1N1 influenza. Vaccination remains a key control strategy.

CNS infections: meningitis, encephalitis, and encephalopathy

Acute infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Viral (enteroviruses, JEV, dengue, HSV, VZV, CMV, EBV, HIV, mumps, measles, rubeola)	<i>Staphylococcus aureus</i> [†]	Free-living amoebae (<i>Acanthamoeba</i> , <i>Balamuthia</i> and <i>Naegleria</i> spp.) ^{§§}
<i>Neisseria meningitidis</i>	Influenza	<i>Listeria monocytogenes</i>
<i>Haemophilus influenzae B</i>	Eosinophilic meningoencephalitis [§]	Rabies
<i>Streptococcus pneumoniae</i>	Typhoid and paratyphoid	<i>Echinococcus granulosus</i>
<i>Mycobacterium tuberculosis</i>	<i>Toxoplasma gondii</i>	Paramyxovirus (Hendra, Nipah)
<i>Streptococcus suis</i>	Postimmunization/vaccine**	
HIV/AIDS and opportunistic infections*	<i>Burkholderia pseudomallei</i> ^{††}	
<i>P. falciparum</i> , <i>P. vivax</i>	<i>Salmonella enterica</i> (nontyphoidal)	
<i>Rickettsia</i> spp.		
<i>Cryptococcus neoformans</i> var <i>neoformans</i> and var <i>gattii</i>		

* HIV is neurotropic and may cause progressive multifocal leukoencephalopathy; also immune reconstitution inflammatory syndrome may occur after starting antiretroviral therapy.

[†] Dissemination often follows skin infections. Community-acquired MRSA is common in some areas.

** Yellow fever, measles, JEV and rabies vaccines.

^{††} In diabetics, patients with renal failure and immunocompromised.

[§] Most common: *Angiostrongylus cantonensis*, *Gnathostoma spinigerum* [1]. Parasites: *T. solium*, *E. alveolaris*, *P. westermanii*, *S. japonicum*, *F. hepatica*, *T. canis*, *T. trichiura*, and *T. spiralis*.

^{§§} Granulomatous amebic encephalitis and primary amebic meningoencephalitis.

CNS infections with symptoms for more than four weeks and in the immunocompromised host

Consider also noninfectious causes like vasculitis and lymphoma.

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
HIV/AIDS and opportunistic infections <i>Mycobacterium tuberculosis</i> <i>Treponema pallidum</i> (neurosyphilis) <i>Taenia solium</i> (neurocysticercosis) <i>Toxoplasma gondii</i>	<i>Cryptococcus neoformans</i> <i>M. tuberculosis</i> (extrapulmonary TB) <i>Toxoplasma gondii</i> <i>Nocardia</i> , <i>Actinomyces</i> spp. <i>Toxocara</i> spp. Free-living amebae* (<i>Acanthamoeba</i> , <i>Balamuthia</i> and <i>Naegleria</i> spp.) CMV <i>Treponema pallidum</i> (neurosyphilis)
* Granulomatous amebic encephalitis and primary amebic meningoencephalitis.	

Ear, nose, and throat infections

Infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Group A streptococcal throat infection	Melioidosis (parotid abscess) [†]	Diphtheria
Otitis media and externa*	<i>Mycobacterium tuberculosis</i>	Nipah virus (outbreak)
Viral (HSV I & II, influenza, adenovirus, enteroviruses, EBV, CMV, HIV, dengue)	Peritonsillar abscess**	Anaerobes: necrotizing stomatitis
<i>Candidia</i> spp. (HIV, antibiotics, diabetes)	Necrotizing fasciitis ^{††}	Noma
<i>B. pertussis</i>	<i>N. gonorrhoeae</i> , syphilis, HPV	
* See Antibiotic resistance. <i>P. aeruginosa</i> and mycosis (<i>Aspergillus</i> , candidiasis) common in otitis externa.		
[†] Melioid parotid abscess common in children.		
** Requires acute ENT evaluation.		
^{††} Requires acute ENT or surgical evaluation.		

Infections with symptoms for more than four weeks and in the immunocompromised host

The main infection to consider in both immunocompetent and immunocompromised subjects is extrapulmonary tuberculosis. TB can affect nose, nasopharynx, oropharynx, middle ear, mastoid bone, larynx, deep neck spaces, and salivary glands. Leprosy targets nose, nasopharynx, and laryngopharynx, but is now rare. Further, candidiasis, HSV, and HIV-associated EBV are differential diagnoses in immunocompromised hosts. Consider noninfectious causes like vasculitis and lymphoma.

Cardiopulmonary infections

Cardiopulmonary infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Pulmonary symptoms		
<i>Streptococcus pneumoniae</i>	Influenza	Diphtheria
<i>Haemophilus influenzae</i>	<i>Legionella pneumophila</i>	<i>Yersinia pestis</i>
<i>Mycoplasma pneumoniae</i>	<i>Cryptococcus neoformans</i>	
<i>Leptospira</i> spp.	<i>Chlamydia psittaci</i>	
<i>Burkholderia pseudomallei</i>	<i>Chlamydia pneumoniae</i>	
<i>Klebsiella pneumoniae</i>	<i>Paragonimus westermanii</i>	
<i>Staphylococcus aureus</i>	<i>Coxiella burnetii</i>	
<i>Rickettsia</i> spp., <i>O. tsutsugamushi</i>		
Endocarditis		
<i>Staphylococcus aureus</i>	<i>Neisseriae gonorrhoeae</i>	
<i>Viridans streptococci</i>	<i>Coxiella burnetii</i>	<i>Propionibacterium</i>
<i>Enterococcus</i> spp.	<i>Streptococcus pyogenes</i>	<i>Neisseria</i> spp.
Coagulase-negative staphylococci (<i>S. epidermidis</i>)*	HACEK group	<i>Campylobacter</i> spp.
<i>Streptococcus pneumoniae</i>	<i>Bartonella</i> spp.	
<i>Candida</i> spp.	<i>E. rhusiopathiae</i>	
* Associated with prosthetic valves.		

Pulmonary symptoms and/or endocarditis for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Pulmonary symptoms*	
COPD	<i>Penicillium marneffeii</i>
<i>M. tuberculosis</i>	<i>Pneumocystis jirovecii</i>
<i>Aspergillus</i> spp.	<i>Aspergillus</i> , candidiasis (neutropenic patients)
<i>Cryptococcus neoformans</i>	<i>M. avium</i> complex and other mycobacteria
<i>Burkholderia pseudomallei</i>	CMV
<i>Paragonimus westermanii</i>	<i>Bartonella henselae</i> , <i>B. quintana</i>
	<i>Burkholderia pseudomallei</i> **
	<i>Histoplasma capsulatum</i>
Endocarditis, pericarditis†	
Coagulase-negative staphylococci (<i>S. epidermidis</i>)	<i>Aspergillus</i> spp.
<i>Viridans streptococci</i>	<i>Trichuris trichiura</i>
<i>Bartonella</i> and <i>Rickettsia</i> spp.	<i>Toxoplasma gondii</i>
<i>Candida</i> spp. (IVDU)	varicella zoster virus
Typhoid (<i>S. enterica</i> , <i>S. typhi</i>)	

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Enterovirus HACEK group	
<p>* Consider noninfectious causes like lung cancer, autoimmune pulmonary fibrosis, vasculitis including Wegener’s granulomatosis. † Rheumatic heart disease (RHD) remains a major predisposition for cardiac infections in SEA. The prevalence of RHD is estimated 21.5/1000 [2]. Consider fever, cough, hemoptysis as a consequence of pulmonary hypertension and/or congestive heart failure with edema without infection. ** Diabetics, renal failure, thalassemia.</p>	

Gastrointestinal infections

Gastrointestinal infections with less than four weeks of symptoms*

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>E. coli</i> (predominantly ETEC, but also EPEC, EIEC, EHEC, EAEC) <i>Salmonella</i> spp. (nontyphoid) <i>Shigella</i> spp. <i>Campylobacter</i> spp. <i>Salmonella enterica</i> , <i>S. typhi</i> ** <i>Vibrio parahaemolyticus</i> <i>Giardia intestinalis</i> <i>Enterobius vermicularis</i> (threadworm) Norovirus, rotavirus <i>Entamoeba histolytica</i> (liver abscess) <i>Cyclospora</i>	Coccidiosis (<i>Isospora</i> , <i>Cryptosporidium</i> , <i>Cyclospora</i>) <i>Staphylococcus aureus</i> toxin <i>Bacillus cereus</i> toxin <i>Vibrio cholerae</i> † <i>Capillaria philippinensis</i> <i>Ascaris lumbricoides</i>	<i>M. tuberculosis</i> <i>Tropheryma whipplei</i> <i>Yersinia enterocolitica</i>
<p>* Repeated negative bacterial cultures and microscopy for parasites suggest noninfectious etiology. Consider inflammatory bowel diseases, malabsorption, celiac disease or neoplasias. Also postinfectious malabsorption (tropical sprue). † Reduced stomach acid production is associated with higher incidence of cholera (children, elderly, proton pump inhibitor and histamine blocker use). ** Symptoms of headache, high fever with abdominal symptoms (diarrhea, constipation) [3].</p>		

Gastrointestinal infections with more than four weeks of symptoms and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Persistent diarrhea (<i>Giardia</i> spp., EAEC, cryptosporidia, <i>Cyclospora</i> , <i>T. trichiura</i> , <i>C. philippinensis</i>) <i>M. tuberculosis</i> (extrapulmonary TB)	Candidiasis HSV
(Continued)	

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Dientamoeba fragilis</i> [†] <i>Tropheryma whipplei</i>	Coccidiosis (<i>Isospora</i> , <i>Cryptosporidium</i>) <i>Strongyloides stercoralis</i> (hyperinfection syndrome)
<i>S. japonicum</i> , <i>S. mekongi</i>	<i>M. tuberculosis</i> (extrapulmonary TB) Microsporidiosis (<i>Enterocytozoon bienersi</i> and <i>Encephalitozoon intestinalis</i>)

* Consider noninfectious causes like postinfectious malabsorption (tropical sprue), inflammatory bowel disease, intestinal malignancies like colon cancer and celiac disease.

† Of uncertain pathogenicity in humans.

Genitourinary infections

Genitourinary infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Cystitis, pyelonephritis, nephritis <i>E. coli</i> (UPEC), [†] <i>Staph. saprophyticus</i> <i>Klebsiella pneumoniae</i> [‡] <i>Enterobacter</i> spp. <i>Enterococcus</i> spp. <i>Proteus mirabilis</i> <i>Chlamydia trachomatis</i> (incl. urethritis, prostatitis) <i>Pseudomonas aeruginosa</i> (hospital-acquired)	Perirenal abscess <i>M. tuberculosis</i> <i>B. pseudomallei</i> (incl. prostatitis)	Hantavirus <i>Schistosoma mekongi</i>
Sexually transmitted infections <i>Chlamydia trachomatis</i> <i>Neisseria gonorrhoeae</i> ^{††} <i>Trichomonas vaginalis</i> Syphilis (<i>Treponema pallidum</i>) Viral (HPV, HSV, HBV, HIV) Chancroid (<i>H. ducreyi</i>) Papillomata (HPV) Parasites (scabies and lice) Pyogenic bacteria (<i>Staphylococcus</i> spp., <i>Streptococcus</i> spp.)	Lymphogranuloma venereum (<i>Chlamydia trachomatis</i>) <i>Entamoeba</i> spp.	

* Consider noninfectious causes, especially malignancies like renal cell carcinoma.

† Throughout Asia *E. coli* can demonstrate MDR to multiple antibiotics.

** *E. coli* and *Klebsiella* spp. associated with ESBL, increasingly common in Asia.

†† See section on antibiotic resistance.

Genitourinary infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Cystitis, pyelonephritis, nephritis Bacterial infections (catheters, renal stones) <i>M. tuberculosis</i> (extrapulmonary TB) Melioidosis (<i>B. pseudomallei</i>)	Candidiasis Melioidosis (<i>B. pseudomallei</i>) <i>M. tuberculosis</i> (extrapulmonary TB)
Sexually transmitted infections Viral: HPV, HSV, HBV, HIV Syphilis (all stages) Chancroid (<i>H. ducreyi</i>) <i>Trichomonas vaginalis</i> <i>Neisseria gonorrhoeae</i> <i>Chlamydia trachomatis</i>	Same panel as immunocompetent patients

Joint, muscle, and soft tissue infections

Joint, muscle, and soft tissue infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Staphylococcus aureus</i> (pyomyositis) Chikungunya <i>Trichinella spiralis</i> Melioidosis (<i>B. pseudomallei</i>) <i>M. tuberculosis</i> (extrapulmonary TB)	Necrotizing fasciitis (GAS, TSST, <i>Vibrio vulnificus</i> , <i>Clostridium perfringens</i> , <i>Bacterioides</i> spp.)* <i>Echinococcus</i> spp. <i>Streptococcus pneumoniae</i> *	Fournier's gangrene (perineum and urogenital) <i>Sarcocystis</i> <i>Sporothrix schenckii</i> <i>Bartonella</i>

*GAS, Group A streptococci; TSST, staphylococcal toxic shock syndrome, consider MRSA.

† Can cause cellulitis, soft tissue infection, scrotal/perineal abscess, arthritis.

Joint, muscle, and soft tissue infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>M. tuberculosis</i> (extrapulmonary TB) <i>M. ulcerans</i> Viral (influenza A and B, chikungunya, dengue, HIV, enterovirus, hepatitis A and B) Melioidosis (<i>B. pseudomallei</i>) Postviral myopathies/chronic fatigue syndrome Madura foot (several different fungi)	<i>Candida</i> spp. <i>M. tuberculosis</i> (extrapulmonary TB) <i>M. avium</i> complex <i>B. pseudomallei</i> (abscess formation)

Skin infections

Skin infections with less than four weeks of symptoms*

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Erysipelas (<i>Staphylococcus aureus</i> , Group A streptococci, <i>Streptococcus pneumoniae</i> [†])	<i>Leishmania</i> spp.	Rat-bite fever (<i>Spirillum minus</i> , <i>S. moniliformis</i>)
Furunculiasis (<i>Staph. aureus</i>)	<i>Cryptococcus neoformans</i>	<i>Erysipelothrix rhusiopathiae</i>
Cutaneous and subcutaneous dermatophytoses	Leptospirosis	Yaws (<i>Trep. pall. pertenue</i>)
<i>N. gonorrhoeae</i>	<i>Strongyloides stercoralis</i> (hyperinfection form)	<i>Leishmania</i> spp.
Syphilis (<i>Treponema pallidum</i>)	Melioidosis (<i>B. pseudomallei</i>)	
<i>Candida</i> spp.	<i>Trichinella spiralis</i>	
<i>Rickettsia</i> spp., <i>O. tsutsugamushi</i> **	<i>Penicillium marneffe</i> [§]	
HIV/AIDS and opp. infections	Gnathostomiasis	
<i>Sporothrix schenckii</i> , <i>S. globosa</i>	Nontuberculous mycobacteria	
<i>M. tuberculosis</i> (extrapulmonary TB)	<i>Streptococcus suis</i>	
Lymphatic filariasis ^{††}		
Scabies (<i>S. scabiei</i>)		
Malaria (<i>Staph. aureus</i> , sweating)		

* A rash due to viral infections was not considered an infection limited to the skin.
[†] Can cause cellulitis, soft tissue infection, scrotal/perineal abscess, arthritis.
^{**} Presence of an eschar only in less than half of patients. Consider DD: insect or spider bite (recluse spider), cutaneous anthrax, cat scratch disease, tuberculosis, tularemia, leishmaniasis, fungal lesion (sporotrichosis, *Aspergillus*, mucormycosis).
^{††} Common in Bangladesh, Myanmar, Indonesia, Timor-Leste.
[§] *Penicillium marneffe* is endemic in Myanmar, Cambodia, Southern China, Indonesia, Laos, Malaysia, Thailand, and Vietnam.

Skin infections with more than four weeks of symptoms and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Syphilis (<i>Treponema pallidum</i>)	<i>Candida</i> spp.
Extrapulmonary tuberculosis	<i>Penicillium marneffe</i> [†]
Melioidosis (<i>B. pseudomallei</i>)	Extrapulmonary tuberculosis
<i>Mycobacterium leprae</i>	Scabies (<i>Sarcoptes scabiei</i> var. <i>hominis</i>)
<i>Pityriasis versicolor</i>	Melioidosis (<i>B. pseudomallei</i>)
Malaria (<i>Staph. aureus</i> , sweating)	<i>M. avium</i> complex
Intertrigo (<i>Candida</i> spp., <i>Corynebacterium</i> spp., dermatophytes)	<i>Sporothrix schenckii</i> , <i>S. globosa</i>

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Folliculitis (<i>Staph. aureus</i>) <i>M. ulcerans</i>	Animal bites** <i>M. ulcerans</i>
<p>* A rash due to viral infections was not considered an infection limited to the skin. † <i>Penicillium marneffe</i> is endemic in Myanmar, Cambodia, Southern China, Indonesia, Laos, Malaysia, Thailand, and Vietnam. ** Stray dogs are common throughout SEA and splenectomized travelers in particular must beware of dog bites (<i>Pasteurella multocida</i> and <i>Captncytophaga canimorsus</i>).</p>	

Adenopathy

Adenopathy of less than four weeks duration

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Regional LN		
Syphilis, <i>H. ducreyi</i> , <i>Chlamydia trachomatis</i> (LGV)	<i>Leishmania</i> spp.	Plague (<i>Y. pestis</i>)
<i>Rickettsia</i> spp., <i>O. tsutsugamushi</i>	<i>Bartonella</i> spp. (cat scratch disease)	<i>Babesia microtus</i>
Skin lesions (fungal, secondary or superinfections)	Lymphatic filariasis (<i>W. bancrofti</i> , <i>B. malayi</i>)	Rat-bite fever*
Nontuberculous mycobacteria	Melioidosis	
Systemic LN		
Viral infection (HIV, EBV, CMV, parvovirus B19, enterovirus, etc.)	<i>M. avium</i> complex	
HIV (incl. primo-infection)	Leishmaniasis	
<i>Rickettsia</i> spp., <i>O. tsutsugamushi</i>	Lymphatic filariasis	
Extrapulmonary tuberculosis	Leptospirosis	
Toxoplasmosis (<i>T. gondii</i>)		
* Caused by <i>Spirillum minus</i> or <i>S. moniliformis</i> .		

Adenopathy of more than four weeks duration and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Toxoplasma gondii</i>	<i>Penicillium marneffe</i>
Extrapulmonary tuberculosis (<i>M. tuberculosis</i>)	CMV
Melioidosis (<i>B. pseudomallei</i>)	<i>M. avium</i> complex
<i>Penicillium marneffe</i>	<i>Toxoplasma gondii</i>
	Extrapulmonary tuberculosis (<i>M. tuberculosis</i>)
	Melioidosis (<i>B. pseudomallei</i>)
* If the diagnosis is not made within a few days, biopsies should be performed to exclude malignancies like lymphoma and carcinomas.	

Fever without focal symptoms

Fever for less than four weeks without focal symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Viral infection (HIV, EBV, CMV, barvovirus B19, enterovirus, etc.) <i>Plasmodium falciparum</i> , <i>P. vivax</i> Flaviviridae (dengue, chikungunya, JEV) <i>Leptospira</i> spp. <i>Rickettsia</i> spp., <i>O. tsutsugamushi</i> HIV/AIDS <i>Toxoplasma gondii</i> Extrapulmonary tuberculosis <i>Burkholderia pseudomallei</i> <i>Salmonella enterica</i> (typhoidal, nontyphoidal)	Nontuberculous mycobacteria <i>Coxiella burnetii</i> <i>Penicillium marneffei</i> <i>Bartonella</i> spp. <i>Brucella</i> spp. <i>P. malariae</i> , <i>P. ovale</i> , <i>P. knowlesi</i>	<i>Neorickettsia sennetsu</i> <i>Babesia microtous</i> Tularemia Ehrlichiosis
Note that deep-seated abscesses may not have focal features, and endocarditis may not have other clinical manifestations.		

Fever for more than four weeks without focal symptoms and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Toxoplasma gondii</i> Tuberculosis (<i>M. tuberculosis</i>) <i>M. leprae</i> Typhoid, paratyphoid (<i>Salmonella</i> spp.) Abscess	<i>M. avium</i> complex <i>Toxoplasma gondii</i> Extrapulmonary tuberculosis <i>Penicillium marneffei</i> Leishmaniasis (visceral > cutaneous forms) Microsporidium spp. <i>Babesia microtous</i> (RF: CD4 <200/ μ L and splenectomy) CMV
*Noninfectious causes should be considered from the beginning, including malignancies like lymphoma and autoimmune diseases.	

Eosinophilia and elevated IgE

Eosinophilia and elevated IgE for less than four weeks*

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Strongyloides stercoralis</i> [†] Hookworm (<i>Ancylostoma</i> , <i>Necator</i>) [†]	<i>Taenia solium</i> (cysticercosis) Streptococcal – scarlet fever	Hydatid disease (<i>Echinococcus granulosus</i>) <i>Anisakis</i> spp.

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Trichuris trichiura</i>	<i>Paragonimus westermanii</i>	Influenza, SARS and bird flu (outbreak settings)
<i>Ascaris lumbricoides</i> Flukes (<i>Opisthorchis viverrini</i> , <i>Clonorchis sinensis</i> , <i>Fasciola hepatica</i>)	<i>Angiostrongylus cantonensis</i> [†] <i>Trichinella spiralis</i>	
Lymphatic filariasis (<i>W. bancrofti</i> , <i>B. malayi</i> and <i>B. timori</i>)	<i>Gnathostoma</i> spp.	
<i>Schistosoma mekongi</i> , <i>S. japonicum</i>	Drug hypersensitivity syndrome (DHS)**	
<i>Enterobius vermicularis</i> <i>Dientamoeba fragilis</i>	Advanced HIV infection	

* Consider "allergic"/hematological/dysplastic/immunological disorders and potential drug associations before starting extensive parasitological examinations.

[†] Larval migration through lungs causes pulmonary symptoms and eosinophilia.

** DHS can be serious. It is characterized by fever, rash, and internal organ involvement. Ensure prompt identification of suspect responsible medicines and avoidance of reexposure. Caveat: cross-reactivity to structurally related medicines is common and first-degree relatives may be predisposed.

Eosinophilia and elevated IgE for more than four weeks and in the immunocompromised host

All helminthic infections mentioned above may cause eosinophilia after four weeks in subjects with adequate immune responses and in immunocompromised hosts. Advanced HIV infection itself (CD4 <200/ μ L) can cause eosinophilia.

Antibiotic resistance

Malaria

South-east Asia is the epicenter of drug resistance in *P. falciparum*, especially MDR and artemisinin resistance in Cambodia and adjacent countries, but risks to travellers are low. Highly chloroquine (CQ)-resistant strains of *P. vivax* are found in parts of Indonesia.

In parts of the Greater Mekong subregion, artemisinin resistance is prevalent and in Cambodia and eastern Myanmar, there are increased failure rates, with the best available treatment for *falciparum* malaria being artemisinin combination therapies (ACTs). Spread or emergence of MDR, including resistance to ACTs, is an urgent public health concern that is threatening the ongoing global effort to reduce the burden of malaria.

Elsewhere in the region, ACTs are highly effective.

Multidrug-resistant *M. tuberculosis*

Around one-third (28%) of the world's MDR-TB cases are in the SEA region. The leading countries in SEA reporting first-line anti-TB drug resistance per 2010 are India with 2.3% MDR among new TB cases (95% confidence interval (CI)) and 17.2% in previously treated TB cases, Myanmar with 4.2% and 10.0%, and Thailand with 1.7% and 34.5% respectively.

In 2014 there were about 480 000 new cases of MDR tuberculosis (MDR-TB). Extensively drug-resistant tuberculosis (XDR-TB) has been identified in 100 countries. On average, an estimated 9% of people with MDR-TB have XDR-TB. Although MDR-TB is a growing concern, it remains largely underreported in SEA, compromising control efforts.

Multidrug-resistant *Salmonella* spp.

Typhoid Plasmid-encoded resistance to chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole in *Salmonella enteritica* serovar *typhi* (MDRST) has been prevalent in SEA for many years. Chromosomal fluoroquinolone resistance (mutations of DNA gyrase *gyrA*) has spread widely in the past decade.

Nontyphoidal salmonellosis (NTS) A MDR strain of *S. typhimurium*, termed definitive phage type 104 (DT104), is emerging worldwide. It is resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracyclines, but is not more virulent than the susceptible strains. Quinolone resistance in NTS strains is common in SEA, mainly due to DNA gyrase and topoisomerase alterations [4]. At present, reports of third-generation cephalosporin resistance are increasing for both typhoidal and nontyphoidal salmonellosis. Azithromycin remains effective in most areas. Clinical management requires careful microbiological assessment.

Drug-resistant *S. pneumoniae*

Resistance of *Streptococcus pneumoniae* to beta-lactams, macrolides, tetracyclines, chloramphenicol, and sulfonamides has been increasing rapidly in SEA. Fortunately, high-level penicillin resistance is still rare in the region. Vancomycin (w/rifampicin) has been required to treat patients with pneumococcal meningitis caused by strains resistant to extended-spectrum cephalosporins (e.g. cefotaxime and ceftriaxone). Korea has the highest frequency of nonsusceptible strains to penicillin, with 80%, followed by Japan, Vietnam, and Thailand. SEA is the world leader in *S. pneumoniae* macrolide resistance (especially Vietnam, Korea, and Japan) [5,6].

Rickettsial disease

Reports of prolonged fever clearance times and potential resistance to doxycycline have been reported from north Thailand, south India, and Korea. Azithromycin is the alternative regimen, including for pregnant women and children [7].

Multidrug-resistant Enterobacteriaceae

The rates of MDR in Enterobacteriaceae have risen drastically in SEA, mainly due to spread of ESBLs among isolates of Enterobacteriaceae from both community and healthcare settings. These enzymes confer resistance to third- and fourth-generation cephalosporins and monobactams, and are frequently associated with co-resistance to other antimicrobials, such as fluoroquinolones (emerging plasmid-mediated quinolone resistance), co-trimoxazole, tetracyclines, and aminoglycosides. The most common organisms affected are *E. coli* and *Klebsiella pneumoniae*.

So far, no evidence for importation of MDR Enterobacteriaceae carrying the *bla*NDM-1 gene (New Delhi metallo-beta-lactamase) from India to SEA has been described (*Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*). Awareness of MDR bacteria carrying NDM-1 is crucial, as they are resistant to most antibiotics, but still appear to respond to colistin and tigecycline.

Untreatable and hard-to-treat infections from carbapenem-resistant Enterobacteriaceae (CRE) bacteria are on the rise among patients in medical facilities. CRE have become resistant to all or nearly all the antibiotics we have today. Almost half of hospital patients who get bloodstream infections from CRE bacteria die from the infection.

Gonorrhoea

Multidrug resistance in *N. gonorrhoeae* (resistance to ciprofloxacin, tetracycline, spectinomycin, and penicillin) has increased rapidly in SEA in recent years, mainly due to high rates of gonorrhoea and uncontrolled use of antibiotics. Many developed countries now recommend the use of third-generation

cephalosporins instead of quinolones for the treatment of gonorrhoea. Gonococcal resistance to third-generation cephalosporins given orally has already emerged in SEA. Treatment failures due to resistance to treatments of last resort for gonorrhoea (third-generation cephalosporins) have been reported from 10 countries. Gonorrhoea may soon become untreatable as no vaccines or new drugs are in development.

HIV/AIDS and immunocompromised people

Antiretroviral therapy (ART) has been available in some SEA countries for almost two decades, but the HIV incidence and ART coverage rates in countries like Cambodia, Laos, and Bangladesh remain limited. In the more developed setting like Thailand, HIV drug resistance threshold surveys based on blood bank and counseling centers show a low prevalence (<5%) of transmitted HIV drug resistance [8]. Travel-associated prophylaxis and antimicrobial treatment may interfere with established HIV drug levels of patients under ART.

Influenza

The constantly evolving nature of influenza means that resistance to antiviral drugs is continuously emerging. By 2012, virtually all influenza A viruses circulating in humans were resistant to drugs frequently used for the prevention of influenza (amantadine and rimantadine). However, the frequency of resistance to the neuraminidase inhibitor oseltamivir remains low (1–2%).

Vaccine-preventable diseases in children

Immunization is among the most successful and cost-effective public health interventions. Nonetheless, during 2002, approximately 1.9 million (76%) of the worldwide 2.5 million vaccine-preventable deaths (VPD) deaths among children aged <5 years occurred in Africa or SEA. Through optimal use of currently existing vaccines alone, further significant reduction of mortality rates among children under five can be achieved [9].

The major VPD in SEA are diphtheria, tetanus, pertussis, poliomyelitis, hepatitis A and B, *Haemophilus influenzae* B, measles, meningococcal and pneumococcal disease, rabies, typhoid, and Japanese encephalitis. Strong emphasis on completing basic vaccination schedules is a required priority. In SEA, the percentage coverage of DTP (three doses) in <1-year-old children was 72% (2010) and hepatitis B coverage stands at 40% (2008) [10]. Although vaccination coverage is improving in some countries, measles transmission persists in SEA. Influenza infections can occur throughout the year in tropical areas. Polio resurfaced in Indonesia in 2005 and imported cases in neighboring countries have occasionally occurred. Unvaccinated people traveling or working in SEA should receive adequate counseling.

Basic economic and demographic data

Country	GNI per capita (USD)*	Life expectancy at birth (total, years)†	School enrollment, primary (% net and year)**
Brunei Darussalam	36 710	77	91 (2013)
Cambodia	1010	64	98 (2012)
Indonesia	3650	72	92 (2012)
Lao PDR	1600	64	97 (2013)
Malaysia	10 660	75	98 (2006)

(Continued)

Country	GNI per capita (USD)*	Life expectancy at birth (total, years) [†]	School enrollment, primary (% net and year)**
Myanmar (Burma)	1270	66	90 (2005)
Philippines	3440	72	90 (2013)
Singapore	55 150	84	NA
Thailand	5410	74	95 (2008)
Timor-Leste	3120	67	91 (2011)
Vietnam	1890	73	98 (2013)

*World Development Indicators database, World Bank, July 2015. <http://data.worldbank.org/indicator/NY.GNP.PCAP.CD>.

[†]World Factbook, CIA, July 2015. www.cia.gov/library/publications/the-world-factbook/rankorder/2102rank.html.

**World Bank, School enrollment, primary, July 2015 (%net). <http://data.worldbank.org/indicator/SE.PRM.NENR>
GNI, gross national income; NA, not available.

Causes of death in children underfive in SEA. Regional average*

The number of deaths among children aged <5 years old in the SEA region (WHO data) was reduced from 1 137 000 in 2000 to 845 000 in 2013 (WHO, World Health Statistics 2015).

Causes of death (<5 years)	%
HIV/AIDS	0.4
Diarrhea	9.5
Measles	2.6
Malaria	0.7
Acute lower respiratory tract infections	13.6
Prematurity	25.5
Birth asphyxia and birth trauma	11.5
Neonatal sepsis	8.3
Congenital abnormalities	7.7
Other communicable, perinatal, and nutritional conditions	8.5
Other noncommunicable diseases	3.7
Injuries	4.6

*WHO Global Health Observatory Data Repository. Regional averages, data from 2013. <http://apps.who.int/gho/data/node.main.CM300REG6?lang=en>.

Ten most common causes of deaths all ages* in three countries of SEA

Data summarized for a low (Cambodia), middle (Thailand), and high (Singapore) GNI per capita.

Common causes of deaths	%		
	Cambodia [†]	Thailand**	Singapore ^{††}
HIV/AIDS	3	4	NS
Tuberculosis	10	NS	NS

Common causes of deaths	%		
	Cambodia [†]	Thailand**	Singapore ^{††}
Diarrheal diseases	7	NS	NS
Perinatal conditions	5	NS	NS
Ischemic heart disease	10	14	18
Lower respiratory infections	8	9	17
Cerebrovascular disease	7	10	9
Chronic obstructive lung disease	NS	5	3
Road traffic accidents	3	5	NS
Meningitis	4	NS	NS
Malaria	2	NS	NS
Diabetes mellitus	NS	4	4
Liver, GI, and lung cancer	2	7	16
Urogenital diseases	NS	3	4
Measles	NS	NS	NS

*WHO statistics. Mortality profile per country.
[†] Cambodia: www.who.int/gho/countries/khm.pdf?ua=1.
** Thailand: www.who.int/gho/countries/tha.pdf?ua=1.
^{††} Singapore: www.who.int/gho/countries/sgp.pdf?ua=1.
NS, not stated, i.e. not included in the 10 most common causes of death.

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Chapter 16

Western Asia and the Middle East

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The Western Asia and Middle East region is both ethnically and geographically diverse. The region stretches from arid deserts in the south to mountainous and temperate areas in the northern part. Nations in this area are characterized by a wide range of cultural backgrounds and religious history. Socioeconomic disparity is wide, including industrialized affluent economies and developing economies. As in most of the destinations, the most common infections in travelers are gastrointestinal conditions. In a key GeoSentinel study published in 2007, the common causes of fever from this region were respiratory and diarrheal illnesses (16% each), while 31% of travelers with fever after traveling to the region remained undiagnosed. Several specific infections endemic in this region, including leishmaniasis, brucellosis, rickettsiosis, relapsing fever, and endemic viral diseases such as West Nile fever, will be discussed further. Chronic and latent infections which should be considered in immigrants from this region include echinococcosis and neurocysticercosis.

Vector-borne diseases

Malaria risk in this area is very low. Most countries in the region are malaria free. In a few countries, malaria exist in some focal areas only, and solely due to *P. vivax* such as in Iran and southern Saudi Arabia. Surprisingly, malaria has not been reported from Syria. Therefore, in our view, malaria prevention in this region should be based on personal protection by mosquito repellents only. In

Infectious Diseases: A Geographic Guide, Second Edition. Edited by Eskild Petersen, Lin H. Chen, and Patricia Schlagenhauf-Lawlor.

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Yemen, *P. falciparum* exists in all areas at altitudes below 2000 meters. Therefore, malaria is a rare cause of fever in travelers returning from the region, but since it is still endemic in some regions it must be included in the differential diagnosis.

Both cutaneous and visceral leishmaniasis are endemic in vast areas of Western Asia and the Middle East [1]. Cutaneous leishmaniasis is widespread in the region. The majority of cases are due to *Leishmani major*, but *L. tropica* was recently reported in Israel and Jordan [2, 3]. Leishmaniasis is very prevalent in refugees from Syria [4]. Visceral leishmaniasis occurs throughout the region and especially in small foci in Iraq, Saudi Arabia, and Syria.

Filariasis (*Wuchereria bancrofti*) is still endemic in some area of Yemen. Tick-borne infections such as *Rickettsia conori*, *R. africae* and relapsing fever (due mainly to *Borrelia persica*) are reported in most areas in the region [5, 6].

Viral arthropod-borne diseases are also among the important pathogens endemic in all these countries. These include West Nile virus [7], Sindbis [8], Toscana virus [9], and Crimean-Congo hemorrhagic fever [10, 11]. Dengue fever outbreaks have been reported from Saudi Arabia and Yemen [12]. It is important to note that the *Aedes albopictus* mosquito, which can transmit dengue and chikungunya, was introduced into the region in the last few years. However, local transmission of chikungunya has not yet been reported.

Hemorrhagic fever virus

The arbovirus that causes Alkhurma hemorrhagic fever emerged in Saudi Arabia in the mid-1990s. In addition to dengue and Kadam viruses [13], which are known to be endemic in Saudi Arabia, it is thought that other flaviviruses exist in the region, though undetected [14, 15].

Soil- and water-associated diseases

Schistosoma mansoni is only present in Yemen, Saudi Arabia, and Southern Oman. *S. haematobium* has a wider distribution in Western Asia and the Middle East. Leptospirosis is pandemic and should be suspected in febrile travelers with a recent history of fresh water or soil exposure [16, 17].¹ Geohelminthic infections (hookworm, strongyloidosis or ascariasis) may occur in exposed travelers.

Zoonotic infections

Several important zoonoses must be considered in travelers returning from the region. Febrile illnesses including endocarditis, osteomyelitis, epididymitis, and orchitis are common manifestations of brucellosis [18]. While Q-fever is a pandemic cause of fever, it is increasingly recognized in travelers and local populations in the region. Rabies is endemic throughout the region and several countries occasionally report outbreaks [19]. Anthrax must be considered in the setting of its classic presentation and is frequently reported from the region [20]. Echinococcosis, caused by the tapeworm *Echinococcus granulosus*, is endemic in Western Asia and the Middle East [21].

Brucellosis is caused by *Brucella* spp. and is transmitted from animals to humans by direct contact with infected animals or consumption of raw animal products such as unpasteurized milk or cheese [22]. It is estimated that the annual incidence of brucellosis in Saudi Arabia is between 9 and 21.4/100000 population [22, 23].

Crimean-Congo hemorrhagic fever (CCHF) was also reported in Oman and United Arab Emirates [24, 25]. Seroprevalence of CCHF among individuals working in animal contact-related jobs was 30.3% of 241 non-Omani citizens and 2.4% of 41 Omani citizens [26].

Hajj – medical aspects

One of the unique aspects of the region is the Hajj pilgrimage. Every year millions of pilgrims from around the world gather under extremely crowded conditions in Makkah, Saudi Arabia, to perform the Hajj [27]. Transmission of infectious diseases during the Hajj is a major concern during the extended stays at Hajj sites due to the physical exhaustion, extreme heat, and crowded accommodation [28]. Two major outbreaks of meningococcal disease occurred in recent years associated with the annual Hajj pilgrimage. The first outbreak occurred in 1987 and was caused by *N. meningitidis* serogroup A. The outbreak resulted in an attack rate of 640 per 100 000 American pilgrims. Subsequently, Saudi Arabia required vaccination against *N. meningitidis* serogroup A as a condition for receiving the Hajj visa [29, 30]. Serogroup W-135 was identified in 6.4% of 483 confirmed cases of meningococcal disease admitted to Makkah hospitals from 1987 through 1997 [31]. However, in the 2000 Hajj, more than 400 cases of W-135 infection in pilgrims and their close contacts were reported from 16 countries, with an attack rate in returning pilgrims of 25–30 per 100 000 persons [31]. Subsequently, quadrivalent vaccine has been required for entry into Saudi Arabia for the Hajj.

A high incidence of respiratory infection, including influenza, has been reported at the Hajj in Makkah, Saudi Arabia. In a study of 260 pilgrims, 150 were from the UK and 110 were Saudi; 38 (25%) UK pilgrims and 14 (13%) Saudi pilgrims had respiratory infections detectable by rtRT-PCR. Rhinovirus infection was present in 13% of the UK group and 3% of the Saudi group. The other isolated viruses included influenza virus, parainfluenza virus, and respiratory syncytial virus [32]. During the Hajj season, there is intense congestion, living in close proximity and an increasing number of elderly pilgrims. These factors may increase the risk of transmission of tuberculosis (TB) [33]. Moreover, many Muslims travel from countries of high TB endemicity. However, the risk of TB transmission during the Hajj season is not known. In a study from Singapore, 10% of 357 pilgrims showed a substantial rise in immune response to QuantiFERON TB assay antigens post-Hajj when compared to a pre-Hajj test [33].

Another respiratory illness that may be important during the Hajj is pertussis. One study showed that 1.4% of pilgrims acquired pertussis [34]. Thus, some authors recommended the administration of acellular pertussis vaccine to pilgrims before the Hajj season [34].

International spread of poliomyelitis through pilgrimage is a major concern for Saudi Arabia. Since poliomyelitis had not been eradicated in Afghanistan, Nigeria, and Pakistan, all pilgrims from these four countries, regardless of age and vaccination status, are required to show a proof of at least one dose of oral polio vaccine (OPV) six weeks or more prior to departure in order to apply for an entry visa for Saudi Arabia. These travelers will also receive a dose of OPV at border points when arriving in Saudi Arabia [35].

Rift Valley fever (RVF) virus is a zoonotic virus causing severe disease, abortion, and death in domestic animals (especially young sheep, cattle, and goats) in Africa and the Arabian Peninsula. The first confirmed cases in the Arabian Peninsula occurred in September 2000 in the south-western coastal part of Saudi Arabia and neighboring areas of Yemen. There were more than 120 human deaths and major losses in livestock populations from disease and slaughter [36, 37].

The emergence of Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 attracted considerable attention as the disease was initially described a few weeks before the Hajj [38]. Vigilance and surveillance during 2013–2016 Hajj seasons increased and samples were taken from all suspected cases and were tested for different viruses, including MERS-CoV [39]. None of the samples was positive for MERS-CoV [39].

CNS infections: meningitis, encephalitis

Acute infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Enteroviruses, Coxsackievirus, herpes virus, varicella zoster virus, Toscana virus <i>Neisseria meningitidis</i> , <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i>	Rabies virus, West Nile virus Neurosyphilis <i>Listeria</i> <i>Mycobacterium tuberculosis</i> , <i>Brucella</i> , <i>Rickettsia</i> <i>proWazekii</i> , <i>R. conorii</i> HIV	Influenza <i>Brucella</i> , <i>Klebsiella pneumoniae</i> , <i>T. whipplei</i> , <i>Rickettsia</i> spp. <i>Naegleria</i> and other free-living ameba

Infection with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than four weeks	Microorganisms in the immunocompromised host
HIV <i>Mycobacterium tuberculosis</i> [10, 11], neuroborreliosis	<i>Mycobacterium tuberculosis</i> <i>Cryptococcus</i> spp., <i>Candida</i> spp., <i>Aspergillus</i> spp., <i>Nocardia</i> , <i>Toxoplasma</i>
*Consider noninfectious causes like lymphoma.	

Ear, nose, and throat infections

Ear, nose, and throat infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Rhinovirus, coronavirus, VRS, myxovirus, herpes virus, adenovirus, enterovirus (tonsillitis, rhinitis, otitis), Epstein–Barr virus (tonsillitis) <i>Streptococcus</i> (tonsillitis, otitis), <i>Haemophilus B catarrhalis</i> (otitis)	Vincent's angina <i>Mycobacterium tuberculosis</i> (tonsillitis, otitis)	Diphtheria (tonsillitis)

Ear, nose, and throat with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Tuberculosis, syphilis (tonsillitis)	<i>Candida</i> spp.
*Consider noninfectious causes like cancer.	

Cardiopulmonary infections

Pneumonia with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Influenza <i>Streptococcus pneumoniae</i> , <i>Mycoplasma pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Staphylococcus aureus</i> , <i>Chlamydia pneumoniae</i> , <i>Coxiella burnetii</i>	<i>Legionella pneumophila</i> <i>Chlamydia psittaci</i> Meloidosis (reported from Iran and Oman)	Diphtheria, <i>Klebsiella pneumoniae</i> (nosocomial)

Endocarditis with less than four weeks of symptoms [13,14]

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Staphylococcus</i> and <i>Streptococcus</i> spp.	<i>Neisseria gonorrhoeae</i> , <i>Coxiella burnetii</i> , HACEK group <i>Brucella</i> , <i>Bartonella</i> spp.	<i>Candida</i> spp. Morbus Whipple

Pulmonary symptoms for more than four weeks and in the immunocompromised host*

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
COPD Tuberculosis <i>Brucella</i> <i>Aspergillus</i>	CMV <i>Coxiella</i> <i>Aspergillus</i> , <i>Candida</i> , <i>Pneumocystis</i>
*Consider noninfectious causes like lung cancer, autoimmune lung fibrosis, Wegener's granulomatosis.	

Endocarditis for more than four weeks and in the immunocompromised host*

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Staphylococcus</i> and <i>Streptococcus</i> spp. <i>Enterococcus</i> , <i>Coxiella burnetii</i> , <i>Bartonella quintana</i> , <i>Brucella</i>	<i>Aspergillus</i> , <i>Candida</i> rhinovirus
*Consider noninfectious causes like sarcoidosis.	

Gastrointestinal infections**Gastrointestinal infections with less than four weeks of symptoms***

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Adenovirus, norovirus and calicivirus, hepatitis A, rotavirus <i>Escherichia coli</i> , ETEC, VTEC, <i>Salmonella typhi</i> and non- <i>typhi</i> , <i>Campylobacter</i> , <i>Shigella</i> , <i>Yersinia</i> <i>Giardia intestinalis</i> , <i>Trichomonas intestinalis</i> , <i>Entamoeba histolytica</i> Hookworms, <i>Ascaris lumbricoides</i> <i>Enterobius vermicularis</i> (pinworm) <i>Bacillus cereus</i> food poisoning, staphylococcal food poisoning	Hepatitis E Morbus Whipple <i>Helicobacter pylori</i> Cryptosporidia spp.	Tuberculosis, Whipple <i>Cyclospora cayentanesis</i>
*Consider noninfectious causes like inflammatory bowel disease and intestinal malignancies like colon cancer.		

Repeated negative bacterial cultures and microscopy for parasites should lead to the consideration that the symptoms may not be caused by an infection. Inflammatory bowel disease like colitis and Mb Chron are differential diagnoses and malabsorption and celiac disease must also be considered.

Gastrointestinal infections with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Hepatitis E Whipple, tuberculosis <i>Giardia intestinalis</i> , <i>Entamoeba histolytica</i> , cryptosporidia, <i>Trichomonas intestinalis</i> , helminths (<i>Ascaris lumbricoides</i> , <i>Trichuris trichiura</i> , <i>Hymenolepis nana</i> , <i>Strongyloides stercoralis</i> , <i>Echinococcus granulosus</i> , <i>Schistosoma mansoni</i> (Sudan and Egypt only) [18]	Herpes virus, CMV <i>Isospora</i> , <i>Microsporidium</i> <i>Candida</i>
*Consider noninfectious causes like inflammatory bowel disease, and intestinal malignancies like colon cancer, malabsorption and celiac disease.	

Infections of liver, spleen, and peritoneum

Acute infections of liver, spleen, and peritoneum with less than four weeks of symptoms

	Frequently found disease	Rare diseases
Jaundice	Hepatitis A, B, C, E* EBV, CMV infection Leptospirosis	Rickettsiosis Syphilis II
Space-occupying lesion in liver	Bacterial liver abscess	Amebic liver abscess
Splenomegaly	Typhoid fever Visceral leishmaniasis (in children) Bacterial endocarditis Viral hepatitis EBV, CMV Brucellosis Tuberculosis	Visceral leishmaniasis (in adults) Relapsing fever (<i>Borrelia recurrentis</i>)

*Hepatitis E is often missed in both travelers and locally infected patients and should be considered.

Chronic infections of liver, spleen, and peritoneum with more than four weeks of symptoms

	Frequently found disease	Rare diseases
Jaundice	Chronic viral hepatitis (B, C) Schistosomiasis*	Brucellosis Q-fever hepatitis Toxocariasis Hepatic tuberculosis [†] Leprosy [†] Histoplasmosis Tuberculosis
Space-occupying lesion in liver		
Ascites	Tuberculous peritonitis	Schistosomiasis*
Splenomegaly	Hepatosplenic schistosomiasis Brucellosis Amebic liver abscess	Tuberculosis

*Hepatic schistosomiasis is most often due to *S. mansoni* and only present in Yemen and western Oman. No data from Syria.

[†]Hepatic TB may occur as miliary, nodular, and solitary abscess forms.

Infections of liver, spleen, and peritoneum in immunocompromised host

Infections in the immunocompromised host are no different from those in the immunocompetent host.

Genitourinary infections

Cystitis, pyelonephritis, and nephritis with less than four weeks of symptoms*

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>E. coli</i> , <i>Klebsiella pneumoniae</i> , <i>Staphylococcus saprophyticus</i> , <i>Proteus mirabilis</i>	<i>Pseudomonas aeruginosa</i> , <i>Enterococcus faecalis</i>	Tuberculosis

*Consider noninfectious causes, especially malignancies like renal cell carcinoma.

Sexually transmitted infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Chlamydia</i> spp., <i>Neisseria gonorrhoeae</i> , <i>Gardnerella vaginalis</i> , syphilis <i>Trichomonas vaginalis</i>	Lymphogranuloma venereum, Ducrey's disease <i>Entamoeba dispar</i> and <i>E. histolytica</i>	

Cystitis, pyelonephritis, and nephritis with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Tuberculosis, <i>Schistosoma haematobium</i> [20]	<i>Candida</i>

*Consider noninfectious causes, especially malignancies like renal cell carcinoma.

Sexually transmitted infections with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
HIV Herpes virus Papilloma virus, HPV Hepatitis B virus Syphilis <i>Neisseria gonorrhoeae</i>	Syphilis Lymphogranuloma venereum <i>Entamoeba histolytica</i> and <i>E. dispar</i>

Joint, muscle, and soft tissue infections

Joint, muscle, and soft tissue infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Staphylococcus aureus</i> <i>Streptococcus</i> (not <i>pneumoniae</i>)		Lice, scabies

Joint, muscle, and soft tissue infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Tuberculosis	<i>Candida</i> , dermatophytes, <i>Cryptococcus</i> , atypical mycobacteria

Skin infections

Skin infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Erysipelas, <i>Streptococcus</i> (not <i>pneumoniae</i>) <i>Staphylococcus aureus</i> <i>Borrelia</i> spp. Dermatomycosis, scabies		Anthrax

We have not listed a rash due to viral infections as this is not considered an infection limited to the skin.

Skin infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Syphilis, tuberculosis, Lepra <i>Leishmania</i> Blastomycosis Scabies	<i>Candida</i> Dermatophytes [23]

Adenopathy

Adenopathy of less than four weeks duration

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Epstein–Barr virus, cytomegalovirus, parvovirus B19, HIV <i>Toxoplasma gondii</i>	Tularemia <i>Bartonella</i>	<i>Ehrlichia</i> Anthrax <i>Yersinia pestis</i> [24]

Adenopathy of more than four weeks duration and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Rubella, <i>Toxoplasma gondii</i> Tuberculosis	Adenovirus, HIV, CMV

If the diagnosis is not made within a few days, biopsies should be performed to exclude malignancies like lymphoma and carcinomas.

Fever without focal symptoms

Fever for less than four weeks without focal symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Salmonella typhi</i> , Mediterranean spotted fever (<i>Rickettsia coronii</i>), <i>Rickettsia</i> spp., <i>Brucella</i> , Crimean-Congo hemorrhagic fever, <i>Streptococcus</i> (endocarditis) <i>Listeria</i> Dengue Chikungunya Malaria (Sudan only) [42], amebiasis	Tuberculosis, <i>Coxiella burnetii</i> , <i>Bartonella quintana</i> Leptospirosis Hantavirus – Old World Armenia, Georgia, Israel (seropositivity among dialysis patients), Kuwait, Turkey <i>Schistosoma</i>	<i>Leishmania</i> (visceral), Toscana virus (reported from Iran, Iraq, Israel, Jordan), Alkhurma virus, Khurma virus, Zika virus

Fever for more than four weeks without focal symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Coxiella burnetii</i> , tuberculosis, <i>Bartonella quintana</i>	Leishmaniasis (visceral), tuberculosis, <i>Mycobacterium</i> (atypical)

Noninfectious causes should be considered from the beginning, including malignancies like lymphoma and autoimmune diseases.

Eosinophilia and elevated IgE

Eosinophilia and elevated IgE for less than four weeks

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Ascaris lumbricoides</i> , <i>Trichuris trichiura</i> , <i>Hymenolepis nana</i>	<i>Toxocara</i> , <i>Fasciola</i>	Myiasis [45], filariasis, <i>Trichinella</i> spp.

Eosinophilia and elevated IgE for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Strongyloides stercoralis</i> , <i>Echinococcus granulosus</i> , <i>Schistosoma mansoni</i> and <i>S. haematobium</i> , <i>Dracunculus medinensis</i> (Sudan only)	

Basic diagnostics in patients with eosinophilia and elevated IgE

Microorganism	Diagnostics
<i>Ascaris</i> spp. <i>Toxocara</i> spp.	Fecal microscopy Serology

Eosinophilia may occur in up to 10% of travelers. Eosinophilia and elevated IgE in travelers are usually caused by helminthic infections. Other causes include allergies and asthma, drug hypersensitivity, infection, and neoplasm. Common causes in West Asia and the Middle East include *Strongyloides*, hookworm infection (during the acute phase), and *Wuchereria bancrofti* (filariasis). Other possible causes include toxocariasis (visceral and ocular larva migrans), trichinosis, and *Ascaris* (during the acute phase). *Schistosoma mansoni* is only present in Yemen, Saudi Arabia, and Oman. If acute schistosomiasis is suspected, it is important to inquire regarding fresh water exposure in these areas. Finally, echinococcosis may cause eosinophilia during spillage or cyst perforation.

Antibiotic resistance

The rate of antimicrobial resistance in major human pathogens is increasing in many parts of the world and specifically in this region. Antimicrobial resistance is a major problem especially among gram-negative bacilli. For example, ciprofloxacin resistance of *Enterobacter cloacae* in Saudi Arabia increased from 8.3% in 2000 to 17.4% in 2006 [40]. Fluoroquinolone resistance is a major concern, with emerging problems in many countries in the Middle East. In one study, *Klebsiella pneumoniae* resistance to ciprofloxacin increased from 2.6% to 23% over time [41]. A high rate (31%) of resistance was also reported among community isolates of urinary isolates of *E. coli* in Oman [42]. However, a much higher rate of ciprofloxacin resistance, reaching 97.4%, was reported from United Arab Emirates in *Pseudomonas aeruginosa* [43].

Resistance among *Streptococcus pneumoniae* is another concern. In a study of invasive pneumococcal disease, the rate of penicillin resistance reached up to 78% [43]. In addition, erythromycin resistance in this region is more prevalent in younger children, ranging from 8% in isolates of older children (under age 14) to 26% in isolates of children under five years of age. Cephalosporin resistance in invasive pneumococci reached 12% in children under age 12 in Qatar [44].

Multidrug-resistant *A. baumannii* is found in 14–35.8% of isolates in Saudi Arabian hospitals [45, 46]. Community-acquired methicillin-resistant *S. aureus* (MRSA) has recently emerged in studies evaluating MRSA carriage among Palestinian populations of the West Bank and Gaza [47]. Possible production of extended-spectrum beta-lactamase among gram-negative bacilli ranges from 6% to 39% [48–51]. NDM-1 cases were described from Oman involving *K. pneumoniae* [52], and VIM was described among *P. aeruginosa* in Saudi Arabia [53] and Kuwait [54] and among Enterobacteriaceae in UAE [55].

Basic economic and demographic data*

Country	GNI	Life expectancy at birth	Percent children in school
Armenia	3350	74	85
Azerbaijan	3830	67	95
Bahrain	17 390	76	98
Georgia	2470	71	94
Iran	3540	71	94
Iraq	NA	68	89
Jordan	3310	73	89
Kuwait	38 420	78	88
Lebanon	6350	72	83
Oman	12 270	76	73
Qatar	NA	76	93
Saudi Arabia	15 500	73	85
Syria	2090	74	95
Turkey	9340	74	92
United Arab Emirates	26 270	79	91
Yemen	950	63	75

*World Bank. www.worldbank.org.

GNI, gross national income; NA, not available.

Causes of death in children under five in Yemen, Armenia, and Saudi Arabia*

	%		
	Yemen	Armenia	Saudi Arabia
Neonatal causes	33	48	100
Pneumonia	20	12	7
Diarrheal diseases	16	10	6
Malaria	7	0	0
HIV/AIDS	0	0	0
Measles	2	0	0
Injuries	4	6	14
Others	17	23	32

*WHO. Regional average, 2000–3. www.who.int/whosis/mort/profiles/en/#P

Top ten causes of deaths all ages* in Yemen, Armenia, and Saudi Arabia

	%		
	Yemen	Armenia	Saudi Arabia
Ischemic and hypertensive heart disease	12	35	17
Cerebrovascular disease	4	16	4
Lower respiratory infections	14	NS	6
Diarrheal disease	11	NS	2
Measles	NS	NS	NS
Chronic obstructive lung disease	NS	3	NS
Nephritis and nephrosis	2	NS	2
Diabetes	NS	6	2
Road traffic accidents	4	NS	6
Cancers	NS	8	NS
Inflammatory heart disease	NS	2	NS
Cirrhosis of the liver	2	2	NS

*WHO 2006. www.who.int/whosis/mort/profiles/en/#P.
NS, not stated.

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Chapter 17

Eastern Europe

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Belarus
Bulgaria
Czech Republic
Hungary
Moldova
Poland
Romania
Russian Federation
Slovakia
Ukraine

The Eastern European region is basically located in a moderate climate. Subtropical climate occurs only at the seashore in the south of Russia and Bulgaria in the Mediterranean region. The north of Russia is located in the subarctic and arctic climatic zones. The landscape is extremely varied, from coastal areas to valleys, steppes, forests, and mountains. Many countries of this region have common features of culture and linguistic roots. According to the World Bank classification (2009–2010), two countries (Moldova and Ukraine) are in the group with low-middle income, two countries have high income (Slovakia and Hungary) and the rest are located in the group of upper-middle income countries. Gross national income (GNI) varies from USD 4700 (Moldova) to 25 200 (Slovakia) per capita. Life expectancy is lowest in Moldova (68.7 years) and highest in Czech Republic (78.1 years). Infectious diseases do not play a significant role in morbidity and mortality in this region.

Bacterial infections

Increasing numbers of *Neisseria meningitidis* serotype C have been isolated in Poland from children, adolescents, and young adults (up to 64% of all isolates), including soldiers and military personnel, particularly a hypervirulent clonal complex ST-11/ET-37 of high invasiveness [1,2]. The most prevalent bacteria isolated from hospitalized patients are extended-spectrum beta-lactamase producing

Enterobacteriaceae (ESBL+), rotavirus and *Acinetobacter baumannii*, mostly diagnosed in neonatal pathology, pediatric departments, intensive care units, infectious diseases and surgical wards for adults. Methicillin-resistant *Staphylococcus aureus* (MRSA) was identified in about 10% of Polish patients, mostly in hemodialysis and ophthalmological wards. *Clostridium difficile* was predominantly observed in ophthalmological, infectious diseases, and nonsurgical wards whereas *Pseudomonas* sp. was observed in burn care surgical wards and less frequently in neonatal pathology and intensive care units for adults [3]. Resistance in gram-positive and gram-negative bacteria is common, including an increasing frequency of MRSA. Tuberculosis is prevalent, with drug-resistant and multidrug-resistant *Mycobacterium tuberculosis* being an increasing epidemiological and therapeutic problem. Infections with *Borrelia* spp. and other tick-borne diseases, including mixed infections, are common in forested areas of Eastern Europe. Recently, in Russia, Poland, and Czech Republic, a new intracellular pathogen, *Neoehrlichia mikurensis*, transmitted by ticks and belonging to the family Anaplasmataceae, has been identified [4].

Small outbreaks of legionellosis have been reported as nosocomial infections in patients with immunosuppression, especially in ophthalmological, neonatal, and oncological clinics [5]. In sero-epidemiological surveys, *Legionella*-specific IgM has been found in 20.4% of cases with respiratory tract symptoms. The infections were mostly associated with stays in a sanatorium or hospital. In the years 2012–13, 13 hotels located in seven voivodeships and 10 cities in Poland were notified to the ECDC as a possible source of potential infection for foreign travelers.

Virus infections

Outbreaks of hepatitis A are recorded regularly and tick-borne encephalitis is seen throughout Russia and most other Eastern European countries. In Russia, Ukraine, and Bulgaria, Crimean-Congo hemorrhagic fever is seen during warm seasons and hemorrhagic fever with renal syndrome (hantavirus) is seen in Russia, Czech Republic, and Slovakia. HIV is increasing among the homeless and intravenous drug abusers.

In Poland, a presence of specific IgG antibodies against Puumala and/or Hantaan hantaviruses has been detected in 8.7–14.9% of asymptomatic forest workers, woodcutters, and zoologists from a high-risk group in the north-east region of the country with documented frequent contact with wild rodents and forest litter. Clinically overt epidemic nephropathy has not yet been registered in Poland [6,7].

Since 2003, no human cases of rabies have been reported in Poland. In 2012, a total of 257 animal rabies infections were registered in wild and domestic animals, predominantly in foxes (78%) and very sporadically in bats (three cases).

West Nile fever is actually spreading from the Mediterranean area to temperate climate territories located in the Russian Federation, Hungary, Romania, Czech Republic, Slovakia, Ukraine, and Belarus. So far, one autochthonous case has been reported in the Varmia-Masuria Province of Poland, and a possibility of a seasonal local transmission is disquieting [8]. West Nile virus outbreaks are reported every year in south-west Russia in the Caucasian region of the Volga and Don basins. Flu-like symptoms progressing to meningitis, encephalitis or myelitis preceded by insect bites in areas with epidemic infections observed in birds or horses should be suspected as West Nile virus neurological disease [9]. Increasing temperatures may thus shift the density and distribution of animal reservoirs and arthropod vectors which could affect human and animal health or cause a shift in the geographical range of disease caused by West Nile virus, hantaviruses, tick-borne encephalitis viruses, *Borrelia burgdorferi*, arboviruses including Sindbis virus, and California serogroup viruses [10].

Key symptoms: high fever, flu-like symptoms, headache, neck stiffness, focal neurological deficits, behavioral changes, disturbances of consciousness, and acute onset.

Parasite infections (protozoans and helminths)

Local transmission of malaria in Russia is low and unstable, and occurs in selected areas at the border with Azerbaijan in the basins of the Rivers Don and Volga, as well as recreational swimming lakes in Moscow city and Moscow region. Autochthonous *Plasmodium vivax* infections were mostly reported among urban populations and constitute nearly 50% of all imported and domestic malaria cases registered in the Russian Federation every year, even though the WHO European Region has now declared that Europe is free of autochthonous malaria. Tertian malaria should be considered in the differential diagnosis of a febrile traveler from Russia in the warmer season from late spring to early autumn.

Key symptoms: fever, chills, weakness, sweating, headache, bone and joint pain, anemia, and acute onset.

Echinococcus granulosus is a main infectious cause of single or multiple cystic lesions in the liver, mostly located in the right lobe. In Poland, about 10% of all space-occupying lesions in the liver are caused by *E. granulosus*. Having a dog on a small private farm and local slaughtering in a household may be helpful factors in an epidemiological interview. Cystic echinococcosis in humans from Central and Eastern Europe is caused by newly recognized “pig” strains of the parasite with genotypes G7 or G9, characterized by low invasiveness. Infections with a “sheep” strain of *E. granulosus*, which dominates in the majority of countries, have not been documented in countries of Eastern Europe.

Key symptoms: abdominal discomfort, right upper quadrant pain, and liver cysts usually accidentally diagnosed by ultrasonography or computed tomography scan, and chronic course.

In recent years, subcutaneous and ocular dirofilariasis has been considered a new emerging infection in Eastern European countries. *Dirofilaria repens* is a predominant species in humans in the region, but *D. immitis* has also been documented in a canine reservoir in Russia, Romania, Bulgaria, Slovakia, and Hungary. Unusual sporadic cases with a completed life cycle and a presence of *D. repens* microfilariae in the peripheral blood have been documented in Polish patients living near the border with Ukraine.

Key symptoms: subcutaneous soft nodule, unilateral periorbital swelling, single or multiple pulmonary nodules, thoracic pain, dyspnea, hypereosinophilia. Insect bites in epidemiological interview.

Many outbreaks of trichinellosis are reported every year in Eastern Europe, mostly related to eating of raw meat from infected wild boars, dogs or brown bears from private hunting without a proven veterinary inspection. *Trichinella spiralis* is a predominant species in domestic pigs, but *T. pseudospiralis* and *T. britovi* have been isolated from wild boars and bears. Mandatory implementation of a digestion technique by the National Sanitary Inspector for all veterinary centers responsible for parasitological examination of meat has significantly reduced the risk of trichinellosis in Poland. Most local infections are reported in family agglomerations, as well as in groups of forest workers, foresters or huntsmen. Seasonal occurrence in spring and autumn and clinical manifestations observed simultaneously in many members of the same family or in occupational groups can be helpful in a clinical diagnosis. The infection requires an obligatory registration by the National Institute of Public Health in Warsaw.

Key symptoms: high fever, severe muscle pain, edema of eyelids, short-term watery diarrhea, subconjunctival hemorrhage, hypereosinophilia, and acute onset.

The intestinal helminths *Ascaris lumbricoides* (roundworms) and *Trichuris trichiura* (whipworm) are frequent in rural areas on organic farms specializing in vegetables and berries. *Enterobius vermicularis* (threadworm) is commonly diagnosed in young children, teachers, and educational workers. *Toxocara cati* and *canis*, responsible for the syndrome of visceral or ocular larva migrans, are mainly observed in children and adolescents, similarly from urban agglomerations and agricultural regions. The clinical picture includes hypereosinophilia with leukocytosis, nonspecific abdominal pain, weight loss, visual impairment, subretinal or liver granulomas, generalized lymphadenopathy, asthma, urticaria, and other allergic disorders. Due to culinary traditions and dietary habits, taeniasis is a common intestinal parasitic infection in Eastern Europe; *Taenia saginata* is the most prevalent species. Small outbreaks in families are reported. Cysticercosis due to a larval form of *Taenia solium* is sporadically observed in agricultural workers from pig-raising areas with single, usually calcified, space-occupying lesions of the brain. Neurocysticercosis should always be considered in a differential diagnosis of impaired

consciousness and focal neurological deficits of unknown origin. Multiple brain lesions characterized by different location and density, including annular enhancing structures with positive Western blot serology, may be helpful in a final diagnosis.

CNS infections: meningitis, encephalitis

Acute infections with less than four weeks of symptoms

Among viral CNS infections, tick-borne encephalitis and enteroviral meningitis are most frequently observed. In 2014 in Russia, 6279 cases of enterovirus group meningitis were registered [11]. In the last 15 years, in the south of Russia and Ukraine, West Nile virus meningitis and encephalitis (more rarely) have been registered, mostly among adults and the elderly. Meningitis and encephalitis due to influenza occur in epidemics. In patients with bacterial meningitis, *Streptococcus pneumoniae*, beta-hemolytic streptococci, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Escherichia coli* are common among adults [12]. *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Streptococcus agalactiae* (newborn infants), and *Staphylococcus aureus* are common in children [13].

Frequently found microorganisms and conditions	Rare microorganisms	Very rare microorganisms
Viral meningitis (enterovirus group)	<i>Mycobacterium tuberculosis</i>	<i>Treponema pallidum</i> (neurosyphilis)
<i>Pneumococcus</i> spp. [12]	HIV	<i>Brucella</i> spp.
Arboviruses (tick-borne encephalitis)* [14]	West Nile virus [8,9]	<i>Listeria monocytogenes</i>
<i>Neisseria meningitidis</i> – serogroup A (rare), B and C (Poland) [1,2]	Influenza viruses	<i>Yersinia</i> spp.
<i>Haemophilus influenzae</i> serotype B [†]	Herpes virus (group I and II)	<i>Gnathostoma spinigerum</i> ** [16]
	<i>Leptospira</i> spp.	<i>Angiostrongylus cantonensis</i> ** [16]
	Enterobacteriaceae	Lymphocytic choriomeningitis virus
	<i>Pseudomonas aeruginosa</i>	Lyssavirus (rabies)
	<i>Borrelia burgdorferi</i> genospecies (mostly <i>B. garinii</i>)	
	<i>Enterococcus</i> spp.	
	<i>Streptococcus agalactiae</i> [15]	

* Except south of Russia and Ukraine.
[†] In children under five years old.
** In the far east of Russia, Kamchatka Peninsula, and Northern Pacific Islands (Kurils).

Infections with symptoms for more than four weeks and in the immunocompromised host

Extrapulmonary tuberculosis is a main cause of CNS infections with symptoms for more than two weeks. Toxoplasmosis is also a frequent etiological factor of space-occupying lesions located in the brain with a long course among immunocompromised hosts. All other infectious agents are significantly less common.

Microorganisms and conditions with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
HIV <i>Mycobacterium tuberculosis</i> Neuroborreliosis Neurobrucellosis* <i>Taenia solium</i> (neurocysticercosis) <i>Toxocara canis</i> and <i>T. cati</i> <i>Acanthamoeba</i> *	Cytomegalovirus Epstein–Barr virus Herpes virus <i>Cryptococcus</i> spp. <i>Toxoplasma gondii</i> <i>Aspergillus</i> spp. <i>Nocardia</i> spp.* <i>Actinomyces</i> spp.* <i>Mucor hiemalis</i>
*Very rare infection.	

Ear, nose, and throat infections

Ear, nose, and throat infections with symptoms for less than four weeks

Seasonal influenza and influenza-like illnesses are the most common viral infections which lead to acute ear, nose, and throat infections [17]. Predominant bacterial pathogens include streptococci and *Haemophilus influenzae* whereas *Moraxella catarrhalis*, *Streptococcus pyogenes*, *Staphylococcus aureus*, anaerobes, etc. are found more rarely.

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Streptococcal throat infection [15,18] Epstein–Barr virus [19]	Peritonsillar abscess* <i>Mycobacterium tuberculosis</i>	<i>Corynebacterium diphtheriae</i> <i>Francisella tularensis</i>
Herpes virus (type I and II)	Necrotizing fasciitis†	<i>Listeria monocytogenes</i>
Seasonal influenza: A(H1N1), A(H1N1 pdm2009), A (H3N2), influenza B Respiratory syncytial virus Parainfluenza virus Adenovirus	<i>Yersinia enterocolitica</i> and <i>Y. pseudotuberculosis</i> Fusiform bacteria and spirochetes (Plaut-Vincent angina) Human metapneumovirus	Human bocavirus
* Requires acute ENT evaluation. † Requires acute surgical evaluation.		

Ear, nose, and throat with symptoms for more than four weeks and in the immunocompromised host

Most frequent chronic ENT infections usually include chronic suppurative otitis media (CSOM), tonsillopharyngitis, and rhinosinusitis. Chronic suppurative otitis media is mostly caused by *S. aureus*, *Pseudomonas aeruginosa* or other gram-negative bacteria. Tonsillopharyngitis is commonly due to

Streptococcus pyogenes infection. Chronic rhinosinusitis usually is caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus* or pathogenic fungi [19].

Microorganisms with symptoms for more than 4 weeks*	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i> Epstein–Barr virus <i>Treponema pallidum</i> (amygdalitis) <i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i> <i>Streptococcus pyogenes</i> <i>Aspergillus</i> spp.	<i>Candida</i> spp. <i>Alternaria</i> spp. <i>Bipolaris</i> spp. Herpes virus (type I and II) Cytomegalovirus
* Consider noninfectious causes like vasculitis and lymphoma.	

Cardiopulmonary infections

Pneumonia with symptoms for less than four weeks

Common causes of acute pneumonia are usually bacteria, such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, and influenza viruses. More rarely, pneumonia is due to *Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Chlamydia pneumoniae* infections [20]. Sporadic cases of pneumonia caused by *Chlamydia psittaci* are also recorded after direct contact with exotic birds.

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Streptococcus pneumoniae</i> pneumonia [12] <i>Mycoplasma pneumoniae</i> [20]	<i>Legionella pneumophila</i> [20] Influenza <i>Toxocara canis</i> and <i>T. cati</i>	<i>Chlamydia psittaci</i> <i>Chlamydia pneumoniae</i>

Endocarditis with less than four weeks of symptoms

The most common predisposing condition for endocarditis is congenital heart disease and rheumatic heart disease, in which *Streptococcus viridans* is the most common microorganism. In intravenous drug users, *Staphylococcus aureus* and *S. epidermidis* as an etiological factor of endocarditis are recorded more frequently. Endocarditis due to fungi (*Candida* spp. and *Aspergillus* spp.) or gram-negative bacteria are recorded in 5–15% of cases [21].

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Beta-hemolytic <i>Streptococcus</i> (<i>Streptococcus viridans</i>) [21] Nonhemolytic streptococci	<i>Pseudomonas aeruginosa</i> Beta-hemolytic <i>Streptococcus</i> (group A, B, C, D) [21]	<i>Bartonella</i> spp. <i>Brucella melitensis</i>

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Enterococcus</i> spp. [21] <i>Staphylococcus aureus</i> [21]	<i>Streptococcus pneumoniae</i> Coagulase-negative staphylococci (<i>S. epidermidis</i>) <i>Listeria</i> endocarditis <i>Borrelia burgdorferi</i> genospecies (mostly <i>B. garinii</i>)*	<i>Neisseria</i> spp. <i>Coxiella burnetii</i> <i>Salmonella</i> spp.
* <i>Borrelia</i> spp. infection may cause atrioventricular blocks.		

Pulmonary symptoms for more than four weeks and in the immunocompromised host

Mycobacterium tuberculosis and *M. avium*, *Pneumocystis jiroveci*, fungal infections, and CMV are the main causes of pneumonia in immunocompromised individuals.

Microorganisms and diseases with symptoms for more than 4 weeks*	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i> <i>Aspergillus</i> spp. <i>Pseudomonas aeruginosa</i> <i>Toxocara canis</i> and <i>T. cati</i> <i>Paragonimus westermani</i> †	<i>Pneumocystis jiroveci</i> Cytomegalovirus Fungi (<i>Aspergillus</i> spp., <i>Candida</i> spp.) <i>Strongyloides stercoralis</i> <i>Mycobacterium avium</i> and <i>M. intracellulare</i> <i>Toxoplasma gondii</i> <i>Actinomyces</i> spp. <i>Nocardia</i> spp. <i>Mucor hiemalis</i>
* Consider noninfectious causes like lung cancer, autoimmune lung fibrosis, and Wegener's granulomatosis. † In the far east of Russia.	

Endocarditis for more than four weeks and in the immunocompromised host*

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Coagulase-negative staphylococci (<i>S. epidermidis</i>) Nonhemolytic streptococci <i>Pseudomonas aeruginosa</i> HACEK group bacteria (<i>Aggregatibacter actinomycetemcomitans</i> , etc.) <i>Bartonella quintana</i> <i>Coxiella burnetii</i> Morbus Whipple	<i>Aspergillus</i> spp. <i>Candida</i> spp.
* Consider noninfectious causes like sarcoidosis.	

Gastrointestinal infections

Gastrointestinal infections with symptoms for less than four weeks*

In recent years, viral gastroenteritis has started to contribute more significantly to the burden of infectious diarrhea. The available data show that rotavirus gastroenteritis (RVGE) is a common disease in Eastern Europe affecting the pediatric population. Among children under 15 years of age, RVGE accounts for between 22.0% and 55.3% of all cases of acute gastroenteritis per year [22,23]. In adult patients viral etiology is registered in 1–6%. For most countries, RVGE is common in the winter months, although it has been reported year round in warmer climate regions like Bulgaria [24].

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Salmonella</i> (non-typhi) [22]	<i>Yersinia enterocolitica</i>	<i>Diphyllobothrium latum</i>
<i>Escherichia coli</i>	<i>Clostridium difficile</i>	<i>Trichuris trichiura</i>
Rotaviruses [†] [23,24]	<i>Bacillus cereus</i> toxin	<i>Anisakis simplex</i> **
<i>Campylobacter</i> spp.	<i>Ascaris lumbricoides</i>	<i>Entamoeba histolytica</i>
<i>Enterobius vermicularis</i>	Norovirus, calicivirus and astroviruses [24]	<i>Cryptosporidium</i> spp.
<i>Staphylococcus aureus</i> toxin	<i>Pseudomonas aeruginosa</i>	<i>Mycobacterium tuberculosis</i>
<i>Giardia intestinalis</i>	<i>Vibrio parahaemolyticus</i>	
<i>Shigella</i> spp.	HIV-associated gastrointestinal infections	

* Consider noninfectious causes like inflammatory bowel disease, and intestinal malignancies like colon cancer.

[†] Basically in children.

** Only in the Baltic, Okhotsk, and Bering Seas pericoastal areas.

Diarrhea is often associated with infections with bacteria, viruses or parasites. Repeated negative bacterial cultures and microscopy for parasites should lead to the consideration that the symptoms may not be caused by an infection. Inflammatory bowel disease like ulcerative colitis and Crohn's disease are differential diagnoses, and malabsorption and celiac disease must also be considered.

Gastrointestinal infections with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms and conditions with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i>	<i>Candida</i> spp.
Morbus Whipple	Herpes virus
<i>Blastocystis hominis</i> [†]	<i>Cryptosporidium</i> spp.
<i>Dientamoeba fragilis</i> [†]	<i>Mycobacterium avium</i> and <i>M. intracellulare</i>
<i>Enterobius vermicularis</i>	Cytomegalovirus
<i>Entamoeba histolytica</i>	<i>Isospora belli</i>
<i>Diphyllobothrium latum</i>	Microsporidia
<i>Taenia saginata</i> , <i>T. solium</i>	<i>Strongyloides stercoralis</i>
<i>Hymenolepis nana</i>	<i>Balantidium coli</i>

* Consider noninfectious causes like inflammatory bowel disease, intestinal malignancies like colon cancer, malabsorption and celiac disease.

[†] Of uncertain pathogenicity in humans.

Acute infections of liver, spleen, and peritoneum with symptoms for less than four weeks

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Hepatitis A virus Hepatitis B virus Hepatitis C virus	Hepatitis E virus <i>Leptospira</i> spp.	<i>Brucella</i> spp.

Chronic infections of liver, spleen, and peritoneum with symptoms for more than four weeks and in the immunocompromised host

Microorganisms and conditions with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i> <i>Fasciola hepatica</i> and <i>F. gigantica</i> <i>Opisthorchis felineus</i> * <i>Clonorchis sinensis</i> † <i>Echinococcus granulosus</i> [25,26] and <i>E. multilocularis</i> ** [27–29] Amebic liver abscess (<i>Entamoeba histolytica</i>) <i>Toxocara canis</i> and <i>T. cati</i>	Herpes virus <i>Mycobacterium avium</i> and <i>M. intracellulare</i> Cytomegalovirus <i>Actinomyces</i> spp.††
* In the basins of rivers in Russia (predominantly Ob, Irtysh, Kama, Volga, and also Don, Donets, Severnaya Dvina, Neman) and Ukraine (Dnepr). † In the far east of Russia. ** In the forests of northern Poland and the Carpathian Mountains. †† Very rare infection.	

Alveolar echinococcosis

Alveolar echinococcosis due to *Echinococcus multilocularis* has become an emerging infection in the majority of Eastern Europe regions; the number of new human cases is constantly increasing in Poland, Slovakia, Czech Republic, and more recently also in Lithuania. Irregular space-occupying lesions of the liver with necrosis, fibrosis, calcifications, and a tendency to infiltration of adjacent tissues and organs, as well as formation of distant metastases in CNS and lungs, make a differential diagnosis difficult because of its clinical similarity to an advanced stage of liver malignancy. Direct demonstration of the parasite in biopsy materials using histopathological investigations which reveal periodic acid-Schiff (PAS) stain-positive structures or detection of *E. multilocularis* nucleic acids using a PCR technique are required for the final diagnosis. Living in forested areas of Eastern Europe or working in forestry occupations, hunting, picking dry twigs, mushrooms or blueberries are the main risk factors. In endemic provinces of northern and southern Poland, the incidence of infection in red foxes varies from 20.1% to 39.6%. In recent years, liver alveococcosis has been documented in children and young people in Poland, indicating the possibility of a more intensive invasion with local *E. multilocularis* strains of a higher pathogenicity and virulence or acquired in very early infancy, which has not been previously reported in other European countries [29].

Key symptoms: abdominal pain, liver insufficiency, jaundice, cachexia, hepatic tumor, in late stages dyspnea and/or seizures because of distant metastases. Slowly progressing chronic disease with potentially fatal prognosis.

Genitourinary infections

Cystitis, pyelonephritis, and nephritis with less than four weeks of symptoms*

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Escherichia coli</i> <i>Klebsiella pneumoniae</i>	Perirenal abscess <i>Enterobacter</i> spp. [30]	<i>Mycobacterium tuberculosis</i> <i>Providencia</i> spp. <i>Morganella</i> spp.
<i>Proteus mirabilis</i> [30]	<i>Pseudomonas aeruginosa</i>	<i>Haemophilus influenzae</i> and <i>H. parainfluenzae</i>
<i>Pseudomonas aeruginosa</i> <i>Staphylococcus aureus</i> <i>Streptococcus epidermidis</i> <i>Streptococcus saprophyticus</i> <i>Enterococcus faecalis</i> <i>Chlamydia trachomatis</i>	<i>Acinetobacter</i> spp. <i>Serratia marcescens</i> <i>Citrobacter</i> spp. <i>Candida albicans</i> <i>Serratia</i> spp. <i>Klebsiella</i> spp. <i>Hantavirus</i> † [6,7] <i>Leptospira</i> spp.	<i>Mycoplasma hominis</i> <i>Bordetella bronchiseptica</i> <i>Pasteurella</i> spp.

* Consider noninfectious causes, especially malignancies like renal cell carcinoma.
† Except south of Russia and Ukraine.

Sexually transmitted infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Chlamydia</i> spp. <i>Neisseria gonorrhoeae</i>	Lymphogranuloma venerum HIV	<i>Haemophilus ducreyi</i> <i>Calymmatobacterium granulomatis</i>
<i>Trichomonas vaginalis</i> <i>Ureaplasma urealyticum</i>	<i>Mycobacterium genitalium</i> and <i>M. hominis</i>	

Cystitis, pyelonephritis, and nephritis with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Bacterial infections in patients with long-term catheters and renal stones <i>Mycobacterium tuberculosis</i> <i>Brucella melitensis</i>	<i>Candida</i> spp. Herpes viruses type I and II <i>Actinomyces</i> spp.

* Consider noninfectious causes, especially malignancies like renal cell carcinoma.

Sexually transmitted infections with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
HIV <i>Treponema pallidum</i> Herpes virus type I and II Papillomavirus type VI and XI Lymphogranuloma venereum	<i>Candida</i> spp.

HIV infection should always be considered. The most common infections with a long incubation period are syphilis, herpes virus, and papillomavirus. In the immunocompromised host, diagnosis can be difficult as the antibody response may be false negative.

Joint, muscle, and soft tissue infections

Joint, muscle, and soft tissue infections with symptoms for less than four weeks

The most common etiological agents of soft tissue infections are *Staphylococcus aureus* and *Streptococcus pyogenes*. *Pseudomonas aeruginosa* and *S. epidermidis* are reported more rarely.

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Staphylococcus aureus</i> [31]	Necrotizing fasciitis (<i>Streptococcus pyogenes</i>)	Fournier's gangrene (perineum and urogenital) [32]
<i>Streptococcus pneumoniae</i>	Group C and G streptococci	
<i>Streptococcus agalactiae</i>	<i>Staphylococcus epidermidis</i>	
<i>Streptococcus pyogenes</i> [31]	<i>Enterococcus faecalis</i>	
<i>Enterobacter</i> spp.	<i>Escherichia coli</i>	
<i>Yersinia pseudotuberculosis</i> and <i>Y. enterocolitica</i>	<i>Pseudomonas aeruginosa</i>	
	<i>Trichinella spiralis</i> , <i>T. pseudospiralis</i> and <i>T. britovi</i> *	

*Outbreaks in family agglomerations or occupational groups (hunters, farmers, butchers).

Joint, muscle, and soft tissue infections with symptoms for more than four weeks and in the immunocompromised host

Lyme disease is widely spread in the territory of Russia and other countries of Eastern Europe [33,34]. Several circumpolar areas located in the north of Russia, Siberia, and Kamchatka Peninsula are the exception, where cases of Lyme borreliosis have not occurred. Since the beginning of the twenty-first century, Lyme disease has been recorded in the south of Russia. Within the last 15–20 years, cases of *Dirofilaria repens* have been diagnosed more frequently in the territory of Russia and Ukraine [35]. The first human cases were recorded in Belarus and Poland [36].

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Borrelia burgdorferi</i> and other species (mostly <i>B. garinii</i> , <i>B. miyamotoi</i>) [33,34]	<i>Candida</i> spp.
<i>Mycobacterium tuberculosis</i>	<i>Actinomyces</i> spp.
<i>Dirofilaria repens</i> [35,36]	<i>Nocardia</i> spp.
<i>Taenia solium</i> (cysticercosis)	

Skin infections

Herpes virus type I, II, and III are the main causes of viral skin diseases. The most common bacteriological etiological agents of skin infections are *Staphylococcus aureus* and *Streptococcus pyogenes*. Erysipelas plays a significant role in hospital morbidity in Russia [37]. The potential reemergence of anthrax associated with historic livestock burial sites is of special concern in the Russian Federation [10] and also may occur in Ukraine, Belarus, and Moldova.

Skin infections with symptoms for less than four weeks

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Erysipelas (<i>Streptococcus pyogenes</i>) [37], <i>S. pneumoniae</i> <i>Staphylococcus aureus</i> [31]	<i>Erysipelothrix rhusiopathiae</i> <i>Haemophilus influenzae</i> type B	Mycoses (<i>Candida</i> , <i>Trichophyton rubrum</i> , <i>Epidermophyton floccosum</i> , etc.) <i>Pasteurella multocida</i>
<i>Borrelia burgdorferi</i> and other species (mostly <i>B. garinii</i> , <i>B. miyamotoi</i>) [10,33,34]	<i>Corynebacterium minutissimum</i>	<i>Mycobacterium leprae</i> * [38]
Herpes virus type I, II, III (VZV)	<i>Propionibacterium acnes</i> Pediculosis <i>Francisella tularensis</i>	Scabies <i>Ancylostoma caninum</i> † <i>Bacillus anthracis</i> [9] <i>Anaplasma phagocytophilum</i>

*Very rare sporadic cases.
†Cutaneous larva migrans syndrome is observed in tourists returning from sandy beaches in Bulgaria, Hungary, and south Russia during the hot season.

We have not listed a rash due to viral infections as this is not considered an infection limited to the skin.

Skin infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Treponema pallidum</i> <i>Mycobacterium tuberculosis</i>	Mycoses (<i>Candida</i> , <i>Trichophyton</i> , <i>Epidermophyton</i>) <i>Strongyloides stercoralis</i>

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium leprae</i> [38] <i>Demodex folliculorum</i> <i>Gnathostoma spinigerum</i> * Cutaneous leishmaniasis†	Atypical mycobacteria <i>Actinomyces</i> spp. <i>Nocardia</i> spp.
* In the far east of Russia, Kamchatka Peninsula, and Northern Pacific Islands (Kurils). † Very rare domestic cases in the south of Russia (Northern Caucasus republics).	

Adenopathy

Most frequently, acute onset of disease with fever and lymphadenopathy is associated with EBV, CMV, and adenoviruses. More rarely, lymphadenopathy is caused by HIV, *Mycobacterium tuberculosis* or *Toxoplasma gondii*. Bacterial tonsillopharyngitis and suppurative infections of ear, nose, and throat can also be accompanied by adenopathy. Sporadic cases of brucellosis related to contact with sick animals are recorded in rural areas of Russia.

Adenopathy of less than four weeks duration

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Epstein–Barr virus [39] Cytomegalovirus [39] <i>Toxoplasma gondii</i> [39] HIV Adenovirus*	<i>Francisella tularensis</i> <i>Bartonella henselae</i> <i>Mycobacterium tuberculosis</i> <i>Toxocara canis</i> and <i>T. cati</i> *	<i>Ehrlichia chaffensis</i> <i>Anaplasma phagocytophilum</i> <i>Babesia divergens</i> and <i>B. microti</i> Parvovirus B19 <i>Brucella</i> spp. <i>Rickettsia slovaca</i> † Lymphocytic choriomeningitis virus
* Mainly in children. † Formerly TIBOLA (tick-borne lymphadenopathy).		

Adenopathy of more than four weeks duration and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Toxoplasma gondii</i> <i>Mycobacterium tuberculosis</i> <i>Brucella melitensis</i>	Adenovirus, HIV Cytomegalovirus <i>Mycobacterium avium</i> and <i>M. intracellulare</i>

If the diagnosis is not made within a few days, biopsies should be performed to exclude malignancies such as lymphoma and carcinomas.

Fever without focal symptoms

The causes of febrile illnesses without localizing symptoms in the region are most commonly EBV and CMV infections, VNF, and septic endocarditis. Other less common infectious diseases include hemorrhagic fever with renal syndrome (HFRS) and Crimean-Congo hemorrhagic fever in the south of Russia, leptospirosis, *Yersinia*, and rickettsiosis. After four weeks of symptoms and in the immunocompromised host, tuberculosis is the most common etiology of prolonged fever.

Fever for less than four weeks without focal symptoms

Frequently found microorganisms and conditions	Rare microorganisms and conditions	Very rare microorganisms and conditions
Endocarditis	<i>Mycobacterium tuberculosis</i>	<i>Francisella tularensis</i>
Epstein–Barr virus	<i>Coxiella burnetii</i>	<i>Salmonella enterica</i> , <i>typhi</i> , <i>paratyphi</i> A, B
Cytomegalovirus	<i>Leptospira</i> spp.	<i>Brucella</i> spp.
<i>Toxoplasma gondii</i>	<i>Yersinia</i> spp.	Parvovirus B19
HIV	<i>Borrelia</i> spp. (Lyme disease)	<i>Plasmodium vivax</i> [†] [41]
<i>Trichinella spiralis</i> ,	Viral hepatitis viruses (HAV, HBV, HCV)	<i>Ehrlichia chaffensis</i> [42]
<i>T. pseudospiralis</i> and	CCHF virus* [40], HFRS virus [10]	<i>Anaplasma phagocytophilum</i> [42]
<i>T. britovi</i> [46]	West Nile fever [8–10]	<i>Babesia divergens</i> and <i>B. microti</i> [43]
		<i>Orientia tsutsugamushi</i> **
		<i>Rickettsia prowazekii</i> , <i>R. slovaca</i> [44], <i>R. heilongjiangensis</i> , <i>R. sibirica</i> ^{††} [45]
		Hantaviruses [6,7]
		<i>Legionella pneumophila</i>

*In the south of Russia.

[†]In the south of Russia there was a rare domestic transmission of *Plasmodium vivax* malaria near the border with Azerbaijan. Also sporadic cases are occasionally registered in the basins of the Don and Volga (“river malaria”). In Moscow city and Moscow region, 30–47.5% of reported malaria infections are locally acquired every year, but new *P. vivax* cases are not reported. Russian travelers infected abroad and local *Anopheles* mosquitoes multiplying in recreational lakes for swimming are the sources of introduced malaria infection. Multiple clinical relapses of *P. vivax* malaria with fever, chills, anemia, and splenomegaly may be seen for a few years in previously infected patients. All the strains of *P. vivax* were sensitive to chloroquine [41]. According to the WHO World Malaria Report, since 2010 the Russian Federation has been in a phase of prevention of reintroduction of malaria and achieved a certification of elimination of indigenous malaria cases in 2012.

**In the far east of Russia.

††In Siberia and the far east of Russia.

Fever for more than four weeks without focal symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i> <i>Brucella melitensis</i>	Cytomegalovirus Adenovirus <i>Ehrlichia chaffensis</i> <i>Neoehrlichia mikurensis</i> [4] <i>Anaplasma phagocytophilum</i> <i>Toxoplasma gondii</i> <i>Legionella pneumophila</i>

Noninfectious causes should be considered from the beginning, including malignancies like lymphoma and autoimmune diseases.

Eosinophilia and elevated IgE

Eosinophilia and elevated titers of IgE are rare symptoms of infectious diseases in the region. The most common causes of eosinophilia are helminthic infections of tissues and internal organs. More rarely, eosinophilia is related to *Mycobacterium tuberculosis*.

Eosinophilia and elevated IgE for less than four weeks

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Ascaris lumbricoides</i> and <i>A. suum</i> <i>Toxocara canis</i> and <i>T. cati</i> <i>Taenia saginata</i> <i>Clonorchis sinensis</i> * <i>Trichinella spiralis</i> , <i>T. britovi</i> , <i>T. pseudospiralis</i> † [46] <i>Opisthorchis felinus</i> ** <i>Enterobius vermicularis</i>	<i>Strongyloides stercoralis</i> <i>Taenia solium</i> <i>Ancylostoma caninum</i> §	<i>Paragonimus westermani</i> * [47] <i>Angiostrongylus cantonensis</i> †† <i>Gnathostoma spinigerum</i> †† [15] <i>Hymenolepis nana</i>

* In the far eaST of Russia.

† Outbreaks related to eating raw meat from wild boars and domestic pigs [46].

** In basins of rivers of Russia (predominantly Ob, Irtysh, Kama, Volga and also Don, Donets, Severnaya Dvina, Neman) and Ukraine (Dnepr).

†† In the far east of Russia, Kamchatka Peninsula, and Northern Pacific Islands (Kurils).

§ Cutaneous larva migrans syndrome is observed in tourists returning from sandy beaches in Bulgaria, Hungary, and south Russia during the hot season.

Eosinophilia and elevated IgE for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Ascaris lumbricoides</i> and <i>A. suum</i> <i>Echinococcus granulosus</i> [25,26] and <i>E. multilocularis</i> * [27–29]	<i>Dirofilaria repens</i> [35,36] <i>Strongyloides stercoralis</i>
<i>Toxocara canis</i> and <i>T. cati</i> <i>Fasciola hepatica</i> and <i>F. gigantica</i> <i>Hymenolepis nana</i> <i>Opisthorchis viverrini</i> and <i>Opisthorchis felineus</i>	<i>Isospora</i> spp.

* In the forests of northern Poland and the Carpathian Mountains.

Antibiotic resistance

Streptococcus pneumoniae demonstrates a low level of resistance to aminopenicillins (0.4%) and third-generation cephalosporins for parenteral administration (0.5–1%), and a high level of resistance to penicillins (8.1–11.2%), third-generation cephalosporins for enteral administration (6.8–12.9%), macrolides (up to 8.2%), and early fluoroquinolones (7.8–16.1%). Up to 29% of *Streptococcus pneumoniae* strains are resistant to tetracycline and more than 39% are resistant to co-trimoxazole [48]. From 33.9% to 45.8% of *Streptococcus pyogenes* isolates are resistant to tetracyclines and not more than 11% to macrolides [49]. *Haemophilus influenzae* shows resistance to co-trimoxazole in 29%, aminopenicillins in 5.4%, and tetracycline in 5% [50].

Up to 30% of *Staphylococcus aureus* strains are resistant to methicillin (MRSA). Resistance of *S. aureus* to co-trimoxazole and fosfomycin is recorded in 10% of cases, chloramphenicol in 22%, macrolides and tetracyclines in 7% [51]. Hospital-isolated MRSA shows a high frequency of resistance to lincosamides, aminoglycosides, and erythromycin and the number of ciprofloxacin-resistant strains among MRSA approaches 88%. Over 60% of strains produce beta-lactamase. Resistance to benzylpenicillin and oxacillin is almost universal [52].

In recent years in Russia, resistance of community-acquired strains of *Escherichia coli* has been found to ampicillin (53%), amoxicillin/clavulanate (46%), ampicillin/sulbactam and piperacillin (47%), co-trimoxazole (31%), ciprofloxacin and levofloxacin (27%), third-generation cephalosporins (11–14%), and gentamicin (11%) [53,54].

The incidence of primary drug-resistant *Mycobacterium tuberculosis* varies from 12% to 18%. Levels of secondary drug resistance are around 56–68%. Multidrug-resistant (MDR) *M. tuberculosis* is detected in 4–19% of newly diagnosed patients and in 37–72% of previously treated persons and reaches up to 80% in the cases of treatment failure. In newly diagnosed patients, resistance to streptomycin, rifampicin, and their combinations is common, whereas among treated patients resistance to isoniazid, rifampicin, and streptomycin is observed in up to 30% of cases. The proportion of MDR cases with extensively drug-resistant (XDR) tuberculosis reaches 16% [55,56]. The level of primary tuberculosis resistant to fluoroquinolones is above 6.4%; in MDR strains it reaches up to 7.4% [57].

More than 60% of *Pseudomonas aeruginosa* strains are resistant to cephoperazon, ciprofloxacin, gentamicin, and netilmicin, and about 40% to piperacillin, ceftazidime, and amikacin. Resistance of *P. aeruginosa* to imipenem and meropenem has been found in up to 30% of isolates. Third-generation

cephalosporins are usually active against *Pseudomonas* spp. [58]. In Russia and Belarus, strains of *P. aeruginosa* producing beta-lactamase increased from 4.5% to 20.3% within a five-year period (2002–2007); most of them are sensitive only to polymyxins [59].

Shigella sonnei shows increasing susceptibility to ampicillin, chloramphenicol, and sulfamethoxazole. *Salmonella typhimurium* is most resistant to antibiotics among all serovars of *Salmonella*. From 47% to 74% of strains in certain years were resistant to chloramphenicol, ampicillin, cefepim, neomycin, carbenicillin, and nalidixic acid. Nosocomial strains of *S. typhimurium* in Russia and Belarus producing extended-spectrum β -lactamase show resistance to multiple antibiotics, including penicillin-inhibitor combinations and various nonbeta-lactam drugs. In particular, these strains demonstrate resistance to quinolones in up to 43% [60].

Neisseria meningitidis strains responsible for recent outbreaks of severe meningococcal sepsis in Poland were mostly susceptible to penicillin; 10.1–32.1% of isolates had lower susceptibility to penicillin [1,2].

Symptomatic legionellosis has become an emerging infection in Poland since 2002, when new outbreaks of up to 100 cases were reported annually in hospitals and recreational or holiday centers. *Legionella pneumophila* strains were susceptible to macrolides and fluoroquinolones [5].

Vaccine-preventable diseases in children

The childhood vaccination programs have a high adherence in the republics of the former Soviet Union (Russia, Belarus, Ukraine, Moldova). Among people who for various reasons have not been vaccinated (migrants, homeless, peoples who refuse vaccinations) or have low levels of protecting antibodies, sporadic cases of diphtheria, mumps, rubella, small outbreaks of measles, and hepatitis A are seen. Vaccination against hepatitis A is not mandatory. The free immunization program for children in Russia includes vaccination against tuberculosis, poliomyelitis, measles, mumps, rubella, diphtheria, whooping cough, tetanus, hepatitis B, pneumococcal disease, and *Haemophilus influenzae* type B (HIB) infection. Also vaccination against rotavirus, chickenpox, and papillomavirus type 16/18 is available on a commercial basis. Seasonal vaccination against influenza is provided to children and at-risk groups. In endemic areas, vaccination against tick-borne encephalitis is recommended. People should be vaccinated in areas where tularemia and plague are enzootic. According to epidemic indications, vaccination is carried out against brucellosis, anthrax, rabies, leptospirosis, Q-fever, typhoid, hepatitis A, shigellosis, and meningococcus group A and C.

A mandatory immunization program in Ukraine and Moldova includes vaccination against tuberculosis, hepatitis B, diphtheria, poliomyelitis, measles, HIB, whooping cough, rubella, and tetanus. Other vaccines (against chickenpox, hepatitis A and B, influenza, rubella, mumps, pneumococcal disease, meningococcus group A and C, rotavirus, papillomavirus, etc.) are available on a commercial basis.

According to the national mandatory immunization program in Belarus, vaccination is carried out against tuberculosis, whooping cough, diphtheria, tetanus, poliomyelitis, hepatitis B, measles, mumps, and rubella. Many regional mandatory immunization schedules in Belarus also include HIB and hepatitis A vaccines.

In Poland, more than 95% of the population are included in the national mandatory and free of charge immunization program for children and young people, which includes prevention of tuberculosis, viral hepatitis B, tetanus, diphtheria, pertussis, HIB, poliomyelitis, mumps, rubella, and measles. Vaccinations against pneumococci, varicella, rotaviruses, hepatitis A, influenza, and human papillomavirus are not included in the routine immunization schedule, but are proposed for parents with full payment. A small number of local outbreaks of chickenpox, hepatitis A, and mumps are reported every year, but their incidence is significantly diminishing.

In recent years, a 10-fold higher incidence of rubella cases has been observed in Poland, mostly in older boys and young men aged 15–29 years who have not been vaccinated in childhood. The National

Institute of Public Health in Warsaw announced an outbreak of rubella in 2013. Actually, two doses of a combined vaccination against rubella, measles, and mumps have been implemented as obligatory in the routine immunization program for the entire population of children, including boys. Congenital rubella is reported sporadically. Current recommendations of the Centers for Disease Control and Prevention (CDC) in Atlanta include an additional vaccination against rubella for nonimmune women of reproductive age traveling to Poland.

Diphtheria was successfully eliminated in the 1970s, and measles is in the process of eradication. Since October 2014, there has been a significant increase in measles cases in Germany, which creates a potential risk of spreading the infection to Poland. The annual number of infected cases varies from 13 to 114, and is significantly lower than in other European countries.

The number of pertussis cases tends to fluctuate, but its actual occurrence is rapidly declining in children and teenagers after the mass introduction of an additional dose of obligatory vaccine at age six years. The increasing incidence of pertussis is actually observed in young people and adults, who were only vaccinated in childhood during the first two years of life. In infants and younger children pertussis is now diagnosed sporadically.

Meningococcal vaccine is not included in the mandatory immunization program. However, since 2003, vaccination against serogroup C meningococci has been recommended for children over two years of age and for asplenic patients. In recent years, outbreaks of severe invasive meningococcal disease associated with a high percentage of cases with fulminant septicemia (up to 62%) and a high case fatality rate of 42.9% have been seen. An increasing number of *N. meningitidis* serotype C have been isolated from children, adolescents, and young adults (up to 64% of all isolates), including soldiers and military personnel, particularly a hypervirulent clonal complex ST-11/ET-37 of high invasiveness [1,2]. Because of the emerging situation of severe meningococcal sepsis in the Polish army, mass introduction of conjugated vaccine against meningococci group C in military recruits is being considering.

For people staying in rural wooded areas of the northern part of the country or seasonally working in forestry occupations, especially soldiers, border guards, hunters, woodcutters, and young people involved in recreational outdoor activities from March to November, vaccination against tick-borne encephalitis (central European encephalitis virus) is strongly recommended.

Basic economic and demographic data*

	GNI per capita (USD)	Life expectancy at birth (total, years)	School enrollment, primary (% net)
Belarus	16810	72.1	94
Bulgaria	15160	74.3	95
Czech Republic	26610	78.1	NA
Hungary	21620	75.1	91
Moldova	4710	68.7	88
Poland	21830	76.8	97
Romania	17700	74.6	94
Russian Federation	22710	70.5	96
Slovakia	25190	76.1	NA
Ukraine	8670	70.9	98

*World Bank, 2012.

GNI, gross national income; NA, not available.

Causes of death in children underfive. Regional average*

	%
Neonatal sepsis	3.1
Acute respiratory diseases	10.6
Diarrheal diseases	0.9
HIV/AIDS	0.2
Measles	0
Prematurity	25.5
Intrapartum-related complications	12.4
Congenital anomalies	30.4
Injuries	7.0
Others	14.3

*WHO. World Health Statistics 2014.

Ten most common causes of deaths all ages* in Moldova, Russian Federation, and Czech Republic

	%		
	Moldova	Russian Federation	Czech Republic
Ischemic and hypertensive heart disease	39.95	35.49	35.91
Cerebrovascular disease	17.32	23.59	13.68
Cancers	13.12	15.64	27.48
Liver cirrhosis	8.26	2.27	2.41
Lower respiratory infections	2.44	1.0	3.52
Tuberculosis	1.38	1.33	0.06
Poisoning	1.09	2.62	0.37
Chronic obstructive pulmonary disease	3.23	1.29	2.46
Falls	0.45	0.55	1.26
Road and traffic accidents	1.34	1.79	1.1
Self-inflicted injuries	1.67	2.02	1.74
Violence	0.68	1.36	0.19

*WHO 2010.

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Chapter 18

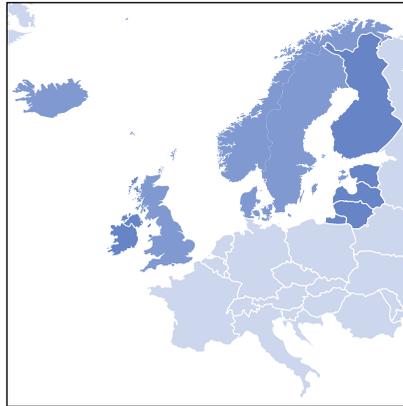
Northern Europe

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Denmark
Estonia
Finland
Iceland
Ireland
Latvia
Lithuania
Norway
Sweden
United Kingdom

The region is located in the temperate climate zone, but with northern Iceland, Norway, Sweden, and Finland stretching into the Arctic. The most common community-acquired infections are respiratory tract infections, including seasonal influenza, gastroenteritis, and urinary tract infections. Viral meningitis due to enterovirus is common and in the Baltic countries and eastern Sweden, tick-borne encephalitis is common. Bacterial meningitis is rare and most often caused by pneumococcus and meningococcus type B. Hepatitis A is rare and hepatitis B are usually sexually transmitted and hepatitis C transmitted by intravenous drug use. Gastroenteritis outbreaks are usually related to contaminated, processed food. *Campylobacter* and *Salmonella* are seen and recently a food-borne outbreak of *Listeria* was described from Denmark. Overall, the prevalence of HIV is below 1% and retroviral treatment is offered free of charge. Tuberculosis is still common in the Baltic countries, where MDR TB is a problem.

Water-borne outbreaks of *Giardia* and *Cryptosporidium* have been described from Norway and Sweden. In the Baltic countries, *Echinococcus granulosus* and *E. multilocularis* are found and *Trichinella spiralis* is seen in home-made meat products.

CNS infections: meningitis, encephalitis

Acute infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Viral meningitis (enterovirus group)	<i>Listeria monocytogenes</i>	Influenza
Pneumococcal meningitis	Neurosyphilis	<i>Naegleria</i> and other free-living amoeba
Herpes virus (group I and II) [1]	HIV	
<i>Borrelia</i> spp.	Tick-borne encephalitis*	Rabies**
<i>Neisseria meningitidis</i>	Tuberculosis	
	<i>Haemophilus influenzae</i> †	

* Especially common in the Baltic countries and parts of Sweden. One case has been reported from Northern Sealand, Denmark.

† Vaccination against *Haemophilus influenzae* has almost eradicated meningitis due to *H. influenzae* in Northern Europe.

** Rabies is found in bats, and persons exposed to bat bites should receive rabies postexposure immunization.

Meningitis and encephalitis with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms and conditions with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
HIV	<i>Nocardia</i>
Tuberculosis	Polyoma virus
Borreliosis	<i>Cryptococcus</i> spp.
	JC, BK virus or papovavirus
	Adenovirus
	<i>Toxoplasma gondii</i>
	CMV

* Consider noninfectious causes like vasculitis and lymphoma.

Ear, nose, and throat infections

Ear, nose, and throat infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Streptococcal throat infection	Peritonsillar abscess*	Diphtheria
Epstein–Barr virus	Tuberculosis	<i>Fusobacterium necrophorum</i>
Herpes virus (type I and II)	Necrotizing fasciitis*	
Adenovirus	<i>Francisella tularensis</i>	

* Requires acute ENT evaluation.

Ear, nose, and throat with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Tuberculosis <i>Actinomyces</i> HIV	<i>Candida</i> Herpes virus HIV Adenovirus <i>Aspergillus</i> Coxsackievirus

* Consider noninfectious causes like vasculitis and lymphoma.

Cardiopulmonary infections

Pneumonia with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Streptococcus pneumoniae</i> pneumonia [2] <i>Mycoplasma pneumoniae</i> [3] <i>Chlamydia pneumoniae</i> <i>Hemophilus influenzae</i>	<i>Legionella</i> Influenza* <i>Chlamydia psittaci</i> Puumalavirus*	Diphtheria <i>Simkania negevensis</i> [4] <i>Anaplasma phagocytophilum</i> <i>Ehrlichia</i> <i>Francisella tularensis</i>
<i>Moraxella catarrhalis</i> <i>Staphylococcus aureus</i>	<i>Klebsiella pneumoniae</i>	

* Puumalavirus belong to the Hantavirus group (Bunyaviridae). It is common in northern Sweden, Finland and the Baltic countries, especially in Estonia, but very rare in Denmark and has not been reported from the UK, Ireland, and Iceland.

Endocarditis with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Staphylococcus aureus</i> [5] Nonhemolytic streptococci Coagulase-negative staphylococci (<i>S. epidermidis</i>) <i>Streptococcus pneumoniae</i> <i>Enterococcus</i>	<i>Neisseria gonorrhoeae</i> <i>Coxiella burnetii</i> <i>Propionibacterium</i> HACEK group* <i>Salmonella</i>	<i>Bartonella</i> spp. <i>Brucella</i>

* *Haemophilus aphrophilus*, *H. paraphrophilis*, *Actinobacillus actinomycetecomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*.

Pulmonary symptoms for more than four weeks and in the immunocompromised host*

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
COPD	<i>Pneumocystis jiroveci</i>
Tuberculosis	CMV
<i>Aspergillus</i>	<i>Aspergillus</i> , <i>Candida</i>
Adenovirus	<i>Pseudomonas aeruginosa</i> , tuberculosis
<i>Chlamydia pneumoniae</i> , <i>Chlamydia psittaci</i>	<i>Toxoplasma gondii</i>
	Influenza
	Herpes simplex

* Consider noninfectious causes like lung cancer, autoimmune lung fibrosis, and Wegener's granulomatosis.

Endocarditis for more than four weeks and in the immunocompromised host*

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Coagulase-negative staphylococci (<i>S. epidermidis</i>)	<i>Aspergillus</i>
<i>Coxiella burnetii</i>	<i>Coxiella burnetii</i>
Nonhemolytic streptococci	
<i>Bartonella henselae</i> and <i>B. quintana</i>	<i>Bartonella henselae</i> and <i>B. quintana</i>

* Consider noninfectious causes like sarcoidosis.

Gastrointestinal infections**Gastrointestinal infections with less than four weeks of symptoms***

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Norovirus and calicivirus	<i>Cryptosporidium</i> spp.	Tuberculosis
<i>Campylobacter</i>	<i>Staphylococcus aureus</i> toxin	Whipple's disease
VTEC	<i>Bacillus cereus</i> toxin	
<i>Giardia intestinalis</i>	<i>Ascaris lumbricoides</i>	
<i>Salmonella</i> (non-typhi)	<i>Entamoeba histolytica/dispar</i>	
<i>Enterobius vermicularis</i>	<i>Schistosoma</i> spp.	
Adenovirus		
Rotavirus		

* Consider noninfectious causes like inflammatory bowel disease and intestinal malignancies like colon cancer.

Autochthonous intestinal and liver amebiasis is very rare in Baltic countries. Repeated negative bacterial cultures and microscopy for parasites should lead to the consideration that the symptoms may not be caused by an infection. Inflammatory bowel diseases like ulcerative colitis and Crohn's diseases are differential diagnoses and malabsorption and celiac disease must also be considered.

Gastrointestinal infections with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Giardia</i> and <i>Cryptosporidium</i> Tuberculosis Whipple's disease <i>Blastocystis</i> † <i>Dientamoeba fragilis</i> † <i>Necator americanus</i>	<i>Candida</i> Herpes virus
* Consider noninfectious causes like inflammatory bowel disease, and intestinal malignancies like colon cancer, malabsorption, intestinal lymphoma, and celiac disease. † Of uncertain pathogenicity in humans.	

Hepatobiliary infections

Hepatitis with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Hepatitis B CMV EBV	Hepatitis A Hepatitis C Hepatitis E	Tuberculosis

Hepatitis with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Hepatitis B Hepatitis C <i>Opisthorchis felineus</i> , <i>Fasciola hepatica</i> †	Herpes virus
* Consider noninfectious causes like autoimmune hepatitis, sarcoidosis, toxic reaction to drugs or other substances. † Consider rare eosinophilic hepatitis cases.	

Echinococcus multilocularis is found in wildlife in the Svalbard islands, but no human cases have been reported [6]. A single case in a fox has been found in Denmark. The known central European endemic area of the tapeworm *E. multilocularis* has expanded during the 1990s, especially to the north and east. Recently, the occurrence of *E. multilocularis* was reported in the Baltic and neighboring regions. *E. multilocularis* was detected in 58% of red foxes and 8% of raccoon dogs in Lithuania. Necrotic lesions in pig livers in 0.4% of cases were identified as *E. multilocularis* by PCR. Since 1997, 215 human cases of *E. multilocularis* have been diagnosed in Vilnius, Lithuania.

Genitourinary infections

Cystitis, pyelonephritis, and nephritis with less than four weeks of symptoms*

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>E. coli</i>	Perirenal abscess	Tuberculosis
<i>Klebsiella pneumoniae</i>	Puumalavirus†	
<i>Staphylococcus saprophyticus</i>	<i>Pseudomonas aeruginosa</i>	
<i>Proteus mirabilis</i>	<i>Chlamydia trachomatis</i>	
<i>Enterococcus faecalis</i>		

*Consider noninfectious causes, especially malignancies like renal cell carcinoma.

†Endemic in northern parts of Scandinavia and the Baltic countries where it causes epidemic nephrotic syndrome.

Sexually transmitted infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Chlamydia</i> spp.	Lymphogranuloma venereum	
<i>Neisseria gonorrhoeae</i>	<i>Entamoeba dispar</i> and <i>E. histolytica</i>	
<i>Trichomonas vaginalis</i>		

Cystitis, pyelonephritis, and nephritis with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Bacterial infections in patients with long-term catheters and renal stones Tuberculosis	<i>Candida</i>

*Consider noninfectious causes, especially malignancies like renal cell carcinoma.

Sexually transmitted infections with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
HIV Herpes virus type I, II Papillomavirus <i>Treponema pallidum</i>	HIV <i>Treponema pallidum</i>

Joint, muscle, and soft tissue infections

Joint, muscle, and soft tissue infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Staphylococcus aureus</i>	Necrotizing fasciitis Group G streptococci increasing numbers of invasive cases (domestic) in Sweden	Fournier's gangrene (perineum and urogenital)
<i>Streptococcus pneumoniae</i>		Sindbis virus

Joint, muscle, and soft tissue infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Borreliosis (Lyme disease), increasing numbers in Sweden Tuberculosis	<i>Candida</i>

Skin infections

Skin infections with less than four weeks of symptoms*

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Erysipelas, <i>Streptococcus pneumoniae</i> <i>Staphylococcus aureus</i> <i>Borrelia</i> spp. <i>Malassezia furfur</i>	Scabies Other fungi <i>Ancylostoma braziliense</i>	Rat-bite fever (<i>Spirillum minus</i>)

*Rash due to viral infections has not been listed.

Skin infections with more than four weeks of symptoms and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Syphilis Tuberculosis	<i>Candida</i>

*Rash due to viral infections has not been listed.

Basic diagnostics of skin infections*

Microorganism	Diagnostics
Erysipelas (streptococcal and <i>S. aureus</i>)	Clinical diagnosis Skin culture usually not helpful, wound culture will reflect contamination not invasive infection, serology useless
<i>Borrelia</i> spp.	Clinical and epidemiological diagnosis, serology useless in cutaneous borreliosis
Scabies	Microscopy of mites removed from the skin
Rat-bite fever	History of rat bite, specific IgG and IgM antibodies

*Consider noninfectious causes like psoriasis. Consult a dermatologist if the condition is unclear.

Adenopathy**Adenopathy of less than four weeks duration**

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Epstein–Barr virus Cytomegalovirus Parvovirus B19 <i>Toxoplasma gondii</i> HIV	Tularemia <i>Bartonella</i>	<i>Ehrlichia</i> <i>Babesia</i>

Adenopathy of more than four weeks duration and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Toxoplasma gondii</i> Tuberculosis	Adenovirus CMV Tuberculosis

If the diagnosis is not made within a few days, biopsies should be performed to exclude malignancies like lymphoma and carcinomas.

Fever without focal symptoms

Fever for less than four weeks without focal symptoms

Frequently found microorganisms and conditions	Rare microorganisms and conditions	Very rare microorganisms and conditions
Endocarditis Epstein–Barr virus Cytomegalovirus Parvovirus B19 <i>Toxoplasma gondii</i> HIV	Tuberculosis <i>Coxiella burnetii</i> Puumalavirus (epidemic nephrotic syndrome)	Tularemia <i>Ehrlichia</i> <i>Babesia</i> Sindbis virus (Ockelbo disease) Anthrax*
*Anthrax from contaminated heroin has been reported in heroin users in the United Kingdom.		

Fever for more than four weeks without focal symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Toxoplasma gondii</i> Tuberculosis	CMV Adenovirus

Noninfectious causes should be considered from the beginning, including malignancies like lymphoma and autoimmune diseases.

Eosinophilia and elevated IgE

Eosinophilia and elevated IgE for less than four weeks

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Ascaris lumbricoides</i> and <i>A. suum</i> <i>Schistosoma</i> spp.*	<i>Toxocara</i> spp. [7] <i>Trichinella spiralis</i> †	<i>Strongyloides stercoralis</i> <i>Isospora belli</i>
*Free-living cercaria cause swimmer's itch. † <i>Trichinella spiralis</i> in humans have been reported from the Baltic countries.		

Eosinophilia and elevated IgE for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Ascaris lumbricoides</i> and <i>suum</i>	<i>Toxocara</i> spp.
<i>Schistosoma</i> spp.*	<i>Strongyloides stercoralis</i>
<i>Trichinella spiralis</i> †	
<i>Echinococcus granulosus</i> ** and <i>multilocularis</i> ††	<i>E. multilocularis</i> detected in a fox in Sweden
Northern Sweden, Norway, and Finland ?	2010, 2011

*Free-living cercaria cause swimmer's itch.

† *Trichinella spiralis* in humans have been reported from the Baltic countries. Between 1999 and 2008, a total of 359 cases were registered, including 66 sporadic cases and 42 outbreaks. During these nine years, the incidence of trichinellosis decreased from 1.7 to 1.2 cases per 100 000 population. Fifty eight percent of the cases were due to consumption of meat from home-raised pigs, 10% due to infected wild boar meat.

** *Echinococcus granulosus* is endemic in reindeers and wolves in Finland, but human cases have not been reported [8]. Human infection with *E. granulosus* is of increasing concern in Lithuania; 13.7% of rural dogs and pigs were found to be infected with *E. granulosus* in south west Lithuania. The pig strain (G7) was identified by sequence analysis in samples from pig livers.

Antibiotic resistance

In Lithuania, penicillin-resistant pneumococci were identified in 6.5% of cases in 2009. Ampicillin and trimethoprim/sulphamethoxazole-resistant *Salmonella* is very common in Lithuania. *E. coli* is ciprofloxacin resistant in 14.6% of culture cases.

Ciprofloxacin-resistant *Campylobacter jejuni* occurred in 21.1% and there was very high resistance of other *Campylobacter* spp. to erythromycin in Lithuania in 2008–2009.

Resistance in TB and malaria is dealt with in the sections above, if appropriate.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is still rare in Scandinavia but increasing, especially in Finland [9]. However, the problem with community-acquired MRSA is increasing, as in other parts of Europe [10]. In Scotland, 7.5% of patients were colonized with MRSA on admission to hospital [11]. In Lithuania, 11.4–12% of *S. aureus* seems to be methicillin resistant. Vancomycin-resistant *Enterococcus faecalis* is rare in Baltic countries, but vancomycin-resistant *E. faecium* is increasing (10.5% cultures of *E. faecium* were resistant in 2009). VRE occurs in Sweden in outbreaks – the highest incidence was 3.38/100 000/year in 2013, MRSA 14.9/100 000/year in 2014, ESBL 0.02/100 000 population per year.

Vaccine-preventable diseases in children

The childhood vaccination programs have high adherence in the Scandinavian and Baltic countries, but small outbreaks due to imported cases are seen in the age groups which are not yet immunized [12]. Measles is increasing in Ireland with substantial transmission [13]. Mumps was reported in the United Kingdom in 2010 and occasional outbreaks of pertussis are also seen. A proportion of children do not follow the childhood immunization program, including polio, tetanus, and diphtheria immunizations. Sporadic cases of measles are seen in nonimmunized children below the age where the first MMR is given, usually 15 months.

Basic economic and demographic data*

	GNI per capita (USD)	Life expectancy at birth (total, years)	School enrollment, primary (% net)
Denmark	59 130	78	96
Estonia	14 270	73	95
Finland	48 120	79	96
Iceland	40 070	81	97
Ireland	49 590	79	96
Latvia	11 860	71	90
Lithuania	11 870	71	91
Norway	87 070	80	99
Sweden	50 940	81	94
United Kingdom	45 390	79	97

*World Bank, 2008.

GNI, gross national income.

Causes of death in children underfive. Regional average*

	%
Neonatal causes	44
Pneumonia	13
Diarrheal diseases	10
HIV/AIDS	0
Measles	0
Injuries	6
Others	25

*WHO. Regional average, 2000–3 data.

Ten most common causes of deaths all ages* in three countries selected for a regional low (Latvia), middle (Iceland), and high (Norway) gross national income per capita

	%		
	Latvia	Iceland	Norway
Ischemic and hypertensive heart disease	30	22	20
Cerebrovascular disease	22	10	11
Lower respiratory infections	NS	5	6
Inflammatory heart disease	2	NS	NS
Alzheimer's and other dementias	NS	5	3

(Continued)

	%		
	Latvia	Iceland	Norway
Chronic obstructive pulmonary disease	NS	4	4
Road traffic accidents	2	NS	NS
Cancers	8	16	13
Falls	NS	1	2
Self-inflicted injuries	2	NS	NS

*WHO 2002.
NS, not stated.

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Chapter 19

Southern Europe

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Albania
Andorra
Bosnia and Herzegovina
Croatia
Cyprus
Gibraltar
Greece
Holy See
Italy
Macedonia
Malta
Montenegro
Portugal
San Marino
Serbia
Slovenia
Spain
Turkey

In this chapter, the countries listed above will be considered as part of Southern Europe as they share common characteristics from the epidemiological standpoint: countries of the Iberian and Italian peninsulas, most of the Balkan countries, Cyprus, Malta, and Turkey. The total population of the region is 220 million inhabitants and the average number of tourists per year is near to 200 million.

Southern Europe is a temperate climate region acting as a bridge between the South and the North, located at the crossroads of migration. Apart from pandemic infections, such as infections with human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), Southern Europe offers peculiar epidemiological features that must be considered. This is mainly due to the presence of specific possible vectors of viral (Tuscany virus, etc.) and protozoan (*Leishmania*, potentially *Plasmodium vivax* malaria) infections. These features put Southern Europe at risk for vector-borne emerging diseases, such as chikungunya, dengue, and West Nile, for which cases have been sporadically reported in past years. Due to its warm climate and long seashores, Southern Europe may also be potentially considered a suitable place for the transmission of fecal-oral pathogens (hepatitis A, typhoid fever, travelers' diarrhea, etc.) although the dramatic improvement in hygienic conditions during the last decades has substantially decreased this risk.

The high antibiotic pressure exerted in the past decades on many bacterial species has given rise to the worrying phenomenon of bacterial drug resistance in the region, particularly in those countries with higher living standards. Unfortunately, epidemiological data on many infectious diseases are limited (*Bartonella*, *Borrelia*), with uncertain prevalence and incidence rates.

Infectious diseases with incubation periods shorter than four weeks

Malaria

In Southern Europe, risk of contracting malaria is present only in the south-eastern part of Turkey from May to October and the infection is exclusively due to *P. vivax*. Turkish provinces with low risk of malaria infection include Diyarbakir, Mardin, and Sanliurfa [1]. For those who travel in this region, WHO type A prevention is recommended which includes only mosquito bite prevention [1]. In Greece, autochthonous transmission of *P. vivax* malaria has been reported since 2009 with the highest number reported in 2011; 20 autochthonous malaria cases were notified in 2011 [2] whereas in 2012 and 2013, fewer cases of local malaria transmission were reported [3]. The risk of contracting malaria in Greece is only very limited and exclusively due to *P. vivax*, from May to October in agricultural areas of the Evrotas delta region in Lakonia district (20km² wide area) with large migrant populations. There is no risk in tourist areas.

An autochthonous case of *P. vivax* malaria was reported in the Aragon region of Spain in October 2010. Autochthonous malaria cases have also been reported in France and Italy [4–6]. Local transmission remains possible in Southern Europe due to the high prevalence of anophelines in many Southern Europe regions. Therefore, surveillance, preparedness, and prevention, including the improvement of health services available to migrants, are very important.

Rickettsial infections

The most common rickettsial infection in Southern Europe is Mediterranean spotted fever due to *Rickettsia conorii*, transmitted to humans by tick bite. The disease is present in Albania, Andorra, Bosnia and Herzegovina, the coastal region of Croatia, in Cyprus and Greece, in Italy, particularly in the islands [7], Macedonia, Malta, Montenegro, and Portugal, in the south of Spain, Serbia, Slovenia, and Turkey. In rural areas of certain countries, the seroprevalence of the infection in humans can be as high as 44% [8]. Murine typhus (*Rickettsia typhi*) is sporadically observed. In Cyprus, *Rickettsia typhi* infections are common [9]. Travelers who have been camping or hiking are to be considered at higher risk of contracting the infection.

Typhoid and paratyphoid fevers

Typhoid fever (due to *Salmonella* enteric serotype *typhi*) and paratyphoid fever are two of the most important infectious diseases in developing countries, whereas in Southern Europe they continue to be uncommon. Most cases (90%) are associated with travel during the exposure period, in particular to the Indian subcontinent [10–12]. The seasonal pattern, with a peak in cases in August–September, also reflects travel during the holiday period, with disease reported after returning home.

Although *S. typhi* is much more common than *S. paratyphi* in developed countries, the notification rate of *S. typhi* and *S. paratyphi* in Europeans is similar; this may be related to *S. typhi* vaccination prior to travel [13]. In the majority of countries of Southern Europe, the incidence rate of *S. typhi* and *S. paratyphi* is low; in Portugal and Cyprus it is 0.13 and 0.12 per 100000 population, respectively, and for Slovenia and Greece, it is 0.05 per 100000 population [14]. The incidence rate for Turkey ranges from two to 40 cases per 100000 population (2000–06); most of the cases are reported from the south-east region [15], where 10000 patients are diagnosed annually with this condition [16].

Although the incidence of typhoid and paratyphoid fever is low, the global diffusion of enteric fevers suggests that the medical practitioner should consider this differential diagnosis for a traveler coming back from this region if clinical findings are suggestive for the disease.

Brucellosis

Brucellosis is present in every country of the region and is due to *Brucella melitensis*, *B. abortus*, and *B. suis*. It is mainly a professional disease and those who work in contact with animals show a seroprevalence of about 3%, as reported in Spain [17]. Among the animals responsible for the transmission

of disease (ovine, bovine, swine), the proportion of affected cattle has been reported to be around 20–30% [18]. The disease occurs in Albania, Bosnia, Croatia, north-western and central regions of Greece, the south of Italy, Macedonia, Montenegro, Portugal, Slovenia, Spain, and Turkey; the highest annual notification rates, although still low, are reported in Greece, Portugal, Spain, and Italy with incidence rates of 1.09, 0.36, 0.13, and 0.01 cases per 100000, respectively (2012). In Andorra, Cyprus, and Malta, no cases have been notified in recent years (2008–12) [19].

Crimean-Congo hemorrhagic fever

Crimean-Congo hemorrhagic fever (CCHF) is endemic in many areas of Africa, the Middle East, central and south-western Asia, and the south-eastern European region. In particular, some Balkan countries (e.g. Albania, Bulgaria, Kosovo under UN Security Council Resolution 1244) and Greece are considered endemic zones for CCHF [8]. During the last decade, CCHF has reemerged in Albania, Greece, Kosovo under UN Security Council Resolution 1244 and countries bordering the Black Sea such as Turkey, Georgia, south-western Russia, and Ukraine. In Greece, detection of the nonpathogenic strain AP92 in ticks in 1975 was followed by notification of the first human CCHF case in June 2008 [20]. However, many of the CCHF cases since 2002 have been recorded in Turkey [21,22]. In nature, CCHF usually circulates between asymptomatic animals and ticks in an enzootic cycle. Humans may become infected through the bite of a tick, mainly of the *Hyalomma* genus, which is present in southern Europe [23].

Tick-borne encephalitis

Tick-borne encephalitis (TBE) is the most common encephalitis due to a flavivirus in Europe. The main subtype is the Central European one, responsible for less severe disease than those due to the Siberian or Far Eastern viruses. The disease starts with an uncharacteristic influenza-like illness. After a symptom-free interval, neurological involvement appears (meningitis, meningoencephalitis, meningoencephalomyelitis or meningoencephaloradiculitis). The disease occurs in the south of Albania, the northern regions of Bosnia and Herzegovina, Croatia, the north of Greece, the north-east of Italy, Macedonia, Serbia and Montenegro, and Slovenia [24]. Countries of the Balkan peninsula show the highest prevalence rates [25]. The country with the highest burden of infection is Slovenia, where the incidence of the disease during 2013 was 15 per 100000 inhabitants [26], with peaks higher than 70 per 100000 inhabitants in northern regions [27]. In Spain and Portugal, TBE is not indigenous. In Turkey, there are no confirmed cases of the disease [28].

Tick-borne encephalitis vaccine should be considered for all persons living in TBE-endemic areas, for those at occupational risk in endemic areas (e.g. farmers, forestry workers, and soldiers) and for travelers to rural endemic areas during late spring and summer [29].

West Nile virus

West Nile virus is transmitted by infected *Culex* mosquitoes and is present in all countries of Southern Europe. The infection can be asymptomatic or associated with an influenza-like illness (fever, headache, vomiting, conjunctivitis, eye pain, and anorexia). In some cases patients can develop neurological signs due to the presence of encephalitis. The virus is present in the coastal region of Albania, in Andorra, Bosnia and Herzegovina, Cyprus, Croatia, Greece, north-eastern regions and islands of Italy with a recent extension of the risk area to the Lombardy region [30], Macedonia, Malta, Montenegro, southern regions of Portugal, Serbia, Slovenia, Spain and the central regions of Turkey. The year 2012 saw a peak of human cases and several European countries reported significant outbreaks [31].

Chikungunya virus

The Chikungunya virus is present in more than 40 countries (mainly in Africa and Asia) and is transmitted by infectious mosquitoes (*Aedes albopictus*, also known as the “tiger mosquito”). In Southern Europe, the disease has been identified only in Italy, where an outbreak occurred in Emilia-Romagna

during 2007, introduced by a man coming from the Indian state of Kerala [32]. The potential for a local transmission of the virus in Southern Europe was subsequently confirmed by a Chikungunya outbreak from a primary imported case occurred in Southern France in Montpellier [33].

Diseases transmitted by sand flies

Sand flies may be responsible for the transmission of many viral, bacterial (bartonellosis), and protozoan (leishmaniasis) diseases. Among viruses responsible for human diseases, in Southern Europe the Tuscany virus and the Sicily and Naples viruses may be encountered. Other viruses have been isolated from asymptomatic carriers, even if currently no data are available on their pathogenicity for the human host: the Corfu virus (identified in Greece and closely related to the Sicily virus), Arbia virus, Punta Toro virus, Chandipura virus, and Changuinola virus. These viruses are endemic in Europe and although a limited number of cases have been reported in few states, their presence could extend to all areas where carriers are present [34]. New viruses, named Adria virus and sand fly fever Turkey virus, were recently identified, the former in Greece in the CSF of a young boy with febrile seizure and the latter in Turkey in a patient with encephalitis [35].

Tuscany virus is generally responsible for asymptomatic infections. However, in some cases a flu-like syndrome occurs and, due to its neurotropism, meningitis and/or encephalitis are also reported. Cases of neurological involvement have been reported in Bosnia and Herzegovina, Croatia, Cyprus, Greece, Italy, Portugal, Spain, and Turkey [36]. In Italy, particularly in spring and summer, Tuscany virus is one of the three most frequent causes of viral meningitis. Tuscany virus infections should always be suspected when a traveler with signs and symptoms of meningoencephalitis returns from Southern Europe.

The illness caused by Sicily or Naples viruses is a flu-like syndrome consisting of fever, eye pain, bone pain, and fatigue, which usually resolves in about a week. Cases of human disease and isolation of vectors are reported in Cyprus, Greece, Italy, Portugal, states of former Yugoslavia (especially Serbia), and Turkey [34].

Rabies

In Southern European countries, rabies infection usually affects wild animals (foxes, bats, and raccoons in particular) rather than domestic ones. The virus affects the central nervous system, causing progressive paralysis, encephalitis, and coma. Based on the WHO assessment of infection risk, Southern European countries can be divided into low risk (Andorra, Cyprus, Greece, Italy, Malta, Portugal, and Spain), medium risk (Slovenia), and high risk (Albania, Bosnia and Herzegovina, Croatia, Macedonia, Serbia, Montenegro, and Turkey) [37].

An outbreak of animal rabies in northern Italy has been documented after many years of absence of the disease in the country; from 2008 to 2011, 287 cases of rabies were reported in wild and domestic animals and one human case in the regions of Friuli Venezia Giulia and Veneto [38]. During the period 2012–14, Italy did not report any rabies cases in animals, indicating that the rabies epidemic that the country experienced in 2008–11 may be over [39]. In October 2012, 25 years after the last reported case, Greece detected one rabid fox in the northern part of the Greek territory. Before the end of 2014, a total of 48 cases (40 cases in wild animals and eight cases in dogs) were reported [39,40]. Rabies remains endemic within a number of countries in south-east Europe. Among these, Turkey is the only one where urban dog-transmitted rabies persists [41].

In cases of exposure to a suspected infected animal, postexposure prophylaxis is mandatory. Pretravel vaccination should be considered according to the estimated risk of travel.

Infectious travelers' diarrhea

Travelers' diarrhea (TD) affects 30–70% of travelers to developing countries. Overall levels of hygiene at the travel destination, including individual eating establishments, are strong predictors for acquisition of TD. TD is a self-limited clinical syndrome caused by a variety of intestinal pathogens. Bacterial

pathogens (*Escherichia coli*, *Campylobacter jejuni*, *Shigella* spp., and *Salmonella* spp., enteroadherent and other *E. coli* species, *Aeromonas* spp., *Plesiomonas*, and *Vibrios*) are the most common and account for 80–90% of TD cases. Intestinal viruses are responsible for only 5–8% of cases, although newly developed diagnostics and their increased use for diagnosing norovirus infections in travelers may modify those percentages in the future. Protozoal pathogens, mainly *Giardia lamblia* and, especially in immunocompromised patients, *Entamoeba histolytica*, follow a more chronic course and account for nearly 10% of diagnoses in longer-term travelers [42]. Southern Europe is a region with an intermediate risk of TD, ranging from 8% to 20% of travelers [43].

Infectious diseases with incubation periods longer than four weeks

Leishmaniasis

Leishmaniasis, a vector-borne disease, is endemic in 98 countries on five continents and is caused by protozoans of the genus *Leishmania*. It is a rare disease in some countries of Europe but endemic in others and may have a great impact on individuals and the potential to spread further.

In Southern Europe, two species have been identified as the cause of leishmaniasis in humans: *Leishmania infantum*, the most widely circulating species, causing over 90% of cases of zoonotic cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL), and *Leishmania tropica* which causes anthroponotic CL and occurs sporadically in eastern Mediterranean countries [44,45]. Leishmaniasis cases have been reported by many countries in the Mediterranean region, including Albania, Bosnia and Herzegovina, Croatia, Cyprus, Greece, Italy, Macedonia, Malta, Montenegro, Portugal, Slovenia, Spain, and Turkey [43]. Imported VL cases in some northern European countries were mainly acquired in southern European countries such as Italy, Spain, Greece, Cyprus, and Malta [46–49]. In Southern Europe, VL also commonly affects HIV-infected patients. In these patients, the less pathogenic strains of *Leishmania* spp. can also spread and cause serious systemic disease [50]. In HIV-infected individuals, VL is not only considered to be an opportunistic infection but it may also reactivate latent infection [51]. A retrospective analysis reported a total of 40 cases diagnosed between 2000 and 2012, the majority of which were identified in Spain, Italy, and Malta [52].

The disease should be monitored carefully through surveillance systems at both national and transnational levels. Surveillance of the disease in dogs is important, because the number of infected animals in an area determines the local risk of human infection.

Tuberculosis

All countries of Southern Europe report cases of tuberculosis, but substantial differences exist among countries. Tuberculosis epidemiological data (cases/100 000 inhabitants per year) distinguish between two different groups of countries: (i) incidence rate less than 10 cases/100 000 (Andorra, Cyprus, Greece, Italy, San Marino, and Slovenia), and (ii) more than 10 cases/100 000 (Albania, Malta, Portugal, Spain, Turkey and ex-Yugoslavian countries, except for Slovenia where tuberculosis vaccination is routinely administered within the normal infant vaccination schedule) [53]. The possibility of active tuberculosis has to be taken into account when subjects with typical symptoms (persistence of cough, fever, and loss of weight) report previous travel to high-prevalence rate countries of the region.

Antibiotic resistance

Although it is very difficult to compare countries with significantly different health expenditures, the drug resistance phenomenon toward the most common pathogen is almost universally present due to the high and often inappropriate use of antibiotics in recent years. For methicillin-resistant *Staphylococcus aureus* (MRSA), data are troubling but stable (usually more than 25% of isolates are MRSA). Regarding gram-negative bacteria, the data are even more alarming: analyzing invasive (from blood and cerebrospinal

fluid) isolates, the phenomenon of multidrug resistance is increasing, especially for *Escherichia coli* and *Klebsiella pneumoniae* (*K. pneumoniae* shows rates of combined resistance to third-generation cephalosporins, fluoroquinolones, and aminoglycosides higher than 25% in Italy, Greece, and Portugal) [54].

Frequency of resistance to antitubercular drugs is different among states in the region. In five countries (Greece, Italy, Portugal, San Marino, and Turkey), strains isolated in notified new tuberculosis cases showed multidrug resistance (MDR) strains in a range of 1–3%; only San Marino and Turkey reported a percentage of MDR strains in previously treated tuberculosis cases higher than 10% [55]. It is important to underline that differences in disease reporting exist from country to country, as a consequence of differences in diagnostic capacity, despite the intense efforts that have been made to enhance the level of monitoring and reporting.

In Southern Europe, since the early 1990s after highly active antiretroviral therapy (HAART) was made available, many HIV strains have become resistant to different classes of drugs, including nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). Recent studies show that as many as 5–20% of new HIV infections in Southern Europe are caused by HIV-resistant strains, requiring resistance testing to be performed before starting therapy in a naive patient [56,57].

Vaccine-preventable diseases

Infants immunization schedules are substantially comparable among the different countries of Southern Europe. Vaccines for tetanus, diphtheria, and whooping cough (usually administered in combination), measles-mumps-rubella (MMR), *Haemophilus influenzae* type B, polio, and hepatitis B are compulsory in all the states in the region, although different coverage rates are recorded from state to state. BCG vaccine against tuberculosis is required only by some states in the region.

Vaccination coverage of the main vaccine-preventable diseases by country, according to WHO/UNICEF estimates, 2013 [58].

	AL	AND	BiH	CY	E	GR	HR	I	M	MK	MNE	P	SLO	SM	SRB	TR
BCG	99	-	96	-	-	-	99	-	-	97	93	99	-	-	97	96
DTP1	99	98	95	99	98	99	98	99	99	99	98	99	98	72	98	99
DTP3	99	96	92	99	96	99	96	97	99	98	94	98	95	69	95	98
HepBB	99	96	96	0	0	0	98	0	0	98	0	98	0	0	99	99
HepB3	99	94	92	96	95	98	96	97	94	97	90	98	0	69	91	97
Hib3	99	96	87	96	96	94	96	96	99	97	94	98	95	69	92	98
Rota (last)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PcV3	99	0	0	0	0	32	0	55	0	0	0	0	0	0	0	97
Pol3	99	99	87	99	96	99	96	97	99	98	94	98	95	69	97	98
MCV1	99	95	94	86	95	99	94	90	99	96	88	98	94	74	92	98
MCV2	99	91	94	88	91	83	97	0	88	96	94	96	95	77	82	85
PAB	87	-	-	-	-	-	-	-	-	-	-	-	-	-	-	90

International countries codes: AL, Albania; AND, Andorra; BiH, Bosnia and Herzegovina; CY, Cyprus; E, Spain; GR, Greece; HR, Croatia; I, Italy; M, Malta; MK, Macedonia; MNE, Montenegro; P, Portugal; SLO, Slovenia; SM, San Marino; SRB, Serbia; TR, Turkey.

Vaccine abbreviations: BCG, Bacillus Calmette–Guérin vaccine; DTP1, first dose of diphtheria-tetanus-pertussis vaccine; DTP3, third dose of diphtheria-tetanus-pertussis vaccine; HepBB, birth dose of hepatitis B vaccine; HepB3, third dose of hepatitis B vaccine; Hib3, third dose of *Haemophilus influenzae* type B vaccine; rota (last), last dose of rotavirus vaccine; PcV3, third dose of pneumococcal conjugate vaccine; Pol3, third dose of polio vaccine; MCV1, first dose of measles-containing vaccine; MCV2, second dose of measles-containing vaccine; PAB, protection at birth against tetanus.

Travelers to Southern Europe should consider specific vaccination is conditions of risk exist with regard to destination, such as hepatitis A, typhoid fever, rabies, and TBE vaccines. All travelers should be up to date with routine vaccination schedules, including MMR, tetanus-diphtheria (Td) and poliomyelitis vaccine. At present, among Southern European countries, only Albania and Malta require a yellow fever vaccination certificate for those entering their national territory and coming from yellow fever-endemic regions [59].

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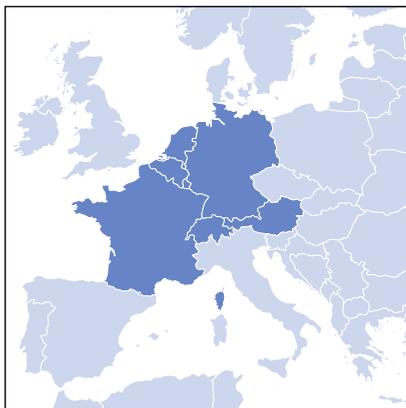
Chapter 20

Western Europe

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Austria
Belgium
France
Germany
Liechtenstein
Luxembourg
Monaco
The Netherlands
Switzerland

The epidemiology of infectious diseases in Western Europe is dominated by infections, typical of industrialized, urbanized regions in the temperate climate zones. Public health policies, including mass vaccination, have reduced the incidence of community-acquired infections. Most infections are air-borne respiratory tract infections. Food-borne gastrointestinal infections are relatively rare although outbreaks may occur. Zoonotic and parasitic infections are rare. Their distribution varies with changing landscape and climate. Vector-borne infections are mainly tick borne but mosquito-borne infections are emerging. Leishmaniasis and *Aedes albopictus*-transmitted dengue and chikungunya have been reported in southern France. Sexually transmitted infections are increasing. Prevalence of antibiotic resistance varies but antibiotic resistance is a growing cause of concern everywhere, most particularly in travelers carrying MDR bacteria, and migrants infected with XDR *Mycobacterium tuberculosis*.

Introduction

The region defined as Western Europe encompasses four different ecological regions:

- the river delta regions of The Netherlands and Belgium (Flanders) and the similar north-western parts of France and Germany flanking the North Sea
- the Pyrenees and alpine mountainous region in Switzerland, Liechtenstein, Austria, and southern parts of Germany and France
- the Mediterranean zone of southern France and Monaco
- the midland that connects the previous three.

The human infections in this region are dominated by diseases of crowding but zoonotic infections and vector-borne diseases are increasingly reported. This is especially true for the lowlands that are characterized by a temperate sea climate, high population densities, intensive bioindustry, and little natural vegetation. The Alpine region, with its highest peak reaching to 4.8 km above sea level, and the Pyrenees in France are far less densely populated and include large forested areas and parks that are frequented by tourists from all over Europe. In the winter season, these regions are cold and covered with snow. The Mediterranean region has a dry subtropical climate suitable for vector-borne diseases, and has variable population densities with large urbanized areas along the coast that attract large flocks of tourists in the summer. The midland is of variable nature but typically a mixture of agricultural land and coniferous and deciduous forests, the habitat for European fauna that may serve as a zoonotic reservoir of particular diseases. Overall, the climate in Western Europe shows a seasonal pattern that affects the transmission patterns of infectious diseases. The effects of global warming on disease transmission are starting to become visible, with the occurrence of autochthonous clusters or outbreaks of dengue, chikungunya, and schistosomiasis in southern France (Corsica).

Overall, eight infectious diseases have been identified as future threats for Europe: extensively drug-resistant bacteria, vector-borne diseases, STI, food-borne infections, a resurgence of vaccine-preventable diseases, healthcare-associated infections, multidrug-resistant tuberculosis, and pandemic influenza [1].

Endemic communicable infections will be discussed in this chapter with frequent reference to EU surveillance data [2]. The large group of ubiquitous, opportunistic or nosocomial infections will only be mentioned if there is a particular condition such as antibiotic nonsusceptibility that deserves discussion.

CNS infections: meningitis, encephalitis, and other infections with neurological symptoms

Acute infections with less than four weeks of symptoms [3]

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Viral meningitis (enterovirus group)	<i>Listeria monocytogenes</i>	<i>Naegleria</i> and other free-living amoeba
Meningococcal meningitis	Neurosyphilis	Influenza
Pneumococcal meningitis	HIV	Toscana virus
Herpes virus (group I and II)		<i>Brucella</i>
Varicella zoster virus		
<i>Borrelia</i> spp.	Tick-borne encephalitis	Malaria (imported)

Enterovirus infections Enterovirus infections are the most common cause of viral meningitis, especially in children. Nonpolio enterovirus infections show a seasonal pattern with peaks in the

summer and early fall extending into the cold season. However, human enterovirus 71 (EV-A71) is emerging in Europe as a cause of encephalitis and poliomyelitis-like paralysis [4].

Meningococcal meningitis *Neisseria meningitidis* serotypes B and C are predominant and the most frequent cause of bacterial meningitis, especially in the younger age group in Western Europe. The introduction of the conjugated meningococcal serogroup C vaccine in some at-risk groups caused a significant decrease in serogroup C infections. A new clone of serogroup C *Neisseria meningitidis* has emerged, at least in European men who have sex with men (MSM) community in Germany and France [5]. Therefore, some public health authorities recommend targeting vaccination against meningococcal infections in MSM as well as individuals more than 25 years old attending social venues that are associated with the MSM community.

Pneumococcal meningitis The notification rate of invasive pneumococcal disease in the EU zone is approximately 6 per 100000, with the highest incidence in winter time [2]. Pneumococcal meningitis is not counted separately. Elderly people and under-fives are the most affected groups.

Viral meningoencephalitis Severe viral CNS infections are predominantly caused by herpes simplex virus (HSV) followed by varicella zoster virus infections and *Mycobacterium tuberculosis* [6].

Neuroborreliosis The causative agents of borreliosis, *Borrelia burgdorferi* sensu stricto, *B. garinii*, and *B. afzelii* and other species in the *B. burgdorferi* s.l. complex, have been isolated from castor bean ticks (*Ixodes ricinus*) and vertebrate hosts from all over Europe, except the Mediterranean coast and altitudes above 1500m [7]. Tick infestation rates are on average 7%, low but rising in the Low Countries and high in the Alpine area [8].

Listeriosis *Listeria monocytogenes* infection may present as a febrile gastroenteritis, associated with consumption of food products such as soft cheese or meat/pork/chicken products. Elderly and immunocompromised individuals are at risk for septicemia and meningoencephalitis [9]. The EU zone average notification rate is 0.34 per 100000, with a small increase over recent years [2].

Tuberculosis Notification rates of tuberculosis are very low in Western Europe and 30–60% of all cases have a foreign origin. Of note, migrants are more at risk of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis.

Syphilis Syphilis incidence has increased over the last decade, mainly among MSM [10]. Syphilis of the central nervous system and ophthalmic syphilis are rare complications that put the patient at risk of vision loss or neurological sequelae.

HIV Central nervous system manifestations of acute and chronic HIV-1 infection (meningitis, cranial nerve involvement, major cognitive or motor disorder, dementia, encephalopathy) are rare but must be systematically evaluated as they indicate drugs that penetrate the CNS.

Tick-borne encephalitis The European subtype of tick-borne encephalitis virus (TBEV-Eu) is transmitted by *Ixodes ricinus*, and is endemic in parts of Austria, Switzerland, and Germany. Sporadic cases have been reported from France [11]. There is no TBEV in the Benelux. Transmission to humans is associated with leisure activities and collecting forest products and is highest during the summer months. Two TBEV-Eu strain-based vaccines are marketed in Western Europe. In Austria, people in risk areas are routinely being vaccinated.

Toscana virus Toscana virus is considered as an emerging pathogen. It is a phlebovirus transmitted by phlebotome bites in Mediterranean areas. Transmission to humans only occurs during the summer months when sandfly populations are active. It is among the three main causes of viral meningitis during the warm season, together with enteroviruses and herpes viruses [12].

Free-living amoeba The chronic granulomatous amebic encephalitis (GAE) caused by *Acanthamoeba* spp. and *Balamuthia mandrillaris* particularly affects immunocompromised individuals. *Naegleria fowleri* may cause an acute, more fulminant, necrotizing, hemorrhagic meningoencephalitis in children and young adults [13].

Acanthamoeba spp. are ubiquitous and have been isolated from soil, fresh and brackish waters, and a range of water-containing appliances. *Balamuthia mandrillaris* has once been reported in Western Europe: a Dutch case with *Balamuthia* brain abscess has just been published. *Naegleria fowleri* proliferates in water at ambient temperatures above 30°C. Swimming in unchlorinated pools or thermal effluents from nuclear power plants is a risk factor, notably during summer.

Influenza Neurological complications of influenza are rare and follow the epidemiology of respiratory influenza, i.e. almost exclusively during the cold season.

Malaria Severe malaria must not be forgotten in every traveler coming back from tropical areas, mainly Africa but also Asia/Oceania and America.

Capnocytophaga canimorsus *Capnocytophaga canimorsus* infection is sporadic and occurs after a dog or cat bite. Sepsis occurs more frequently than meningitis. Male sex, asplenia, and alcohol abuse are risk factors [14].

Brucellosis Brucellosis is extremely rare in Western Europe. Sporadic cases are often imported from endemic areas or associated with imported food products that bypass the routine food control systems.

Meningitis and encephalitis with symptoms for more than four weeks and in the immunocompromised host [6]

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
HIV	<i>Nocardia</i>
Tuberculosis	Polyoma virus
Neuroborreliosis	<i>Cryptococcus</i> spp.
	Adenovirus
	Toxoplasmosis

Nocardiosis Nocardiosis is ubiquitous. Inhalation, ingestion, and intravenous inoculation by IV drug users and direct skin inoculation are means of infection. The incidence is very low in Western Europe.

Polyoma viruses JC virus causes progressive multifocal leukoencephalopathy and is probably transmitted via close human-to-human contact. It is a very common infection that causes disease almost exclusively in AIDS and otherwise immunocompromised patients [15]. Polyoma viruses remain latent in the urinary tract. IgG prevalence rates were 58% for Swiss healthy blood donors and asymptomatic urinary shedding was 19% [16].

Cryptococcosis *Cryptococcus neoformans* meningitis used to be one of the most common opportunistic infections of the CNS in AIDS patients. Sporadic cryptococcal infection of the CNS may occur in otherwise immunocompromised patients.

Adenovirus Adenovirus infections are very common and usually cause a mild upper respiratory tract infection, gastroenteritis and/or conjunctivitis, especially in infants and young children. Severe disease may occur in immunocompromised patients and is mainly associated with serotypes 3 and 7 [17].

Toxoplasmosis *Toxoplasma gondii* encephalitis used to be the most common opportunistic infection of the CNS in countries where the prevalence of latent infection is high in the general population, such as France. It gives rise to brain abscesses, encephalitis, retinitis, pneumonia, and in some instances disseminated disease.

Ear, nose, and throat infections

Ear, nose, and throat infections with less than four weeks of symptoms

Frequently found microorganisms	Microorganisms and conditions	Very rare microorganisms
Acute otitis media	VZV	Diphtheria
Streptococcal throat infection	Peritonsillar abscess	
Epstein–Barr virus	Tuberculosis	
Herpes virus (type 1)	Necrotizing fasciitis	
	Lemierre's syndrome	

Acute otitis media Acute otitis media is most commonly caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.

Bacterial infections of the ENT Group A beta-hemolytic *Streptococcus pyogenes* infections of the throat are common in Western Europe, peaking during the winter. Ample use of antibiotics has reduced the incidence of rheumatic fever. Severe bacterial infection of the cervical regions, necrotizing fasciitis, and Lemierre's syndrome, caused by fusobacteria, are rare conditions.

Diphtheria Diphtheria is no longer endemic in Western Europe but may reappear in unvaccinated persons.

Epstein–Barr virus Epstein–Barr virus infections rank third among the causes of tonsillitis in Europe, after *Streptococcus* and adenovirus infections [17]. There is no seasonal fluctuation.

Herpes Herpes labialis, caused by HSV-1, is common in Western Europe. Seroprevalence of HSV-1 is high, in most countries over 50% among the general population.

Ear, nose, and throat infections with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Tuberculosis	<i>Candida</i>
Leishmaniasis	Herpes virus
	Zoster virus
	EBV (oral hairy leukoplakia)

Cardiopulmonary infections

Pneumonia with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Streptococcus pneumoniae</i>	<i>Legionella pneumophila</i>	Diphtheria
<i>Mycoplasma pneumoniae</i>	Influenza, parainfluenza, RSV	Anaerobes
<i>Chlamydia pneumophila</i>	<i>Staphylococcus aureus</i>	

Streptococcus pneumoniae Pneumococcal pneumonia is a rather common disease in Western Europe. Underlying (pulmonary) disease, alcohol abuse, compromised immune system, and recent viral respiratory tract infections are risk factors. Older age, meningitis, nonsusceptibility to penicillin, and specific serotypes (that differ between children and adults) are significantly associated with death in Europe [18].

Atypical pneumonia *Mycoplasma pneumoniae* is the most common cause of primary atypical pneumonia. It is typically a disease of crowding, which is why the incidence in young children increases parallel to the increase of attending day care centers [19]. *Chlamydia pneumophila* is a rather common cause of mild respiratory tract infections.

(Para-)Influenza The epidemiology of influenza in Western Europe follows that of influenza in the northern hemisphere. The peak season is in winter time, from October to April. Influenza A virus H1N1 circulated in Western Europe in 2009–10. Oseltamivir-resistant H1N1 influenza virus has been isolated in Western Europe. During the following years, the pandemic virus (A H1N1) continued to circulate widely, and was the dominant type A virus in Europe, co-circulating with influenza A H3N2 and an increasing proportion of type B viruses at the end of the season [2].

Human H5N1 influenza was not reported from Western Europe but infected birds have been isolated. An outbreak of H7N7 avian flu in the poultry industry led to a series of human infections in 2003, a few with fatal outcome. Outbreaks of avian flu, caused by different virus strains, occur repeatedly but in recent years no human infections have occurred.

Q-fever *Coxiella burnetii* is a gram-negative intracellular coccobacillus. Ruminants are the main zoonotic reservoir. Humans become infected by inhalation of infectious spores. Ruminant farmers, laboratory workers, dairy workers, and veterinarians are particularly at risk. In The Netherlands, a seroprevalence study showed high rates of seropositivity: 87% in farmers, 54% in their spouses, and 44% in their children [20]. The rapidly expanded goat industry in The Netherlands caused the largest and longest outbreak of Q-fever in history, starting in 2007, with 2357 human cases notified in 2009 [21]. Incidence of human disease peaks in the months following the birth of goat kids, especially when weather conditions are dry. Abortion waves on dairy goat farms are the primary source of infection for humans, primarily affecting people living close (under 5 km) to such a farm [20]. The large-scale culling of pregnant goats on infected farms and the vaccination of goats since 2010 have curbed the epidemic.

Legionellosis *Legionella pneumophila* and other *Legionella* species may cause atypical pneumonia. They are ubiquitous gram-negative bacteria that live in water and moist conditions. Inhalation of aerosolized water such as in showers is the most common mode of infection. Regulations for prevention of water infection in public spaces are in place in Western Europe. The notification rates, however, are still rather stable, in the range of approximately 10–20 per 1 million population [2,22].

Tuberculosis Tuberculosis is rare in Western Europe. Notification rates of tuberculosis in Western Europe are below or at the European average of 8 per 100 000 population. The proportion of HIV-infected patients among TB patients is not exactly known for all countries. Contagious pulmonary forms of MDR and XDR tuberculosis are more and more commonly described in migrants. The two main predisposing factors are a history of TB and being a native from a country endemic for MDR TB, i.e. at the European level, most of the countries of the former Soviet Union. In Western Europe more particularly France, around 90% of the MDR treated patients have already been treated for TB in their country of origin mainly Eastern Europe [23].

Endocarditis with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Staphylococcus aureus</i>	<i>Bartonella</i> spp.	<i>Tropheryma whipplei</i>
Nonhemolytic streptococci	<i>Coxiella burnetii</i>	<i>Brucella</i>
Coagulase-negative staphylococci (<i>S. epidermidis</i>)		<i>Streptococcus pneumoniae</i>
<i>Streptococcus gallolyticus</i> (ex <i>S. bovis</i>)	HACEK group	<i>Neisseria gonorrhoeae</i>
<i>Enterococcus faecalis</i> , <i>E. faecium</i>		<i>Propionibacterium acnes</i>

Endocarditis for more than four weeks and in the immunocompromised host

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Coagulase-negative staphylococci (<i>S. epidermidis</i>)	<i>Aspergillus</i>
Nonhemolytic streptococci	<i>Candida</i>

Endocarditis Infective endocarditis with underlying rheumatic heart disease is declining whereas the proportion of patients undergoing valve surgery has increased over recent decades. Intravenous drug use is a separate risk factor. The causative agents of endocarditis do not show an epidemiological pattern that is particular for Western Europe, except Q-fever. Non-HACEK gram-negative endocarditis is rare and associated with intravascular medical devices and IV drug use.

Pulmonary symptoms for more than four weeks and in the immunocompromised host

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
COPD	<i>Pneumocystis jiroveci</i>
Tuberculosis	Tuberculosis
<i>Aspergillus</i>	<i>Aspergillus</i> , <i>Candida</i>

COPD-associated infections The most important geographical difference is the variable antibiotic susceptibility reported by country. This is, however, outweighed by individual factors such as previous use of antibiotics, recent hospitalization, and living in nursing homes.

Pneumocystis pneumonia (PCP) *Pneumocystis jirovecii* is an ubiquitous agent with exposure in early life. There is geographic variation in prevalence but no particular ecological niche. Colonization is more common among patients with chronic disorders such as COPD. PCP occurs in patients with untreated AIDS and other immunodeficiencies.

Pulmonary aspergillosis *Aspergillus* infections of the lungs only occur in immunocompromised patients, especially those with hematological disorders and after bone marrow transplantation.

Gastrointestinal infections

Gastrointestinal infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Norovirus and caliciviruses	<i>Cryptosporidium</i> spp.	Tuberculosis
<i>Campylobacter jejuni</i>	<i>Staphylococcus aureus</i> toxin	Whipple disease
ETEC/VTEC	<i>Bacillus cereus</i> toxin	<i>Entamoeba histolytica</i>
<i>Giardia intestinalis</i>	<i>Yersinia enterocolitica</i>	<i>Ascaris lumbricoides</i>
<i>Salmonella</i> (non-typhi)	<i>Shigella</i> spp.	<i>Cyclospora cayentanensis</i>
<i>Enterobius vermicularis</i> (threadworm)	<i>Clostridium difficile</i> (post antibiotherapy)	

Norovirus infections Norovirus infections (family Caliciviridae) of the gastrointestinal tract are highly contagious and secondary infections are frequent [24]. Outbreaks are a bit more prominent in the cold season but there is little seasonality.

Campylobacter infections *Campylobacter jejuni* is one of the most common causative agents of food-borne illness in Western Europe, with notification rates approaching 70 per 100000 population, predominantly in the younger age groups [25]. Infections often come in outbreaks associated with consumption of infected poultry and meat products. The highest incidence is reported during summer.

ETEC/VTEC Enterohemorrhagic or verocytotoxin-producing *Escherichia coli* (ETEC and VTEC) infections are rare, with a peak during the summer and young children being most vulnerable. Occasional outbreaks are associated with a common source of infected food. The clinical spectrum following infection with Shiga toxin-producing *E. coli* (STEC) is wide ranging and includes hemorrhagic colitis and life-threatening hemolytic uremic syndrome (HUS). VTEC serogroup O 157 infections that predispose for HUS are prevalent in Western Europe. Infections are usually acquired through consumption of infected meat or mutton but handling infected (pet) animals has also been reported. Of 8400 German patients with STEC infection, 2454 (29%) were hospitalized and 30 (0.4%) died. This study provides population-based and age-adjusted evidence for the exceptionally high virulence of STEC O157 in relation to non-O157 STEC other than O104 [26].

Giardia intestinalis (duodenalis) Giardiasis is uncommon, but prevalence of carriership may be high in child day care centers. There is some seasonality, with most cases being reported during late summer and early autumn. *G. intestinalis* may be transmitted by oroanal sex.

Salmonellosis *Salmonella enterica* serovar *typhi* and *paratyphi* infections are almost exclusively imported from outside Western Europe whereas intestinal non-*typhi*/*paratyphi* infections are common,

with peaks during the summer season. Infants and children are most affected. The majority of infections are caused by the serovars *enteritidis* and *typhimurium*, are associated with certain food products such as poultry/eggs, and tend to come in outbreaks.

Enterobius vermicularis Infections by *Enterobius vermicularis* (oxyuriasis) are not routinely notified. However, this infection is very common among infants and children in day care centers and primary schools.

Cryptosporidium spp. Cattle are the main reservoir of *Cryptosporidium* spp. Oocysts are particularly resistant, also against several disinfectants, and can be found in fresh surface water in Western Europe. Ingestion of contaminated swimming or drinking water is the route of infection. Cryptosporidiosis is usually self-limiting. Immunosuppression, notably AIDS, may seriously aggravate the disease.

Staphylococcus aureus toxin food poisoning *Staphylococcus aureus* growth is inhibited in the presence of other bacteria. Proliferation of *S. aureus* occurs in partially heated and not cool stored protein-rich food; this may produce one of the 21 currently known heat-stable enterotoxins [27]. This is a rare event in the professional food industry because of strict regulations and control. Domestic infections do occur.

Bacillus cereus toxin food poisoning Survival of *B. cereus* endospores in improperly cooked food is another source of short incubation time food poisoning. *B. cereus* is considered a biohazard group 2 organism by the European Commission. Several *B. cereus* toxins have been identified that cause diarrhea or vomiting. The latter is associated with consumption of improperly cooked and stored rice. Outbreaks of *B. cereus* toxin food poisoning are rare.

Gastrointestinal infections with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Tuberculosis <i>Tropheryma whipplei</i>	Cytomegalovirus, HSV <i>Cryptosporidium parvum</i> <i>Isospora belli</i> <i>Enterocytozoon bienersi</i> <i>Encephalocytozoon intestinalis</i> <i>Mycobacterium avium</i> complex

Tuberculosis *Mycobacterium bovis* infections of cattle are rare. The Netherlands and Belgium have achieved “officially tuberculosis-free bovine herd” status (prevalence among cattle farms <0.1%) despite a recent small outbreak in cattle. Cattle infection rates in other Western European countries are very low and pasteurization of milk effectively prevents transmission to humans. *M. bovis* also occurs in wild animals. *M. bovis* infections in AIDS patients may present as *M. tuberculosis* infections and may occasionally spread from human to human.

Whipple’s disease This is a rare disease in Western Europe, caused by the ubiquitous *Tropheryma whipplei*. There is no known geographic limitation [28].

Protozoa with controversial pathogenicity (*Blastocystis hominis*, *Dientamoeba fragilis*)

Blastocystis hominis is an ubiquitous intestinal protozoon. Pathogenicity may depend on genotype. Carrier rates are rather high (30%) [24].

Dientamoeba fragilis can also be acquired in Europe. Transmission is probably through food but person-to-person transmission is also possible. Infection may be asymptomatic but also causes diarrhea or a chronic syndrome resembling irritable colon syndrome. Carrier rates are lower than for *B. hominis* (15%).

Candidiasis *Candida* esophagitis used to be a frequent problem in patients with untreated AIDS.

CMV enteritis, herpes esophagitis, and other microorganisms in immunocompromised hosts

Cytomegalovirus enteritis and herpes esophagitis are common opportunistic GI infections in patients with advanced immunosuppression. Beside CMV, other causes of enteritis include *Mycobacterium avium* complex, *Isospora belli*, *Cryptosporidium parvum* and microsporidia (*Enterocytozoon bieneusi*, *Encephalocytozoon intestinalis*). The clinical management of enteritis in immunocompromised hosts relies on direct examination of repeated stool samples with adequately oriented use of particular staining, and colonoscopy.

Infections of the liver**Infections of the liver with symptoms for less than four weeks**

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
EBV	<i>Coxiella burnetii</i>	Varicella virus
CMV	Leptospirosis	HSV
	Hepatitis A virus	Hantavirus
	Hepatitis E virus	

Infections of the liver with symptoms for more than four weeks

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
	Hepatitis B virus	Hepatitis D virus
	Hepatitis C virus	<i>Fasciola hepatica</i>

Hepatitis A Hepatitis A is no longer endemic in Western Europe. Elderly people are also seronegative. Small outbreaks after the holiday season associated with introduction by travelers, particularly those who visited friends and relatives in endemic countries, are regularly reported.

Hepatitis E Hepatitis E is mainly seen as a rare travel-related disease but locally acquired infections by rare zoonotic strains are repeatedly reported. Over recent years, HEV has been recognized in Western Europe. Pigs in particular serve as a zoonotic reservoir with prevalence rates as high as 77% in Dutch pigs [29]. Seroprevalence of anti-hepatitis E IgG among Dutch blood donors was 13% below the age of 30 and 43% among donors older than 65 [30]. In contrast, the rate of infection in blood donors in France has been found to be very low, with 24 positive HEV RNA among 53234 blood donations [31].

EBV Epstein–Barr virus infections are common and although hepatic involvement is common, overt hepatitis is rare.

CMV Cytomegalovirus infections in immunocompetent patients almost always involve the liver, as indicated by slightly elevated blood transaminase concentrations. Overt hepatitis is rare.

Hepatitis B Hepatitis B is a rare disease in Western Europe and confined to certain risk groups and behavior. IV drug users, MSM, hemodialysis patients, and immigrants make up the most affected groups. All countries have introduced hepatitis B vaccination which caused a further decline of notification rates.

Hepatitis C The notification of hepatitis C is slightly higher than for hepatitis B. This is mainly due to the late diagnosis. Transfusion hepatitis no longer occurs.

Hepatitis D (delta agent) Hepatitis D virus, an incomplete virus that depends on the presence of HBV, is very rare in Western Europe.

Other viral infections of the liver Varicella used to be an infection of childhood. Immigrants from low endemic countries may develop chickenpox at later age, and with more severe forms. This may be complicated by hepatitis. With the introduction of varicella vaccination, local transmission will soon come to a halt, with the exception of regions with religious objections against vaccination, such as the “bible belt” in The Netherlands, or countries that did not recommend varicella vaccination in the general population.

Life-threatening herpes simplex virus-related hepatitis has been reported particularly among pregnant women during the third trimester.

Fascioliasis In Europe, human *Fasciola hepatica* cases are very rare despite high prevalences among cattle, especially in the northern and western parts of the region [32]. Late-stage fascioliasis may cause symptoms that mimic chronic biliary tract disease. A triclabendazol-resistant *Fasciola* human infection has been reported from The Netherlands. Among cattle, this is a much larger problem.

Genitourinary infections

Cystitis, pyelonephritis, and nephritis with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>E. coli</i> <i>Klebsiella pneumoniae</i>	Perirenal abscess Hantavirus	Tuberculosis Leptospirosis

Cystitis, pyelonephritis, and nephritis with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Bacterial infections in patients with long-term catheters and renal stones Tuberculosis	<i>Candida</i>

Common bacterial infections of the genitourinary tract The incidence of urinary tract infections in Western Europe does not show any difference from other regions. Common pathogens are

Escherichia coli, *Proteus* spp., and *Klebsiella* spp. Underlying disease and invasive procedures are risk factors. Hospitalization, living in nursing homes or preceding antibiotic therapy increase the risk of antimicrobial resistance.

Hantavirus infection There are three hantaviruses known to cause hemorrhagic fever with renal syndrome (HFRS) in Europe [33]. The predominant one is the puumalavirus (PUUV), causing nephropathia epidemica and hepatitis. The rodent reservoir, the bank vole, is prevalent in all countries of Western Europe except the Mediterranean coast. Rodent infestation rates are variable. Tula virus, Seoul virus, Dobrava, and Saaremaa virus have been identified in rodents in various parts of Western Europe but human infections have not been confirmed unequivocally [34].

Leptospirosis Leptospirosis is a relatively rare disease in Europe except in France during summer time [35]. The most virulent serotype is *L. icterohaemorrhagiae*, the causative agent of Weil's disease, but other serotypes such as *L. grippityphosa* and *L. hardjo* have also been recognized. Leptospirosis is acquired through leisure activities, mainly by exposure to contaminated fresh surface water, or through occupational exposure (slaughter house workers, farmers, rat catchers, etc.). Active screening programs for cattle and dairy products are in place.

Sexually transmitted infections

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Chlamydia trachomatis</i> D-K HPV (genital warts) HSV (genital herpes) <i>Neisseria gonorrhoeae</i> <i>Treponema pallidum</i> (syphilis)	<i>Mycoplasma genitalium</i> <i>Trichomonas vaginalis</i>	<i>Chlamydia trachomatis</i> L (lymphogranuloma venereum) <i>Haemophilus ducreyi</i>

Chlamydia infections *Chlamydia* infections serotypes D–K are the most frequently reported STI in Europe as well as genital warts and to a lesser extent genital herpes. For Western Europe, the notification rates are much lower than from Scandinavia and the UK. The age group of 15–44 years is most affected, with a slight overrepresentation of females.

Lymphogranuloma venereum Lymphogranuloma venereum (LGV) is caused by *Chlamydia trachomatis* serotypes L1 to L3. LGV is a rarely imported disease in Western Europe. LGV proctitis caused by serotype L2 occurs among men having sex with men, mostly HIV positive [36].

Neisseria gonorrhoeae Gonorrhea notification rates are approximately fourfold lower than for *Chlamydia trachomatis* but with the highest incidence in the same age groups. Rates are slightly higher for males than for females. However, there has been a continuous increase of gonorrhea notification since the 2010s. In addition, MDR clones of *N. gonorrhoeae* (including decreased susceptibility to cephalosporins) are emerging in Western Europe. For instance, in Switzerland, the prevalence of MDR isolates increased from 7% in 1998–2001 to 70% in 2009–12 [37].

Syphilis Syphilis is reemerging in at-risk populations, among prostitutes, and MSM, mostly HIV positive. Patients are more often diagnosed at a secondary stage, or when presenting with acute neurosyphilis or ophthalmic involvement.

Joint, muscle, and soft tissue infections

Joint, muscle, and soft tissue infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Staphylococcus aureus</i>	Necrotizing fasciitis Group G streptococci	Fournier's gangrene (perineum and urogenital)
<i>Streptococcus pyogenes</i> (group A streptococcus)	Septic arthritis: <i>Neisseria gonorrhoeae</i> <i>Borrelia burgdorferi</i> <i>Streptococcus pneumoniae</i>	Septic arthritis: <i>Mycobacterium tuberculosis</i> , <i>Pseudomonas aeruginosa</i> , <i>Mycoplasma hominis</i> , <i>Sporothrix schenckii</i> (fungal infection)
Viral arthritis: parvovirus B19	Hepatitis B virus Rubella virus Mumps virus	Reactive arthritis: <i>Campylobacter</i> , <i>Yersinia</i> , salmonellae, shigellae, <i>Chlamydia trachomatis</i>

Joint, muscle, and soft tissue infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Borreliosis (Lyme disease) Tuberculosis	Fungal infections <i>Capnocytophaga canimorsus</i>

Parvovirus B19 Parvovirus B19 virus infections may cause long-standing arthropathy, especially in adults. Seroprevalence is high in Western Europe [38]. Most acute infections occur during childhood, known as fifth disease, and peak in late winter and spring.

Necrotizing fasciitis The incidence of invasive streptococcal infections varies over time, suggesting a variation in virulence. In Europe, the overall crude incidence rate is 2.79 per 100 000 population with slightly higher rates in the North than in the South [39].

Group G streptococci Group G streptococci may cause skin infections and serious systemic infections that are predominantly seen in patients with underlying disease such as cancer, alcoholism, and diabetes mellitus.

Fournier's gangrene Fournier's gangrene is a rare polymicrobial necrotizing infection or gangrene of the perineum that predominantly occurs in elderly patients with concurrent disease. *Staphylococcus aureus* pyomyositis is very rare in Western Europe.

Reactive arthritis Reactive arthritis is a mono- or oligoarthritis of large joints or spine, often with other symptoms, in response to a previous infection of other organs. Risk factors are HLA B27 positivity seropositivity. White young adult males are at risk. *Chlamydia* infections are probably the most common trigger in Western Europe, but bacillary enteritis caused by *Campylobacter*, *Salmonella* and *Yersinia* spp. has also been reported.

Trichinellosis *Trichinella* spp. infections have become rare in Western Europe and are mostly of foreign origin. Pigs and horses, however, may still be infected and meat inspection does not detect all cases. Small outbreaks do occur, mainly associated with (imported) meat or eating wild animals (boar).

Skin infections

Skin infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Erysipelas, <i>Streptococcus pyogenes</i> (GAS)	Scabies Pasteurellosis (<i>Pasteurella multocida</i>)	Rat-bite fever (<i>Spirillum minus</i>)
<i>Staphylococcus aureus</i>	Herpes zoster	<i>Bacillus anthracis</i> (anthrax, IV drug addicts)
<i>Borrelia</i> spp. (erythema migrans) Viral exanthematous infections	Trichobilharzia Rickettsiosis	

Erysipelas Erysipelas is a rather common streptococcal infection in Western Europe. In contrast to streptococcal pharyngitis, skin infections peak in the summer.

Staphylococcus aureus *Staphylococcus aureus* infections of the skin are common in Western Europe. Less than 5% of *S. aureus* isolates are Panton-Valentine leukocidin (PVL) positive, an exotoxin associated with severe disease. However, the majority of isolates from hospitalized patients with abscesses are PVL positive.

Scabies Scabies, caused by *Sarcoptes scabiei*, is rare in Western Europe with the exception of France where it is increasingly reported. Otherwise, outbreaks in nursing homes or other institutions are repeatedly reported everywhere. Lindane resistance has been reported but the drug has been redrawn by the European Medicines Agency [40]. Permethrin, benzylbenzoate, sulfur, and ivermectin are available in Western Europe.

Trichobilharzia (swimmer's itch) Avian *Schistosoma* species are endemic in Western Europe, especially in lakes in The Netherlands, Germany, Switzerland, and France. Swimming in those waters during the summer may cause acute cercarial dermatitis.

Rat-bite fever Rat-bite fever is a zoonosis caused by *Streptobacillus moniliformis* or *Spirillum minus*. Rats and other rodents, and sometimes also nonrodent mammals, are the source of infection. Infections may be acquired either by consumption of contaminated water, milk or other food (Haverhill fever) or after direct contact with rats, by scratches or bites. Rat-bite fever is a sporadic ubiquitous infection with no specific geographic distribution [41].

Anthrax Outbreaks of *Bacillus anthracis* infections are no longer reported. In contrast, injectional anthrax has emerged since 2009 in European intravenous drug addicts, with 70 confirmed cases between 2012 and 2013 and a 37% case fatality rate [42]. Otherwise, incidental human infections rarely occur, mostly limited to skin infection after handling infected animals.

Viral exanthematous infections The main causes of viral infection with exanthema are measles, parvovirus B19, rubella, and varicella. A huge outbreak of measles occurred in Western Europe, mainly France and the neighboring countries, at the end of the twenties. Amongst the 22.178 notified cases (median age 12–16 years old, 20% vaccinated), there were 11% complications, 22% hospitalizations, and 10 death (0.45 death/1000 cases)[43].

However, dengue, Zika, and chikungunya may also emerge in the coming years. Indeed, the geographic distribution of the vector *Aedes albopictus* includes increasing parts of France and Switzerland. The first

locally acquired cases of dengue and chikungunya were reported in 2010, and since then cases have been reported nearly every year, the most important outbreak involving 12 persons in October 2014 [44].

Rickettsioses Rickettsioses are caused by *Rickettsia*, and mainly transmitted by ticks. Most give rise to skin lesions, either an ulcer at the inoculation site or a maculopapular exanthema during the febrile phase [45].

Mediterranean spotted fever (MSF) is caused by *Rickettsia conorii* (and other subspecies such as *R. conorii caspia* and *R. conorii israelensis*) and *Rickettsia massiliae*.

Dermacentor-borne necrosis erythema and lymphadenopathy/tick-borne lymphadenopathy (DEBONEL/TIBOLA) is caused by *R. slovaca*, *R. raoultii*, and *R. rioja* and has been described in several countries where *Dermacentor marginatus* ticks are present.

Rickettsia helvetica has also been involved as a human pathogen in cases of fever with and without rash and in patients with meningitis and carditis.

Other rickettsioses such as lymphangitis-associated rickettsioses (LAR), caused by *R. sibirica monolitimonae*, have been diagnosed in France and other European countries

Skin infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Syphilis	Fungal infections
Tuberculosis	Tuberculosis
Nontuberculous mycobacterial infections	Nontuberculous mycobacterial infections

Adenopathy

Adenopathy of less than four weeks duration

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Epstein–Barr virus	Tularemia	<i>Ehrlichia</i>
Cytomegalovirus	<i>Bartonella</i>	<i>Babesia</i>
Parvovirus B19	<i>Borrelia burgdorferi</i>	Measles, rubeola
<i>Toxoplasma gondii</i>	<i>Treponema pallidum</i> (syphilis)	Lymphogranuloma venereum
HIV	Tuberculosis	<i>Haemophilus ducreyi</i>
	<i>Rickettsia</i>	

Toxoplasmosis *Toxoplasma gondii* infections are common in Western Europe and a common cause of generalized lymphadenopathy. Seropositivity rates are highest in France and Belgium, ranging up to 90%. They are much lower in Switzerland, Austria, and The Netherlands (up to 54%). Notification of acute disease is incomplete. Toxoplasmosis during pregnancy or immunosuppression is the most important disease presentation. Screening during pregnancy is in place. Risk factors are eating underdone meat products or contact with cats, especially young cats.

Tularemia Human tularemia, caused by *Francisella tularensis*, has become very rare in Western Europe, despite the prevalence of *F. tularensis* (subsp. *holarctica*) [46]. Transmission takes place after contact with

infected (dead) animals or by consumption of contaminated food or water. From 2002 to 2012, 433 cases were notified in France, the most frequent clinical presentations being glandular tularemia (46%) and ulceroglandular tularemia (26%). Most frequent at-risk exposures were handling hares (41%) and outdoor leisure exposure to dust aerosols (50%). Tick bites were reported by 19% of the patients. Ten clusters (39 cases) were detected over the 10-year period, as well as a national outbreak during winter 2007–08 [47].

Cat scratch disease *Bartonella henselae*, the causative organism of cat scratch disease, is endemic in Western Europe. Acute locoregional lymphadenitis after a cat scratch is a classic presentation. Extensive chronic disease may mimic lymphoreticular disease.

Rickettsioses Rickettsioses giving rise to lymphatic spread include *Dermacentor*-borne necrosis erythema and lymphadenopathy/tick-borne lymphadenopathy (DEBONEL/TIBOLA) caused by *Rickettsia slovaca*, *R. raoultii*, and *R. rioja* and lymphangitis-associated rickettsioses (LAR) caused by *R. sibirica mongolitimonae* [45].

Fever without focal symptoms

Fever for less than four weeks without focal symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Endocarditis	Tuberculosis	Tularemia
Epstein–Barr virus	<i>Coxiella burnetii</i>	<i>Ehrlichia</i> spp.
Cytomegalovirus	<i>Tropheryma whipplei</i>	Babesiosis
Parvovirus B19		
<i>Toxoplasma gondii</i>		
HIV		

Most of the causes of acute fever offer some specific clue for the experienced clinician. Endocarditis is difficult to diagnose but a recent history of exposure (e.g. dental procedures, IV drug use) may offer a clue.

Cytomegalovirus The nonspecific presentation of CMV infections in immunocompetent individuals may reveal its cause to the skilled clinician. The seroprevalence in Western Europe is among the lowest in the world, with an overall seroprevalence between 40% and 50% [48]. This increases with age and is slightly higher for females. Blood transaminase concentrations are almost always slightly elevated, indicative of minor hepatitis.

Rare organisms that may cause fever Tuberculosis, Q-fever, trench fever, pasteurellosis, Whipple's disease, and tularemia are rare causes of prolonged fever.

Human granulocytic anaplasmosis (ehrlichiosis) Anaplasmosis is a tick-borne zoonosis caused by the pathogen *Anaplasma phagocytophilum* (formerly named *Ehrlichia phagocytophila* and *Ehrlichia equi*). In Western Europe, it is transmitted by *Ixodes ricinus*. It has infrequently been reported from Western Europe but not all human infections may have been detected [49].

Babesiosis In Western Europe, three species have been identified as the cause of human babesiosis: *Babesia microti*, *B. divergens*, and *B. spp* EU1, also called *B. venatorum*. *Ixodes ricinus* is thought to be the main vector.

Fever for more than four weeks without focal symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Toxoplasma gondii</i> Tuberculosis HIV infection	CMV Adenovirus Q-fever <i>Bartonella quintana</i> <i>Leishmania infantum</i> <i>Tropheryma whipplei</i> Tuberculosis Nontuberculous mycobacterial infections

Chronic fever due to infections that are not diagnosed within four weeks is rare and the approach should be that of fever of unknown origin. The differential diagnosis includes endocarditis, Q-fever, abscesses, brucellosis, tuberculosis, and bartonellosis.

Bartonella quintana, the causative agent of trench fever, has become a very rare disease with the exception of the homeless population where its vector, the body louse, is often present even in Western Europe.

Leishmaniasis *Leishmania infantum* is endemic in the Mediterranean region. Historically, it was mainly children who became infected but immunocompromised adult patients are also at risk. Since the introduction of ARV therapy, HIV-leishmania co-infection has become rare. Mobile patients with immunosuppressant medication are currently an at-risk group.

Eosinophilia and elevated IgE

Eosinophilia and elevated IgE for less than four weeks

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
	<i>Toxocara</i> spp.	Anisakiasis <i>Ascaris lumbricoides</i> and <i>suum</i> <i>Schistosoma haematobium</i>

Eosinophilia and elevated IgE for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Ascaris lumbricoides</i> and <i>suum</i> Anisakiasis <i>Echinococcus granulosus</i> <i>Echinococcus multilocularis</i> <i>Dirofilaria repens</i>	Strongyloidiasis

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Fascioliasis Hookworm-related larva cutanea migrans <i>Toxocara</i> spp.	

Eosinophilia is a sign of invasive helminthic infection. Intestinal nematode infections cause eosinophilia mostly during their initial tissue invasion (Löffler's syndrome). Helminth infections have become rare in Europe.

Ascariasis Prohibiting the use of human waste (water) as fertilizer effectively eliminated *Ascaris lumbricoides* infections in Western Europe. *Ascaris suum* infection of pigs is rather common in Western Europe. Morphologically indistinguishable from *A. lumbricoides*, most presumed human *A. suum* infections were probably *A. lumbricoides*.

Toxocarasis *Toxocara canis* infection of pet animals is very common in Western Europe. Transmission to humans occurs by ingestion of eggs, especially by children who play in contaminated sandboxes.

Anisakiasis Deep freezing of sea fish effectively prevents human infection by *Anisakis* spp. (herring worm). Since the professional fishing industry started to adhere to these EU laws, anisakiasis has become a very rare disease. Rare infections may occur by consumption of self-caught fish or fish imported through uncontrolled channels.

Dirofilaria repens Subcutaneous nodules, caused by *Dirofilaria repens*, is a rare infection in humans. It occurs in the southern parts of France. It is transmitted by *Aedes* mosquitoes.

Baylisascaris procyonis *Baylisascaris procyonis* is well established among American raccoons living freely in Europe, especially in Germany. Human infections have not been reported thus far.

Fascioliasis Human *Fasciola hepatica* infections are rare. Livestock, especially sheep, are not free from *Fasciola hepatica*, despite massive treatment. Infection is acquired by eating contaminated water-plants or ingestion of contaminated water. Triclabendazole-resistant *F. hepatica* has been reported in sheep in The Netherlands and an occasional human infection.

Strongyloidiasis *Strongyloides stercoralis* is not endemic in Western Europe. Because under immune suppression *S. stercoralis* may proliferate long after infection was acquired, all people with past exposure who are to undergo immunosuppressive therapy should be screened or presumptively treated for the presence of *S. stercoralis*.

Hookworm-related cutaneous larva migrans Hookworm-related cutaneous larva migrans is rare in Western Europe. Incidental infections have been reported in France.

Echinococcosis *Echinococcus multilocularis* has been demonstrated in wild animals (foxes) all over Western Europe, with the highest endemicity in the northern Alpine region and the mountainous areas of the middle region. Infection rates of foxes in The Netherlands and northern Germany are low but the geographic distribution is expanding [50]. Human infection, alveolar echinococcosis, is a sporadic infection in Western Europe and is acquired by eating wild berries contaminated by fox dung.

Echinococcus granulosus, the causative agent of hydatid echinococcosis, used to be prevalent in Western Europe but locally acquired human infections have not been reported for a long time.

Schistosomiasis Cases of urinary schistosomiasis were reported during the summers of 2012 and 2013, after exposure in the Cavu river in Corsica [51]. Cases are due to a hybrid of *S. haematobium*/*S. bovis*. They were diagnosed by urinalysis, and were cured with praziquantel.

Antibiotic resistance

Antimicrobial resistance is variable in Western Europe and changes over time. The most recent aggregated data are available from the European Antimicrobial Resistance Surveillance System [52,53]. The driving forces for the selection of resistant microbes are the unrestricted use of antimicrobials for human and veterinary infections. Use of antifungal agents in agriculture may select resistant fungi that may cause human infections.

There are large differences in prescribing practices in Western Europe. The most extreme example is The Netherlands where restricted use of antibiotics in medical practice parallels the low frequency of resistant microorganisms in human infections but where the use of antimicrobial agents in the extremely intensive bioindustry is still common practice.

The lowest rates of penicillin-resistant pneumococci are found in The Netherlands and south-east Austria (<1%). Rates in Belgium are a little bit higher (4%) but in other regions can be much higher, up to 38%. In the case of amoxicillin resistance, amoxicillin-clavulanic acid is also not effective.

The proportion of pneumococci not susceptible to penicillin and macrolides varies significantly. The two correspond because penicillin resistance induces macrolide prescription which subsequently selects for macrolide resistance. In France, reported rates of macrolide resistance have been up to 30% whereas in The Netherlands and Austria, this was less than 5%. Dual nonsusceptibility is generally low.

The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) varies over Western Europe. Hospital-acquired MRSA is very common in Belgium, Luxembourg, Germany, and Switzerland (rates up to 25 % of clinical isolates), less common in Austria and France (5–10%), and rare in The Netherlands (<1%). Dutch hospitals still maintain a search and destroy policy, which means that patients attending Dutch hospitals after recent hospitalization in any other country will be admitted in strict isolation until MRSA carriage has been excluded by repeated culturing of skin and orifices. Community-acquired MRSA, which seems to be less virulent, is rather common in the cattle industry so that patients with exposure to these animals will also be subjected to MRSA isolation policies.

Invasive *Enterococcus faecalis* infections are far more frequent than *E. faecium* infections, but both show high rates of resistance to aminoglycosides in Western Europe, between 25% and 50%.

Reported rates of vancomycin-resistant enterococci (VRE) are low or even nil in Western Europe; the highest rates are found in the Alpine countries (<5%). However, outbreaks of VRE infections regularly occur in various hospital settings with important consequences.

Antimicrobial resistance of *E. coli* to third-generation cephalosporins (mostly ESBL producing) is generally below 5% in Western Europe (EARSS 2008). Rates of fluoroquinolone-resistant *E. coli* range between 10% and 25% in Western Europe and are increasing. Multiply resistant *E. coli* is increasingly frequent. There is a link between travel, most particularly in Asia, and carriage of ESBL. The chance of carrying ESBL increases in case of travelers' diarrhea, and when TB has been treated by antibiotics.

Overall, the frequency of resistant gram-negative bacteria is slightly higher than in Scandinavia and lower than in southern and central-eastern Europe. A similar geographic north/south axis is seen for resistance rates of *Pseudomonas aeruginosa*.

Extended-spectrum beta-lactamase producing *Klebsiella pneumoniae* has long been reported and also in *E. coli*. The frequency is rising rapidly now. Carbapenem-resistant *Klebsiella pneumoniae* (KPC-2-carbapenemase-gene and New-Delhi-metallo-carbapenemase-gene, NDM-1) has been reported from patients in Western Europe who acquired these outside the region.

Multidrug-resistant/extensively drug-resistant TB is more commonly diagnosed in patients of foreign origin.

Vaccine-preventable diseases in children

Country	DTP, IPV, MMR	Hib	HBV	HAV	PCconj	PCps	HPV	MenC	Varicella	Influenza	TBE	Rotavirus
Austria	Yes	Yes	Yes		Yes		Girls	Yes		Elderly and risk groups	Risk areas	Yes
Belgium	Yes	Yes	Yes		Yes		Girls	Yes		"		Yes*
France	Yes	Yes	Yes		Yes		Girls	Yes		"		Yes†
Germany	Yes	Yes	Yes		Yes	>60	Girls	Yes	Yes	"	Risk areas	
Luxembourg	Yes	Yes	Yes		Yes	≥60	Girls	Yes		"		Yes
Netherlands	Yes	Yes	Yes		Yes		Girls	Yes		"		
Switzerland	Yes	Yes	Yes		Yes	>65	Girls	Yes	Adolescents	"	Risk areas	
Monaco	Yes	Yes	Yes	Risk groups		2 months	Girls	Yes		"		

DTP, diphtheria, tetanus and acellular pertussis vaccine; IPV, parenteral polio vaccine; MMR, measles, mumps and rubella; Hib, *Haemophilus influenzae* vaccine; HBV, hepatitis B virus vaccine; HAV, hepatitis A vaccine; PCconj, conjugated pneumococcal vaccine; PCps, polysaccharide pneumococcal vaccine; TBE, tick-borne encephalitis vaccine.

* Some differences between Flanders/Wallony and German-speaking community.

† Recommended but not or only partially reimbursed.

http://apps.who.int/immunization_monitoring/en/globalsummary/scheduleResult.cfm

Basic economic and demographic data*

	GNI per capita (USD)	Life expectancy at birth (total, years)	School enrollment, primary (% gross)
Austria	50 390 (2013)	81 (2013)	102 (2013)
Belgium	47 030 (2014)	80 (2013)	104 (2013)
France	43 080 (2014)	82 (2013)	108 (2013)
Germany	47 640 (2014)	81 (2013)	100 (2013)
Liechtenstein	116 030 (2009)	82 (2013)	104 (2012)
Luxembourg	69 880 (2013)	82 (2013)	97 (2012)
Monaco	186 950 (2008)	NA	NA
Netherlands	51 210 (2014)	81 (2013)	104 (2013)
Switzerland	90 670 (2013)	83 (2013)	103 (2012)

*World Bank, 2008.
GNI, gross national income; NA, not available.

Causes of death in children under-five. Regional average*

	%
Neonatal causes	44
Pneumonia	13
Diarrheal diseases	10
HIV/AIDS	0
Measles	0
Injuries	6
Others	25

*WHO. Regional average, 2000–03 data.

Ten most common causes of deaths all ages in Western Europe*

	%									
	Austria	Belgium	France	Germany	Luxembourg	Monaco	Netherlands	Switzerland		
Ischemic and hypertensive heart disease	22	15	9	21	13	10	14	18		
Neoplasms	27	28	30	28	27	28	30	26		
Cerebrovascular disease	11	9	7	10	11	8	9	7		
Lower respiratory infections	2	5	4	3	3	4	6	4		
Alzheimer's and other dementias	0	4	3	1	3	0	4	5		
Chronic obstructive pulmonary disease	3	5	3	3	3	3	5	3		
Falls	1	1	2	1	1	2	1	1		
Diabetes mellitus	0	1	2	0	1	2	1	1		

*WHO, 2010.

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Chapter 21

The Caribbean

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Antigua and Barbuda	Jamaica
Aruba	Netherlands Antilles
Bahamas	Puerto Rico
Barbados	St. Kitts and Nevis
Bermuda	St. Lucia
Cayman Islands	St. Vincent and the Grenadines
Dominica	Trinidad and Tobago
Dominican Republic	Virgin Islands
Grenada	
Haiti	

In the Caribbean Sea, there are more than 700 islands which are geopolitically organized in various ways, including as sovereign states, overseas departments, and dependencies. The Caribbean islands have unique disease endemicities, reflective of historical influences and variation in economies.

Important regional infections

HIV and HTLV-1

The Caribbean has been more heavily affected by HIV than any region outside sub-Saharan Africa. In 2011, an estimated 230 000 people were living with HIV, 13 000 were newly infected, and 10 000 died from AIDS. Five countries account for 96% of all people living with HIV in the region: Cuba, the Dominican Republic, Haiti, Jamaica, and Trinidad and Tobago [1, 2]. Sex between men is emerging as a major route of transmission in Caribbean countries, with many new infections also linked with commercial sex work. Cultural and behavioral patterns (such as early sexual debut and taboos related to sex and sexuality), gender inequalities, stigmatization, and economic need are some of the factors influencing vulnerability to HIV and AIDS in the Caribbean.

Human T-lymphotropic virus type 1 (HTLV-I) is also prevalent in the Caribbean region. HTLV-1 predisposes to infection and is linked to adult T-cell leukemia/lymphoma and a demyelinating disease called HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP). HTLV-1 is transmitted

vertically (predominantly through breastfeeding), and through sexual intercourse, transfusion, and sharing needles and syringes. The general population prevalence ranges from 0.1% to 2% [3].

Dengue

Dengue fever is also an important febrile infection of the Caribbean region. Transmitted by the day-biting mosquitoes *Aedes aegypti* which are prevalent in urban areas, dengue causes an acute febrile illness with headache, myalgias, rash, with case fatality rate <1%. The incubation is most commonly of 3–8 days, followed by a sudden onset of fever, headache, muscle/joint pains, and variable CNS symptoms. Within a few days of illness onset, a maculopapular rash develops in about half of patients. Serious complications (e.g. hemorrhage and shock syndromes) may occur in those who have infections with multiple strains.

Chikungunya

Chikungunya virus is also transmitted by *Aedes* mosquitoes. First recognized in the Caribbean in St Martin in 2013, widespread outbreaks are now reported [4]. Chikungunya may be associated with severe febrile illness followed by a prolonged arthralgia-dominated disease. Distinct from dengue, the disabling arthralgia can persist for weeks or months.

Zika

Another flavivirus transmitted by *Aedes* mosquitoes, Zika had been known to be endemic in Africa for decades, but underwent explosive spread throughout the Americas following arrival in Brazil in 2015. Zika is asymptomatic in 80% of those infected but may cause a mild illness of rash, fever, headaches, and myalgia, similar to dengue [5]. But Zika is unique for recent recognition of sequelae of infection including Guillain–Barré syndrome through direct neurotoxicity, and congenital Zika syndrome, including microcephaly and ocular malformations. Disease control tools, including strategies to protect pregnant women, vaccines, improved diagnosis and treatments, are emerging.

Leptospirosis

Leptospirosis is endemic in the Caribbean, with outbreaks especially likely following flooding. Leptospire are spirochete bacteria which cause a biphasic febrile illness with an average incubation of seven days (range 2–29 days) following exposure to contaminated environmental water. Besides fever, headache, and myalgia, leptospirosis can be associated with anemia and rash, and may progress untreated to renal failure, meningitis, hepatic failure, and respiratory distress. Leptospirosis is often misdiagnosed due to the wide range of nonspecific symptoms.

Fish toxins

Some fish toxins merit consideration in travelers with suspected infections returning from the Caribbean. Ciguatera is caused by eating fish (especially grouper, snapper, amberjack, and barracuda) contaminated with toxins produced by microorganisms that live around coral reefs. The toxins that cause ciguatera do not affect the appearance, taste, or smell of fish, and are not inactivated by thorough cooking. Within three hours after eating the contaminated fish, the patient usually develops nausea, vomiting, diarrhea, and classic neurological symptoms, such as tingling, itching, feeling as if the teeth are loose, and blurred vision.

Scombroid is another seafood toxin that can occur during travel to the Caribbean. The flesh of fish that has not been properly refrigerated can harbor bacteria that in turn convert the fish's naturally high levels of the amino acid histidine to histamine. Contaminated fish may taste peppery, sharp, metallic or bitter, but it may also look and taste normal. Histamine is not destroyed by heat, so even

thoroughly cooked fish is a risk. Within an hour after eating contaminated fish (most commonly mackerel, tuna, bonito), a syndrome mimicking an allergic reaction occurs. Symptoms include facial flushing, headache, heart palpitations, itching, blurred vision, cramps, and diarrhea. Symptoms are usually self-limited but can be treated with antihistamines.

Myiasis

Myiasis is a subcutaneous infestation by developing *Diptera* fly larvae. In the Caribbean, myiasis is most commonly caused by *Dermatobia hominis* (human botfly). The unique life cycle of the botfly is remarkable: the female fly catches a blood-sucking arthropod, usually a mosquito, midflight and attaches her eggs to its abdomen. When the mosquito takes a blood meal, the eggs hatch and drop to the skin of the host, enter and grow painlessly. Each larva may appear as a furuncle, unique in that patients sometimes perceive movement or vibration within the lesion.

A note about Haiti

Haiti is the poorest country in the Western hemisphere, with 80% of the population living under the poverty line and 54% in abject poverty [6]. Vaccination coverage is only 50% and only 40% of the population has access to basic healthcare. Nearly half the deaths in Haiti are attributable to HIV/AIDS, respiratory infections, meningitis, and diarrheal diseases. Control of disease has been hindered by the severe poverty, lack of available diagnostics and treatments, and weak health service infrastructure, all made worse by the January 2010 earthquake, chronic political unrest, and natural disasters such as Hurricane Matthew (2016).

Most travel to Haiti is related to humanitarian missions and visiting friends and relatives, either of which may be for longer duration and therefore higher risk than typical Caribbean vacations. Haiti is endemic for several important infections that are otherwise rare in the Caribbean region. At least 2% of the population in Haiti is HIV infected, and the TB rate is 200 cases per 100,000 population, the highest in the Western hemisphere [6, 7]. During 2010–12, Haiti also had the highest incidence of human rabies transmitted by dogs in the Western hemisphere: 40% (16/40) of all cases [8].

Cholera is an acute, diarrheal illness caused by intestinal infection with the bacterium *Vibrio cholerae*. Tragically, during relief efforts following the 2010 earthquake in Haiti, cholera was introduced into the Artibonite River and spread rapidly throughout the country. To date in Haiti, there have been more than 700,000 cases and more than 9,000 deaths [9]. Evidence suggests (and the United Nations has conceded) that the bacterium was most likely brought to Haiti by Nepalese UN humanitarian relief workers [10]. Currently, two oral cholera vaccines (Dukoral® and ShanChol®) are WHO prequalified, and a live-attenuated oral cholera vaccine (Vaxchora®) has recently been licensed by the FDA in the US.

A recent diphtheria epidemic was also attributed to the earthquake conditions [11]. This outbreak of unknown magnitude prompted a targeted vaccination campaign for those at risk. In addition, there is a relatively high incidence of neurocysticercosis in Haiti, with a frequency of *T. solium* antibodies in serum samples from adults in Port-au-Prince in 2009 of 2.8% [12]. Filariasis (*Wuchereria bancrofti* and *Mansonella ozzardi*), chloroquine-sensitive *falciparum* malaria, and anthrax can also be acquired in Haiti.

CNS infections acquired in the Caribbean region

The most common causes of acute central nervous system (CNS) infections acquired in the Caribbean include typical viral and bacterial causes. West Nile virus infections first appeared in human residents of the Cayman Islands and the Florida Keys in 2001 [13]. Subsequent activity was detected in birds, mammals, and/or humans in Jamaica, the Dominican Republic, Guadeloupe, the Bahamas, Trinidad, Cuba, Puerto Rico, and Haiti.

In developing countries where pig tapeworm, *Taenia solium*, is common, such as in the Caribbean, neurocysticercosis is the most common parasitic disease of the nervous system and is the main cause

of acquired epilepsy. Humans develop neurocysticercosis when they eat undercooked infected pork or ingest eggs excreted in the stool of people infected with the adult tapeworm. Risk for disease appears relatively high in Haiti, as above.

Angiostrongylus cantonensis, also known as the rat lungworm, is a parasitic nematode that is primarily transmitted between rats and mollusks (such as slugs or snails). Humans become infected following ingestion of raw or undercooked infected snails or slugs, or foods contaminated by infected snails or slugs. The larvae are transported via the blood to the central nervous system, where they are the most common cause of eosinophilic meningitis that can lead to death or permanent brain damage. Most cases of human infection are diagnosed in South-east Asia and the Pacific Basin, but the parasite has also been found in the Caribbean [14].

Acute CNS syndromes and infections with less than four weeks of symptoms

Frequently found organisms	Rare organisms	Very rare organisms
Viral meningoencephalitis: enterovirus group	Eosinophilic meningitis (e.g. <i>Angiostrongyloides cantonensis</i>)	Neurocysticercosis (<i>Taenia solium</i>)
Bacterial meningitis: <i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i> , <i>Haemophilus influenzae</i>	Neurosyphilis (<i>Treponema pallidum</i>)	Cryptococcal meningitis: <i>Cryptococcus neoformans</i> and <i>Cryptococcus gatii</i>
Ciguatera reef fish toxin poisoning	Rabies encephalitis	Amebic meningoencephalitis (e.g. <i>Naegleria fowleri</i> and other free-living amebae)
West Nile virus encephalitis, aseptic meningitis, and flaccid paralysis; Guillain–Barré syndrome	Dengue virus encephalitis and meningitis	
Herpes simplex virus meningitis and encephalitis	Zika virus and Guillain–Barré syndrome and encephalitis	

CNS syndromes and infections with symptoms for more than four weeks and more common in the immunocompromised host

Syndromes presenting in the immunocompetent host with symptoms typically for more than 4 weeks	Syndromes in the immunocompromised host
<i>Mycobacterium tuberculosis</i>	<i>Mycobacterium tuberculosis</i>
Neurosyphilis (<i>Treponema pallidum</i>)	Neurosyphilis (<i>Treponema pallidum</i>)
Cryptococcal meningitis or cryptococcomas (<i>Cryptococcus neoformans</i> and <i>Cryptococcus gatii</i>)	Cryptococcal meningitis or cryptococcomas (<i>Cryptococcus neoformans</i> and <i>Cryptococcus gatii</i>)
	<i>Nocardia</i> spp. brain abscess and meningitis
	Cytomegalovirus encephalitis
	Toxoplasmosis (<i>Toxoplasma gondii</i>)
	<i>Listeria monocytogenes</i> meningitis
	HIV-associated neurocognitive disorder (HAND)
	HTLV-associated myelopathy and tropical spastic paraparesis (HAM/TSP)
	Progressive multifocal leukoencephalopathy (JC virus)

Ear, nose, and throat infections

Ear, nose, and throat infections with less than four weeks of symptoms, shown by anatomical region

Infection by anatomical region	Frequently found microorganisms	Rare microorganisms	Microorganisms in the immunocompromised host
Otitis and sinusitis	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i>	Gram-negative bacteria (e.g. <i>Pseudomonas aeruginosa</i> , <i>Klebsiella pneumoniae</i> and <i>Enterobacter</i> spp.), <i>Staphylococcus aureus</i>	<i>Rhizopus</i> spp., <i>Mucor</i> spp., <i>Candida</i> spp., <i>Aspergillus</i> spp.
Pharyngitis	Respiratory viruses (e.g. rhinovirus, adenovirus, influenza, parainfluenza, coronavirus), group A <i>Streptococcus</i> ,* adenovirus, cytomegalovirus, Epstein–Barr virus	<i>Mycoplasma pneumoniae</i> , <i>Neisseria gonorrhoeae</i> , acute HIV	<i>Candida</i> spp.
Tonsillitis	Alpha-hemolytic <i>Streptococcus</i> , beta-hemolytic <i>Streptococcus</i> , respiratory viruses (e.g. rhinovirus, adenovirus, influenza, parainfluenza, and coronavirus)	<i>Staphylococcus</i> spp., <i>Mycoplasma pneumoniae</i> , <i>Neisseria gonorrhoeae</i>	
Laryngitis, tracheitis, epiglottitis	<i>Haemophilus influenzae</i> , <i>Streptococcus pneumoniae</i> , <i>Streptococcus pyogenes</i> , <i>Neisseria meningitidis</i>	<i>Bordetella pertussis</i> or <i>parapertussis</i>	Tuberculosis (<i>Mycobacterium tuberculosis</i>)
Oral lesions	Herpes simplex virus, cytomegalovirus	Secondary syphilis (<i>Treponema pallidum</i>), <i>Candida</i> spp., acute HIV	Cytomegalovirus, <i>Candida</i> spp.

*Group A *Streptococcus* is *Streptococcus pyogenes*, also known as Group A beta-hemolytic *Streptococcus* (GABHS).

Cardiopulmonary infections

Tuberculosis, cryptococcal pneumonia, and histoplasmosis should be considered in both immunocompetent and immunocompromised hosts who have prolonged pulmonary symptoms.

Löffler's syndrome is a process of transient pulmonary infiltrates often associated with cough and wheezing in which eosinophils accumulate in response to a parasitic infection. Typical parasites present in the Caribbean region causing Löffler's syndrome include *Ascaris lumbricoides*, *Strongyloides stercoralis*, hookworms, and *Toxocara canis* and *cati*.

Causes of pneumonia acquired in the Caribbean region

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms	Microorganisms in the immunocompromised host
<i>Streptococcus pneumoniae</i>	Influenza and parainfluenza	Tuberculosis (<i>Mycobacterium tuberculosis</i>)	
<i>Mycoplasma pneumoniae</i>	Human metapneumovirus	Cryptococcal pneumonia (<i>Cryptococcus neoformans</i> or <i>Cryptococcus gattii</i>)	
<i>Legionella pneumophila</i>	<i>Staphylococcus aureus</i>	Löffler's syndrome	<i>Toxoplasma gondii</i>
<i>Haemophilus influenzae</i>	Adenovirus	<i>Entamoeba histolytica</i>	<i>Pneumocystis jiroveci</i>
<i>Klebsiella pneumoniae</i>	<i>Chlamydia pneumoniae</i>	<i>Schistosoma mansoni</i>	
		Melioidosis (<i>Burkholderia pseudomallei</i>)	

Etiologies of endocarditis in the Caribbean region

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Streptococcus</i> and <i>Staphylococcus</i> spp. <i>Enterococcus</i> spp.	HACEK group (<i>Haemophilus</i> spp., <i>Aggregatibacter</i> spp., <i>Cardiobacterium</i> spp., <i>Eikenella corrodens</i> , <i>Kingella</i> spp.) <i>Abiotrophia defectiva</i> Gram-negative bacteria	<i>Bartonella</i> spp. <i>Brucella</i> spp. Q-fever (<i>Coxiella burnetii</i>) <i>Candida</i> spp.

The causes of endocarditis in the Caribbean appear to be similar to global causes, especially staphylococci and streptococci.

Gastrointestinal infections

The etiologies of gastrointestinal infections acquired in the Caribbean include typical bacterial, viral, and parasitic causes. Coccidian parasites are spore-forming single cell obligate intracellular protozoan parasites, of which the most important human pathogens include *Cryptosporidium parvum* and *hominis*, *Cyclospora cayetanensis*, and *Isospora belli*. Cholera should be considered among patients living in or in humanitarian response to Haiti; recent outbreaks have also occurred in the Dominican Republic and Cuba [15].

Schistosomiasis, introduced to the Caribbean due to the slave trade with Africa, is considered endemic in St Lucia, but transmission has been interrupted in Antigua, Montserrat, Martinique, Puerto Rico, Guadeloupe, and the Dominican Republic.

Gastrointestinal infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Viral infections (norovirus, rotavirus, calicivirus)	<i>E. coli</i> O157:H7 and other verotoxin-producing <i>E. coli</i>	<i>Yersinia enterocolitica</i>
Bacterial infections (nontyphoidal <i>Salmonella</i> spp., <i>Campylobacter</i> , enterotoxigenic <i>E. coli</i> , <i>Shigella</i> , <i>Aeromonas</i> and <i>Plesiomonas</i> spp.)	Viral hepatitis (A, B+/-D, C and E)	<i>Vibrio vulnificus</i> <i>Vibrio cholerae</i>
Protozoan parasitic infections (<i>Giardia lamblia</i> , <i>Entamoeba histolytica</i>)	Nematode infestation (<i>Strongyloides stercoralis</i> , <i>Ascaris lumbricoides</i>)	
Coccidian parasites	<i>Salmonella enterica</i> serovar <i>typhi</i> and nontyphoidal serotypes	
Preformed toxin disease (<i>Staphylococcus aureus</i> , <i>Bacillus cereus</i>)		
<i>Clostridium difficile</i>		

Gastrointestinal infections and syndromes with symptoms for more than four weeks and in the immunocompromised host

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Nematodes (<i>Strongyloides stercoralis</i> , <i>Trichuris trichiura</i> , <i>Schistosoma mansoni</i>)	Protozoan parasitic infections (<i>Giardia lamblia</i> , <i>Entamoeba histolytica</i> , <i>Dientamoeba fragilis</i>)
Gastritis (<i>Helicobacter pylori</i>)	Coccidian parasites
Whipple's disease (<i>Tropheryma whipplei</i>)	Histoplasmosis
Postinfectious irritable bowel syndrome	Enteroaggregative <i>Escherichia coli</i>
Brainerd diarrhea	Cytomegalovirus
	<i>Strongyloides stercoralis</i>

Infections of liver, spleen, and peritoneum

Yellow fever in humans has not recently been reported from the Caribbean region. However, in 2009, yellow fever was found in dead monkeys in Trinidad [16]. Therefore, the US Centers for Disease Control and Prevention suggests that there is risk of yellow fever in certain parts of Trinidad.

Acute infections of liver, spleen, and peritoneum with less than four weeks of symptoms, shown by anatomical region

Infection by anatomical region	Frequently found microorganisms	Rare microorganisms
Hepatitis	Acute viral hepatitis A, B (+ hepatitis D co-infection), C, E; <i>Plasmodium</i> spp., <i>Leptospira</i> spp.	<i>Salmonella enterica</i> serovar <i>typhi</i> , dengue, herpes viruses,* <i>Schistosoma mansoni</i> , <i>Ascaris lumbricoides</i> , <i>Fasciola hepatica</i>
Hepatic abscess	Bacteria (<i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Enterococcus</i> spp., anaerobes); <i>Entamoeba histolytica</i>	<i>Brucella</i> spp., polycystic hepatic hydatid disease (<i>Echinococcus vogeli</i>), <i>Salmonella enterica</i> serovar <i>typhi</i> , nontyphoidal <i>Salmonella</i> spp., <i>Burkholderia pseudomallei</i>
Cholecystitis/ascending cholangitis	<i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Enterobacter</i> spp.	Bacteria (<i>Burkholderia pseudomallei</i> , <i>Leptospira</i> spp., anaerobes, <i>Salmonella</i> spp.), <i>Ascaris lumbricoides</i> , <i>Fasciola hepatica</i>
Spleen	Malaria (<i>Plasmodium falciparum</i>), mononucleosis (cytomegalovirus, Epstein–Barr virus)	Leptospirosis (<i>Leptospira</i> spp.), <i>Burkholderia pseudomallei</i>
Peritonitis	<i>Escherichia coli</i> , <i>Klebsiella</i> spp., <i>Streptococcus pneumoniae</i> , <i>viridans</i> group streptococci, <i>Enterococcus</i> spp.	

*Herpes viruses include cytomegalovirus, Epstein–Barr virus, herpes simplex virus, and varicella zoster virus.

Chronic infections of liver, spleen, and peritoneum with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Hepatitis B virus (+ hepatitis D virus co-infection)	Herpes viruses*
Hepatitis C virus	<i>Candida</i> spp.
<i>Schistosoma mansoni</i>	HIV-associated cholangiopathy
<i>Brucella</i> spp.	Histoplasmosis
<i>Fasciola hepatica</i>	Adenovirus
<i>Salmonella enterica</i> serovar <i>typhi</i>	Coccidian parasites
<i>Toxocara canis</i> and <i>cati</i>	Mycobacterial spp.

*Herpes viruses include cytomegalovirus, Epstein–Barr virus, herpes simplex virus, and varicella zoster virus.

Genitourinary infections

The differential diagnosis of sexually transmitted infections acquired in the Caribbean region is similar to the global spectrum of such illnesses. However, it is worth noting that *Mycoplasma genitalium* (distinct from *M. hominis*) has been increasingly recognized as a sexually transmitted infection that causes urethritis (especially in men), cervicitis, and pelvic inflammatory disease [17]. Infection should be suspected in cases of persistent or recurrent urethritis and may be considered in persons with persistent or recurrent cervicitis and pelvic inflammatory disease. Recently, sexual transmission of Zika virus has been documented in many countries, necessitating advice on prevention of sexual transmission, preconception planning, and pregnancy exposures [18,19].

Sexually transmitted infections

Frequently found microorganisms	Rare microorganisms and conditions
<i>Chlamydia cervicitis</i> (<i>Chlamydia trachomatis</i>) Nongonococcal urethritis (<i>Mycoplasma genitalium</i> , <i>Ureaplasma urealyticum</i> , <i>Trichomonas vaginalis</i> , herpes simplex virus) Gonorrhea (<i>Neisseria gonorrhoeae</i>) Syphilis (<i>Treponema pallidum</i>) Acute HIV Zika virus	Lymphogranuloma venereum (<i>Chlamydia trachomatis</i>) Scabies (<i>Sarcoptes scabiei</i>) and pubic lice (<i>Phthirus pubis</i>) <i>Entamoeba histolytica</i> among men who have sex with men (MSM) Molluscum contagiosum Chancroid (<i>Haemophilus ducreyi</i>)

Musculoskeletal infections

Frequently found microorganisms	Rare microorganisms
<i>Staphylococcus aureus</i> Group A <i>Streptococcus</i>	Trichinellosis (<i>Trichinella</i> spp.) Lymphatic filariasis (<i>Wuchereria bancrofti</i>) Tetanus Haverhill fever or epidemic arthritic erythema (<i>Streptobacillus moniliformis</i>)

Skin infections

Infections for which skin manifestations occur as part of a more systemic illness such as dengue, chikungunya, Katayama fever (*Schistosoma mansoni*), and rat-bite fever (*Streptobacillus moniliformis*) are shown elsewhere. Travelers may encounter some noninfectious conditions that require differentiation from infectious etiologies, and these are also included in the tables below.

Primary skin lesions with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Bacterial cellulitis, impetigo (<i>Staphylococcus aureus</i> and group A <i>Streptococcus</i>) and erysipelas (group A <i>Streptococcus</i>)	Swimmer's itch* Seabather's eruption† Phytophotodermatitis	Anthrax (<i>Bacillus anthracis</i>) <i>Mansonella ozzardi</i> (Haiti) African tick bite fever eschar (<i>Rickettsia africae</i>)
Bacterial skin abscess		
Arthropods (e.g. myiasis caused by <i>Dermatobia hominis</i> and <i>Cochliomyia hominivorax</i> ; scabies caused by <i>Sarcoptes scabiei</i> ; and tungiasis (<i>Tunga penetrans</i> or sand or jigger flea)		
Allergic rash or reaction		
Herpes simplex virus		
Cutaneous larva migrans (<i>Ancylostoma braziliense</i> , <i>Ancylostoma caninum</i>)		

*Swimmer's itch is a hypersensitivity reaction to nonhuman schistosomatidae.
†Seabather's eruption is caused by hypersensitivity to cnidarian nematocysts and is typically seen on skin covered by a bathing suit.

Primary skin lesions with more than four weeks of symptoms and in the immunocompromised host

Microorganisms causing symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Superficial mycoses Syphilis (<i>Treponema pallidum</i>) <i>Mycobacterium marinum</i>	Histoplasmosis <i>Candida</i> spp. Norwegian scabies (<i>Sarcoptes scabiei</i>)

Adenopathy

Toxoplasma gondii is highly endemic in the Caribbean. African tick bite fever also occurs.

Infectious syndromes primarily characterized by adenopathy of less than four weeks duration

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Herpes viruses*	Histoplasmosis	African tick bite fever
Parvovirus B19	Tuberculosis	(<i>Rickettsia africae</i>)
<i>Bartonella</i> spp.	(<i>Mycobacterium tuberculosis</i>)	–lymphadenopathy proximal to eschar
Nontuberculous mycobacterial spp.	Toxoplasmosis	HTLV
Lymphogranuloma venereum (<i>Chlamydia trachomatis</i>) – inguinal and femoral nodes	(<i>Toxoplasma gondii</i>)	Mansonellosis
	Primary or secondary syphilis (<i>Treponema pallidum</i>)	(<i>Mansonella ozzardi</i>)
	Rubella	

*Herpes viruses include cytomegalovirus, Epstein–Barr virus, herpes simplex virus, and varicella zoster virus.

Infectious syndromes characterized primarily by adenopathy of more than four weeks duration and in the immunocompromised host

Microorganisms causing symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Lymphatic filariasis (<i>Wuchereria bancrofti</i>)	Herpes viruses*
Toxoplasmosis (<i>Toxoplasma gondii</i>)	HIV
Brucellosis (<i>Brucella</i> spp.)	Tuberculosis (<i>Mycobacterium tuberculosis</i>)
Herpes viruses*	Secondary syphilis (<i>Treponema pallidum</i>)
HIV	Adenovirus
Tuberculosis (<i>Mycobacterium tuberculosis</i>)	Histoplasmosis
Secondary syphilis (<i>Treponema pallidum</i>)	HTLV-1

*Herpes viruses include cytomegalovirus, Epstein–Barr virus, herpes simplex virus, and varicella zoster virus.

Fever without focal symptoms

Malaria, although less common than dengue, must remain on the differential diagnosis of any febrile illness in patients from Haiti and eastern Dominican Republic [20]. As described in more detail above, Zika virus is widespread throughout the Americas, including the Caribbean [21].

Fever with nonspecific signs and symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Chikungunya	Parvovirus B19	Katayama fever
Dengue	Acute HIV	(<i>Schistosoma mansoni</i>)
Malaria (<i>Plasmodium</i> spp.)	African tick bite fever	Yellow fever (Trinidad only)
Leptospirosis (<i>Leptospira</i> spp.)	(<i>Rickettsia africae</i>)	Rat bite fever (<i>Streptobacillus moniliformis</i>)
Zika virus		

Causes of prolonged febrile illness without focal symptoms and in the immunocompromised host

Microorganisms causing prolonged symptoms	Microorganisms more common in the immunocompromised host
Amebic liver abscess (<i>Entamoeba histolytica</i>)	Mononucleosis (Epstein–Barr virus and cytomegalovirus)
Brucellosis (<i>Brucella</i> spp.)	Tuberculosis (<i>Mycobacterium tuberculosis</i>)
Q-fever (<i>Coxiella burnetii</i>)	<i>Bartonella</i> spp.
Enteric fever (<i>Salmonella enterica</i> serovar <i>typhi</i> or <i>paratyphi</i>)	Toxoplasmosis (<i>Toxoplasma gondii</i>)
Endocarditis	Babesiosis (<i>Babesia</i> spp.)
Malaria (<i>Plasmodium</i> spp.)	<i>Cryptococcus</i> spp.
Melioidosis (<i>Burkholderia pseudomallei</i>)	Nontuberculous <i>Mycobacterium</i> spp.
Trichinellosis (<i>Trichinella</i> spp.)	Histoplasmosis
Visceral larval migrans (<i>Ancylostoma braziliense</i> , <i>Ancylostoma caninum</i>)	

Eosinophilia

Microorganisms and syndromes that can cause eosinophilia and elevated IgE

Helminthic parasites during tissue invasive stages of development and extraintestinal migrations, including nematodes (e.g. <i>Ascaris lumbricoides</i> , <i>Necator brasiliense</i> , <i>Strongyloides stercoralis</i> , <i>Toxocara</i> spp., <i>Trichinella spiralis</i> , and the microfilaria (e.g. <i>Dirofilaria immitis</i> , <i>Wuchereria bancrofti</i> and <i>Mansonella ozzardi</i>), trematodes (e.g. <i>Schistosoma mansoni</i> and <i>Fasciola hepatica</i>), and cestodes (e.g. <i>Taenia solium</i>)
Allergic bronchopulmonary aspergillosis (<i>Aspergillus fumigatus</i>)
Gastrointestinal pathogens including <i>Dientamoeba fragilis</i> , <i>Isospora belli</i> , <i>Sarcocystis</i> spp.
HIV

Economic and demographic data for Caribbean countries

The World Bank region of the Caribbean small states, with an overall population of 7.039 million in 2014, had a collective gross national income per capita of 9219 USD [22]. Forty two percent of the population was urban, with an overall life expectancy of 72 years; 91% of the relevant age group completed education.

Caribbean region countries' Gross National Income (GNI), life expectancy, and primary school enrollment

	GNI per capita (USD)	Life expectancy at birth (total, years)	School enrollment, primary (% net)
Antigua and Barbuda	13 360	76	98
Aruba	NA	75	104
Bahamas	21 010	75	108
Barbados	14 880	75	105
Cayman Islands	NA	NA	NA
Cuba	NA	79.2 (2013)	98
Dominica	7 070	73.5	118
Dominican Republic	5 950	73	103
Grenada	7 850	73	103
Haiti	830	63	112
Jamaica	5 220	73	96
Puerto Rico	19 310	79	90
St Kitts and Nevis	14 540	71	85
St Lucia	7 090	75	100
St Vincent and the Grenadines	6 560	73	105
Trinidad and Tobago	15 640	70	106
Turks and Caicos	NA	NA	NA
Virgin Islands (US)	NA	80	120

GNI, gross national income per capita (formerly GNP per capita). GNI shown are 2014 data although most recent available data for Puerto Rico and Trinidad are from 2013 while Barbados data are from 2012. NA, not available.

The mortality rate for children under five years (the probability per 1000 live births that a newborn baby will die before reaching age five) has been declining, and was 20.1 in 2013. For reference, the analogous mortality rate for the United States was 6.9 [23,24].

Causes of death among children aged less than five years in 2013, comparing the WHO region of the Americas with the global distribution

	Region of the Americas (%)	Global (%)
Prematurity	21	17
Intrapartum complications	9	11
Neonatal sepsis	6	7
Congenital anomalies	21	7

	Region of the Americas (%)	Global (%)
Acute respiratory infections	11	15
Diarrhea	4	9
Malaria	<1	7
HIV/AIDS	<1	2
Measles	0	2
Injuries	8	6
Other diseases	20	17

Common causes of death all ages in three countries selected for a low (Haiti), middle (Dominican Republic), and high (Bahamas) GNI per capita [25]

Common causes of death	%		
	Haiti	Dominican Republic	Bahamas
HIV/AIDS	7.4	1.5	0.3
TB	2.5	0.4	0
Diarrheal diseases	4.6	0.4	0
Neonatal conditions	6.4	2.6	0
Ischemic heart disease	5.6	9.1	0.3
Lower respiratory infections	7.7	2.0	0.1
Cerebrovascular disease	10.7	5.5	0.2
Chronic obstructive lung disease	0.4	0.8	0
Road injury	1.4	3.7	0
Meningitis	1.8	0.1	0
Malaria	0.4	0	0
Diabetes mellitus	4.4	2.1	0.1
All cancers	6.0	8.1	0.4
Genitourinary diseases	1.7	1.2	0.1
Measles	0	0	0

Note that many of the indicators shown are associated with significant uncertainty, the margins of which are available on the Global Health Observatory website (www.who.int/gho).

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Chapter 22

Central America

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Belize
Costa Rica
El Salvador
Guatemala
Honduras
Mexico
Nicaragua
Panama

There are a number of neglected tropical pathogens in Central America which need serious attention in the hope of achieving improved control or elimination in the future. This chapter will highlight the profiles of certain infectious agents that are potentially problematic in exposed individuals residing in or traveling to Belize, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, and Panama.

Bacterial infections

Typhoid fever, leptospirosis, listeriosis, and rickettsial infections are all common. Tuberculosis is common and whenever it is diagnosed, co-infection with HIV should be considered. Tuberculosis is particularly high in some areas of the region, such as Belize and Honduras. Brucellosis is still a public health problem in Mexico, where recent epidemiological studies have shown incidence rates of 2–3 cases per 100 000 population in the last decade.

Viral infections

Dengue fever is common in Central America where it gives rise to repeated outbreaks. Hantavirus infections give rise to hantavirus pulmonary syndrome and hemorrhagic fever with renal syndrome. West Nile virus is seen in Mexico, but has the potential to spread further south. Human exposure to rabies-infected dogs is reported throughout the region. HIV is a risk in all countries in the region. Recently, chikungunya virus has been reported in many countries in the region, including El Salvador, Guatemala, and Honduras, among others. Influenza occurs throughout the region. In Central America, the most common animal species that carry rabies are unvaccinated dogs or cats and wild animals.

As is happening in South America, Zika is affecting all the countries in Central America, particularly Mexico, Honduras, Costa Rica, El Salvador, Guatemala, Nicaragua, and Panama. Clusters of microcephaly cases and other neurological disorders (including Guillain–Barré syndrome) have been associated with Zika virus transmission, and a causal relationship between Zika infection during pregnancy and microcephaly has been scientifically accepted (www.paho.org; www.cdc.org/Zika; www.who.int/emergencies/zika-virus/en/). In February 2016, the meeting of the WHO Emergency Committee (EC) under the International Health Regulations (2005) (IHR 2005) declared that the recent clusters of neurological disorders and neonatal malformations reported in the Americas region, potentially associated with Zika virus infection, constitute a Public Health Emergency of International Concern (PHEIC). Some Zika virus-associated cases of microcephaly have been reported in this region.

Parasitic infections

Malaria has declined dramatically in recent years. In most areas, it is due predominantly to *Plasmodium vivax* in more than 90% but varies within regions, including altitudes below 1000–1500 m (in Honduras and Guatemala) [1]. Although *Plasmodium falciparum* is seen in less than 10% of cases, chloroquine-resistant strains have been reported in the Darien and San Blas provinces of Panama [2]. Hookworms are endemic (including dog hookworm that is commonly the cause of cutaneous larva migrans), as are the two tapeworms *Taenia saginata* and *T. solium*, the latter being the cause of cysticercosis. American trypanosomiasis (Chagas' disease) and leishmaniasis (cutaneous, mucosal, and visceral forms) are seen throughout the region and onchocerciasis (river blindness) is found mainly in Guatemala. Recently, *Trichinella* spp. have been reported from pigs in Mexico.

Fungal infections

Pulmonary coccidioidomycosis is seen in dry and desert-like environments, and histoplasmosis is seen sporadically throughout the region.

CNS infections: meningitis, encephalitis, and neurological syndromes

CNS infections with less than four weeks of symptoms*

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Virus: enterovirus, dengue virus, HSV, VZV, CMV, EBV, HIV, mumps, measles, rubeola, chikungunya, Zika	<i>Listeria monocytogenes</i>	Influenza
<i>Streptococcus pneumoniae</i>	Eosinophilic meningoencephalitis	West Nile virus
<i>Neisseria meningitidis</i>	(<i>Angiostrongyloides cantonensis</i>)	Rabies
<i>Haemophilus influenzae</i> b	<i>Treponema pallidum</i>	Free-living amebae: <i>Naegleria</i> , <i>Angiostrongylus</i> , <i>Baylisascaris</i> , <i>Balamuthia</i>

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
<i>Mycobacterium tuberculosis</i> <i>Plasmodium falciparum</i>	<i>Leptospira</i> <i>Brucella</i> spp. <i>Salmonella enterica</i>	<i>P. vivax</i>

*The association of Zika virus infection with neurological disorders, especially Guillain–Barré syndrome and fetal microcephaly, has recently been accepted.

CNS infections with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i> <i>Taenia solium</i> (neurocysticercosis) HIV/AIDS <i>Cryptococcus neoformans</i> <i>Treponema pallidum</i> <i>Toxoplasma gondii</i> <i>Taenia solium</i> (cysticercosis)	<i>Cryptococcus neoformans</i> <i>Mycobacterium tuberculosis</i> <i>Toxoplasma gondii</i> CMV, JC virus, VZV, EBV <i>Nocardia</i> , <i>Actinomyces</i> <i>Aspergillus</i> <i>Treponema pallidum</i> Free-living amoebae

*The association of Zika virus infection with neurological disorders, especially Guillain–Barré syndrome and fetal microcephaly, has recently been established.

Cysticercosis Humans, the usual definitive host of the parasite, may also become an intermediate host by direct ingestion of *T. solium* eggs in food contaminated by human feces. This is particularly dangerous since the larval forms of the parasite cause cysticercosis, presenting with varying CNS symptoms including seizures, seen in <0.1% throughout Central America [3].

Rabies Rabies continues to be reported throughout Central America and a Mexican woman died in the US in 2010 from rabies and another fatal case was reported from Guatemala in 2007. In May and August 2008, cases in one dog and two horses, respectively, were confirmed in Belize [1]. The occurrence of rabies in bovids and wildlife, such as vampire bats and foxes, represents an ongoing public health threat.

Ear, nose, and throat infections

Ear, nose, and throat infections with less than four weeks exposure

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Group A streptococci Influenza, parainfluenza, rhinovirus EBV, CMV, HIV HSV I/II, HPV <i>Neisseria gonorrhoeae</i> <i>Leptospira</i>	Peritonsillar abscess with various organisms Necrotizing fasciitis <i>Mycobacterium tuberculosis</i>	Diphtheria <i>Haemophilus influenzae</i>

Ear, nose, and throat infections for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i> <i>Mycobacterium leprae</i> Mucocutaneous leishmaniasis	<i>Candida albicans</i> HSV, EBV Human herpes virus 8 (Kaposi's sarcoma) <i>Pseudomonas aeruginosa</i> <i>Aspergillus, Mucor, Rhizopus</i>

Mucosal leishmaniasis affects the nasal, oral, and pharyngeal mucosa leading to a disabling and mutilating disease.

Cardiopulmonary infections

Cardiopulmonary infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Pulmonary symptoms <i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Legionella pneumophila</i> <i>Mycoplasma pneumoniae</i> <i>Chlamydomphila pneumoniae</i> Respiratory viruses	Influenza <i>Staphylococcus aureus</i> Aerobic gram-negative bacilli (e.g. <i>Klebsiella pneumoniae</i>) <i>Ascaris lumbricoides</i> (Löffler's syndrome) <i>Wuchereria bancrofti</i> Hantavirus pulmonary syndrome	<i>Histoplasma capsulatum</i> <i>Coccidioides immitis</i> <i>Yersinia pestis</i> Melioidosis (<i>Burkholderia pseudomallei</i>) <i>Rickettsia psittaci</i>

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Endocarditis, pericarditis, myocarditis		
Viridans streptococci	<i>Streptococcus pneumoniae</i>	<i>Bartonella</i> spp.
<i>Staphylococcus aureus</i>	<i>Neisseria gonorrhoeae</i>	<i>Coxiella burnetii</i>
<i>Enterococcus</i>	HACEK group	
Coagulase-negative staphylococci	Nutritionally variant streptococci	
Coxsackievirus	<i>Brucella</i>	
	Chagas' disease	

Avian/human influenza has been recently reported in Central America [1].

Pulmonary symptoms and endocarditis for more than four weeks and in the immunocompromised host

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Pulmonary symptoms	
<i>Mycobacterium tuberculosis</i>	<i>Mycobacterium tuberculosis</i>
<i>Cryptococcus neoformans</i>	<i>Pneumocystis jiroveci</i>
<i>Aspergillus</i>	<i>Aspergillus</i> , <i>Candida</i>
<i>Nocardia</i>	<i>Mycobacterium avium</i> complex
Nontuberculous mycobacteria	CMV
	<i>Histoplasma capsulatum</i>
	<i>Pseudomonas aeruginosa</i>
	<i>Coccidioides immitis</i>
Endocarditis, pericarditis, myocarditis	
Coagulase-negative staphylococci	<i>Aspergillus</i>
Viridans streptococci	<i>Toxoplasma gondii</i>
<i>Bartonella</i>	
<i>Candida</i>	
<i>Trypanosoma cruzi</i>	

Infection from *Coccidioides immitis* is transmitted by inhalation of fungal conidia from dust, can be asymptomatic in nature or present as influenza-like illness, or overwhelming pulmonary and disseminated disease. Activities that increase the risk are those that result in exposure to dust, such as construction, excavation or dirt biking.

Infection associated with *Histoplasma capsulatum* is transmitted via inhalation of spores from soil contaminated with bat guano or bird droppings and is found throughout Central America. It is particularly seen in persons who are exposed to bird droppings and bat guano, including high-risk activities such as spelunking, mining, and construction and excavation works. An outbreak of histoplasmosis among guests in a contaminated hotel has been described from Mexico.

Infection caused by *Trypanosoma cruzi* is transmitted by blood-sucking triatomine bugs ("kissing bugs"). The vector is found mainly in rural areas of Central America where it lives in the walls of poorly constructed housing. There are reported cases of oral transmission in areas where the vector is present

by ingestion of unprocessed freshly squeezed sugarcane or açai berries. It causes a chronic illness with progressive myocardial damage leading to cardiac arrhythmias and cardiac dilatation, and gastrointestinal involvement leading to megaesophagus and megacolon. Across Central America, a prevalence rate of 1.6% has been reported [4]. Suspect the disease in the proper settings, and in cases when a traveler is exposed during trekking, camping or use of poor-quality accommodation.

Gastrointestinal infections

Gastrointestinal infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>E. coli</i> (ETEC, EPEC, EIEC, EHEC, EAEC)	<i>Vibrio cholerae</i>	<i>Tropheryma whipplei</i>
Nontyphoidal <i>Salmonella</i>	<i>Anisakis</i> spp.	<i>Yersinia enterocolitica</i>
<i>Campylobacter</i> spp.	<i>Cystoisospora</i>	
<i>Shigella</i> spp.	<i>Cryptosporidium</i>	
<i>Salmonella typhi</i>	<i>Cyclospora</i>	
<i>Giardia intestinalis</i>	<i>Angiostrongylus costaricensis</i>	
<i>Entamoeba histolytica</i>		
<i>Staphylococcus aureus</i>		
<i>Ascaris lumbricoides</i>		
<i>Enterobius vermicularis</i>		
Norovirus, rotavirus		

Giardia intestinalis infection usually occurs through ingestion of cysts in water or food contaminated by the feces of infected humans or animals. *Cyclospora cayetanensis* has been the source of outbreaks from consuming fruits and berries contaminated with cysts.

Gastrointestinal infections with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Giardia</i>	<i>Candida</i> spp.
<i>Cryptosporidium</i>	<i>Cryptosporidium</i>
<i>Cyclospora</i>	<i>Cystoisospora</i>
<i>Ascaris lumbricoides</i>	<i>Microsporidium</i> spp.
Hookworms	<i>Salmonella</i>
<i>Taenia solium</i> and <i>T. saginata</i>	CMV
<i>Mycobacterium tuberculosis</i>	<i>Mycobacterium tuberculosis</i>
HIV-associated opportunistic GI infections	<i>Strongyloides stercoralis</i>
	HSV
	HHV 8

The tapeworm *Taenia saginata* is acquired by consumption of raw or undercooked beef from cattle that harbor the larval form of the parasite. *T. solium* is similarly acquired from raw or undercooked pork. Cattle and pigs become infected with the larval stages of tapeworm as a result of access to human feces, from which they ingest tapeworm eggs, spread by human tapeworm carriers.

Infection may also be acquired by handling soil-contaminated foods, in street markets, or by contaminated water. Guatemala has the highest prevalence of ascariasis and trichuriasis which may partly explain why the nation has the highest prevalence of underweight children [4].

Infections of liver, spleen, and peritoneum

Acute infections of liver, spleen, and peritoneum with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms
Hepatitis A virus, hepatitis B virus (isolated or delta virus co-infection/superinfection), hepatitis C virus, dengue virus <i>Leptospira</i> <i>Mycobacterium tuberculosis</i> <i>Salmonella typhi</i>	Herpes viruses (CMV, EBV, HSV, VZV, adenovirus), HIV, hepatitis E virus Rickettsia, nontuberculous mycobacteria, <i>Brucella</i> , <i>Salmonella</i> <i>Toxocara</i> (larva migrans), <i>Fasciola hepatica</i> , <i>Ascaris lumbricoides</i> <i>Plasmodium falciparum</i> , <i>P. vivax</i>

Chronic infections of liver, spleen, and peritoneum with more than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms	Microorganisms in the immunocompromised host
Hepatitis B virus (with or without delta virus co-infection/superinfection), hepatitis C virus <i>Salmonella typhi</i> <i>Mycobacterium tuberculosis</i>	Torque teno (TT) virus, hepatitis G virus Nontuberculous mycobacteria, <i>Salmonella typhi</i> , <i>Brucella</i> , <i>Borrelia</i> , <i>Treponema pallidum</i> <i>Entamoeba histolytica</i> , <i>Fasciola hepatica</i> , <i>Toxocara</i> (larva migrans)	Herpes viruses (CMV, EBV, HSV, VZV), HIV <i>Salmonella typhi</i> , <i>Mycobacterium tuberculosis</i> , nontuberculous mycobacteria, <i>Treponema pallidum</i> <i>Histoplasma</i> , <i>Cryptococcus</i> , <i>Candida</i> , <i>Cryptosporidium</i> , <i>Microsporidium</i>

Genitourinary infections

Genitourinary symptoms with less than four weeks duration

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Cystitis, pyelonephritis, nephritis <i>E. coli</i> <i>Staphylococcus saprophyticus</i>	<i>Enterococcus</i> spp. <i>Staphylococcus aureus</i>	Hantavirus

(Continued)

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Klebsiella pneumoniae</i>	Perianal abscess	
<i>Proteus</i> spp.		
<i>Chlamydia trachomatis</i>		
<i>Pseudomonas aeruginosa</i>		
<i>Leptospira</i> spp.		
Sexually transmitted infections		
<i>Chlamydia</i> spp.	<i>Lymphogranuloma venereum</i> (LGV)	
<i>Neisseria gonorrhoeae</i>	<i>Entamoeba histolytica</i>	
<i>Treponema pallidum</i>	<i>Granuloma inguinale</i>	
HSV II		
<i>Haemophilus ducreyi</i>		
HPV		
<i>Trichomonas vaginalis</i>		
Ectoparasites (scabies, lice)		

Genitourinary symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Cystitis, pyelonephritis, nephritis	
Bacterial infections (catheters, renal stones)	<i>Candida</i> spp.
<i>Mycobacterium tuberculosis</i>	<i>Mycobacterium tuberculosis</i>
HIV-associated nephropathy	HHV 8
Sexually transmitted infections	
<i>Treponema pallidum</i>	Same as in immunocompetent host
HPV	
HSV	
HIV	
<i>Haemophilus ducreyi</i>	
<i>Chlamydia trachomatis</i>	
<i>Neisseria gonorrhoeae</i>	
<i>Trichomonas vaginalis</i>	

Sexually transmitted infections There is inadequate data on STIs in most areas in Central America. The inability to determine trends is thought to be due to the emphasis on HIV disease, and thus neglecting the other infections acquired through unsafe sexual contacts. Data from 2007 revealed that *Trichomonas* infections in women, and nonspecific genital infections in both sexes, were the most common STIs reported [5].

Recently, sexual transmission of Zika virus has been reported from many countries not considered to have Zika virus circulation [6]. However, this is difficult to distinguish from mosquito-borne Zika virus infection in Central America.

Joint, muscle, and soft tissue infections

Joint, muscle, and soft tissue infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Staphylococcus aureus</i> <i>Neisseria gonorrhoeae</i> Chikungunya	Necrotizing fasciitis (GAS) <i>Vibrio vulnificus</i> <i>Clostridium perfringens</i> <i>Echinococcus</i> spp. <i>Streptococcus pneumoniae</i> <i>Trichinella spiralis</i> Virus (parvovirus, rubella, HBV, enterovirus) <i>Salmonella</i> spp.	Fournier's gangrene

Joint, muscle, and soft tissue infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i> <i>Brucella</i> spp. Virus (influenza, dengue fever, HBV, enterovirus, HIV) Postviral myopathy, chronic fatigue syndrome <i>Coccidioides immitis</i> Chikungunya	<i>Candida</i> spp. <i>Mycobacterium tuberculosis</i> <i>Mycobacterium avium</i> complex <i>Cryptococcus</i> spp.

Skin infections

Skin infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Staphylococcus aureus</i> Beta-hemolytic streptococci Dermatophytes <i>Treponema pallidum</i> <i>Neisseria gonorrhoeae</i> Spotted fever group rickettsioses <i>Sarcoptes scabiei</i> Helminths Tinea versicolor (<i>Malassezia furfur</i>)	<i>Leishmania</i> spp. <i>Cryptococcus neoformans</i> <i>Strongyloides stercoralis</i> <i>Trichinella spiralis</i> <i>Onchocerca volvulus</i> Hookworms	<i>Erysipelothrix rhusiopathiae</i> Yaws Rat-bite fever (<i>Spirillum minus</i> , <i>S. moniliformis</i>) <i>Bacillus anthracis</i>

(Continued)

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
HIV-associated opportunistic infections <i>Candida</i> spp. <i>Leptospira</i> spp. Chikungunya Zika		

Skin infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Treponema pallidum</i> <i>Mycobacterium tuberculosis</i> <i>Mycobacterium leprae</i> Nontuberculous mycobacteria Pityriasis versicolor <i>Candida</i> spp. <i>Mycetoma</i> (actinomycosis) <i>Nocardia</i> HIV Leishmaniasis	<i>Candida</i> spp. HHV 8 <i>Histoplasma capsulatum</i> <i>Mycobacterium tuberculosis</i> <i>Cryptococcus neoformans</i> <i>Bartonella</i> spp. <i>Mycobacterium avium</i> complex <i>Sarcoptes scabiei</i> var. <i>hominis</i>

Leishmaniasis is transmitted by the bite of female phlebotomine sandflies. Dogs, rodents, and other mammals, including humans, are reservoir hosts for leishmaniasis. Sandflies acquire the parasites by biting infected reservoirs. Transmission from person to person by infected blood or contaminated syringes and needles is also possible.

Cutaneous leishmaniasis is the most common presentation and causes skin sores and chronic ulcers. It is one of the highest disease burdens among the neglected tropical diseases in Central America, with 62000 infected population presenting mainly as cutaneous disease and 5000 cases as visceral disease, in some areas [4].

Zika virus infections, recently documented in Central America and Mexico and spreading rapidly through the region, often present with rash and conjunctivitis.

Adenopathy

Adenopathy of less than four weeks duration

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Regional adenopathy <i>Treponema pallidum</i> Staphylococci, streptococci Fungal infections Nontuberculous mycobacteria	<i>Leishmania</i> spp. <i>Bartonella</i> spp. <i>Wuchereria bancrofti</i> <i>Brucella</i> spp.	<i>Yersinia pestis</i> <i>Babesia microti</i> Rat-bite fever (<i>S. minus</i> , <i>S. moniliformis</i>)

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Systemic adenopathy HIV EBV, CMV, enterovirus Parvovirus B19 Rickettsioses <i>Mycobacterium tuberculosis</i> Chikungunya		

Adenopathy of more than four weeks duration and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
HIV <i>Mycobacterium tuberculosis</i> <i>Treponema pallidum</i>	HIV <i>Mycobacterium tuberculosis</i> <i>Mycobacterium avium</i> complex <i>Mycobacterium leprae</i> <i>Toxoplasma gondii</i> EBV, CMV HHV 8 Fungal infections (<i>Histoplasma capsulatum</i>)

Tuberculosis remains a major health threat in persons living with HIV/AIDS, with prevalence of co-infection of about 12.4% in 2008 [7]. It has started to decline in recent years due to improved strategy in screening, treatment by directly observed therapy, and effective antiretroviral therapy. Political commitment is also strongly reinforced in the hope of curbing the infection rates and emergence of drug-resistant tuberculosis.

Global surveillance of HIV and AIDS through the joint effort of WHO and UNAIDS has developed a core framework of national indicators to monitor the availability, coverage, outcomes, and impact of health sector interventions for prevention, treatment, and care of people living with this disease. In general, there is a steady increase of new cases per year with HIV. In Central America, Belize has the highest HIV prevalence among adults aged 15–49 years (<http://aidsinfo.unaids.org/#>). Transmission occurs primarily through heterosexual contact.

Fever without focal symptoms

Fever for less than four weeks without focal symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Viral infections (HIV, EBV, CMV, enterovirus, parvovirus B19) <i>Mycobacterium tuberculosis</i>	<i>Brucella</i> spp. Nontuberculous mycobacteria	<i>Babesia</i> spp.

(Continued)

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Plasmodium falciparum</i> , <i>P. vivax</i> Dengue fever <i>Leptospira</i> spp. Rickettsioses <i>Toxoplasma gondii</i> <i>Salmonella</i> spp. Chikungunya, Zika	<i>Bartonella</i> spp. <i>Coxiella burnetii</i>	

Rickettsia rickettsii infections, known in Mexico as “fiebre manchada,” have been identified in northern Mexico, Costa Rica, and Panama. *R. prowazekii* causes louse-borne typhus, transmitted by the human body louse. Louse-borne typhus fever is the only rickettsial disease that can cause explosive epidemics. Although rare, it can be seen in colder regions of Central and South America, and in conditions of overcrowding and poor hygiene, such as prisons and refugee camps.

Dengue fever transmission often occurs in both rural and urban areas. Dengue infections are most often reported from urban settings with lower risk at altitudes above 1000m. Usually dengue causes a mild illness, but it can be severe and lead to dengue hemorrhagic fever (DHF) which can be fatal if not treated.

In 2002, the WHO reported an increase in endemic dengue disease in El Salvador. About 1200 cases of DF and 101 cases of DHF from serotype 1 have been laboratory confirmed, with children between the ages of five and nine years most affected. During the same year, Honduras experienced an outbreak with reports of 3993 cases of DF, including eight deaths, and 545 cases of DHF. About three years later, a smaller outbreak in Belize with 652 cases, including the first confirmed case of the hemorrhagic type, was reported [1].

West Nile Virus is found in Mexico and may spread in other parts of Central America, presenting as febrile syndrome and/or encephalitis. The ongoing Zika virus epidemic has spread throughout Central America. Transmission, especially to pregnant women, most probably causes microcephaly in the fetus in a proportion of cases. Guillain-Barré syndrome and lately ADEM have also been linked to Zika virus infections.

Malaria occurs at least 7–9 days after being bitten by an infected mosquito. Malaria in most parts of Central America is due predominantly to *Plasmodium vivax* in more than 90% but varies within regions, including altitudes below 1000–1500m (in Honduras and Guatemala) [1]. Although *Plasmodium falciparum* is seen in less than 10% of cases, chloroquine-resistant strains have been reported in the Darien and San Blas provinces of Panama [2].

Leptospirosis is acquired through contact between the skin or mucous membranes and water, wet soil, or vegetation contaminated by the urine of infected animals, notably rats. Occasionally, it may also result from direct contact with urine or tissues of infected animals or from consumption of food contaminated by the urine of infected rats. Leptospirosis is present throughout Central America, and outbreaks have occurred in whitewater rafters in Costa Rica and US troops training in Panama [1].

Hantavirus infection is found in tropical and subtropical regions of Central America. Hantaviruses are carried by various species of rodents, and infection occurs through direct contact with the feces, saliva, or urine of infected rodents or by inhalation of the virus in rodent excreta. It causes damage to the vascular endothelium, leading to increased vascular permeability, hypotension, bleeding, and shock. Two distinct syndromes are well-known associations: hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome.

The WHO reported 12 suspected cases including three deaths from hantavirus pulmonary syndrome in March 2000 in areas of Panama, particularly from Las Tablas and Guarare districts, and Los Santos

Province. The diagnosis was confirmed by serological tests (positive IgM and IgG) on samples from three surviving patients [1].

Visceral leishmaniasis involves the spleen, liver, bone marrow, and lymph nodes, producing fever and anemia. Leishmaniasis shows one of the highest disease burdens among the neglected tropical diseases in Central America, with 62000 infected population presenting mainly as cutaneous disease, and 5000 cases as visceral disease [4].

Fever for more than four weeks without focal symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i>	<i>Mycobacterium tuberculosis</i>
HIV	<i>Mycobacterium avium</i> complex
<i>Toxoplasma gondii</i>	<i>Cryptococcus neoformans</i>
<i>Salmonella</i>	EBV
<i>Leishmania</i>	CMV
Brucellosis	<i>Babesia microti</i>
<i>Mycobacterium leprae</i>	

Brucellosis has been reported from Mexico after consumption of unpasteurized cheese. *Mycobacterium bovis* has also been reported in humans after consuming cheese from Mexico produced from unpasteurized milk.

Eosinophilia and elevated IgE

Eosinophilia and elevated IgE for less than four weeks

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Strongyloides stercoralis</i>	<i>Trichinella spiralis</i>	<i>Anisakis</i> spp.
Hookworms	HIV	
(<i>Ancylostoma</i> , <i>Necator</i>)	<i>Echinococcus granulosus</i>	
<i>Wuchereria bancrofti</i>	Drug hypersensitivity reaction	
<i>Schistosoma</i> spp.	<i>Angiostrongylus</i> spp.	
Neurocysticercosis		
(<i>Taenia solium</i>)		
<i>Trichuris trichiura</i>		
<i>Toxocara</i> spp.		

Eosinophilia and elevated IgE for more than four weeks and in the immunocompromised host

All helminthic infections can present with chronic eosinophilia in immunocompetent and immunocompromised host. Advanced HIV infection, with CD4 count of less than 200/ μ L, can also cause some degree of eosinophilia.

Filariasis is transmitted through the bite of infected mosquitoes, which introduces larval forms of the nematodes during a blood meal [4]. The prevalence of filariasis in Central America is approximately 0.1%. Typical manifestations in symptomatic cases include filarial fever, lymphadenitis, and retrograde lymphangitis. Chronic cases can present as lymphedema, hydrocele, chyluria, tropical pulmonary eosinophilic syndrome, and, in rare instances, renal damage.

Hookworms, particularly *Necator* and *Ancylostoma* species, may be a risk especially in places where beaches are polluted by human or canine feces. Humans become infected by larval parasites that penetrate the skin. *A. caninum* produces a characteristic skin lesion, cutaneous larva migrans.

Onchocerca volvulus, onchocerciasis, is transmitted through the bite of infected blackflies. The adult worms are found in fibrous nodules under the skin where they discharge microfilaria which migrate through the skin, causing dermatitis, and can reach the eye, causing damage that results in blindness. Although this disease is mainly seen in Western and Central Africa, sporadic cases can be found in Central and South America, in less than 5% of cases characterized by low worm burden with little eye disease presenting as classic keratoiridocyclitis [3]. Guatemala has the greatest number of cases, with 0.2 million at risk [4].

Trichinella is found throughout the region in wild animals and appears occasionally in domesticated pigs.

Antibiotic resistance

Resistance of certain pathogens to the current pharmacological armamentarium presents therapeutic dilemmas to clinicians worldwide, and is particularly troublesome in developing countries. Resistance is an ecological phenomenon stemming from the response of a microorganism to the widespread use of antimicrobials and their presence in the environment. The underlying problems are economic and societal, and no ready solutions are available. The Environmental Protection Agency reported that thousands of pounds of antibiotics were being sprayed onto fruit trees all across the globe, including Central America [8,9]. The end result is excellent conditions for the selection of drug resistance. Compounding this problem is the widespread and inappropriate use of antimicrobials in the setting where their use is likely to be futile.

Malaria

Chloroquine-resistant strains have been reported in the Darien and San Blas provinces of Panama [10]. Primaquine is the preferred drug after glucose-6-phosphate dehydrogenase deficiency has been ruled out. Alternatively, atovaquone-proguanil, doxycycline, and mefloquine can be used.

Tuberculosis

The Americas have been reported as an area with the lowest proportions of new cases of multidrug-resistant tuberculosis (MDR-TB) with the notable exception of Guatemala with 3.0% [7]. In general, absolute numbers of extensively drug-resistant tuberculosis (XDR-TB) are low in Central America.

Staphylococcus aureus

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a growing problem in the Americas. Information gathered by the Pan American Health Organization (PAHO)-sponsored program on nosocomial infections demonstrated the prevalence of MRSA as follows: Costa Rica, 58%; Guatemala, 64%; Honduras, 12%; Panama, 28%; and Nicaragua, 20% [11,12].

Gram-negative enteric bacteria

During the last 25 years, outbreaks of disease due to multidrug-resistant strains of enteric bacterial pathogens have occurred with alarming frequency in less affluent areas of the world. The outbreaks

have involved most of the important etiological agents of bacterial diarrhea. Drug-resistant *Shigella* and *Salmonella* species are widespread in Central America [13]. The problem was brought dramatically to the world's attention in 1969, when a pandemic of bacillary dysentery began in Guatemala and eventually spread to involve six Central American countries and southern Mexico before subsiding the following year [14,15]. The epidemic strain was resistant to sulfonamides, streptomycin, tetracycline, and chloramphenicol.

The rate of multidrug-resistant Enterobacteriaceae is sporadically seen mostly in countries around Latin America with efficient surveillance systems. The mechanism is mainly related to extended-spectrum beta-lactamases (ESBL) among isolates from both the community and hospital settings.

Vaccine-preventable infections in children

Immunization is one of the most successful and cost-effective interventions that has shown significant reduction of mortality rates. Children should be considered for vaccination at all times against the same diseases as adults, although be aware that the specific product, dose, and administration details may vary.

As programs around the nation are reinforcing basic vaccination schedules, global health agencies as well as local health sectors have joined efforts in the hope of controlling disease outbreaks in the future.

The risk of major vaccine-preventable diseases has been reduced through a steady increase in vaccination coverage against measles, mumps, rubella, diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, *Haemophilus influenzae* type b, pneumococcal disease, and varicella. Each has a coverage level above 90%. Depending on the risk involved, rabies and influenza vaccines may be given. Rotavirus vaccine has been included in the immunization schedule since October 2010 [16,17].

There have been no reported cases of measles, diphtheria, and poliomyelitis in the last decade. Overall, all Central American countries had significant numbers of reported cases of mumps in 2009, except Belize and Guatemala. Likewise, pertussis is still prevalent in Costa Rica, Guatemala, Nicaragua, and Panama [1].

Basic economic and demographic data, 2015 [16–18]

Country	Human Development Index (HDI)	Life expectancy at birth	Expected years of schooling	Mean years of schooling	Gross national income (GNI) per capita
	Value (2014)	(years) (2014)	(years) (2014)	(years) (2014)	(PPP \$) (2011)
Belize	0.715	70.0	13.6	10.5	7614
Costa Rica	0.766	79.4	13.9	8.4	13413
El Salvador	0.666	73.0	12.3	6.5	7349
Guatemala	0.627	71.8	10.7	5.6	6929
Honduras	0.606	73.1	11.1	5.5	3938
Mexico	0.756	76.8	13.1	8.5	16056
Nicaragua	0.631	74.9	11.5	6.0	4457
Panama	0.780	77.6	13.3	9.3	18192

Causes of deaths in children under five years (%) (data from 2010) [16–18]

Cause	Costa							
	Belize	Rica	El Salvador	Guatemala	Honduras	Mexico	Nicaragua	Panama
HIV/AIDS	0	0	4	2	2	0	0	0
Diarrhea	10	1	5	7	5	4	9	11
Measles	0	0	0	0	0	0	0	0
Malaria	0	0	0	0	0	0	0	0
Pneumonia	7	3	11	15	11	12	14	9
Prematurity	0	20	15	22	22	17	19	14
Birth asphyxia	48	8	6	14	8	6	7	5
Neonatal sepsis	0	1	5	7	7	6	6	7
Congenital abnormalities	7	37	24	9	18	23	18	24
Other diseases	15	25	20	17	24	22	23	23
Injuries	12	4	11	8	3	9	4	6

Top 10 causes of deaths, all ages [16–18]

Causes	
Belize	Diabetes
	Hypertension
	Diseases of the pulmonary circulation and other forms of heart disease
	HIV/AIDS
	Cerebrovascular diseases
	Transport accidents
	Ischemic heart disease
	Acute respiratory disease
	Injury, undetermined
	Injury, purposely inflicted
Costa Rica	Ischemic heart disease
	Cerebrovascular diseases
	HIV/AIDS COPD
	Road traffic accidents
	Stomach cancer
	Diabetes mellitus
	Hypertensive heart disease
	Lower respiratory tract infections
	Perinatal conditions
	El Salvador
Lower respiratory tract infections	
Violence	
HIV/AIDS	

Causes	
Guatemala	Perinatal conditions
	Road traffic incidents
	Nephritis and nephrosis
	Cerebrovascular diseases
	Diabetes mellitus
	Alcohol use disorders
	COPD
	HIV/AIDS
	Lower respiratory tract infections
	Violence
Honduras	Perinatal conditions
	Diarrheal diseases
	Ischemic heart diseases
	Cerebrovascular diseases
	Diabetes mellitus
	Cirrhosis of liver
	Ischemic heart disease
	HIV/AIDS
	Perinatal conditions
	Cerebrovascular diseases
Mexico	Diabetes mellitus
	Ischemic heart disease
	Stroke
	Interpersonal violence
	Cirrhosis of the liver
	Chronic obstructive pulmonary disease
	Lower respiratory infections
	Hypertensive heart disease
	Road injury
	Kidney diseases
Nicaragua	Ischemic heart disease
	Cerebrovascular disease
	Lower respiratory tract infections
	Perinatal conditions
	Diarrheal diseases
	Diabetes mellitus
	Nephritis and nephrosis
	Road traffic accidents
	Hypertensive heart disease
	Self-inflicted injuries

(Continued)

Causes	
Panama	<p>Ischemic heart disease</p> <p>Cerebrovascular disease</p> <p>Diabetes mellitus</p> <p>Perinatal conditions</p> <p>Lower respiratory tract infections</p> <p>COPD</p> <p>Road traffic accidents</p> <p>Prostate cancer</p> <p>Violence</p> <p>Stomach cancer</p>

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Chapter 23

South America

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Argentina
Bolivia
Brazil
Chile
Colombia
Ecuador
French Guyana
Guyana
Paraguay
Peru
Suriname
Uruguay
Venezuela

South America is a large and heterogenous subcontinent that extends from 12°27' north to 53°54' south, islands excluded from consideration, and from 34°77' west to 81°19' west, islands also excluded. Its landmass is 17 840 000 square kilometers (6 890 000 square miles), or almost 3.5% of the Earth's surface, with a population of roughly 370 million.

Intense urbanization occurred during the twentieth century and is still ongoing, and increasing migration has contributed to the present distribution of infectious disease in the subcontinent.

Although there has been significant improvement in health conditions, several infectious diseases are still endemic and epidemic in South America. Their distribution is far from homogeneous and considerable differences in disease surveillance account for much of this distribution. In this setting, urbanization of tropical diseases, previously limited to rural areas, has been an emerging aspect in this region (e.g. seen in malaria, Chagas' disease, and leishmaniasis, among others) [1].

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Infectious Diseases: A Geographic Guide, Second Edition. Edited by Eskild Petersen, Lin H. Chen, and Patricia Schlagenhaut-Lawlor.

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South America travel and travelers

Data from the World Tourism Organization show a significant increase in the number of arrivals to South American countries over the years. In 2013, of 1087 million international arrivals around the world, 27.4 million had a South American country as destination. More indicative, however, is the increase from 2005 to 2013, of 5.2% for the Americas overall. The greatest increases between 2012 and 2013 were in Peru (11.2%), Ecuador (7.4%), Paraguay (5.3%), and Colombia (5.2%) [2].

Fever is the most frequent clinical sign of illness acquired among returned travelers [3,4]. In ill travelers returning from the Caribbean and Central and South America, fever was reported in 3–18% of cases [3,4]. Another retrospective study identified fever as the most important clinical sign in 8.5% of patients [5]. Fever is usually associated with a nonspecific clinical picture, a challenge during etiological investigation of febrile acute disease in this increasing group of patients.

Among acute febrile patients, malaria is one of the most common specific diagnoses when an endemic area is visited [3–5]. However, in South America, dengue fever has reemerged in all countries and dengue fever and more recently Zika and chikungunya fevers figure as the most important vector-borne diseases and one of the most relevant differential diagnosis of acute nonspecific, exanthematic or hemorrhagic febrile syndromes. According to WHO data from 2008, there were 826 535 notified cases of dengue fever, 16 737 of them dengue hemorrhagic fever, with 225 deaths. This explains why since the 1980s dengue fever has been more frequent than malaria in travelers returning from any region except Africa and Central America [6,7]. Also, chikungunya and Zika have emerged recently in the region and have disseminated widely particularly in tropical countries (www.paho.org) [8]. Zika virus infection has caused explosive outbreaks in South America, with associated microcephaly and other congenital defects due to infection during pregnancy; Zika virus has also been associated with Guillain-Barré syndrome and other neurological sequelae (www.who.int/emergencies/zika-virus/en/).

Other vector-borne diseases (arbovirolosis, rickettsial diseases, trypanosomiasis) are endemic in many regions of South America, although mostly rural or sylvatic, and with a lower incidence [3–5,9]. Although tropical diseases are an important differential diagnosis, diseases with universal distribution (e.g. herpes viruses, HIV, toxoplasmosis, influenza, leptospirosis, salmonellosis, pneumococcal, influenza) account for the majority of travel-related illnesses, and for this reason they should be always considered and, if the clinical and epidemiological picture is consistent, investigated [4,7,9].

A large retrospective study using the GeoSentinel database observed the most frequent clinical syndromes among ill travelers returning from countries of South America as follows: dermatological disorders (264/1000 patients), acute diarrhea (219/1000 patients), systemic febrile illness (143/1000 patients), respiratory disorders (50/1000 patients) [5].

When considering the interval of time from returning to the first medical evaluation, many retrospective studies show that most patients sought medical assistance within a month after travel, the majority within two weeks (77–84.4%) [3,5,9], but a significant proportion (10%), due to an indolent disease or a longer incubation period, were first evaluated after six months or more [4,5].

Reported disease activity in the last 10 years (isolated cases, clusters, and epidemics), by country [10] [9]

Country	Disease
Argentina	Anthrax (cutaneous)
	Arenavirus (Junin)
	Chagas' disease (vector borne)
	Chikungunya
	Coccidioidomycosis
	Dengue fever
	Hantavirus
	Malaria
	Measles
	Mucocutaneous leishmaniasis
	St Louis encephalitis
	Trichinellosis
	Visceral leishmaniasis
	West Nile virus
	Yellow fever (jungle)
	Zika
Bolivia	Arenavirus (Chapare, Machupo)
	Chagas disease (vector-borne)
	Chikungunya
	Dengue
	Hantavirus
	Malaria
	Mucocutaneous leishmaniasis
	Visceral leishmaniasis
	Plague
	Yellow fever
Zika	
Brazil	Bat-transmitted rabies
	Brazilian spotted fever (<i>Rickettsia rickettsii</i>)
	Chagas' disease (including oral infection)
	Chikungunya
	Dengue fever
	Diphyllobothriosis
	Filariasis (<i>W. bancrofti</i>)
	Hantavirus
	Hepatitis D
	Lepstospirosis
	Malaria (<i>P. falciparum</i> , <i>P. vivax</i> , <i>P. malariae</i>)
	Mayaro, Oropouche
	Measles
	Melioidosis (Ceará State)
	Meningococcal disease
	Mucocutaneous leishmaniasis
	Onchocerciasis
Oropouche	
Plague	

(Continued)

Country	Disease
Chile	St Louis encephalitis
	Schistosomiasis (<i>S. mansoni</i>)
	Visceral leishmaniasis
	Yellow fever
	Zika
	Coccidioidomycosis
	Chikungunya (Easter Island)
	Dengue (Easter Island)
	Hantavirus
	Listeriosis
Colombia	Trichinellosis
	<i>Vibrio parahaemolyticus</i>
	Zika (Easter Island, one case)
	Anthrax (cutaneous)
	Bartonellosis (Carrion's disease; Oroya fever)
	Bat-transmitted rabies
	Chagas' disease (including oral infection)
	Chikungunya
	Cutaneous leishmaniasis
	Dengue
	Hantavirus (north Caribbean)
	Leptospirosis
	Malaria
	Measles
	Mucocutaneous leishmaniasis
Ecuador	Spotted fever (<i>R. ricketсии</i>)
	Tuberculosis
	Visceral leishmaniasis
	Zika
	<i>Angiostrongylus</i> meningitis
	Bartonellosis (Carrion's disease; Oroya fever)
	Bat-transmitted rabies
	Chikungunya (some areas)
	Dengue fever
	Histoplasmosis
French Guyana	Malaria (very low risk)
	Onchocerciasis
	Oropouche
	Zika
	Chikungunya
Guyana	Malaria
	Measles
	Yellow fever
	Zika
	Chikungunya
	Dengue fever
Leptospirosis	
Malaria	
Mucocutaneous leishmaniasis	
Zika	

Country	Disease
Paraguay	Chikungunya
	Dengue
	Diphtheria
	Hantavirus pulmonary syndrome
	Malaria
	Visceral leishmaniasis
	Yellow fever
Peru	Zika
	Bartonellosis (Carrion's disease; Oroya fever)
	Bat-transmitted rabies
	Chikungunya (north)
	Epidemic typhus (<i>R. prowazekii</i>)
	Leptospirosis
	Oropouche
	Plague
	Spotted fever (<i>R. rickettsii</i>)
	Yellow fever
	Zika
Suriname	Chikungunya
	Dengue
	Schistosomiasis
	Yellow fever
	Zika
Uruguay	Anthrax (cutaneous)
	Coccidioidomycosis
	Dengue
	Hantavirus
	Histoplasmosis
	Meningococcal disease
	<i>Rickettsia parkeri</i>
Venezuela	Arenavirus (Guanarito) 2002
	Chagas' disease (including oral infection)
	Chikungunya
	Cutaneous leishmaniasis
	Dengue
	Eastern equine encephalitis
	Malaria
	Mayaro
	Onchocerciasis
	Venezuelan equine encephalitis
Yellow fever	
Zika	

Universal distribution: amebiasis, cryptosporidiosis, histoplasmosis, leptospirosis, salmonellosis, viral hepatitis (A, B, C), mononucleosis syndromes, influenza, tuberculosis.

Emerging issues in South America

- Acute Chagas' disease acquired through oral transmission [10–12]
- Chikungunya and Zika [8,13]
- Dengue and dengue hemorrhagic fever [14–16]

- Expansion and urbanization of visceral (kala-azar) leishmaniasis
- Increasing yellow fever activity (nonhuman primate epizooty, clusters of human cases in expanding transmission area) [17]

Information about South American malaria-risk areas can be found at the CDC website [18] and information about dengue epidemiological activity in South America can be found at Healthmap [19].

CNS infections: meningitis, encephalitis

Acute infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
<p>Virus: arboviruses (dengue, yellow fever*), enteroviruses (echoviruses, Coxsackieviruses, parvovirus), mumps, herpes viruses (HSV1, HSV2, varicella, CMV), HIV, chikungunya, Zika**</p> <p>Bacteria: <i>Pneumococcus</i>, <i>Meningococcus</i>, <i>Haemophilus influenzae</i>, leptospirosis</p> <p>Other agents: <i>Toxoplasma</i>, <i>Plasmodium falciparum</i></p>	<p>Virus: arboviruses (St Louis, Rocio), rabies, measles, influenza virus</p> <p>Bacteria: neurosyphilis, <i>Staphylococcus aureus</i>, <i>Streptococcus pyogenes</i>, <i>Salmonella</i>, <i>Rickettsia</i>, <i>Brucella</i></p> <p>Other agents: <i>Cryptococcus</i>, American trypanosomiasis (acute), <i>P. vivax</i></p>	<p>Virus: West Nile, alphaviruses (Eastern equine encephalitis, Western equine encephalitis, Venezuelan equine encephalitis)</p> <p>Bacteria: <i>Listeria monocytogenes</i></p> <p>Other agents: Naegleria and other free-living amoebae, <i>Angiostrongylus cantonensis</i></p>
<p>*Only jungle cycle. Bolivia and Paraguay had possible urban transmission in the last 10 years.</p> <p>**Guillain-Barré syndrome is associated with Zika virus. Microcephaly and other congenital neurological abnormalities are related to vertical transmission of Zika virus.</p>		

CNS infections: meningitis, encephalitis with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<p>Virus: HIV, rabies, HTLV-1 (tropical spastic paraparesis)</p> <p>Bacteria: <i>Mycobacterium tuberculosis</i>, <i>Borrelia</i>, neurosyphilis</p> <p>Other agents: <i>Schistosoma mansoni</i>, <i>Toxoplasma</i>, <i>Taenia solium</i> (cysticercosis), <i>Lagochilascaris minor</i>, <i>Toxocara</i> spp.</p>	<p>Virus: polyomavirus, JC virus, cytomegalovirus, poliovirus</p> <p>Bacteria: <i>Nocardia</i>, <i>Mycobacterium tuberculosis</i>, <i>Borrelia</i>, neurosyphilis, <i>Listeria</i></p> <p>Other agents: <i>Cryptococcus</i> spp., American trypanosomiasis, <i>Toxoplasma</i>, <i>Strongyloides stercoralis</i></p>
<p>*Consider noninfectious causes like vasculitis and lymphoma.</p>	

Ear, nose, and throat infections

Ear, nose, and throat infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<p>Common cold: rhinovirus, adenovirus, parainfluenza virus, respiratory syncytial virus, influenza virus</p> <p>Pharyngitis: rhinovirus, adenovirus, parainfluenza virus, influenza virus, Epstein–Barr virus, <i>Streptococcus</i> group A beta-hemolytic</p> <p>Peritonsillar abscess:* <i>Chlamydomphila pneumoniae</i>, <i>Mycoplasma pneumoniae</i></p> <p>Laryngitis: rhinovirus, influenza virus, parainfluenza virus, adenovirus</p> <p>Acute otitis media: <i>Streptococcus pneumoniae</i>, <i>Moraxella catarrhalis</i>, <i>Streptococcus</i> group A, <i>Staphylococcus aureus</i></p> <p>Otitis externa: <i>Staphylococcus aureus</i>, <i>Staphylococcus epidermidis</i>, <i>Corynebacterium</i>, anaerobics</p> <p>Acute sinusitis: rhinovirus, influenza virus, adenovirus, parainfluenza virus, <i>Streptococcus pneumoniae</i>, <i>Moraxella catarrhalis</i>, <i>Streptococcus pyogenes</i>, <i>Staphylococcus aureus</i>, <i>Haemophilus influenzae</i> (unencapsulated), gram-negative bacteria, anaerobic bacteria</p>	<p>Pharyngitis: herpes simplex virus 1 and 2, Coxsackievirus A, cytomegalovirus, HIV-1, <i>Corynebacterium diphtheriae</i>, <i>Neisseria gonorrhoeae</i>, <i>Chlamydomphila pneumoniae</i>, <i>Mycoplasma pneumoniae</i></p> <p>Laryngitis: <i>Chlamydomphila pneumoniae</i>, <i>Mycoplasma pneumoniae</i>, <i>Chlamydomphila pneumoniae</i>, <i>Mycoplasma pneumoniae</i></p> <p>Epiglottitis: <i>Haemophilus influenzae</i></p> <p>Otitis externa: <i>Pseudomonas aeruginosa</i></p>	<p>Common cold: coronavirus, human metapneumovirus</p> <p>Pharyngitis: coronavirus, <i>Yersinia enterocolitica</i>, <i>Francisella tularensis</i></p> <p>Laryngitis: coronavirus, human metapneumovirus</p> <p>Vincent’s angina:* mixed infection</p> <p>Ludwig’s angina*</p> <p>Lemierre’s disease:* <i>Fusobacterium necrophorum</i></p>
<p>* Requires acute ENT evaluation.</p>		

Ear, nose, and throat with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<p>Sinusitis: <i>Aspergillus</i>, <i>Zygomycetes</i> (<i>Mucor</i> spp., <i>Rhizopus</i> spp.), <i>Streptococcus pneumoniae</i>, <i>Haemophilus influenzae</i>, gram-negative bacteria</p> <p>Laryngitis: <i>Paracoccidioides brasiliensis</i>, tegumentary leishmaniasis, <i>Mycobacterium tuberculosis</i>, human papillomaviruses, <i>Corynebacterium diphtheriae</i></p> <p>Nose/oral ulcers: <i>Paracoccidioides brasiliensis</i>, tegumentary leishmaniasis, <i>Mycobacterium tuberculosis</i>, syphilis, herpes simplex virus, <i>Candida</i> spp., <i>Corynebacterium diphtheriae</i>, <i>Actinomyces</i>, <i>Streptococcus</i>, anaerobic bacteria, <i>Mycobacterium leprae</i></p>	<p>Bacteria: <i>Streptococcus pneumoniae</i>, <i>Haemophilus influenzae</i>, gram-negative bacteria, <i>Mycobacterium tuberculosis</i>, nontuberculous <i>Mycobacterium</i>, syphilis</p> <p>Viral: herpes simplex virus, human papillomavirus, cytomegalovirus</p> <p>Other pathogens: <i>Aspergillus</i>, <i>Zygomycetes</i> (<i>Mucor</i> spp., <i>Rhizopus</i> spp.), <i>Candida</i>, <i>Fusarium</i></p>
<p>* Consider noninfectious causes like vasculitis and lymphoma.</p>	

Cardiopulmonary infections

Pneumonia with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<p>Viral: influenza virus, respiratory syncytial virus (in children)</p> <p>Bacteria: <i>Streptococcus pneumoniae</i>, <i>Streptococcus pyogenes</i>, <i>Staphylococcus aureus</i>, <i>Haemophilus influenzae</i>, <i>Pseudomonas aeruginosa</i>, <i>Mycoplasma pneumoniae</i>, <i>Chlamydia pneumoniae</i>, <i>Mycobacterium tuberculosis</i></p>	<p>Viral: adenovirus, parainfluenza virus, hantavirus, varicella zoster virus</p> <p>Bacteria: <i>Moraxella catarrhalis</i>, <i>Legionella</i>, <i>Leptospira</i> spp., <i>Chlamydia psittaci</i>, nontuberculous <i>Mycobacterium</i>, <i>Bordetella pertussis</i></p> <p>Other agents: <i>Aspergillus</i> spp., <i>Paracoccidioides brasiliensis</i>, <i>Histoplasma capsulatum</i>, <i>Toxoplasma gondii</i>, <i>Ascaris lumbricoides</i>, <i>Strongyloides stercoralis</i>, <i>Toxocara canis</i></p>	<p>Virus: coronavirus, metapneumovirus, measles, adenovirus</p> <p>Bacteria: <i>Bacillus</i> spp., <i>Corynebacterium</i>, <i>Coxiella</i>, <i>Burkholderia pseudomallei</i>,* <i>Yersinia pestis</i></p>
*Only reported in Ceará State, Brazil.		

Endocarditis with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<p><i>Staphylococcus aureus</i>, coagulase-negative staphylococci (<i>S. epidermidis</i>), viridans streptococci, <i>Streptococcus pneumoniae</i>, <i>Enterococcus</i> spp., other streptococci</p>	<p><i>Neisseriae gonorrhoeae</i>, <i>Coxiella burneti</i>, HACEK group (<i>Haemophilus parainfluenzae</i>, <i>H. aphrophilus</i>, <i>Actinobacillus</i>, <i>Cardiobacterium</i>, <i>Eikenella</i>, <i>Kingella</i>), <i>Propionibacterium</i>, <i>Candida</i> spp.</p>	<p><i>Bartonella</i> spp., <i>Brucella</i> spp.</p>

Selected cardiac infections (myocarditis) other than infectious endocarditis include the following.

- **Viral:** hantavirus, Chikungunya, Coxsackieviruses, dengue virus, yellow fever virus, arenavirus, influenza virus
- **Bacteria:** *Leptospira*, *Rickettsia*, *Borrelia*, *Mycoplasma*, *Chlamydia*, *Salmonella*, *Coxiella*, *Corynebacterium diphtheriae*, *Streptococcus pyogenes*, *Staphylococcus aureus*
- **Other agents:** American trypanosomiasis (acute presentation), *Toxoplasma*, *Trichinella*

Pulmonary symptoms for more than four weeks and in the immunocompromised host*

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<p>Bacteria: <i>Mycobacterium tuberculosis</i>, <i>Bordetella pertussis</i>, <i>Chlamydia</i></p> <p>Other agents: COPD, <i>Aspergillus</i> spp., <i>Histoplasma capsulatum</i>, <i>Paracoccidioides brasiliensis</i>, <i>Toxoplasma gondii</i>, <i>Ascaris lumbricoides</i>, <i>Strongyloides stercoralis</i>, <i>Toxocara canis</i></p>	<p>Virus: cytomegalovirus</p> <p>Bacteria: <i>Mycobacterium tuberculosis</i>, nontuberculosis <i>Mycobacterium</i>, <i>Rhodococcus equi</i>, <i>Nocardia</i></p> <p>Other agents: <i>Pneumocystis jiroveci</i>, <i>Aspergillus</i>, <i>Cryptococcus</i>, <i>Toxoplasma</i>, <i>Strongyloides</i></p>
<p>* Consider noninfectious causes like lung cancer, autoimmune lung fibrosis, Wegener's granulomatosis, allergic pneumonitis, and sarcoidosis.</p>	

Endocarditis for more than four weeks and in the immunocompromised host*

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Coagulase-negative staphylococci (<i>S. epidermidis</i>), nonhemolytic streptococci	<i>Aspergillus</i> , <i>Candida</i> spp.
<p>* Consider noninfectious causes like sarcoidosis and systemic lupus.</p>	

Gastrointestinal infections

Gastrointestinal infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<p>Viral: calicivirus (norovirus), rotavirus</p> <p>Bacteria: <i>Campylobacter</i>, VTEC, enterotoxigenic <i>Escherichia coli</i>, <i>Salmonella</i> (non-typhi), <i>Staphylococcus aureus</i> toxin, <i>Shigella</i>, <i>Streptococcus</i> group A</p> <p>Other agents: <i>Giardia intestinalis</i>, <i>Enterobius vermicularis</i> (threadworm), <i>Ascaris lumbricoides</i></p>	<p>Bacteria: <i>Bacillus cereus</i> toxin, <i>Vibrio cholerae</i>, <i>Clostridium perfringens</i>, <i>Salmonella typhi</i>, invasive <i>Escherichia coli</i>, <i>Escherichia coli</i> O157, <i>Vibrio parahaemolyticus</i>, <i>Listeria</i></p> <p>Other agents: <i>Cryptosporidium</i> spp., <i>Cyclospora</i>, <i>Trichinella</i>, <i>Schistosoma mansoni</i>, chemical agents (toxins, heavy metals)</p>	<p>Bacteria: <i>Yersinia enterocolitica</i>, <i>Corynebacterium diphtheriae</i>, <i>Mycobacterium tuberculosis</i></p>

Gastrointestinal infections with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<p>Bacteria: <i>Mycobacterium tuberculosis</i>, <i>Salmonella typhi</i></p> <p>Other agents: <i>Blastocystis</i>, <i>Dientamoeba fragilis</i>, <i>Cryptosporidium</i>, <i>Entamoeba histolytica</i>, <i>Giardia</i>, <i>Trichinella</i></p>	<p>Bacteria: <i>Clostridium difficile</i>, <i>Campylobacter jejuni</i>, nontuberculosis <i>Mycobacterium</i>, <i>Mycobacterium tuberculosis</i>, <i>Listeria</i></p> <p>Other agents: <i>Candida</i>, herpes viruses, <i>Strongyloides stercoralis</i>, <i>Cryptosporidium</i>, <i>Cyclospora</i>, <i>Microsporidium</i>, <i>Isospora</i>, <i>Histoplasma</i></p>

Genitourinary infections

Cystitis, pyelonephritis, and nephritis with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<p><i>Escherichia coli</i> (most frequent), <i>Klebsiella</i>, <i>Proteus</i>, <i>Pseudomonas</i>, <i>Enterobacter</i></p>	<p>Staphylococci, <i>Mycobacterium tuberculosis</i>, perirenal abscess</p>	<p>Adenovirus, <i>Ureaplasma</i>, <i>Mycoplasma</i></p>

Sexually transmitted infections with less than four weeks of symptoms*

Frequently found microorganisms	Rare microorganisms and conditions
<p>Urethritis, vulvovaginitis: <i>Neisseria gonorrhoeae</i>, <i>Chlamydia trachomatis</i>, <i>Ureaplasma urealyticum</i>, <i>Trichomonas vaginalis</i>, <i>Mycoplasma genitalium</i>, herpes simplex virus, <i>Candida</i> (vulvovaginitis), <i>Gardnerella vaginalis</i> (bacterial vaginosis)</p> <p>Epididymitis/orchitis: mumps, <i>Neisseria gonorrhoeae</i>, <i>Chlamydia trachomatis</i>, <i>Escherichia coli</i>, <i>Klebsiella pneumoniae</i>, <i>Pseudomonas aeruginosa</i>, staphylococci, streptococci</p> <p>Ulcers: syphilis, herpes simplex 1 and 2, <i>Haemophilus ducreyi</i> (chancroid)</p> <p>Wart: human papillomavirus</p>	<p><i>Chlamydia trachomatis</i> (lymphogranuloma venereum), <i>Calymmobacterium granulomatis</i> (granuloma inguinale)</p> <p>Orchitis: Coxsackievirus, lymphocytic choriomeningitis virus, <i>Brucella</i></p>

* Zika virus transmission through sexual contact has occurred in areas without mosquito-transmitted Zika; the extent of sexual transmission in South America is unclear.

Cystitis, pyelonephritis, and nephritis with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<p>Bacterial infections in patients with long-term catheters and renal stones, <i>Mycobacterium tuberculosis</i></p>	<p><i>Candida</i>, <i>Mycobacterium tuberculosis</i>, JC virus, BK virus</p>

Sexually transmitted infections with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<p>Ulcers: syphilis</p> <p>Wart: human papillomavirus</p> <p>Epididymitis/orchitis: <i>Mycobacterium tuberculosis</i>, <i>Paracoccidioides brasiliensis</i></p> <p>Prostatitis: <i>Enterococcus faecalis</i>, <i>Staphylococcus saprophyticus</i>, <i>Escherichia coli</i>, <i>Neisseria gonorrhoeae</i>, <i>Chlamydia trachomatis</i>, <i>Ureaplasma urealyticum</i>, <i>Trichomonas vaginalis</i>, <i>Mycoplasma genitalium</i>, <i>Mycobacterium tuberculosis</i>, <i>Paracoccidioides brasiliensis</i></p>	<p>Cytomegalovirus, <i>Mycobacterium</i>, <i>Candida</i>, <i>Cryptococcus</i>, <i>Salmonella</i></p>

Joint, muscle, skin, and soft tissue infections

Joint, muscle, skin, and soft tissue infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<p>Skin and soft tissues:* <i>Staphylococcus aureus</i>, group A streptococci, Scabies</p> <p>Arthritis: <i>Staphylococcus aureus</i>, <i>Neisseria gonorrhoeae</i>, <i>Neisseria meningitidis</i>, <i>Streptococcus pneumoniae</i>, chikungunya, Zika</p> <p>Myositis: dengue virus, <i>Leptospira</i>, <i>Staphylococcus aureus</i>, group A streptococci</p>	<p>Skin and soft tissues:* <i>Pseudomonas aeruginosa</i>, <i>Pasteurella multocida</i> (post animal bites), <i>Leishmania</i> spp., <i>Paracoccidioides brasiliensis</i>, <i>Borrelia</i></p> <p>Arthritis: <i>Brucella</i>, parvovirus B19, HIV (acute infection), dengue virus, <i>Borrelia</i>†</p> <p>Necrotizing fasciitis: group A/G streptococci</p> <p>Myositis: group B/C/G streptococci, echovirus, influenza virus, Coxsackievirus, <i>Rickettsia</i>, <i>Toxoplasma</i></p> <p>Tropical pyomyositis: <i>Staphylococcus aureus</i></p> <p>Scarlet fever syndromes: <i>Staphylococcus aureus</i>, group A streptococci</p> <p>Gas gangrene: <i>Clostridium perfringens</i></p>	<p>Skin and soft tissues:* <i>Corynebacterium diphtheriae</i>, <i>Bartonella</i>, <i>Bacillus anthracis</i>, <i>Sporothrix</i>, nontuberculous <i>Mycobacterium</i>, <i>Burkholderia pseudomallei</i>, <i>Spirillum minus</i></p> <p>Arthritis: Mayaro virus, <i>Bartonella</i></p> <p>Fournier's gangrene</p> <p>Myositis: <i>Trichinella</i>, <i>Taenia solium</i>, influenza virus, <i>Mycobacterium</i></p>

* Impetigo, folliculitis, furuncles, paronychia, ecthyma, erysipelas, cellulitis, ulcers.

† Transmission, epidemiology, and clinical picture not completely understood in South America.

Joint, muscle, skin, and soft tissue infections with more than four weeks of symptoms and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<p>Skin and soft tissues: syphilis, yaws[†] (<i>Treponema pertenu</i>), pinta** (<i>Treponema carateum</i>), onchocerciasis,^{††} paracoccidioidomycosis, verruga peruana (<i>Bartonella bacilliformis</i>), <i>Mycobacterium tuberculosis</i>, <i>Mycobacterium leprae</i>, <i>Sporothrix</i>, <i>Leishmania</i></p> <p>Arthritis: <i>Borrelia</i>,[†] <i>Mycobacterium tuberculosis</i>, syphilis, <i>Nocardia</i>, <i>Brucella</i>, nontuberculous <i>Mycobacterium</i> (including <i>M. leprae</i>), <i>Sporothrix</i>, <i>Paracoccidioides brasiliensis</i>, reactive arthritis (Reiter's syndrome – post <i>Chlamydia trachomatis</i>, and Enterobacteriaceae infection), chikungunya</p>	<p>Skin and soft tissues: <i>Candida</i>, <i>Histoplasma</i>, <i>Cryptococcus</i>, <i>Fusarium</i>, <i>Bartonella hensellae</i>, <i>Mycobacterium tuberculosis</i>, nontuberculous <i>Mycobacterium</i>, varicella virus, herpes virus, Mayaro, Zika</p>
<p>* Consider other inflammatory noninfectious arthritides: Still's disease, rheumatic fever, rheumatoid arthritis, Kawasaki syndrome. [†] Rare: Ecuador, Colombia, Suriname, Guyana. ^{**} Rare: Amazon region, cases reported almost exclusively in Indians. ^{††} Limited area: Brazil (Roraima State), Venezuela (most cases in Yanomami Indians).</p>	

Adenopathy

Adenopathy of less than four weeks duration

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<p>Virus: Epstein–Barr virus, cytomegalovirus, parvovirus, HIV, rubella, adenovirus, Zika</p> <p>Bacteria: <i>Mycobacterium tuberculosis</i>, <i>Treponema pallidum</i></p> <p>Other agents: <i>Toxoplasma gondii</i>, <i>Paracoccidioides brasiliensis</i></p>	<p>Virus: dengue virus</p> <p>Bacteria: <i>Bartonella</i>, <i>Haemophilus ducreyi</i>, <i>Rickettsia parkeri</i></p> <p>Other agents: <i>Trypanosoma cruzi</i> (acute infection), <i>Schistosoma mansoni</i> (acute infection), leishmaniasis kala-azar</p>	<p>Filariasis, onchocerciasis, <i>Francisella tularensis</i>, <i>Yersinia pestis</i>, <i>Ehrlichia</i></p>

Adenopathy of more than four weeks duration and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Toxoplasma gondii</i> , <i>Paracoccidioides brasiliensis</i> , <i>Mycobacterium tuberculosis</i> , <i>Leishmania chagasi</i> , Kikuchi's disease, leprosy	cytomegalovirus, parvovirus, HIV, adenovirus, <i>Mycobacterium tuberculosis</i> , nontuberculous <i>Mycobacterium</i> , histoplasmosis, <i>Bartonella</i> , <i>Leishmania chagasi</i>

Fever without focal symptoms

Fever for less than four weeks without focal symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<p>Viral: Epstein–Barr virus, cytomegalovirus, dengue virus, HIV, chikungunya, Zika</p> <p>Bacterial: <i>Mycobacterium tuberculosis</i>, <i>Salmonella</i> (typhoid and paratyphoid fevers), infective endocarditis</p> <p>Other agents: <i>Plasmodium vivax</i>, <i>Plasmodium falciparum</i>, <i>Leishmania chagasi</i>, <i>Toxoplasma gondii</i></p>	<p>Viral: Oropouche virus, parvovirus B19, herpes virus 6, Mayaro virus, Guaroa virus,* Venezuelan equine encephalitis virus, St Louis virus</p> <p>Bacterial: <i>Coxiella burnetii</i>, organ abscess</p> <p>Other agents: <i>Trichinella spiralis</i>†</p>	<p><i>Francisella tularensis</i>, <i>Yersinia pestis</i>,** <i>Ehrlichia</i>, <i>Babesia</i>, <i>Rickettsia prowazekii</i>††</p>
<p>* Amazon region. † Argentina and Chile, mostly. Exposure to locally produced pork or wild boar meat. ** Peru, Bolivia, and Colombia reported recent human cases. †† Remote high-altitude Andean region. No recent activity.</p>		

Fever for more than four weeks without focal symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Toxoplasma gondii</i> Tuberculosis	CMV Adenovirus

Eosinophilia and elevated IgE

Eosinophilia and elevated IgE for less than four weeks

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Ascaris lumbricoides</i> and <i>suum</i> * <i>Strongyloides stercoralis</i> <i>Necator americanus</i>	<i>Toxocara</i> spp. <i>Schistosoma mansonii</i> * <i>Paracoccidioides brasiliensis</i> † <i>Trichinella spiralis</i>	<i>Wuchereria bancrofti</i> (lymphatic filariasis)
* Acute phase. † Disseminated (juvenile) form.		

Eosinophilia and elevated IgE for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Ascaris lumbricoides</i> and <i>suum</i> , <i>Angiostrongylus costaricensis</i>	<i>Toxocara</i> spp., <i>Strongyloides stercoralis</i>

Hemorrhagic and icterohemorrhagic fever

Hemorrhagic fever	Icterohemorrhagic fever
Viral: dengue virus, Chikungunya, arenavirus, hantavirus* Bacteria: meningococci, staphylococci, <i>Rickettsia rickettsii</i> Other agents: <i>Plasmodium falciparum</i>	Virus: yellow fever virus, arenavirus, hepatitis A virus, hepatitis B/D Bacteria: <i>Rickettsia rickettsii</i> , <i>Leptospira</i> , <i>Salmonella</i> Other agents: <i>Plasmodium falciparum</i> , <i>Plasmodium vivax</i> (uncommon)
* In South America, cardiopulmonary syndrome.	

Selected endemic tropical infections in South America

Disease	Transmission	Clinical picture	Clinical alert signs and complications	Laboratorial diagnosis
Dengue Fever (Flavivirus DENV1, DENV 2, DENV3, DENV 4)	Vectorial (<i>Aedes aegypti</i>) Urban transmission Endemic/epidemic	Incubation period: median 5–6 days (3–15 days) General signs and symptoms: Fever, headache, prostration, ocular pain, prostration, exanthema, joint and muscle pain, diarrhea, vomiting, pruritus	Alert signs: Abdominal pain, vomiting, hypothermia, altered mental status, hemorrhagic signs, hemoconcentration, hepatomegaly, thrombocytopenia. Complications: hypoalbuminemia, hypovolemic hypotension, pulmonary effusion, hemorrhage, encephalitis, myocarditis, idiopathic thrombocytopenic purpura, hepatitis (including fulminant forms).	– Viral isolation – PCR – Antigen NS1 detection – IgM detection Immunohistochemistry (tissue)
ZIKA (Flavivirus)	Vectorial (<i>Aedes aegypti</i> and <i>Aedes albopictus</i>) Urban transmission Endemic/epidemic Vertical and perinatal transmission have been reported Possible sexual and transfusion transmission have been reported.	Incubation period: not well established; estimated to be 2–7 days (up to 14 days) General signs and symptoms: High proportion of asymptomatic infections (~80%) Symptomatic cases usually present a mild and self-limiting illness which includes fever, maculopapular rash, pruritus, arthralgia, conjunctivitis, myalgia and headache	Severe disease is uncommon. Cases of Guillain-Barré syndrome have been reported in patients following suspected Zika virus infection. A possible association between Zika virus and miscarriages, congenital central nervous system malformation and microcephaly has been postulated	Viral isolation Reverse transcriptase- polymerase chain reaction (RT-PCR) Virus-specific IgM and neutralizing antibodies. Plaque-reduction neutralization testing can be performed to discriminate cross- reaction with other related flaviviruses

(Continued)

Disease	Transmission	Clinical picture	Clinical alert signs and complications	Laboratorial diagnosis
Chikungunya (Alphavirus)	Vectorial (<i>Aedes aegypti</i> and <i>Aedes albopictus</i>) Urban transmission Endemic/epidemic	Incubation period: average incubation period of 3 to 7 days (range: 1–12 days) General signs and symptoms: Acute disease (duration 3–10 days): sudden onset of high fever, severe joint pain. Headache, diffuse back pain, myalgias, nausea, vomiting, polyarthrits, rash, and conjunctivitis may occur. Subacute and chronic Disease (after the first 10 days): relapse of symptoms that include distal polyarthrits, exacerbation of previous joints and bones diseases, hypertrophic tenosynovitis, depressive symptoms, fatigue, weakness. Chronic disease is defined by symptoms that persist for more than 3 months Chronic disease is defined by symptoms that persist for more than 3 months	Neurological manifestations: meningoencephalitis, encephalopathy, seizures, Guillain-Barré syndrome, cerebellar syndrome, paresis, palsies, neuropathy Cardiovascular manifestations: myocarditis, pericarditis, heart failure, arrhythmias, hemodynamic instability Ocular manifestations: optic neuritis, iridocyclitis, episcleritis, retinitis, uveitis Dermatological manifestations: photosensitive hyperpigmentation, intertriginous aphthous-like ulcers, vesiculobullous dermatosis Other manifestations: bleeding dyscrasias, pneumonia, respiratory failure, hepatitis, pancreatitis, nephritis, syndrome of inappropriate secretion of antidiuretic hormone, hypoadrenalism	– virus isolation – reverse transcriptase-polymerase chain reaction (RT-PCR) – serology: IgM and IgG immunoglobulin detection
Malaria (<i>Plasmodium falciparum</i> , <i>Plasmodium vivax</i> , and <i>Plasmodium malarie</i>)	Vectorial (<i>Anopheles spp</i>) Jungle, rural, and, rarely, urban transmission Endemic	Incubation period*: – <i>P. falciparum</i> : 8–12 days – <i>P. vivax</i> : 13–17 days – <i>P. malarie</i> : 18–30 days *the use of antimalarial chemoprophylaxy may extend the IP. General signs and symptoms: Fever, headache, joint and muscle pain, prostration, chills, diarrhea, vomiting	Alert signs: Hypoglicemia, anemia, thrombocytopenia, jaundice, hemorrhagic signs, altered mental status, oliguria, Complication: Respiratory distress, Disseminated intravascular coagulation, hemorrhages, severe anemia, cerebral edema, seizures, hypotension, shock, acute renal failure	– Blood films (including thick films) (parasite observation) – Rapid test antigen detection – PCR

Yellow Fever (Flavivirus)

Vectorial (*Haemagogus*, *Sabethes*, *Aedes*)
 Sylvatic (jungle) transmission;
 Recent outbreaks and epidemics in many countries.

Incubation period:

3–6 days

General signs and symptoms:

Fever, headache, joint and muscle pain, lowback pain, prostration, vomiting, diarrhea

Alert signs:

Intense nausea and vomiting, hematemesis, oliguria, albuminuria, thrombocytopenia, jaundice, hemorrhagic signs, altered mental status

Complication:

Respiratory distress, disseminated intravascular coagulation, hemorrhages, encephalopathy, coma, hypotension, shock, acute renal failure, liver failure

Acute Chagas Disease

(*Trypanosoma cruzi*)

Vectorial, food-borne, vertical, parenteral (eg, transfusion)

Sporadic clusters and outbreaks

Incubation period:

– **Vectorial:** 4–15 days

– **Enteral/oral:** 3–22 days

General signs and symptoms:

prostration, diarrhea, vomiting, lymphadenopathy, hepatomegaly, splenomegaly, diarrhea, muscle pain, exanthema

Complication:

Acute: facial edema, anasarca, myocarditis, pericarditis, cardiomegaly, arrhythmia, cough, dyspnoea, congestive heart insufficiency, digestive hemorrhage, meningoencephalitis,

Chronic:

– **Myocardiopathy** (dilatation, aneurysms, arrhythmia, cardiac congestive insufficiency)

– **Digestive tract** dysfunction (megacolon, megaesophagus)

– **Reactivation in immunocompromised** patients (mostly cardiac and neurologic damage)

– Blood films (parasite observation)
 – IgM detection
 – IgG increasing antibodies titers (paired samples)
 – PCR

– Viral isolation

– PCR

– IgM detection

– Immunohistochemistry (tissues)

Special considerations: malaria

As observed in many endemic areas, the emergence of *Plasmodium* species has increased in South America. *P. falciparum* should always be considered chloroquine resistant. In addition, *P. vivax* malaria is the most frequent etiological agent, with possible cases of severe or complicated disease [20].

Antibiotic resistance

As seen worldwide, the emergence of an increasing number of pathogens resistant to a wide spectrum of antimicrobials is a critical issue in many countries of South America. Despite the heterogeneous nature of information among countries, some systems of surveillance and information have been contributing to knowledge of frequency, distribution, clinical and therapeutic implications.

Pneumococcus

The Sistema Regional de Vacunas (Regional System of Vaccines, SIREVA), a multicenter, international laboratory-based surveillance project on invasive *Streptococcus pneumoniae*, monitors circulating serotypes and susceptibility pattern to antibiotics [21]. From 2000 to 2005, SIREVA determined 38.8% as the continental index of *S. pneumoniae* strains with diminished susceptibility to penicillin (CLSI, 2006) (21.5% intermediate; 17.3% high) for pneumonia, sepsis, and bacteremia; for meningitis, it was 30.5% (19.3% intermediate; 17.3% high) [22].

Other gram-positive bacteria

In a SENTRY study of Brazilian hospitals from 2005 to 2008, there was 31% oxacillin (MRSA) resistance among *S. aureus* strains, most also resistant to clindamycin, ciprofloxacin, levofloxacin, and trimethoprim/sulfamethoxazole (68.1%); all strains were susceptible to vancomycin, daptomycin, and linezolid [23]. Among coagulase-negative staphylococci, 80% were resistant to oxacillin. A significant increase in vancomycin resistance has been observed in enterococci. Despite strong evidence of spread of MRSA in Latin America with a wide range of clones, especially in Brazil, Argentina, Chile, Colombia, and Paraguay, more consistent data, including prevalence studies, are lacking [24].

Meningococcus

SIREVA II (2000–2005) found 65.8% and 99.2% susceptibility to penicillins and rifampicin, respectively; there was 34.1% intermediate resistance to penicillin and only 0.2% resistant [25].

Salmonella

Nalidixic acid-resistant *Salmonella* strains are common. According to the SENTRY Antimicrobial Surveillance Program, 1997–2004, the overall *Salmonella* resistance to nalidixic acid with reduced susceptibility to ciprofloxacin in Latin America was 15% [26]. In the same study, it was observed that all strains were susceptible to cefepime, carbapenems, gentamicin, and fluoroquinolones.

Vaccine-preventable diseases in children

The childhood vaccination programs in South America are above the average of developing countries in other continents, both in number of vaccines available and coverage.

Only two of the 12 countries and one overseas department (French Guyana) qualify as GAVI-dependent countries.

The work of the Pan American Health Organization (PAHO) has been fundamental in achieving high-quality standards. Polio, measles and rubella have been eliminated. Occasional imported cases of measles with secondary cases may occur but no wild polio cases have been detected since the early 1990s.

Most countries have a vaccination schedule that includes ID-BCG, DTP, Hib, OPV, HepB, rotavirus, measles, and rubella. Pneumococcal conjugate vaccine has been introduced in several countries and many have annual influenza vaccination for the elderly.

Updated vaccination schedules by country, as well as vaccine coverage in children and incidence of selected vaccine-preventable diseases, can be found on the PAHO's website [27].

Yellow fever vaccine is part of the childhood schedule in children above one year of age in risk areas (areas where yellow fever has been detected in humans or monkeys) in Argentina, Brazil, Bolivia, Peru, Paraguay, Ecuador, and Colombia. Venezuela vaccinates only travelers to risk areas.

Human papillomavirus vaccine (HPV) has not yet been introduced in public programs in South American countries.

In 2008, the region reported 16 cases of neonatal tetanus, a good indicator of the effectiveness of a vaccination program, from five countries (Brazil, Colombia, Ecuador, Paraguay, and Peru), down from 130 cases in seven countries reported 10 years earlier, in 1999.

Basic economic and demographic data, 2014 – II

Indicator	Human Development Index (HDI)	Life expectancy at birth	Mean years of schooling	Expected years of schooling	Gross national income (GNI) per capita
Country	Value	(years)	(years)	(years)	(2013 PPP \$)
Argentina	0.836	76.7	9.8	17.9	17,297 (2011)
Bolivia	0.662	67.8	8.2	13.2	5,750
Brazil	0.755	74.5	7.7	15.2	14,750
Chile	0.832	80.5	9.8	15.2	21,060
Colombia	0.720	74.4	7.3	13.5	11,960
Ecuador	0.732	77	7.6	14.2	10,720
Guyana	0.636	66.6	8.5	10.3	6,610
Paraguay	0.679	72.4	7.7	11.9	7,670
Peru	0.734	75.4	9.0	13.1	11,160
Suriname	0.714	71.4	7.7	12.7	15,960
Uruguay	0.793	77.5	8.5	15.5	18,940
Venezuela	0.762	74.9	8.9	14.2	17,900

UNDP, 2015 [30].

Causes of death in children under-five

	%
Neonatal causes	44
Influenza/Pneumonia	5.08
Sepsis	2.28
Acute Respiratory diseases	1.97
Vaccine preventable diseases	0.37
Diarrhoeal diseases	0.22
Others	46

PAHO, 2013.

All top ten causes of deaths all ages* in three countries elected for a low (Guyana), middle (Bolivia) and high (Brazil) BNI per capita

	%		
	Guyana	Bolivia*	Brazil
Ischemic heart disease	10.77	1.68	8.86
Cerebrovascular diseases	10.89	93.72	8.51
Respiratory infections (including influenza and pneumonia)	3.38	3.25	5.23
Diabetes mellitus	8.94	0.89	4.82
Violence	2.27	–	4.69
Hypertensive heart disease	6.86	0.26	3.85
Road traffic accidents	2.57	0.16	3.78
Chronic obstructive lung disease	0.87	0.31	3.51
Chronic heart disease	0.74	2.39	2.66
All cancers	–	2	2.35

PAHO, 2013.
[http://ais.paho.org/phis/viz/mort_causasprincipales_lt_oms.asp].
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Chapter 24

Northern America

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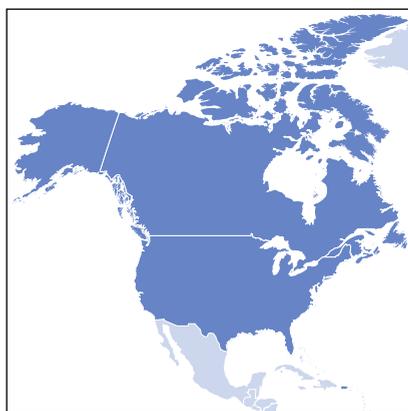
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Canada
United States

Northern America consists of two major industrialized nations, Canada and the United States, with populations of 35 million and over 318 million, respectively. The UN definition of the region includes Bermuda, Greenland, Saint Pierre, and Miquelon. For this book, Greenland is included in the chapter on the Arctic and Antarctica, and Bermuda is included in the chapter on the Caribbean. Infectious agents in Northern America are typical of those identified in most developed countries, but some regionally specific pathogens exist. Agents and illnesses specific to Northern America (or less commonly recognized in other world regions) include *Babesia*, *Ehrlichia*, *Anaplasma*, Lyme, Rocky Mountain spotted fever, and *Coccidioides*. West Nile virus has become established in the region since its initial identification in 1999. Food-borne factors cause an estimated 48 million illnesses in the United States annually, with the majority attributed to infectious agents including *Salmonella* spp., norovirus, Shiga toxin-producing *Escherichia coli*, *Campylobacter* spp., *Clostridium perfringens*, *Giardia*, and *Cyclospora*. Community-acquired *Clostridium difficile* diarrhea has emerged, whereas previously this had been a consequence of antibiotic therapy. Antimicrobial resistance is a common concern when treating infections in Northern America, especially vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus*.

Acute infections within four weeks of exposure

Infectious agents in Northern America are typical of those identified in most developed countries, but some pathogens and illnesses exist that are less commonly recognized in other world regions, including *Babesia*, *Ehrlichia*, *Anaplasma*, Lyme, Rocky Mountain spotted fever, *Coccidioides*, St. Louis encephalitis, eastern equine encephalitis, and western equine encephalitis. With the globalization of food procurement within the United States, an estimated 48 million food-borne illnesses with 9.4 million due to known pathogens occur annually [1]. Clonal outbreaks have become dispersed over wide geographic areas and sometimes have involved enormous numbers of people. Thus, increased clinical suspicion should be maintained for persons presenting with acute gastrointestinal complaints. Furthermore, diagnosis and reporting of gastrointestinal pathogens have gained importance in detecting outbreaks and implementing control measures.

While the burden of HIV infection has not reached the heights seen in other parts of the world, at the end of 2012, an estimated 1.2 million persons 13 and older were living with HIV infection in the United States, including 156300 persons whose infections had not been diagnosed [2]. Increased surveillance and recognition, especially in major metropolitan areas, have identified more acute cases and, given its nonspecific symptoms, HIV should be contemplated in anyone with fever and other nonspecific complaints [3].

Additionally, several bacterial infections have increased prevalence in the community setting within North America and should be considered in patients presenting from this region with compatible clinical complaints. The frequency of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) isolates has increased. As of 2011, 20.6% of invasive MRSA infections were community associated and 84% of these were bacteremia [4]. The incidence of *Clostridium difficile* infections is rising both in hospitalized patients and in the community, and must be considered in the differential diagnosis of diarrhea in Northern America [5,6]. Pertussis has reemerged, with 18000–48000 cases annually in the US since 2011 [7]. Finally, measles cases persist with 50–220 cases/year reported from 2000 to 2012, often acquired via international travel or in outbreaks associated with travel-related cases [8].

Diversity within the region: important regional infections with particular exposures

Food-borne outbreaks cause an estimated 48 million illnesses in the United States annually, and of those with identifiable causes, 9.4 million are attributed to infectious agents [1]. Recent multistate outbreaks have implicated many foods and have identified *Salmonella* (ground beef, chicken, tilapia fish, pistachios), *Escherichia coli* O157:H7 (ground beef, prepackaged leafy greens), *Vibrio parahaemolyticus* (raw oysters), and *Listeria monocytogenes* (Latin-style soft cheeses) [1].

Within the subcontinent, some organisms have limited distribution, particularly tick-borne diseases and some mosquito-borne infections. Many ecological factors influence vector survival and feeding, which in turn affect pathogen transmission. For example, outbreaks of human flea-borne typhus have occurred in southern California, caused by *Rickettsia typhi* or *Rickettsia felis*, carried by rats, cats, opossums, and other wild animals (www.cdph.ca.gov/HealthInfo/discond/Documents/Flea-borneTyphusCaseCounts.pdf). The distribution of these pathogens reflects the range of their vectors and/or the range of preferred animal reservoir hosts, as well as human activities. Although overall incidence of the tick-borne diseases may be low relative to other infectious etiologies, infection may be common in endemic areas during spring, summer, and fall. Some fungal infections have regional predominance. Also, a rare infection associated with widely present rodents, hantavirus pulmonary syndrome, occurs predominantly (but not exclusively) west of the Mississippi River.

Notable tick-borne infections

Lyme disease is the most frequently diagnosed tick-borne infection in the US. *Borrelia burgdorferi*, the causative bacterial agent, is transmitted by *Ixodes* ticks. Most cases of Lyme disease (90%) are reported from the north-east and upper mid-west of the US [9] (Figure 24.1). Lyme disease may present from

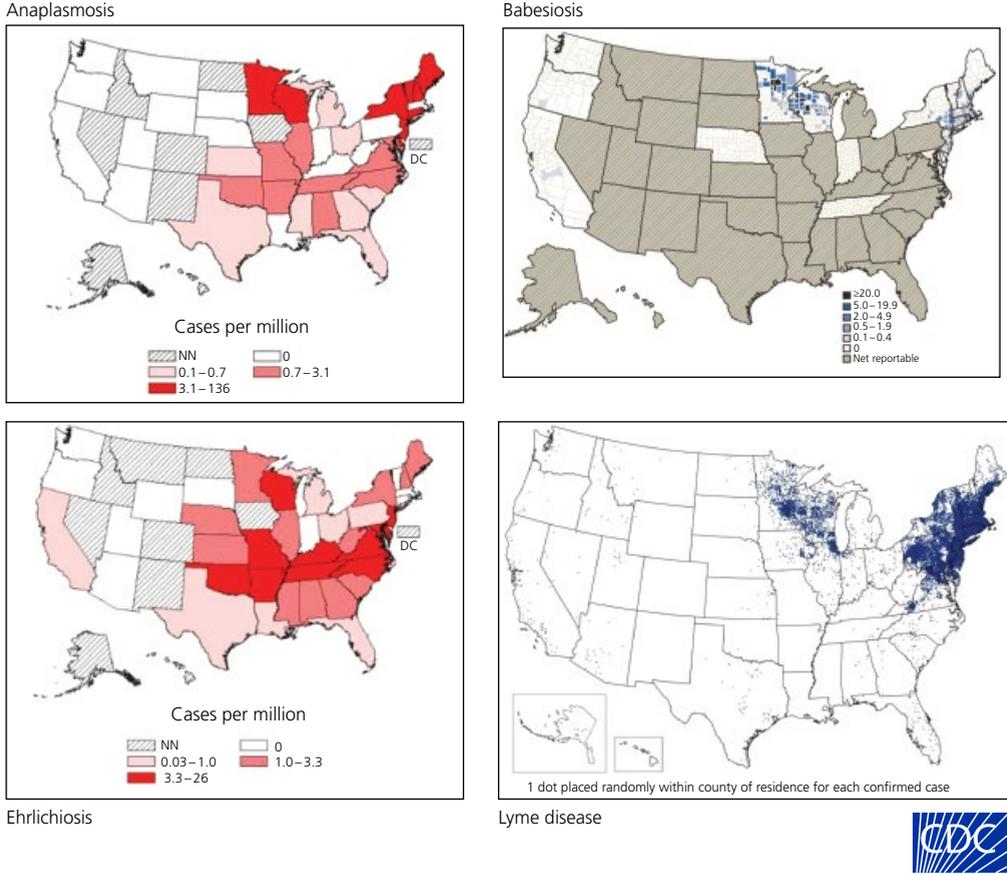


Figure 24.1 Selected tick borne diseases reported to CDC as of 2016 (Sources: www.cdc.gov/anaplasmosis/stats/#casesbyyear; www.cdc.gov/mmwr/preview/mmwrhtml/mm6127a2.htm; www.cdc.gov/lyme/stats/maps/map2013.html; www.cdc.gov/ehrlichiosis/stats/#geography).

3–30 days after tick bite as an early localized stage with erythema migrans rash, fatigue, fever, chills, headache, myalgia, and adenopathy. Days to weeks after tick bite, untreated infection may lead to early disseminated stage with rashes elsewhere, facial or Bell’s palsy, meningismus, pain/swelling in large joints, shooting pains, or arrhythmia/carditis. Months to years after tick bite, untreated infections may present as large joint arthritis, chronic neurological complaints such as neuralgia, numbness, tingling, and memory impairment [10]. *Borrelia mayonii*, a new species identified in Minnesota and Wisconsin, also causes Lyme disease (www.cdc.gov/ticks/diseases/index.html).

Babesia microti is the most frequently identified *Babesia* species in the United States, primarily parts of New England, New York State, New Jersey, Wisconsin, and Minnesota, and is transmitted by *Ixodes scapularis* (deer tick). In the north-east, babesiosis occurs in both inland and coastal areas, including the off-shore islands [9] (Figure 24.1). Many infections by this intracellular protozoa are asymptomatic. When symptomatic, patients present with nonspecific flu-like illness including fever, chills, headache, myalgias, anorexia, and fatigue. More severe illness occurs in persons with asplenia or immune suppression, or who are elderly [10].

Anaplasmosis is caused by the intracellular bacterium *Anaplasma phagocytophilum* and transmitted by the tick *Ixodes scapularis*, and occurs generally in the upper mid-west and coastal New England [9]

(Figure 24.1). After an incubation period of up to two weeks, patients may present with fever, headache, myalgia, malaise, chills, nausea, cough, confusion, and rarely a rash [10].

Ehrlichiosis, most commonly caused by *Ehrlichia chaffeensis* and *Ehrlichia ewingii*, and transmitted by *Amblyomma americanum* (lone star tick), occurs mainly in the lower mid-west, south-east, and East Coast [9] (Figure 24.1). The incubation period is typically 1–2 weeks, and illness can be fatal. Symptoms may include fever, chills, headache, malaise, myalgia, nausea, vomiting, diarrhea, confusion, conjunctival injection, and rash. Severe disease including respiratory and bleeding disorders can develop if untreated in previously healthy persons. Additionally, persons with immune suppression or splenectomy are at high risk for severe disease [11].

Rocky Mountain spotted fever (RMSF) is caused by *Rickettsia rickettsii*. RMSF is reported from nearly all contiguous US states, and is transmitted by infected *Dermacentor variabilis* (American dog tick), *Dermacentor andersoni* (Rocky Mountain wood tick) or *Rhipicephalus sanguineus* (brown dog tick). After an incubation period of 2–14 days, patients may present with fever, rash (macular or petechial), headache, nausea, vomiting, abdominal pain, myalgia, anorexia, and conjunctival injection. If not treated, the disease can progress to fatality within days [11].

Tick-borne relapsing fever is caused by *Borrelia* spp. and occurs in western US. *Borrelia miyamotoi* is a recently identified relapsing fever group spirochete that appears to be an emerging threat transmitted by *Ixodes* ticks [12]. Human infection has been reported from Russia, USA, Japan, and The Netherlands. Most human cases in the US documented to date have been from the north-east, in the same distribution as Lyme disease, anaplasmosis, and babesiosis. *B. miyamotoi* causes a febrile illness that may be associated with fatigue, headache, chills, myalgia, arthralgia, nausea, and meningoencephalitis [12]. Seroprevalence studies suggest that it may be more widespread than recognized.

Finally, some emerging tick-borne viral infections include Powassan virus, a flavivirus, Heartland virus, a phlebovirus, and Bourbon virus, a thogotovirus. The latter two were identified in Missouri and Kansas, respectively.

Notable mosquito-borne infections West Nile virus (WNV) was introduced into New York in 1999, but spread throughout the United States and southern Canada over just a few years. In recent years, WNV incidence has been higher in the upper mid-west. The incubation period for WNV disease is 2–14 days. Although many infections are asymptomatic, patients may present with West Nile fever (fever, headache, weakness, myalgia, arthralgia, gastrointestinal symptoms, rash) or neuroinvasive disease (meningitis, encephalitis, or acute flaccid paralysis).

Eastern equine encephalitis, St Louis encephalitis, La Crosse encephalitis, and Western equine encephalitis are zoonotic infections that are transmitted to humans accidentally via mosquito bites. Symptoms from infection with these viruses resemble those of WNV neuroinvasive disease. The names indicate their primary identification and distribution in the United States.

Dengue virus has typically been an imported disease in Northern America, acquired when travelers to warmer regions are bitten by the *Aedes* mosquito. One vector, *Aedes albopictus*, is present in many southern states, allowing local acquisition of dengue virus infections within Northern America. Such transmissions have occurred in Florida, Texas, and Hawaii, including outbreaks in 2009–2010 in Key West, Florida [13]. The US territory of Puerto Rico is endemic for dengue and more recently chikungunya (see below). Its close connection and high travel volume to/from mainland US contribute to some travel-associated dengue infections recorded in the US. Dengue virus should be considered in the differential diagnosis among febrile individuals who have visited these areas within the incubation period of two weeks.

Chikungunya, an alphavirus, was identified in Saint Martin in 2013 and subsequently spread to the Caribbean, Central, and South America. Chikungunya has led to local transmission in Florida (11 cases in 2014), although most cases in Northern America have been imported [14,15].

Zika, a flavivirus identified in Uganda in 1947 with subsequent outbreaks in South-east Asia and the Western Pacific, was first noted by the World Health Organization (WHO) to have local transmission in the Americas in May 2015, in Brazil (www.who.int/emergencies/zika-virus/en/; www.cdc.gov/zika/).

By January 2016, locally transmitted disease had spread to include Puerto Rico and as of early 2017, there have been over 125 locally transmitted cases within the continental US confined to southern Florida and Texas (www.cdc.gov/zika/geo/united-states.html).

Notable fungal respiratory infections

Dimorphic fungi such as *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Cryptococcus gattii* are acquired via inhalation of the spores. They cause a spectrum of illness from sub-clinical to disseminated infection, the latter particularly in immunosuppressed hosts. These fungi have demonstrated predominance in certain areas. For example, coccidioidomycosis is endemic to the south-western states, particularly California and Arizona, but also Nevada, Utah, Arizona, New Mexico, and Texas. Cases have been reported in other states in travelers returning from endemic areas [9]. The alkaline soil and climate in south-western US support the growth of coccidioidomycosis, and when the soil is disrupted, fungal conidia become air-borne (Figure 24.2). In Northern America, *H. capsulatum* is endemic in the Mississippi and Ohio River valleys. The endemic areas of blastomycosis appear to be the Mississippi and Ohio River valleys of the south central and mid-western US, and both American and Canadian sides of the St Lawrence valley. *Cryptococcus gattii* is endemic in many tropical and sub-tropical areas, and in the US, infections have been recognized in the Pacific North-west since 2004.

Infections in the Canadian Arctic and Alaska

The arctic regions of North America are endemic for several infections which are otherwise rare in the rest of the continent. In addition, several more common types of infections are far more prevalent in northern regions. This is due to the intersection of poverty, which is often extreme among the indigenous peoples of the arctic, the unique lifecycles of several arctic fauna and their associated parasites, and the particular hunting and food preferences in the area. The definition of “arctic” for this discussion is generally the region north of the 10°C July isotherm, which corresponds roughly to the “tree line.”

Rates of diagnosis of acute otitis media are twofold higher, and hospital admission rates for lower respiratory infection in the Canadian arctic are 10-fold higher than other Canadian populations. Invasive infections with *H. influenzae* type a have emerged in Alaska and northern Canada after the success of vaccination against type b. Hepatitis B and C are relatively prevalent in the north, but incidence of hepatitis B and especially hepatitis A has decreased since the widespread implementation of vaccination in schools (personal communication, Michael Libman). A seroprevalence rate of 3% for hepatitis E was reported among the Inuit. *H. pylori* infection appears to be linked to particularly high rates of iron deficiency anemia [17].

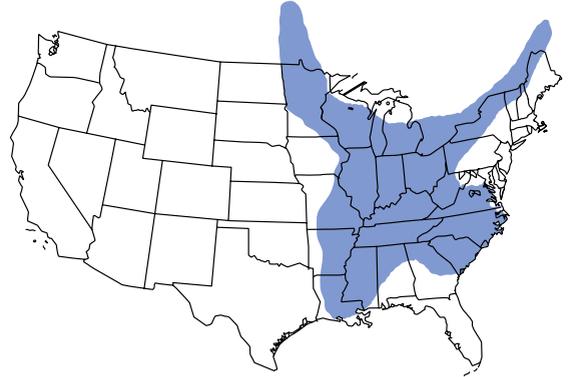
Several helminthic infections are far more common in the north than in the rest of Canada, mostly zoonoses [18]. Trichinellosis outbreaks are common, and are linked to consumption of raw polar bear and walrus. The organism is generally *T. nativa* rather than *T. spiralis*. Repeated infection produces a syndrome of chronic diarrhea, rather than the more classic symptoms of this disease [19]. *Trichinella* outbreaks have decreased, as hunters have been trained to collect meat samples for testing by local experts, before allowing distribution and consumption of the carcass [20]. Diphyllorhynchiasis (fish tapeworm) is still endemic, and occasionally worms are mistaken for tumors on barium enema. Both cystic and alveolar forms of *Echinococcus* still occur. *E. granulosus* tends to occur in a “semi-sylvatic” cycle which involves wild cervids and domestic hunting dogs. The northern biotype of *E. granulosus* appears to produce less virulent disease than elsewhere in the world. Incidence appears to be decreasing as hunters are educated not to feed raw offal to their dogs. *E. multilocularis* is rare, but foci exist across the western arctic [21]. An unusual gastrointestinal syndrome due to consumption of raw freshwater fish infected with *Metorchis conjunctus* has been described well south of the tree line [22].

Seroprevalence of toxoplasmosis has been reported to be up to 60%, far higher than the rest of the continent [18]. The arctic lifecycle of this parasite remains mysterious given the near total absence of felines in the region. Screening programs in pregnancy appear to have rendered congenital infection

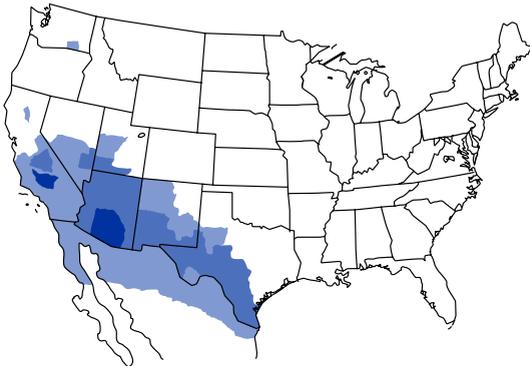
Possible areas endemic for *cryptococcus gattii*



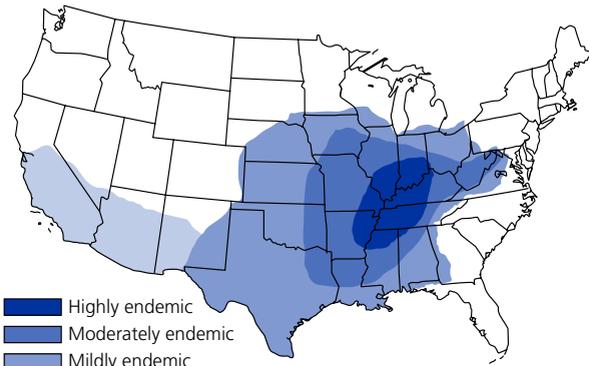
Areas endemic for blastomycosis



Areas endemic for coccidioidomycosis



Areas endemic for histoplasmosis



Highly endemic
 Moderately endemic
 Mildly endemic
 Suspected endemic

Highly endemic
 Established endemic
 Suspected endemic

Figure 24.2 Distribution of endemic fungi in the United States. Data sources: CDC (clockwise): www.cdc.gov/fungal/diseases/cryptococcosis-gattii/causes.html www.cdc.gov/fungal/diseases/blastomycosis/causes.html www.cdc.gov/fungal/diseases/histoplasmosis/causes.html www.cdc.gov/features/valley-fever-10-things/.

very rare. Very recently, diarrheal disease due to cryptosporidiosis has been recognized in the north. The local species appear to be different from those in the south, and transmission may be both zoonotic and anthroponotic. The animal reservoir has not yet been identified [23].

Botulism remains a recurring problem linked to improper fermentation of traditional foods made mostly from walrus and seal, or other marine mammals. These animals general harbor bacteria producing type E toxin, which is important when contemplating administration of specific antitoxin to affected individuals [24]. Rabies also remains endemic in the north, with the main reservoir being the arctic fox, and occasional introductions into the domestic dog population or other small mammals [25].

Infections in southern Canada

The epidemiology of most infectious diseases in southern Canada resembles that described in the United States. Infections which have specific distributions include Lyme disease, which is uncommon in Canada, but appears to be increasing as climate change improves conditions for dissemination. It has moved from a single focus north of Lake Erie to scattered southern parts of Ontario, Quebec, Nova Scotia, Manitoba, and south-eastern New Brunswick. Foci are also emerging near the west coastal region. Blastomycosis is endemic in central Canada, with almost all cases originating from Quebec, Ontario or Manitoba. Histoplasmosis occurs mainly in the central provinces, uncommonly in the Maritimes and the north, and rarely in western Canada. Western British Columbia, especially Vancouver Island, has emerged in the last 15 years as an endemic focus for *Cryptococcus gattii* which had previously been found mostly in tropical and subtropical climates. Clinical cases of West Nile virus infection were reported from Manitoba, Ontario, and Quebec [26].

CNS infections: meningitis, encephalitis, and other infections with neurological symptoms

Infections of the central nervous system (CNS) can be life threatening and associated with a high incidence of morbidity and mortality. Therefore, prompt recognition, diagnosis, and institution of appropriate therapy are mandated to avoid negative consequences. The presentation of infection of the CNS may be acute, subacute or chronic and correct identification of the signs and symptoms of a CNS infection involves assessment of the patient's complaints in conjunction with a compatible physical examination. In most cases, sampling of the cerebrospinal fluid (CSF) is key in the diagnostic evaluation, in conjunction with imaging.

Acute infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Viral meningitis (enterovirus group)	<i>Listeria monocytogenes</i>	<i>Naegleria</i> and other free-living amebae
<i>Streptococcus pneumoniae</i>	<i>Treponema pallidum</i>	Influenza
<i>Neisseria meningitidis</i>	<i>Rickettsia rickettsii</i>	<i>Baylisascaris procyonis</i>
Herpes simplex	<i>Borrelia burgdorferi</i>	<i>Clostridium botulinum</i>
Herpes zoster	<i>Anaplasma phagocytophilum</i>	<i>Cryptococcus gattii</i>
<i>Haemophilus influenzae</i>	La Crosse encephalitis	Rabies
West Nile virus	Eastern equine encephalitis	Western equine encephalitis
	St Louis encephalitis	Deer tick virus
	Powassan virus	Jamestown Canyon virus
		Zika virus (Florida)

CNS infections: meningitis and encephalitis with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
HIV <i>Mycobacterium tuberculosis</i> <i>Borrelia burgdorferi</i> <i>Treponema pallidum</i>	<i>Nocardia</i> spp. JC virus (John Cunningham virus) <i>Cryptococcus neoformans</i> <i>Toxoplasma gondii</i>

* Consider noninfectious causes like vasculitis and lymphoma.

Ear, nose, and throat infections

Because of the proximity of the structures in the head and their interconnectedness, the symptoms of the many pathogens that affect this area may be interrelated. The most common illness for which adults visit their physicians is acute pharyngitis. Many organisms both bacterial and viral can cause acute pharyngitis, either in isolation or as part of a more widespread disease process [27]. The most often implicated organisms are group A streptococcus (GAS), Epstein–Barr virus (EBV), herpes simplex virus (HSV), *N. gonorrhoeae*, cytomegalovirus, HIV, *Mycoplasma pneumoniae* and, very rarely, *Corynebacterium diphtheriae*. In the immunocompromised host, candidal infections also play a larger role. In addition to pharyngitis, rhinosinusitis and otitis are prominent conditions for which adults seek medical treatment. Rhinosinusitis affects 31 million adults in the United States annually [28]. Most often, viral causes such as rhinovirus predominate and bacteria including *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Moraxella catarrhalis* only account for 2% of these infections [29].

Cardiopulmonary infections

A leading cause of hospitalization and death in the United States is pneumonia and those aged ≥ 65 years are most susceptible to pneumonia-related morbidity and mortality [30]. Population-based data on community-acquired pneumonia are limited and data derived from most published studies reflect a variety of selection biases [31–33]. In cases where symptoms have been present for more than four weeks and alternative diagnoses such as malignancy, autoimmune disease, and vasculitis are ruled out, organisms such as *Mycobacterium tuberculosis*, *Histoplasma capsulatum*, *Aspergillus* spp., and atypical mycobacteria should be considered. In the immunocompromised, consideration should also be given to *Pneumocystis jiroveci*, CMV, *Candia albicans*, and *Aspergillus* spp.

Pneumonia with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Streptococcus pneumoniae</i> <i>Mycoplasma pneumoniae</i> <i>Haemophilus influenzae</i> <i>Legionella pneumophila</i> <i>Coccidioides immitis</i> *	Influenza <i>Staphylococcus aureus</i> <i>Chlamydophila pneumoniae</i> <i>Chlamydophila psittaci</i> <i>Cryptococcus neoformans</i>	<i>Corynebacterium diphtheriae</i> <i>Francisella tularensis</i> <i>Coxiella burnetii</i> Hantavirus (predominantly south-west) <i>Cryptococcus gattii</i>

* Regional distribution as noted earlier.

Infective endocarditis can be a highly morbid and potentially deadly infection, accounting for 1 in 1000 hospitalizations each year in the United States totaling about 15 000 new cases yearly [34]. Like pneumonia, data on endocarditis trends may be extrapolated from population-based studies [35]. While typically, most of the organisms listed here will present within four weeks, some may cause more protean manifestations and take longer to present to care: coagulase-negative *Staphylococcus*, nonhemolytic streptococci, *Bartonella* spp. and *Brucella* spp. In addition, in susceptible hosts, fungi such as *Candida* spp. and *Aspergillus* spp. may rarely cause endocarditis.

Endocarditis with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Staphylococcus aureus</i> Viridans group streptococci Coagulase-negative staphylococci* (<i>S. epidermidis</i>) <i>Streptococcus pneumoniae</i> <i>Enterococcus</i> spp.	HACEK group (<i>Haemophilus</i> spp., <i>Actinobacillus</i> <i>actinomycetemcomitans</i> , <i>Cardiobacterium hominis</i> , <i>Eikenella corrodens</i> , and <i>Kingella</i> spp.) <i>Coxiella burnetii</i> <i>Propionibacterium</i> Beta-hemolytic streptococci	<i>Bartonella</i> spp. <i>Brucella</i> spp.
*Predominantly on prosthetic valves.		

Gastrointestinal infections

Gastroenteritis manifesting as diarrhea is fairly common and can be due to many causes other than just infection. Many times, changes in bowel function caused by gastrointestinal infection are short-lived and often resolved without specific treatment. That said, food-borne disease outbreaks, especially multistate outbreaks, have been attributable to organisms such as *E. coli* O157:H7, *L. monocytogenes*, *Salmonella*, and norovirus [1]. When investigating for the infectious causes listed in the tables below, repeated negative bacterial cultures and microscopy for parasites should lead to the consideration that the symptoms may not be caused by an infection. Inflammatory bowel disease, malabsorption, and celiac disease must also be considered.

Gastrointestinal infections with less than four weeks of symptoms*

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Norovirus and calicivirus Rotavirus (in children) <i>Campylobacter</i> spp. Enterohemorrhagic <i>E. coli</i>	<i>Cryptosporidium</i> spp. <i>Bacillus cereus</i> toxin <i>Ascaris lumbricoides</i> †	<i>Vibrio</i> , non-cholera (predominantly <i>V. parahaemolyticus</i>)** <i>Cyclospora cayatanensis</i> <i>Aeromonas</i> spp.

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Giardia intestinalis</i> <i>Salmonella</i> (non-typhi) spp. <i>Clostridium difficile</i> <i>Staphylococcus aureus</i> toxin	<i>Shigella</i> spp. <i>Yersinia enterocolitica</i>	<i>Plesiomonas</i> spp. <i>Entamoeba histolytica</i>
<p>* Consider noninfectious causes like inflammatory bowel disease and intestinal malignancies like colon cancer. † <i>Ascaris</i> may cause nonspecific gastrointestinal discomfort but not diarrhea. ** Infection is associated with salt water.</p>		

Gastrointestinal infections with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i> <i>Tropheryma whipplei</i> <i>Blastocystis</i> * <i>Dientamoeba fragilis</i> * <i>Giardia lamblia</i> <i>Salmonella</i> spp. <i>Cryptosporidium</i> spp.	<i>Candida</i> spp. Herpes simplex Cytomegalovirus <i>Cryptosporidium</i> <i>Cystoisospora belli</i> Microsporidiosis
* Of uncertain pathogenicity in humans.	

Infections of liver, spleen, and peritoneum

A frequent cause of infection of the liver is viral hepatitis, most frequently caused by hepatitis A, B or C in North America. The incidence of acute infections is decreasing due to vaccination; within the US in 2013, newly identified cases of hepatitis A, hepatitis B, and hepatitis C were only 3473, 3050, and 2138 respectively [36]. Whereas hepatitis A used to be more prevalent in the western US, increased vaccination has resulted in similar rates throughout the country [36]. In Canada, the incidence of HAV is low and also declining, as is the incidence of HBV, although it is about 20 times more prevalent in northern natives compared to whites in southern Canada [37]. Hepatitis E is considered prevalent but rarely pathogenic in the US as data from the Third National Health and Nutrition Examination survey (NHANES), 1988–1994, showed that 21% of US residents are seropositive for HEV while the CDC only reports five cases of acute HEV in the US from 1997 to 2006 [38] although in recent years, with different methods of surveillance, others have argued that the seroprevalence is actually 6% [39]. In comparison, the prevalence of HEV in Canadian Inuits is about 3% [40]. Acute EBV infection may cause hepatitis and splenomegaly and is most common in the United States in teenagers aged 15–19, accounting for about 68% of the cases of acute mononucleosis [41].

In addition to viral infections, the spleen and liver may become infected with bacterial or fungal organisms through hematogenous or embolic spread leading to abscess. Most cases of acute peritonitis are either spontaneous and monobacterial in the presence of ascites, or polymicrobial when secondary to a perforated viscus.

Genitourinary infections

Urinary tract infection (UTI), that is infection of the urinary system (urethra, bladder, ureters or kidneys), is one of the most common bacterial infections, accounting for 7 million office visits in 1997 [42]. However, because UTIs are not reportable, the true incidence is difficult to project accurately. *Escherichia coli* causes 80% of all community-acquired UTI, yet a wide range of bacteria such as *Pseudomonas*, *Staphylococcus*, *Proteus mirabilis*, and *Enterobacter* grow well in urine and may successfully invade the urinary system and potentially lead to complications such as perinephric abscess [43]. Rarely, *Candida* spp. can cause infections in immunocompromised hosts. Additionally, *Mycobacterium tuberculosis* and hanta virus very infrequently can cause symptomatic UTI.

Regardless of one's country of origin, sexually transmitted infections (STIs) have serious health effects. In the US, half of STI cases excluding HIV occur among young people under age 25. Cases of *Chlamydia*, gonorrhea, and syphilis are reportable to public health authorities in Canada and the US [44]. *Chlamydia* is the most frequently reported among all age groups. Gonorrhea is the second most commonly reported followed by syphilis [44]. In 2009, national rates of gonorrhea reached a historic low at 98.1 cases per 100 000. Yet, between 2009 and 2012, the rate increased each year to 106.7 per 100 000 and remained relatively stable in 2013 at 106.1 per 100 000, mostly attributable to the decrease in infections among women [45]. The case count and rate of primary and secondary syphilis in 2013 were the highest recorded since 1995 [46]. Among cases of primary and secondary syphilis for whom the sex of the sex partner is known, men who have sex with men (MSM) accounted for 75% [46]. The highest rate of syphilis in 2013 was seen in the 20–24 years and 25–29 years age groups [46].

Other causes that should be considered in evaluating a patient with a suspected STD include HSV, *Trichomonas vaginalis*, *Lymphogranuloma venereum*, *Haemophilus ducreyi* (chancroid), HPV, and *Entamoeba histolytica*. Bacterial vaginosis and *Candida* cause genital symptoms that are generally not sexually transmitted. Recently, sexual transmission of Zika virus has been documented in many countries, necessitating advice on prevention, preconception planning, and exposure in pregnancy (www.who.int/emergencies/zika-virus/en/; <http://www.cdc.gov/zika/>).

Joint, muscle, and soft tissue infections

Several pathogens including bacteria and viruses can precipitate inflammation of the musculoskeletal system. Septic arthritis is rare but most often due to hematogenous spread of bacteria such as *Staphylococcus aureus*, *Streptococcus pyogenes* and occasionally *Streptococcus pneumoniae*. Rarely these organisms may cause infection of the muscle and fascia and lead to necrotizing fasciitis or, in the case of *Clostridium perfringens*, myonecrosis. In patients with joint prostheses, the same pathogens are found, but coagulase-negative *Staphylococcus* and other streptococcal spp. may also be isolated [47]. Diabetics may present with synergistic gangrene of the perineum that is usually polymicrobial. Lyme (*Borrelia burgdorferi*) disease is a common cause of arthralgia during the summer months, especially on the East Coast and upper mid-west [48,49]. If not recognized and treated early, it can lead to a more chronic arthritis. In sexually active individuals, *Neisseria gonorrhoeae* may cause an acute monoarticular arthritis. Certain viruses, such as parvovirus B19, rubella, EBV, CMV, and Zika, may cause acute arthralgias without frank arthritis. Rarely, *Candida* spp. and *Mycobacterium tuberculosis* can lead to arthritis that is usually indolent. Finally, several bacterial pathogens including *Campylobacter*, *Salmonella*, and *Shigella* may lead to reactive arthritis and a detailed history of recent gastrointestinal symptoms should be sought in those presenting with polyarticular complaints [50].

Skin infections

The most frequently encountered primary skin infection is cellulitis which is a common cause of antibiotic therapy and hospitalization. The following table lists the most frequently implicated organisms, including those that can cause skin findings resembling cellulitis. Less frequent but still important

etiologies of skin infections include *Treponema pallidum* (syphilis), *Mycobacterium* spp., and *Candida* spp. We have not listed a rash due to viral infections such as varicella zoster, measles, or rubella, or bacterial infections such as *Rickettsia rickettsia* (Rocky Mountain spotted fever) and other rickettsial infections or Lyme disease as they are not considered infections limited to the skin. Finally, one of the challenges facing any clinician is a noninfectious skin condition mimicking cellulitis. In these cases, consultation with a dermatologist may be necessary.

Skin infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Group A <i>Streptococcus</i> Beta-hemolytic <i>Streptococcus</i> (particularly B* and G) <i>Staphylococcus aureus</i> <i>Borrelia</i> spp. Gram-negatives in patients with diabetes, (particularly Enterobacteriaceae and <i>Pseudomonas</i>)	<i>Sarcoptes scabiei</i> (scabies) <i>Vibrio vulnificus</i> Southern tick- associated rash illness (STARI)	<i>Spirillum minus</i> and <i>Streptobacillus</i> (rat-bite fever) <i>Corynebacterium</i> <i>minutissimum</i> (erythrasma) <i>Erysipelothrix rhusiopathiae</i> (erysipeloid)
* More common in older individuals with underlying co-morbidities.		

Adenopathy

The potential infectious etiologies causing lymphadenopathy are broad but may be narrowed by anatomical location. Several infectious processes may cause generalized lymphadenopathy. Reactive adenopathy can occur from infections draining to regional nodes. If an infectious diagnosis is not made quickly, then biopsies of a lymph node may be necessary to exclude malignancy which may mimic infection.

Adenopathy of less than four weeks duration

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Epstein-Barr virus Cytomegalovirus Parvovirus B19 <i>Toxoplasma gondii</i> HIV	<i>Francisella tularensis</i> <i>Bartonella</i> spp. Rubella Rubeola <i>Treponema pallidum</i> , secondary	<i>Ehrlichia</i> spp. <i>Babesia</i> spp.

Adenopathy of more than four weeks duration and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Toxoplasma gondii</i> <i>Mycobacterium tuberculosis</i>	Adenovirus Cytomegalovirus

Fever with nonspecific complaints

Fever is a common reason for adults and children to present to medical care. Fever of unknown origin, however, is a more rare entity and is usually subdivided into four major categories, of which infection is the most common. It is important to be mindful of the potential for less common manifestations of certain diseases such as extrapulmonary tuberculosis or occult abscesses. For newborns, serious bacterial infections (presenting simply with fever or with additional localizing findings) are usually due to group B streptococci, *Escherichia coli*, or, rarely, *Listeria*. For young children, bacteremia is caused by *Meningococcus*, *Pneumococcus*, and *Haemophilus influenzae* type b; the latter two organisms have become less common with immunizations widely available.

Fever with nonspecific complaints

Frequently found microorganisms and conditions	Rare microorganisms and conditions	Very rare microorganisms and conditions
Endocarditis (many organisms) Epstein–Barr virus Cytomegalovirus Parvovirus B19 <i>Toxoplasma gondii</i> HIV	<i>Mycobacterium tuberculosis</i> <i>Coxiella burnetii</i> <i>Brucella</i> spp. West Nile virus <i>Rickettsia</i> spp. including Rocky Mountain spotted fever <i>Anaplasma phagocytophilum</i> * <i>Babesia</i> spp.* <i>Ehrlichia</i> spp.* <i>Leptospira</i> spp.	<i>Francisella tularensis</i> Relapsing fever <i>Borrelia</i> spp. <i>Borrelia miyamotoi</i> Colorado tick fever Heartland virus Bourbon virus (recently identified) Adenovirus (immunocompromised) Dengue virus (Florida, Texas) Chikungunya virus (Florida) Zika virus (Florida)

*Infection may occur very commonly in the endemic areas during spring, summer, and fall, although overall incidence may be low relative to other infectious etiologies.

Eosinophilia and elevated IgE

Eosinophilia may be caused by a number of conditions including fungal infections, parasites, mycobacteria, and malignancy. The fungal infections within Northern America, including coccidioidomycosis, cryptococcosis, and histoplasmosis, have been identified as potential etiologies to eosinophilia. While

the majority of parasitic diseases within the United States are identified in travelers and immigrants, there are several parasites that are endemic and should be considered in the correct clinical context. While *Trichinella* spp. have declined overall in the subcontinent, there are reservoirs in wildlife and noncommercial pork and thus continued case outbreaks [51,52]. *Toxocara* is the most common parasitic worm infection in the United States, affecting mostly those living in poverty [53]. *Baylisascaris procyonis* has caused eosinophilic encephalitis in Illinois and California [54]. *Echinococcus granulosus* is endemic to south central Canada and the northern mid-western US, with reservoirs in wolves and thus also domesticated sheep and dogs. Several reports of human disease in these areas are documented. *Strongyloides* transmission continues in the Appalachian area of the US where transmission has been demonstrated in previous serostudies [55].

Antibiotic resistance

Resistance patterns vary between continents and within various parts of Northern America. Group A streptococci remain completely susceptible to penicillin. Macrolide resistance is found in approximately 5–8% of group A streptococci, but resistance rates vary temporally and geographically as the prevalence of various streptococcal M types varies [56,57]. Macrolide treatment failure has been associated with acute rheumatic fever [58]. Clindamycin resistance is less common, approximately 1% [56]. For penicillin- and cephalosporin-allergic patients with streptococcal pharyngitis, clindamycin is now recommended [56].

In the United States, up to 30% of *Streptococcus pneumoniae* are resistant to at least one antibiotic [59]. *Pneumococcus* is uniformly susceptible to vancomycin, 99.8% susceptible to levofloxacin, 97% susceptible to cefotaxime, 90% susceptible to tetracycline, 72% susceptible to erythromycin, and 95% susceptible to penicillin [60]. In Canada, 86% of pneumococci from positive blood cultures were penicillin susceptible based on breakpoints for meningitis, and 99% were susceptible using levels other than for meningitis [61]. Most antibiotic resistance is found in serotype 19A, which is included in the currently used 13-valent pneumococcal conjugate vaccine [59].

Approximately one-third of *Haemophilus influenzae* produce beta-lactamase in the United States [62]. Macrolide resistance has also been identified among *Mycoplasma pneumoniae* in the United States, but such resistance is still much less common than in Asia and Europe [63].

Methicillin-resistant *Staphylococcus aureus* (MRSA) accounts for 80 000 invasive infections and 11 000 deaths each year in the United States [64]. Vancomycin resistance among MRSA has been identified but is very rare in Canada, and daptomycin and linezolid are still uniformly effective [61].

Gram-negative organisms causing urinary tract infection are becoming increasingly resistant to antimicrobial treatment. As of 2006, 50% were susceptible to ampicillin, 78% to trimethoprim-sulfamethoxazole, and over 90% to a quinolone [65]. Since then, however, quinolone resistance is increasing in at least some American settings, especially when the infections are associated with healthcare [66]. Among hospitalized patients, extended-spectrum beta-lactamase-producing *Escherichia coli* cases (per 1000 hospitalizations) increased from 0.51 in 2000 to 1.81 in 2009; carbapenem-resistant Enterobacteriaceae were identified and rose to 0.51 cases per 1000 hospitalizations [67]. In Canada, extended-spectrum beta-lactamase-producing Enterobacteriaceae seem to pose a significant threat, and nearly 19% of healthcare-associated Enterobacteriaceae infections in the US are now caused by extended-spectrum beta-lactamase-producing strains [64,68].

Gonococcal resistance is also increasing, with approximately 30% now being resistant to at least some antibiotics (23% resistant to tetracycline) [64]. Approximately 1% of gonococcal strains in the United States are resistant to cefixime, and about 0.4% are resistant to ceftriaxone [69].

Most *Mycobacterium tuberculosis* infections in the United States are linked to immigrants. Resistance patterns of tuberculosis infections vary with the geographical source of the infection [70]. Approximately 1.2% of new infections are multidrug resistant [71].

Vaccine-preventable diseases in children

The incidences of many vaccine-preventable diseases are at record low levels in North America, but problems still occur. In 2014, for instance, the United States CDC reported one case of diphtheria, 3158 cases of invasive *Haemophilus influenzae* (not all type b), 1123 cases of hepatitis A, 2636 cases of hepatitis B, 628 cases of measles, 1151 cases of mumps, 947 cases of invasive pneumococcal disease in children less than five years of age, 28 660 cases of pertussis, eight cases of rubella, and 9058 cases of varicella [72].

The persistence of pertussis relates to waning protective immunity from vaccines [69]. Booster doses of pertussis vaccine are now recommended for adolescents and for pregnant women in the United States.

Outbreaks of mumps and measles are often linked to internationally traveling index cases who import the infection [69,73]. As sadly demonstrated by the 2014–15 California amusement park-associated measles outbreak affecting over 130 people, though, infections can spread widely when there are susceptible subjects; people in seven US states and in two adjoining countries were infected during that outbreak [74,75].

Childhood vaccination schedules are similar in the United States and Canada, but Canadian schedules vary somewhat by province [76,77]. Throughout Northern America, childhood vaccination is recommended for diphtheria, tetanus, pertussis, polio (using injectable vaccine), *Haemophilus*, hepatitis B, meningococcal disease (infants in Canada, older children in the US), *Pneumococcus* (using the 13-valent vaccine), rotavirus, influenza, measles, mumps, rubella, varicella, and human papillomavirus (only girls in Canada, suggested for boys and girls in the US). In the US, hepatitis A vaccine is also routinely given after one year of age.

Immunization in compliance with recommended schedules is common for standard infant vaccines (>90), but lower for newer vaccines (73% for rotavirus, 83% for hepatitis A at one year of age); coverage rates vary between states [78]. There are also geographical variations in immunization rates related to parental refusal of vaccination [79]. There is growing public support for removal of nonmedical exemptions from vaccination.

Basic economic and demographic data

Basic demographics*	GNI per capita 2014 (USD)	Life expectancy at birth (total, years)	School enrollment, primary (% net)
Canada	51 690	81	99.0
United States	55 200	79	98.0

*World Bank.

GNI, gross national income; NA, not available.

Causes of death in children under five*

	Canada (%)	USA (%)
Prematurity	29	28
Congenital	27	25
Other causes	22	23
Injuries	5	12

	Canada (%)	USA (%)
Birth asphyxia/trauma	10	5
Acute lower respiratory infections	2	3
Neonatal sepsis	3	2
Diarrheal diseases	<1	2
Malaria	0	<1
HIV/AIDS	0	<1
Measles	0	0

*WHO. Regional average, 2013 data. Available at: www.who.int/countries/usa/en/

Top 10 causes of deaths all ages*

	%	
	Canada 2012	United States 2012
Chronic obstructive lung disease	5	6
Lower respiratory infections	2	2
Tracheal, bronchial and lung cancers	8	7
Breast cancer	2	
Cerebrovascular diseases	5	5
Ischemic heart disease	14	15
Alzheimer's and other dementias	10	10
Diabetes mellitus	3	3
Hypertensive heart disease	NS	3
Colon and rectal cancers	4	2
Falls	2	NS

* www.who.int/countries/can/en/; <http://www.who.int/countries/usa/en/>
NS, not stated.

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Chapter 25

Australia, New Zealand

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Australia
New Zealand

Australia has both temperate areas in the southern and coastal regions and tropical areas in central and northern Australia. The New Zealand climate, however, is temperate in the main. Temperate Australia and New Zealand (NZ) have similar health services and diseases, with the risks of most common community illnesses (e.g. gastroenteritis, respiratory viruses) being similar to those in other developed countries globally. However, a number of diseases found in temperate Australia have never been reported from NZ, including Ross River virus, Murray Valley encephalitis, Barmah Forest virus, Q-fever, tick typhus, scrub typhus, Hendra virus, lyssavirus and *Mycobacterium ulcerans*. The tropical areas of Australia are sparsely populated, have relatively basic medical services outside major cities and urban areas, and have different disease patterns. Infections such as *Strongyloides stercoralis*, HTLV-1, rheumatic fever, trachoma, melioidosis, and scabies are not infrequent among Australian Aborigines.

Bacterial and mycobacterial infections

Brucellosis (due to *Brucella suis*) is uncommon and occurs almost exclusively in association with hunting feral pigs. The 2014 notification rate in Australia was 0.1/100 000 population with virtually all infections acquired in rural areas of Queensland followed by northern New South Wales (NSW) [1,2].

Melioidosis, caused by *Burkholderia pseudomallei*, is endemic in northern Australia (Northern Territory, Far North Queensland, Western Australia) and the Torres Strait Islands. Melioidosis is the most common cause of fatal community-acquired pneumonia in Darwin. In the top end of the Northern Territory, cases most frequently occur during the summer monsoonal wet season (November through April) [3–5].

Bartonellosis (cat scratch disease, caused by *Bartonella henselae*) is widespread throughout Australia and NZ. It is associated with bites/scratches from domestic cats.

The overall prevalence of tuberculosis in Australia (5.7 cases per 100 000 population in 2014) and New Zealand (6.6 cases per 100 000 population in 2014) is low [1,2]. *M. tuberculosis* strains are usually sensitive to all major antituberculosis agents.

Mycobacteria ulcerans occurs almost entirely in south-eastern Australia, especially in Victoria (Bairnsdale, Phillip Island, Bellarine, and Mornington Peninsulas). The annual number of cases in Victoria is increasing, although the overall rate of infection is low (1.1/100 000 per year) [6]. The infection has also been reported in Cairns in Far North Queensland, although residents of Cairns are only at risk if they visit the coastal strip north of Cairns between Mossman and just north of the Daintree river. Infections often occur in clusters, but the exact mode of *M. ulcerans* transmission is unknown, but the risk to travelers is low.

Rickettsial infections have been reported from all states of Australia and occur in travelers to rural, forested, and coastal areas [7]. Infections are divided into the spotted fever group spread by ticks and the typhus group spread by fleas from mice and rats.

- **Spotted fever group:** Queensland tick typhus is caused by *Rickettsia australis* and has been reported from Queensland, New South Wales, coastal areas of eastern Victoria and Tasmania. Flinders Island spotted fever, caused by *Rickettsia honei*, has been reported from Flinders Island in southern Australia, Tasmania, and south-eastern Australia.
- **Typhus group:** murine typhus, caused by *Rickettsia typhi*, is present throughout Australia but predominantly in Queensland and Western Australia. Scrub typhus, caused by *Orientia tsutsugamushi*, occurs through coastal northern Queensland (north of Townsville), and tropical northern Australia, including the top end of the Northern Territory (in particular, Litchfield Park south of Darwin) and the Kimberley region of Western Australia. *Rickettsia felis* is present in Western Australia. In NZ, infection has occurred almost exclusively in people living in a rural environment, usually in the warmer climes of the Waikato and Auckland regions [8].

In Australia, the epidemiology of meningococcal disease follows the pattern seen in most other industrialized nations [9]. In 2000, the incidence of notified meningococcal disease reached 3.3 per 100 000, and the incidence of serogroup C disease was around 1.1 per 100 000 in the years prior to 2003 when the vaccine was introduced [10]. Disease incidence has declined markedly since the introduction of the meningococcal C conjugate vaccine, and the incidence of invasive meningococcal infections in Australia in 2014 was 0.7/100 000 population [1]. The case fatality rate is approximately 4%. In contrast, NZ had high rates of meningococcal disease during the 1990s due to the emergence of a serogroup B clone, which by 2000 accounted for 85% of cases. Cases were disproportionately seen among Maori and Pacific Islands children in the North Island of NZ, and infants <1 year had an age-specific rate of 124/100 000 in 2003 [11]. This led to the development of a strain-specific vaccine, MeNZBTM, and a vaccination program between 2004 and 2008 that significantly reduced the rate of meningococcal disease to 1.9/100 000 in 2012, the lowest rate in 20 years: 63% type B and 34% type C, Maori and Pacific Islanders still with significant though lower numbers [12].

Although overall rates of acute rheumatic fever (ARF) in Australia and NZ are low, the rates of ARF among indigenous people are among the highest in the world [13,14]. The average annual incidence

rate of confirmed ARF in Australia between 1996 and 2010 was 26/100000 population. However, the incidence is substantially higher in Aboriginal and Torres Strait Islanders in the top end of the Northern Territory, especially among those aged 5–14 years who account for 58% of all notifications [15]. In New Zealand, the incidence among Maoris is 8 per 100000, 10 times higher than occurs among people of European descent [13].

Leptospirosis occurs in all parts of Australia, mainly as an occupational disease among livestock and agricultural workers. Most cases (>70%) occur in Queensland, with serovars *zanoni*, *australis*, and *hardjo* accounting for most of the disease. Since 1999 in Australia there has been a downward trend in notifications of leptospirosis [16], which has been attributed to recent persistent drought conditions. The incidence of leptospirosis in Australia in 2014 was reported at 0.4/100000 population, with the highest rate reported in Queensland (1.2/100000 population) [1]. In NZ, the incidence of the disease is reported as 2.2 per 100000 population, with the most common serovars causing human infection in NZ being *L. borgpetersonii* sv. *hardjo* and *ballum*, and *L. interrogans* sv. *Pomona* [8,16,17].

Although not previously thought to be endemic in Australia, two cases of tularemia caused by *Francisella tularensis* subspecies *holarctica* were reported in 2011 in Tasmania associated with bites from ringtail possums [18].

Viral infections

Australia and NZ have relatively small HIV epidemics. The adult HIV prevalence in the general population in these countries is about 0.2% [19]. Transmission is primarily through sexual contact between men.

Australia is the only country in the world that has reported cases of Hendra virus. The natural reservoir for the Hendra virus is the fruit bat. It can be transmitted to horses and has occasionally been reported among horses in Queensland and New South Wales. Illness has occurred in humans working with infected horses, mostly among veterinarians, leading to either an acute respiratory illness or a meningoencephalitis. The risk to travellers is extremely low.

Dengue virus is not endemic in Australia, but the presence of mosquito vectors in northern Australia has resulted in epidemics following the introduction of dengue virus by travelers returning from other endemic countries. Outbreaks of dengue fever are periodically reported from northern Queensland in the region extending from the Torres Strait south to Cairns, Townsville, and Charters Towers [19]. A major dengue outbreak occurred in the northern suburbs of Cairns between December 2008 and May 2009, with 1026 cases reported in 2009 [19]. Cases were also reported from Townsville, Port Douglas, Yarrabah, Injinoo, and Innisfail. In the rest of the country, dengue fever is predominantly a disease of returned travelers. In 2014 the Australian notification rate was 7.3/100000 population [19].

Ross River virus (RRV) is the most common arboviral disease in Australia and is characterized by fever, rash, and arthralgias. RRV has become established in most parts of Australia and has resulted in several outbreaks [20]. In May 2010, a fourfold increase in the number of RRV cases was reported from the Riverina Murray region in New South Wales, due to greater rain and a larger number of mosquitoes. The incidence of RRV disease in Australia in 2014 was 22.7/100000 [1], although this varied widely according to season and geographical regions (e.g. Queensland 24–146 cases/100000/year; Northern Territory 32–208 cases/100000/year) [19]. An outbreak occurred in Queensland and New South Wales in 2015, with record numbers of cases reported (>7000) in the first six months of the year [19].

Barmah Forest virus (BFV) is a closely related arbovirus that is spread by the same mosquito vectors and hence epidemics of mixed RRV and BFV infections have been reported. BFV is less common with an annual notification rate of about 6.5 (3.2–18.3)/100000/year [19]. The incidence of BFV in the Northern Territory varies from 12.3 to 167/100000/year, in Queensland from 10 to 47.8/100000/year, and in NSW from 2.2 to 9.4/100000/year [19]. BFV also occurs in Western Australia (including the Kimberley, Pilbara, and Gascoyne regions). Incidence peaks between the months of February to May.

Murray Valley encephalitis (MVE) is an infrequent disease. Over the last decade, cases have been reported from the Northern Territory (South Australia, north-west Western Australia, outback Queensland, and outback NSW). Usually only one or two cases are reported annually, but in 2011 there were 16 cases [20], three-quarters of which were in Western Australia [1], associated with heavy rainfall and flooding [21]. The risk period is maximal from February to early April in central Australia but can persist until June.

Kunjin virus infection is uncommon and only sporadic cases have been reported from Northern Territory, Western Australia, and QLD. The Australian notification rate is $<0.1/100\,000$ population [1].

Japanese encephalitis (JE) is not endemic either on mainland Australia or in NZ but 11 cases have been notified since 2000 [1]. Four of these were reported from Badu Island in the Torres Strait. One locally acquired case was reported in a resident of the Cape York Peninsula of Far North Queensland. The remaining cases were reported in travelers who had acquired infection overseas [20].

Australia and NZ are rabies free, but the Australian bat lyssavirus (ABL) has been isolated from insectivorous and fruit-eating bats in NSW, Northern Territory, Queensland, Victoria, and Western Australia, and has caused three human fatalities. Potential exposure is most likely among professional bat handlers although inadvertent exposure following handling of bats by individuals in the general community has also been reported. There has been one case of ABL over the last 10 years [1,22].

Parasite infections

Infection with the dog hookworm, *Ancylostoma caninum*, has a worldwide distribution but so far the only reports of it also causing an eosinophilic infiltration of the gut wall have been from Australia, mainly from Northern Queensland [23].

Cases of *Angiostrongylus cantonensis*, the rat lungworm, have been reported from Australia, particularly from Queensland and New South Wales [24]. It is acquired by eating contaminated leafy vegetables (in salads), infected snails and slugs (often inadvertently), and land crabs. Symptoms include paraesthesia and an eosinophilic meningitis.

High rates of *Strongyloides stercoralis* are found in some indigenous communities in central Australia. Complicated strongyloidiasis often occurs in association with HTLV-1 infection as these two infections are co-endemic [23].

Australia and NZ are free of endemic malaria and human schistosomiasis.

In addition to infectious outcomes listed in the tables below, travelers also need to be aware of the risks of toxins, envenomations, and bites (spiders and snakes).

CNS infections: meningitis, encephalitis, and other infections with neurological symptoms

Acute infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Viral meningitis (enterovirus group)	<i>Listeria monocytogenes</i>	<i>Naegleria fowleri</i> and other free-living amoebae including <i>Acanthamoeba</i> spp. and <i>Balamuthia mandrillaris</i>
<i>Streptococcus pneumoniae</i> (meningitis)	<i>Treponema pallidum</i> (neurosyphilis)	Influenza

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Herpes virus (group I and II) <i>Neisseria meningitides</i>	HIV Murray Valley encephalitis	<i>Brucella suis</i> <i>Burkholderia pseudomallei</i> Hendra virus Australian bat lyssavirus Japanese encephalitis (Torres Strait Islands only) Kunjin virus <i>Angiostrongylus cantonensis</i>

CNS infections: meningitis and encephalitis with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
HIV <i>Mycobacterium tuberculosis</i> <i>Tropheryma whipplei</i>	<i>Nocardia</i> spp. Polyomavirus <i>Cryptococcus</i> spp. JC virus <i>Mycobacterium tuberculosis</i> <i>Toxoplasma gondii</i> <i>Acanthamoeba</i> spp.

* Consider noninfectious causes like vasculitis and lymphoma.

Ear, nose, and throat infections

Ear, nose, and throat infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Group A streptococci (streptococcal throat infection) Epstein-Barr virus Herpes simplex virus (type I and II)	Peritonsillar abscess* <i>Mycobacterium tuberculosis</i> <i>Fusobacterium necrophorum</i> (Lemierre's syndrome)	<i>Corynebacterium diphtheriae</i>

* Requires acute ENT evaluation.

Ear, nose, and throat with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i>	<i>Candida</i> spp. Herpes simplex virus

*Consider noninfectious causes like vasculitis and lymphoma.

Cardiopulmonary infections**Pneumonia with less than four weeks of symptoms**

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Streptococcus pneumoniae</i>	<i>Coxiella burnetii</i> (Q-fever)	<i>Corynebacterium diphtheriae</i>
<i>Mycoplasma pneumoniae</i>	Influenza virus	<i>Burkholderia pseudomallei</i>
<i>Chlamydia psittaci</i>	Parainfluenza virus	Hendra virus
<i>Legionella pneumophila</i>		
<i>Chlamydia pneumoniae</i>		

Endocarditis with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Staphylococcus aureus</i>	<i>Neisseria gonorrhoeae</i>	<i>Bartonella</i> spp.
Viridans group streptococci and <i>S.bovis</i>	<i>Coxiella burnetii</i> *	<i>Brucella</i> spp.
Coagulase-negative <i>Staphylococcus</i> (<i>S. epidermidis</i>)	<i>Propionibacterium</i>	<i>Tropheryma whipplei</i>
<i>Enterococcus</i> spp.	HACEK group	
	<i>Streptococcus pneumoniae</i>	

*Q-fever has not been reported from New Zealand.

Pulmonary symptoms for more than four weeks and in the immunocompromised host*

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i>	<i>Pneumocystis jiroveci</i>
<i>Bordetella pertussis</i>	CMV
<i>Aspergillus</i> spp.	<i>Aspergillus</i> spp.
	<i>Candida</i> spp.

*Consider noninfectious causes like lung cancer, autoimmune lung fibrosis, and Wegener's granulomatosis.

Endocarditis for more than four weeks and in the immunocompromised host*

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Viridans</i> group streptococci and <i>S.bovis</i> Coagulase-negative staphylococci (<i>S. epidermidis</i>) <i>Coxiella burnetii</i> [†] <i>Bartonella</i> spp.	<i>Aspergillus</i> spp. <i>Tropheryma whipplei</i>
* Consider noninfectious causes like sarcoidosis. † Q-fever has not been reported from New Zealand.	

Gastrointestinal infections**Gastrointestinal infections with less than four weeks of symptoms***

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Norovirus and calicivirus, rotavirus <i>Campylobacter</i> spp. Enteropathogenic <i>E. coli</i> <i>Giardia intestinalis</i> [†] <i>Salmonella</i> spp. (non-typhi) <i>Enterobius vermicularis</i> (pinworm)	<i>Cryptosporidium</i> spp. <i>Staphylococcus aureus</i> toxin <i>Bacillus cereus</i> toxin <i>Ascaris lumbricoides</i> <i>Strongyloides stercoralis</i> <i>Ancylostoma caninum</i> <i>Shigella</i> spp. <i>Trichuris trichiura</i> <i>Aeromonas</i> spp. <i>Entamoeba dispar</i>	<i>Mycobacterium tuberculosis</i> <i>Tropheryma whipplei</i>
* Consider noninfectious causes like inflammatory bowel disease and intestinal malignancies like colon cancer. † <i>Giardia intestinalis</i> can occur throughout Australia and New Zealand, but it is particularly endemic in Tasmania.		

Diarrhea is often associated with infections with bacteria, viruses, and parasites. Repeated negative bacterial cultures and microscopy for parasites should lead to the consideration that the symptoms may not be caused by an infection. Inflammatory bowel diseases like ulcerative colitis and Crohn's disease are part of the differential diagnosis and malabsorption and celiac disease must also be considered.

Gastrointestinal infections with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i> <i>Tropheryma whipplei</i> <i>Blastocystis hominis</i> [†] <i>Dientamoeba fragilis</i> [†]	<i>Candida</i> spp. Herpes virus, cytomegalovirus
(Continued)	

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Echinococcus granulosus</i> <i>Enterobius vermicularis</i> <i>Strongyloides stercoralis</i> ** <i>Ancylostoma duodenale</i> (hookworm)** <i>Ascaris lumbricoides</i> ** <i>Trichuris trichiura</i> **	
* Consider noninfectious causes like inflammatory bowel disease, intestinal malignancies like colon cancer, malabsorption, and celiac disease. † Of uncertain pathogenicity in humans. ** Mainly occur in the tropical north of Australia.	

Infections of liver, spleen, and peritoneum

Acute infections of liver, spleen, and peritoneum with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Hepatitis A Hepatitis B Hepatitis C	<i>Entamoeba histolytica</i>	<i>Fasciola hepatica</i> Hepatitis E

Chronic infections of liver, spleen, and peritoneum with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i> <i>Tropheryma whipplei</i>	<i>Mycobacterium avium</i> complex
Infections in the immunocompromised host are generally similar to those in the immunocompetent host.	

Genitourinary infections

Cystitis, pyelonephritis, and nephritis with less than four weeks of symptoms*

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>E. coli</i> <i>Klebsiella pneumoniae</i>		<i>Mycobacterium tuberculosis</i>
* Consider noninfectious causes, especially malignancies like renal cell carcinoma.		

Sexually transmitted infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Chlamydia</i> spp. <i>Neisseria gonorrhoeae</i> Herpes simplex	<i>Treponema pallidum</i>	

Cystitis, pyelonephritis, and nephritis with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i>	<i>Candida</i> spp.
* Consider noninfectious causes, especially malignancies like renal cell carcinoma.	

Sexually transmitted infections with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Treponema pallidum</i>	

Joint, muscle, and soft tissue infections**Joint, muscle, and soft tissue infections with less than four weeks of symptoms**

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Staphylococcus aureus</i>	Necrotizing fasciitis Group G streptococci	
<i>Streptococcus pneumoniae</i> Ross River virus Barmah Forest virus	Dengue	

Joint, muscle, and soft tissue infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i>	<i>Candida</i> spp.

Skin infections

Skin infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Erysipelas (<i>S. pyogenes</i>), <i>Streptococcus pneumoniae</i> <i>Staphylococcus aureus</i>	Scabies Necrotizing fasciitis caused by group A streptococcal spp.	<i>Vibrio vulnificus</i>

We have not listed a rash due to viral infections as this is not considered an infection limited to the skin.

Skin infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Treponema pallidum</i> <i>Mycobacterium tuberculosis</i> <i>Mycobacterium ulcerans</i> *	<i>Candida</i> spp.
* <i>Mycobacterium ulcerans</i> has not been reported from New Zealand.	

Adenopathy

Adenopathy of less than four weeks duration

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Epstein–Barr virus Cytomegalovirus Parvovirus B19 <i>Toxoplasma gondii</i> HIV	<i>Bartonella henselae</i>	

Adenopathy of more than four weeks duration and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Toxoplasma gondii</i> <i>Mycobacterium tuberculosis</i> Nontuberculous mycobacteria spp.	CMV <i>Mycobacterium avium</i> complex

If the diagnosis is not made within a few days, biopsies should be performed to exclude malignancies like lymphoma and carcinomas.

Fever without focal symptoms

Fever less than four weeks without focal symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Endocarditis	<i>Mycobacterium tuberculosis</i>	
Epstein–Barr virus	<i>Coxiella burnetii</i> *	
Cytomegalovirus	<i>Bartonella henselae</i>	
Parvovirus B19	Leptospirosis	
<i>Toxoplasma gondii</i>	<i>Rickettsial</i> spp.	
HIV	Dengue virus	
	<i>Brucella suis</i>	

*Q-fever has not been reported from New Zealand.

Fever for more than four weeks without focal symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Toxoplasma gondii</i> <i>Mycobacterium tuberculosis</i>	CMV

All patients with adenopathy should have a CT or MR scan of the thorax and abdomen performed soon to determine the extent of the adenopathy and to enable decision of the best approach to biopsy. PET-CT will provide clues for inflammatory foci and malignancies. Noninfectious causes like lymphoma, other malignancies, and autoimmune diseases should be considered early.

Eosinophilia and elevated IgE

Eosinophilia and elevated IgE for less than four weeks

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
	<i>Toxocara</i> spp. <i>Ascaris lumbricoides</i> , <i>Trichuris trichiura</i> , hookworm <i>Strongyloides stercoralis</i>	<i>Fasciola hepatica</i>

Eosinophilia and elevated IgE for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Ascaris lumbricoides</i> , <i>Trichuris trichiura</i> , hookworm <i>Strongyloides stercoralis</i>	<i>Toxocara</i> spp.

Basic diagnostics in patients with eosinophilia and elevated IgE

Microorganism	Diagnostics
<i>Ascaris lumbricoides</i> , <i>Trichuris trichiura</i> , hookworm <i>Toxocara</i> spp. <i>Strongyloides stercoralis</i> <i>Fasciola hepatica</i>	Fecal microscopy Serology Fecal microscopy, serology Fecal microscopy, serology, imaging

Antibiotic resistance

Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is not an infrequent cause of *S. aureus* infections in patients presenting to medical practitioners and hospitals. The spectrum of infections includes skin and soft tissue infections, bacteremia, and community-acquired pneumonia. The highest rates have been reported from Western Australia, the Northern Territory and Queensland, but CA-MRSA skin infections have now also been reported from Brisbane, Sydney, Canberra, and Melbourne. In Western Australia, the notification rate for CA-MRSA in the metropolitan areas of Perth is as high as 144/100 000 population. In Darwin, CA-MRSA has accounted for up to 20% of community-onset *S. aureus* bacteremias, with a substantial proportion of patients having infective endocarditis. National surveillance has shown significant increases in the proportion of CA-MRSA isolates over the last 10–15 years. The most frequent clonal isolates have included ST1-MRSA-IV (Western Australia, Northern Territory, and South Australia) followed by ST93-MRSA-IV (Queensland and New South Wales) and ST30-MRSA-IV (Northern Territory, Queensland, and New South Wales). ST129-MRSA-IV and ST5-MRSA-IV are most frequently encountered in Victoria, Tasmania, and Western Australia [25].

Although cases of high-level penicillin-resistant *Pneumococcus* causing pneumonia or meningitis have been reported, they are infrequent (<5%). ESBL and MBL gram-negative infections are also uncommon and are seen almost exclusively as nosocomial infections or in travelers returning from areas such as South and South-east Asia.

Vaccine-preventable diseases in children

Australia has a national immunization program schedule (funded by the Australian government) which currently includes vaccines against a total of 16 diseases. There is also an Australian Childhood Immunization Register (the ACIR), which aims to provide (i) an accurate measure of the immunization

coverage of children in Australia under seven years of age and (ii) an effective management tool for monitoring immunization coverage and service delivery. The childhood vaccination schedule consists of the vaccines listed below [26] and over 90% of children are fully vaccinated.

- Birth: hepatitis B
- 2, 4, and 6 months: diphtheria, tetanus, pertussis, polio, Hib, hepatitis b, pneumococcal, rotavirus
- 12 months: measles, mumps, rubella, Hib, meningococcal C
- 18 months: varicella, measles, mumps, rubella
- 12–24 months: hepatitis A and pneumococcal polysaccharide (23vPPV) (only for Aboriginal and Torres Strait Islander children in high-risk areas)
- 4 years: diphtheria, tetanus, pertussis, polio (plus measles, mumps, rubella if not given previously)
- 10–15 years: diphtheria, tetanus, pertussis, human papillomavirus, varicella

The NZ national immunization schedule (New Zealand Ministry of Health, 2006, 2008) currently includes vaccines against a total of 13 diseases offered free to babies, children, adolescents, and adults. NZ also has a National Immunization Register. Approximately 93% of children are fully immunized by two years of age [27].

- 6 weeks, 3 and 5 months: diphtheria, tetanus, acellular pertussis, polio, *Haemophilus influenzae* type b, hepatitis B
- 6 weeks, 3 and 5 months: rotavirus
- 6 weeks, 3 and 5 and 15 months: 13-valent pneumococcal conjugate vaccine
- 15 months: *Haemophilus influenzae* type b
- 15 months: measles, mumps, rubella
- 4 years: measles, mumps, rubella, diphtheria, tetanus, acellular pertussis
- 11 years: tetanus, diphtheria, acellular pertussis
- 12 years (girls only): human papillomavirus (three doses)
- 45 and 65 years: adult tetanus and diphtheria
- All adults 65 years and over and high-risk other groups: seasonal influenza[xbl]

There are additional scheduled vaccines offered.

- BCG to babies who will be living in a household or family with a person with either current TB or a past history of TB, have one or both parents who are of Pacific ethnicity, have parents or household members who, within the past five years, lived for a period of six months or longer in a country with a high incidence of TB, during their first five years will be living for three months or longer in a country with a high incidence of TB.
- Babies of HBsAg-positive mothers need HBIG and hepatitis B vaccine at birth; then they continue with the usual schedule at six weeks, three and five months.
- Women of childbearing age who are nonimmune to rubella are offered the MMR vaccine.

Basic economic and demographic data*

	GNI per capita (USD)	Life expectancy at birth (total, years)	School enrollment, primary (% net)
Australia	40 350	81	97
New Zealand	27 940	80	99

*World Bank (www.worldbank.org)
GNI, gross national income.

Causes of death in children under five in Australia*

	%
Neonatal causes	56
Pneumonia	1
Diarrheal diseases	0
Malaria	0
HIV/AIDS	0
Measles	0
Injuries	11
Others	

*WHO 2006. www.who.int/whosis/mort/profiles/en/#P

Most common causes of deaths all ages in Australia

	%
Ischemic and hypertensive heart disease	20
Cerebrovascular disease	9
Lower respiratory infections	2
Perinatal conditions	NS
Tuberculosis	NS
Diarrheal disease	NS
Measles	NS
Chronic obstructive lung disease	4
Malnutrition	NS
Diabetes	3
Alzheimer's and other dementias	3
Nephritis and nephrosis	NS
Cancers	14
Asthma	NS
Endocrine disorders	NS

NS, not stated.

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Chapter 26

Oceania

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- American Samoa
- Cook Islands
- Fiji
- Guam
- Kiribati
- Marshall Islands
- Micronesia (Federated States of)
- Northern Mariana Islands
- New Caledonia
- Nauru
- Niue
- Palau
- Papua New Guinea
- Pitcairn
- Samoa
- Solomon Islands
- Tahiti (French Polynesia)
- Tonga
- Tuvalu
- Vanuatu
- Wallis and Futuna

Oceania comprises over 20 countries with differing levels of healthcare, socioeconomics, disease surveillance, and intensity of various infections. Whereas some risks occur throughout the region, such as travelers' diarrhea, there is marked nonuniformity in the risks of other diseases. This is well highlighted by malaria: most Oceanic countries pose no malaria risk, but the Solomon Islands, Papua New Guinea, and Vanuatu have high intensity of both *P. falciparum* and *P. vivax* malaria. There is likely to be underreporting by many countries in the region regarding malaria and other monitored diseases, but information regarding specific diseases that are reported has been summarized in the text and tables below to indicate where in the region infectious diseases risks are likely to be greatest.

Bacterial and mycobacterial infections

Travelers diarrhea is a frequent problem for travelers to Oceania, often due to bacterial pathogens (enterotoxigenic *E. coli*, *Campylobacter* spp., *Salmonella* spp., *Shigella* spp.). Cholera is uncommon, but sporadic cases and outbreaks are reported, particularly in Papua New Guinea (PNG). Typhoid fever also occurs; Fiji, Tonga, and Samoa in particular have reported a significant number of typhoid cases in recent years.

Cases of yaws still occur in some parts of Oceania. Eradication campaigns have strongly reduced the geographic extension and global burden, with a few resisting foci of cases occurring in PNG, Solomon Islands, and Vanuatu [1–3].

Melioidosis has been reported from the Western Province of PNG, with most cases occurring in children. Cases of melioidosis have also recently been reported from the Northern Province of New Caledonia [4].

Scrub typhus, caused by *Orientia tsutsugamushi* and transmitted by a chigger bite, has been reported from PNG. The remaining regions of Oceania have traditionally been thought of as being relatively free of rickettsial infections [5–7]. However, a recent study reviewing human case reports, human serosurveys, and PCR-based testing of vectors and host animals for both *Rickettsia* spp. and *O. tsutsugamushi* within the Oceania region suggested widespread distribution of these pathogens, thus implying a significantly higher burden of disease in Oceania than is currently appreciated [8].

Cat scratch disease, caused by *Bartonella henselae*, occurs throughout Oceania and is transmitted by the bite or scratch of domestic cats.

Leptospirosis is endemic in much of Oceania, with occurrence of both sporadic cases and outbreaks [9]. In particular, New Caledonia, Wallis and Futuna, American Samoa, French Polynesia, and PNG have reported this infection [10–12]. An investigation in livestock found a dominance of serovar *hardjo*, whilst the dominant presumptive serovars in other regions of Oceania were *L. icterohaemorrhagiae* and *australis*, indicating linkage to a rodent reservoir [12]. Foci of leptospirosis have also been described in Fiji, Vanuatu, Palau, Guam, the Commonwealth of the Northern Mariana Islands, and the Federated States of Micronesia.

The overall prevalence of tuberculosis varies throughout Oceania, from about 20/100 000 population to over 400/100 000 population. The country with the highest prevalence in the region is Papua New Guinea, with an estimated prevalence of about 420/100 000. For Fiji, the Cook Islands, Samoa, Guam, French Polynesia, Tonga, and New Caledonia, the prevalence is about 20–40/100 000 [13]. Drug resistance is an emerging problem, especially in Papua New Guinea.

Leprosy is endemic in most countries within Oceania, although underreporting makes exact prevalence rates difficult to determine. Reported rates are highest in PNG, Micronesia, Kiribati, and Marshall Islands [14].

In the Asia-Pacific region, *Mycobacterium ulcerans* infection is most commonly reported from PNG. The majority of cases occur in children 15 years of age or younger and infection in travelers to these regions has been reported [15,16].

Acute rheumatic fever (ARF) continues to be a huge public health burden on many Pacific Island countries [17–20]. Prevalence rates of rheumatic heart disease (RHD) are high in Samoa (77.8/1000), Tonga (30/1000), the Cook Islands (18.5/1000), and New Caledonia (10/1000). Indigenous Fijians are also disproportionately affected. ARF incidence data suggest the following: 113–236/100 000 in French Polynesia, 98/100 000 in New Caledonia, and 206/100 000 in Samoan children. RHD causes around 115 000 deaths per year in the Western Pacific Region [20].

Viral infections

Hepatitis A infection occurs in the region, and outbreaks are intermittently reported. Hepatitis E may be endemic in some countries, but levels of endemicity are unknown. Hepatitis B is endemic throughout the Pacific region, with HBsAg carrier rates above 8% for most countries and islands in the region. However, chronic carrier rates have started to decline since the introduction of HBV vaccination programs.

It is estimated that 0.4% of the adult population of Oceania is living with HIV/AIDS, with the highest incidence occurring in PNG (estimate of 0.7% of adults aged 15–49), according to the 2013 UNAIDS report [21]. Heterosexual transmission is the predominant means of infection [22].

Dengue is reported from most countries in Oceania, and the number of cases reported annually has varied widely in recent years (1975 cases (incidence 6/100000 population) in 2004 to 13959 (39.5/100000) in 2009 and 1902 (5.3/100000) in 2010) [23]. Highest rates are reported from French Polynesia, Fiji, American Samoa, Cook Islands, PNG, New Caledonia, and Tonga. Outbreaks have also been reported from Kiribati, Micronesia, Nauru, Palau, Samoa, Solomon Islands, Marshall Islands, and Vanuatu. Given that reported cases are undoubtedly an underestimation of the true number of cases, travelers visiting Oceania are at risk of infection, especially during the rainy seasons.

Chikungunya virus has recently emerged in the region, with many large outbreaks occurring in the last few years affecting over half the countries in the Pacific Islands, including the Cook Islands, Kiribati, Samoa, American Samoa, New Caledonia, Nauru, Tonga, Micronesia, French Polynesia, Fiji, and Marshall Islands [24]. As with dengue, cases are likely underestimated, and given the pace of spread in both the Pacific and other global areas, it must be presumed that travelers to the region in general are at risk regardless of whether or not chikungunya has been officially reported in the specific country being visited.

Japanese encephalitis has been reported from Palau, Guam, and the Northern Mariana Islands since 1990 [25]. This zoonotic flavivirus has spread down through the Indonesian archipelago to Papua New Guinea (as well as to the Torres Strait of northern Australia) [26].

Ross River virus is a mosquito-transmitted alphavirus that is endemic and enzootic in Australia and PNG. It has also been reported to cause large epidemics in Fiji, New Caledonia, Samoa, and the Cook Islands in the South Pacific [27,28].

Murray Valley encephalitis (MVE) has been reported from PNG. The virus in PNG is closely related to MVE in Australia although separate foci of MVE evolution and greater strain variation exist in PNG [29].

Zika virus is a flavivirus that was first isolated in 1947 from a rhesus monkey in the Zika Forest near Entebbe, Uganda [30]. No transmission of Zika virus had been reported outside Africa and Asia until 2007, when physicians in the Federated States of Micronesia reported an outbreak of illness characterized by rash, conjunctivitis, subjective fever, arthralgia, and arthritis. The virus emerged unexpectedly on the island of Yap and adjoining islands of Ulithi, Fais, Earpik, Woleai, and Ifalik with over 150 cases [2]. Over the last few years it has also emerged in Vanuatu, New Caledonia, French Polynesia, the Solomon Islands, Easter Island, American Samoa, Fiji, Samoa, Marshall Islands, Papua New Guinea, Palau, Tonga, and Cook Islands, with occurrence of large outbreaks in some areas [24]. It is transmitted to humans by infected *Aedes* mosquitoes [31,32]. Prominence of this arbovirus in Oceania in recent years demands a presumption that travelers to the region are, in general, at risk of contracting the disease independently of whether or not Zika is reported in the visited country.

All countries in Oceania are considered rabies free, although for many areas there is minimal surveillance.

Parasite infections

The soil-transmitted helminths hookworm, *Ascaris lumbricoides*, and *Trichuris trichiura* are common and represent a significant public health problem in many countries of Oceania, particularly in rural and small village settings of Fiji, Vanuatu, Solomon Islands, and PNG [11]. While school-based deworming efforts have been scaled up in many countries, travelers who have walked barefoot may still be at particular risk of infection. *Strongyloides stercoralis* infection is also endemic in many regions.

Both *falciparum* and *vivax* malaria are present in three Oceanic countries: PNG, Solomon Islands, and Vanuatu. In PNG, malaria occurs in areas below <1800m, and increased risk occurs along coastal areas and in the lowlands, especially during the wetter months (December through February). In the Solomon Islands and Vanuatu, malaria occurs countrywide, including in many urban areas. *Vivax* malaria from Oceania is becoming increasingly resistant to chloroquine, precluding its use as a first-line therapy for *vivax* malaria acquired in this region. Reduced susceptibility to primaquine is also common.

Lymphatic filariasis is a major public health problem in many countries in Oceania, caused by infection with either *Wuchereria bancrofti* or *Brugia malayi*. Adult worms develop in the lymphatic vessels, causing severe damage and swelling, and in late stages painful, disfiguring swelling of the legs and genital organs (elephantiasis). Countries endemic for filariasis include PNG, Niue, Tonga, Vanuatu, Fiji, French Polynesia, New Caledonia, Samoa, Cook Islands, American Samoa, Nauru, Tuvalu, Kiribati, and the Solomon Islands, with most of the people at risk being in PNG. In recent years, efforts to eliminate the disease through annual mass drug administration have been carried out in most of the endemic countries. Short-term travelers are usually at very low risk of infection.

Infection due to *Angiostrongylus cantonensis*, the rat lungworm, occurs in Oceania, and has in particular been reported from PNG [33]. It is acquired by eating contaminated leafy vegetables (in salads), infected snails and slugs, and land crabs. Symptoms include paresthesiae and eosinophilic meningitis.

The major intestinal protozoan infections in Oceania are amebiasis, balantidiasis, cryptosporidiosis, and giardiasis. Epidemic foci of *Balantidium coli* infection have been reported from swine-producing areas of PNG, and an outbreak of balantidiasis was described after a typhoon on Truk resulted in contamination of ground and surface water with pig feces. Giardiasis is also common in populations in Oceania, and diarrhea secondary to the infection and that of *Entamoeba histolytica* also occurs [11].

Oceania is free of human schistosomiasis.

In addition to specific infectious outcomes listed, travelers also need to be aware of the risks of toxins, envenomations, and bites (spiders and snakes). Safety of blood supplies is not guaranteed.

CNS infections: meningitis, encephalitis, and other infections with neurological symptoms

Acute infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
Viral meningitis (enterovirus group)	<i>Listeria monocytogenes</i>	<i>Naegleria</i> and other free-living amoeba
Pneumococcal meningitis	Neurosyphilis	Influenza
Herpes virus (group I and II)	HIV	<i>Burkholderia pseudomallei</i>
<i>Neisseria meningitidis</i>	MVE	Japanese encephalitis
		<i>Angiostrongylus cantonensis</i>

CNS infections: meningitis and encephalitis with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
HIV <i>Mycobacterium tuberculosis</i>	<i>Nocardia</i> spp. Polyomavirus <i>Cryptococcus</i> spp. [†] JC virus

* Consider noninfectious causes like vasculitis and lymphoma.

[†] In PNG, *Cryptococcus gattii* infection occurs relatively more frequently than *Cryptococcus neoformans*.

Ear, nose, and throat infections

Ear, nose, and throat infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Streptococcal throat infection	Peritonsillar abscess*	
Epstein–Barr virus	Tuberculosis	
Herpes virus (type I and II)	Diphtheria†	

* Requires acute ENT evaluation.
 † Papua New Guinea has more diphtheria cases than other countries in the region.

Ear, nose, and throat with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i>	<i>Candida</i> spp. Herpes simplex virus

* Consider noninfectious causes like vasculitis and lymphoma.

Cardiopulmonary infections

Pneumonia with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Streptococcus pneumoniae</i> pneumonia	<i>Legionella</i>	<i>Corynebacterium diphtheriae</i>
<i>Mycoplasma pneumoniae</i>	Influenza	<i>Burkholderia pseudomallei</i> Tropical pulmonary eosinophilia

Endocarditis with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Staphylococcus aureus</i>	<i>Neisseria gonorrhoeae</i>	<i>Bartonella</i> spp.
Nonhemolytic streptococci	<i>Coxiella burnetii</i>	
Coagulase-negative staphylococci (<i>S. epidermidis</i>)	<i>Propionibacterium</i> spp.	
<i>Streptococcus pneumoniae</i>	HACEK group*	
<i>Enterococcus</i> spp.		

*HACEK is an abbreviation of the initials of the genera of a group of gram negative bacteria: Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella.

Pulmonary symptoms for more than four weeks and in the immunocompromised host*

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i> <i>Aspergillus</i> spp.	<i>Pneumocystis jiroveci</i> CMV <i>Aspergillus</i> spp., <i>Candida</i> spp.
* Consider noninfectious causes: lung cancer, autoimmune lung fibrosis, Wegener's granulomatosis.	

Endocarditis for more than four weeks and in the immunocompromised host*

Microorganisms and diseases with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Coagulase-negative staphylococci (<i>S. epidermidis</i>) Nonhemolytic streptococci <i>Coxiella burnetii</i> <i>Bartonella</i> spp.	<i>Aspergillus</i> spp.
* Consider noninfectious causes like sarcoidosis.	

Gastrointestinal infections

Gastrointestinal infections with less than four weeks of symptoms*

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Norovirus, calicivirus, rotavirus <i>Campylobacter</i> VTEC, ETEC <i>Giardia intestinalis</i> <i>Salmonella</i> (non-typhi) <i>Salmonella typhi</i> <i>Shigella</i> Enteropathogenic <i>E. coli</i> <i>Enterobius vermicularis</i> <i>Strongyloides stercoralis</i> Hookworm <i>Ascaris lumbricoides</i> <i>Trichuris trichiura</i> <i>Entamoeba histolytica</i> Hepatitis A virus	<i>Cryptosporidium</i> spp. <i>Staphylococcus aureus</i> toxin <i>Bacillus cereus</i> toxin <i>Vibrio cholerae</i>	<i>Mycobacterium tuberculosis</i> <i>Tropheryma whipplei</i>
* Consider noninfectious causes like inflammatory bowel disease and intestinal malignancies like colon cancer.		

Diarrhea is often associated with infections with bacteria, viruses, and parasites. Repeated negative bacterial cultures and microscopy for parasites should lead to the consideration that the symptoms may not be caused by an infection. Inflammatory bowel diseases like ulcerative colitis and Crohn's disease are part of the differential diagnosis and malabsorption syndromes and celiac disease must also be considered.

Gastrointestinal infections with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i> <i>Tropheryma whipplei</i> <i>Blastocystis hominis</i> † <i>Dientamoeba fragilis</i> † <i>Entamoeba histolytica</i> <i>Enterobius vermicularis</i> <i>Strongyloides stercoralis</i> Hookworm <i>Ascaris lumbricoides</i> <i>Trichuris trichiura</i>	<i>Candida</i> Herpes virus <i>Strongyloides stercoralis</i>
*Consider noninfectious causes like inflammatory bowel disease, intestinal malignancies like colon cancer, malabsorption and celiac disease. †Of uncertain pathogenicity in humans.	

Infections of liver, spleen, and peritoneum

Acute infections of liver, spleen, and peritoneum with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
Hepatitis A Hepatitis B Hepatitis C Hepatitis E* <i>Entamoeba histolytica/dispar</i>	Hydatid infection due to <i>Echinococcus granulosus</i>	<i>Fasciola hepatica</i>
*Hepatitis E is probably present, but has not been reported so far.		

Chronic infections of liver, spleen, and peritoneum with more than four weeks of symptoms

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i> <i>Tropheryma whipplei</i>	

Infections in the immunocompromised host are generally similar to those in the immunocompetent host.

Genitourinary infections

Cystitis, pyelonephritis, and nephritis with less than four weeks of symptoms*

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>E. coli</i> <i>Klebsiella pneumoniae</i>		<i>Mycobacterium tuberculosis</i>
Consider noninfectious causes, especially malignancies like renal cell carcinoma.		

Sexually transmitted infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Chlamydia</i> spp. <i>Neisseria gonorrhoeae</i>	L-serovars of <i>Chlamydia trachomatis</i> (lymphogranuloma venereum)	

Cystitis, pyelonephritis, and nephritis with symptoms for more than four weeks and in the immunocompromised host*

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
Bacterial infections in patients with long-term catheters and renal stones <i>Mycobacterium tuberculosis</i>	<i>Candida</i> spp.
* Consider noninfectious causes, especially malignancies like renal cell carcinoma.	

Sexually transmitted infections with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Treponema pallidum</i>	Lymphogranuloma venereum

Joint, muscle, and soft tissue infections

Joint, muscle, and soft tissue infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Staphylococcus aureus</i>	Necrotizing fasciitis	Fournier's gangrene
<i>Streptococcus pneumoniae</i>	Group G streptococci	(perineum and urogenital)
Ross River virus		<i>Trichinella</i> species (<i>T. papuae</i>)*

* *T. papuae* is found in Papua New Guinea in domestic and feral pigs and can cause human infection.

Joint, muscle, and soft tissue infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Mycobacterium tuberculosis</i>	<i>Candida</i> spp.

Skin infections

Skin infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Erysipelas, <i>Streptococcus pneumoniae</i>	Scabies	Cutaneous diphtheria
<i>Staphylococcus aureus</i>	Cutaneous larva migrans	Lepa*

* Reported from Papua New Guinea.

We have not listed a rash due to viral infections as this is not considered an infection limited to the skin.

Skin infections with more than four weeks of symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Treponema pallidum</i> <i>Mycobacterium tuberculosis</i> <i>Mycobacterium leprae</i> <i>Mycobacterium ulcerans</i> Yaws Dermatophytes	<i>Candida</i> spp.

Adenopathy

Adenopathy of less than four weeks duration

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Epstein–Barr virus Cytomegalovirus Parvovirus B19 <i>Toxoplasma gondii</i> HIV	<i>Bartonella</i> spp.	

Adenopathy of more than four weeks duration and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Toxoplasma gondii</i> <i>Mycobacterium tuberculosis</i> Lymphatic filariasis	CMV Atypical mycobacteria

If the diagnosis is not made within a few days, biopsies should be performed to exclude malignancies like lymphoma and carcinomas.

Fever without focal symptoms

Fever for less than four weeks without focal symptoms

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Epstein–Barr virus Cytomegalovirus	<i>Mycobacterium tuberculosis</i> <i>Coxiella burnetii</i>	Zika virus

(Continued)

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
Parvovirus B19 <i>Toxoplasma gondii</i> HIV Dengue virus Malaria Enteric fever Influenza virus Chikungunya virus Zika virus	<i>Bartonella</i> spp. Leptospirosis <i>Rickettsia</i> , <i>Orientia</i> Hepatitis A Amebic liver abscess	

Fever for more than four weeks without focal symptoms and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
HIV <i>Mycobacterium tuberculosis</i>	CMV

Noninfectious causes should be considered from the beginning, including malignancies like lymphoma and autoimmune diseases.

Eosinophilia and elevated IgE

Eosinophilia and elevated IgE for less than four weeks

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms and conditions
<i>Ascaris lumbricoides</i> , <i>Trichuris trichiura</i> , hookworm Filariasis, tropical pulmonary eosinophilia <i>Strongyloides stercoralis</i>	<i>Toxocara</i> spp.	<i>Trichinella spiralis</i>

Eosinophilia and elevated IgE for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
<i>Ascaris lumbricoides</i> , <i>Trichuris trichiura</i> , hookworm <i>Strongyloides stercoralis</i> Filariasis, tropical pulmonary eosinophilia	<i>Toxocara</i> spp.

Antibiotic resistance

Penicillin-resistant *Streptococcus pneumoniae* is prevalent in parts of Oceania, especially in PNG; this should be taken into account when travelers develop pneumonia or meningitis.

Vaccine-preventable diseases in children

Vaccine schedules for Oceania are similar for all countries in the region, with primary prevention against the following diseases being a focus: tetanus, diphtheria, hepatitis B, *Haemophilus influenzae* type b (Hib), pertussis, measles, mumps, rubella, polio, and tuberculosis. Vaccine coverage rates in the Western Pacific for hepatitis B are as high as 92%, 97% for polio, and 92% for measles but only 27% for Hib [34]. Specific data can be extracted from the WHO Vaccine Preventable Diseases Monitoring System Global Summary (http://apps.who.int/immunization_monitoring/en/globalsummary/countryprofileselect.cfm).

Basic economic and demographic data*

	GNI per capita (USD)	Life expectancy at birth (total, years)	School enrollment, primary (% net)
American Samoa	NA	NA	NA
Cook Islands	NA	NA	NA
Fiji	3930	69	91
Guam	NA	76	NA
Kiribati	2000	61	97
Marshall Islands	3270	65	66
Micronesia (Federated States of)	2340	69	NA
Nauru	NA	NA	NA
New Caledonia	14020	76	NA
Niue	NA	NA	NA
Northern Mariana Islands	NA	NA	NA
Palau	8650	69	96
Papua New Guinea	1010	57	NA
Pitcairn	NA	NA	NA
Samoa	2780	72	90
Solomon Islands	1180	64	62
Tahiti (French Polynesia)	NA	NA	NA
Tonga	2560	72	96
Tuvalu	NA	NA	NA
Vanuatu	2870	70	87

*World Bank (www.worldbank.org).
GNI, gross national income; NA, not available.

Causes of death in children underfive in Papua New Guinea and Fiji*

	%	
	Papua New Guinea	Fiji
Neonatal causes	35	41
Pneumonia	18	9
Diarrheal diseases	15	11
Malaria	1	0
HIV/AIDS	0	0
Measles	2	0
Injuries	2	3
Others	25	36

*WHO. Regional average, 2000–03 (www.who.int/whosis/mort/profiles/en/#P).

Most common causes of deaths all ages* in Papua New Guinea and Fiji

	%	
	Papua New Guinea	Fiji
Ischemic and hypertensive heart disease	11	20
Cerebrovascular disease	4	13
Lower respiratory infections	8	5
Perinatal conditions	10	3
Tuberculosis	7	NS
Diarrheal disease	5	NS
Measles	2	NS
Chronic obstructive lung disease	2	2
Malnutrition	2	NS
Diabetes	NS	4
Alzheimer's and other dementias	NS	NS
Nephritis and nephrosis	NS	4
Cancers	NS	NS
Asthma	NS	3
Endocrine disorders	NS	2

NS, not stated.

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Chapter 27

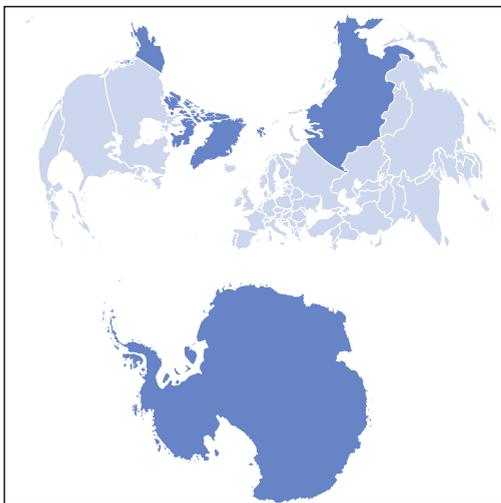
Arctic and Antarctica

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Alaska (United States)
Greenland (Home Rule/Denmark)
Northern Canada (Nunavut, Nunavik,
Northwest Territories, Yukon)
Siberia (Russian Federation)
Svalbard (Norway) Antarctica

Arctic parts of Russia (Siberia), Alaska, Canada, and Greenland are characterized by indigenous populations living in small isolated settlements where household crowding is high. People living in Svalbard and the Antarctic are predominantly Caucasians. The main infectious diseases that occur in excess numbers in indigenous populations in the Arctic compared with Northern European/American populations include invasive bacterial diseases caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*, tuberculosis, chronic otitis media, respiratory tract infections including RSV and influenza, hepatitis B virus infection, sexually transmitted infections, *Helicobacter pylori* infection, parasitic infections such as giardiasis and toxoplasmosis, and bacterial zoonoses such as tularemia. Infectious disease patterns in people living in Svalbard and Antarctica mainly reflect those of their native countries.

The regions

The Arctic denotes the northern “top of the world.” While no uniform definition of “Arctic” exists, the treeline, the 10° July isotherm, and the line of continuous permafrost have been used interchangeably to refer to this region. This covers most of Alaska, northern Canada, Greenland, Svalbard, Siberia, Iceland, and the northern portions of Sweden, Norway, and Finland.

The Arctic and Antarctic regions are characterized by sparse populations living in small, isolated settlements which tend to have crowded households. Arctic regions of Alaska, Canada (Nunavut, Nunavik, Northwest Territories and Yukon), Siberia, and Greenland are populated by indigenous populations and also Caucasians mostly originating from their southern counterparts (USA, Canada, Russia, and Denmark, respectively). Although there are regional differences, living conditions and disease patterns for these populations are relatively comparable. The population of Svalbard mainly consists of northern Europeans. Iceland and northern portions of Sweden, Norway, and Finland are populated by Caucasians and health conditions are described in the Northern Europe chapter. In the following, “Arctic” refers to Alaska, northern Canada, Greenland, Svalbard, and Siberia.

Most health facilities in the Arctic (hospitals, etc.) are small, geographically separated by large distances, and often served by staff on short-term contracts. Diagnostic capacity is often lacking, and when laboratories are available, services are frequently limited to basic clinical chemistry and microbiology. Laboratories must also contend with long distances over which specimens must be transported, which can result in poor survival of bacterial specimens, lower culture positivity rates, and delayed reporting of results back to healthcare providers. Furthermore, the actual numbers of infectious disease cases across the Arctic are small relative to other regions of the world, due in large part to limited populations. Health statistics from Arctic regions are often lacking or are very sparse when compared to their southern counterparts (e.g. southern USA, southern Canada, and Denmark for Greenland).

Scientific studies on infectious diseases in Arctic regions inhabited by indigenous people are most often performed on high-incidence diseases. A number of infectious diseases such as invasive disease caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*, tuberculosis, chronic otitis media, hepatitis B virus, sexually transmitted infections, *Helicobacter pylori*, parasitic infections, and bacterial zoonoses occur at higher rates in Arctic regions than in their southern counterparts. While firm knowledge exists on the epidemiology of these particular diseases in the Arctic, our understanding of less common diseases is limited.

There is much travel between northern Europe and Greenland, and between Arctic and subarctic areas in Alaska, Canada, and Siberia. Correspondingly, many pathogens that appear in northern Europe exist in Arctic areas too.

The following chapter describes infections with known high prevalence in the Arctic regions of Alaska, Canada, Greenland, and Siberia and will be viewed as supplementing the Northern Europe, Northern America, and Russian Federation chapters. Among the Arctic countries, there is far more information on infectious diseases available for Alaska, Canada, and Greenland than for Siberia.

Knowledge on infectious diseases in the immunocompromised host for this region is limited.

The infectious disease patterns for persons living in and traveling to Svalbard and the Antarctic reflect those of their corresponding populations (e.g. Norway for Svalbard and countries of origin for persons traveling to the Antarctic). For these regions please see relevant chapters.

Diagnostic principles for infectious diseases in Arctic regions are identical to those of Western countries, except that access to microbiological laboratories, X-ray and other diagnostic facilities is limited due to long distances and low numbers of such facilities. Diagnostic work-up will therefore not be described in this chapter.

Risk for travelers

Virtually no information is available specifically regarding infectious disease risk in persons traveling to Arctic areas. For the same reason, national travel recommendations from a range of Western countries span from no advice regarding specific vaccinations to consider vaccination against hepatitis A and B,

tuberculosis, rabies, diphtheria, and tetanus. While hepatitis A infection is no longer endemic in the Arctic, the presence of hepatitis B infection, tuberculosis, and rabies in humans and wildlife may, for persons with longer stay and/or at special risk such as health workers or persons with exposure to wildlife, warrant vaccination against these agents. Updated protection against diphtheria and tetanus is recommended for travel anywhere in the world, although no specific figures for the risk for these diseases in Arctic areas exist. In addition to vaccine-preventable diseases, a range of sexually transmitted infections may pose risks to travelers, as may contact with wildlife and handling or consumption of raw or fermented game meat and fish.

Important infections in the Arctic [1]

Invasive disease and respiratory agents

Invasive pneumococcal disease (IPD) is a leading cause of pneumonia, septicemia, meningitis, and other invasive diseases (e.g. endocarditis, cellulitis, and septic arthritis), with incidence rates being higher among indigenous persons compared with nonindigenous persons [2,3]. In addition, otitis media that may be caused by *S. pneumoniae* is highly prevalent in Arctic indigenous populations [4]. Vaccine campaigns with the 7-valent (PCV7) then 13-valent pneumococcal conjugate vaccine (PCV13) have markedly reduced rates of vaccine type IPD across many Arctic countries, and the increase in invasive disease caused by nonvaccine serotypes observed after use of PCV7 [2] has not yet been observed in the post-PCV13 period [5].

Rates of invasive disease caused by *Haemophilus influenzae* type b (Hib) among native populations of the northern American Arctic were among the highest in the world, but decreased markedly after vaccine introduction in the 1980s and 1990s. However, serotype replacement with non-type B strains has resulted in epidemics of *H. influenzae* serotype A [6–8]. Common manifestations of invasive *H. influenzae* disease include meningitis, pneumonia, and septic arthritis.

Indigenous people of the north American Arctic suffer disproportionately from bacterial meningitis caused by *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae* [9].

Respiratory syncytial virus (RSV) is particularly incident among Canadian and Alaskan indigenous infants [10–12].

Alaskan indigenous people have an average of 2–3-fold higher mortality rates due to seasonal pneumonia and influenza than nonindigenous Alaskans [13,14].

Increased crowding, especially during colder fall and winter months, may facilitate transmission of respiratory pathogens [15]. Increased rates of pandemic influenza A H1N1 (pH1N1) were documented in indigenous populations of Canada and Alaska in 2009 [16,17].

Tuberculosis

While tuberculosis was the single major cause of morbidity and mortality in Arctic regions in the first part of the twentieth century [18], the incidence fell markedly following massive targeted efforts in Alaska, Arctic Canada, and Greenland; lowest incidence rates were reached in the 1980s. However, in the 1990s TB incidence increased from about 30 to more than 100/100 000 in Greenland and since then, the incidence has remained high, ranging from 106 to 205/100 000 person-years [19]. In a recent outbreak in East Greenland, the local incidence increased in 2011 to more than 1600/100 000 [20]. Today, rates of TB are markedly higher in Arctic areas than in their southern counterparts. In Alaska, TB incidence is highest among the states of the USA, with the highest rates among Alaskan natives [21]. In Canada, the Inuit have the highest reported incidence (156/100 000) whereas Metis and American Indians experience incidences <10/100 000 [22]. Drug resistance is rare in most Arctic regions [23] but in Siberia where TB incidence rates are similarly high as in Greenland, multidrug-resistant TB is a considerable public health problem [24]. BCG vaccination, that is part of the national childhood vaccination program in Greenland, has been shown to reduce the risk of both tuberculosis infection and disease in Greenlanders [25].

Viral hepatitis

Viral hepatitis is frequent in the Arctic. Hepatitis A virus (HAV) infection tends to occur in epidemics, the latest in Greenland in 1970–4 with 11% of the population developing clinical hepatitis [26], and in Canada in 1991–2 when 20% of children aged 2–20 years in affected communities developed clinical hepatitis [27]. Serosurveys show that 50–70% of Arctic indigenous populations have been exposed to HAV. In 1992, a vaccine campaign among young persons living in one of 25 Alaska villages was able to stop an epidemic within three weeks, and later introduction of HAV to the childhood vaccine program markedly reduced the incidence [28].

Hepatitis B virus (HBV) infection is endemic in Arctic populations. Serosurveys have shown rates of HBV exposure and chronic infection, respectively, of 42–75% and 7–20% of the population of Greenland 1965–2008, and 25% and 5% of the population of Canada 1980–99 [1]. Rates of chronic infection of 6–14% among Alaskan indigenous peoples led Alaska to introduce statewide vaccination programs in 1984, leading to a dramatic reduction in the incidence of clinical hepatitis in affected populations [29]. In 2001, hepatitis B vaccination was included in the childhood vaccination program in Canada and in 2010 in Greenland. Chronic HBV infection is associated with increased risk of cirrhosis and liver cancer. In Greenland, HBV infection is similarly associated with increased risk of these diseases, but for unknown reasons at lower rates than expected. In contrast to other high-incidence countries, where neonatal transmission is substantial, in Greenland HBV appears primarily to be transmitted in adolescence and adulthood, which may partly explain the lower risk of long-term sequelae [30]. Superinfection with hepatitis D is common in Greenland [31] and Siberia, but rare in Canada and Alaska.

Seroprevalence of hepatitis C virus (HCV) is estimated to be 1–1.9% in Canada, highest among indigenous people [32]. The prevalence is lower in Alaska and Greenland and probably considerably higher in Siberia. HCV infection is mainly associated with IV drug use and blood transfusion [33].

Sexually transmitted infections

Rates of sexually transmitted infections are high in Arctic populations, with Greenland having the highest rates [34]. Targeted efforts against gonorrhea and syphilis in the 1970s led to markedly lower rates of gonorrhea that have, however, increased slowly since 1996–2000 to reach an incidence of approximately 2200/100 000 (2013) [19]. Rates are somewhat lower in Canada and Alaska [34]. Syphilis is generally a rare disease with on average one yearly case in Greenland, but since 2011, a marked increase in cases has been noted in Greenland, showing that syphilis still occurs in epidemics in Arctic areas [19,35]. Chlamydia remains the most prevalent STI with increasing incidence rates since the 1990s in Greenland to a present rate of 6000/100 000 (2013) which is 10 times the incidence of Denmark [19]. Incidence rates of *Chlamydia* in Canada and Alaska are somewhat lower, but also increasing.

HIV

HIV was suspected to reach alarmingly high levels in Arctic populations, but in Greenland the yearly incidence remained stable at 10–12/100 000 for several years followed by a decrease to 4/100 000 in recent years [19]. In Greenland, transmission is mainly heterosexual (75%) and most patients are middle-aged at the time of diagnosis [36]. The estimated HIV incidence is 10/100 000 in Canada [37] and in Alaska about 5/100 000, one-third of the incidence in the USA [38]. Men having sex with men account for about half of the infections in these countries, and injection drug use for about 15–20%. HIV incidence is very high in Siberia and most registered cases are associated with injection drug use [39].

Zoonotic and parasitic infections

With the strong hunting traditions of northern indigenous populations, a range of zoonotic and parasitic diseases occur in humans residing in the Arctic, although at different rates by region [40]. Less reliance on hunting for and consumption of subsistence food may result in a lower incidence of such

diseases, but present and future climate changes affecting temperature, humidity, flooding, and wildlife composition may increase the incidence of these infections in humans [41].

Botulism

Botulism is caused by ingestion of a neurotoxin produced by the anaerobic bacterium *Clostridium botulinum*, which grows in meat and fish under special conditions such as an anaerobic environment and low acidity [42]. In the Arctic, traditional food preparation includes fermentation of meat and fish by anaerobic storage at low temperatures above freezing without salting, which may lead to outbreaks of botulism in Alaska, Canada, and Greenland. In recent years in Alaska, incidence and death rates from botulism have decreased [43]. However, botulism cases continue to occur among Alaskan native persons which may be due to a shift from traditional fermenting techniques towards the use of plastic containers, which facilitates growth of anaerobic bacteria [44]. In Greenland, incidence rates have decreased although lethal cases of botulism were seen in 2013.

Bacterial and viral zoonoses

Seroprevalence studies have shown that seropositivity to *Coxiella burnetii*, *Leptospira* spp., *Francisella tularensis*, and arbovirus (Jamestown Canyon and Snowshoe Hare) occurs in Greenland, Canada, and Alaska [45–49], although the extent of clinical disease from these organisms is unknown. *Brucella* has been observed in Siberia, Alaska, and northern Canada, and both marine (*Brucella ceti* and *pinnipedialis*) and terrestrial strains (*Brucella suis*) have been identified [50,51].

Protozoans In Arctic Canada and Alaska, the most frequent protozoan infections include *Toxoplasma gondii* and in lower numbers *Giardia* [40]. As in other areas of the world, microsporidial species, *Cryptosporidium parvum*, and *Pneumocystis jiroveci* are observed in immunocompromised/HIV patients. However, water-borne infections such as *Giardia*, *Cryptosporidium*, and *Toxoplasma* may be emerging causes of human disease in a warming North [52].

Helminths *Trichinella nativa*, the freeze-resistant variant of *Trichinella*, is widespread in Arctic game, mainly polar bear and walrus [40]. Clinical manifestations of trichinellosis in Arctic populations differ from those of other populations by the fact that the diarrheal phase, which precedes the classic myopathic and fever phase, is often the only sign, possibly because of repeated exposures to *Trichinella*. Diphyllobothriasis includes at least six species, with *Diphyllobotrium dendriticum* being particular common, infecting 80% in some indigenous communities [52]. Hydatid disease includes *Echinococcus granulosus* (cystic echinococcosis) and *E. multilocularis* (alveolar echinococcosis) and exists in Siberia, Alaska, and Arctic Canada, with western Alaska being hyperendemic for *E. multilocularis* [53]. *E. granulosus* exists in two forms: the northern or cervid form that is widely distributed in northern regions and infects a range of wild animals, and the European form that is associated with husbandry [40]. Although endemic in Alaska, northern Canada, and Greenland, the reported incidence of these endemic helminth zoonoses is declining.

Other nematodes include *Toxocara canis*, Anisachidae, and *Enterobius vermicularis* [52]. In addition, *Strongyloides* may be seen in the immunocompromised patient. In Siberia, *Opisthorchis felineus* (mainly in western Siberia) is common [40].

CNS infections: meningitis, encephalitis, and other infections with neurological symptoms

A number of mainly bacterial pathogens cause acute CNS infections in Arctic areas (see table below). Some viral pathogens (e.g. CMV, herpes simplex virus 1 and 2, VZV, echovirus) are known to cause CNS infections in Arctic populations [54–56], but prevalence is unknown. Zoonotic infections with possible CNS symptoms exist (rabies virus, *Echinococcus multilocularis* and *granulosus*, *Toxoplasma*) [40,57].

Acute infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms	Very rare microorganisms
<i>Streptococcus pneumoniae</i> <i>Neisseria meningitidis</i> <i>Haemophilus influenzae</i> * Herpes simplex Varicella zoster	<i>Listeria monocytogenes</i> <i>Escherichia coli</i> <i>Mycobacterium tuberculosis</i> Botulism [58]	Influenza HIV† Streptococci
* Hib rare, other serotypes more frequent. † HIV as cause of CNS symptoms is very rare in Greenland.		

CNS infections: meningitis and encephalitis with symptoms for more than four weeks and in the immunocompromised host

Microorganisms with symptoms for more than 4 weeks	Microorganisms in the immunocompromised host
HIV and opportunistic infections <i>Mycobacterium tuberculosis</i>	<i>Mycobacterium tuberculosis</i> Polyoma virus (JC virus)

Ear, nose, and throat infections

Upper respiratory tract infections (bacterial and viral [4]) are highly prevalent in Arctic populations, in children mainly as the common cold and chronic suppurative otitis media (CSOM), with cumulative incidence of CSOM up to 14% at age four [59]. Epstein–Barr virus infects most children at a very young age and infectious mononucleosis is consequently rarely observed.

Ear, nose, and throat infections with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions
Otitis media (acute and chronic) <i>Streptococcus pneumoniae</i> <i>Moraxella catarrhalis</i> <i>Haemophilus influenzae</i> Streptococci	<i>Mycobacterium tuberculosis</i> <i>Staphylococcus aureus</i> Infectious mononucleosis <i>Chlamydia</i> <i>Neisseria gonorrhoeae</i> , HSV, HPV
Respiratory virus (rhinovirus, enterovirus, adenovirus, influenza, parainfluenza, RSV, hMPV, coronavirus, Epstein–Barr virus)*	
* Epstein–Barr virus highly prevalent, median age at infection three years, but most often just symptoms of common cold. Mononucleosis is rare.	

Cardiopulmonary infections

Arctic populations have high rates of lower respiratory tract infections, as shown in both hospitalization rates and outpatient clinic-based rates [60,61] Main pathogens include both bacteria and virus, in particular *S. pneumoniae* and RSV.

Pneumonia with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms
<i>Streptococcus pneumoniae</i>	<i>Bordetella pertussis</i>
<i>Haemophilus influenzae</i>	<i>Mycoplasma pneumoniae</i>
<i>Moraxella catarrhalis</i>	Streptococci
Respiratory virus (RSV, rhinovirus, enterovirus, adenovirus, influenza, parainfluenza, hMPV, coronavirus)	<i>Klebsiella pneumoniae</i>
<i>Mycobacterium tuberculosis</i>	Legionella
<i>Pneumocystis jiroveci</i> (in immunocompromised host)	Chlamydia
	<i>Staphylococcus aureus</i>

Endocarditis with less than four weeks of symptoms

Compared with Caucasian populations, *S. pneumoniae* is a significantly more frequent cause of endocarditis in Inuit populations, responsible for 16–24% of cases [62,63]. Clinical course and outcome of *S. pneumoniae* endocarditis are comparatively more severe than in Caucasian populations [63]. Pericarditis caused by *M. tuberculosis* is relatively frequent in Greenland.

Frequently found microorganisms	Rare microorganisms and conditions	Very rare microorganisms
<i>Streptococcus pneumoniae</i>	<i>Escherichia coli</i>	<i>Coxiella burnetii</i>
<i>Staphylococcus aureus</i>	Coagulase-negative staphylococci	
<i>Streptococcus viridans</i>	Enterococci	

Gastrointestinal infections

Gastrointestinal infections with less than four weeks of symptoms

Gastrointestinal infections in Arctic areas may be caused by bacteria, viruses, helminths, or protozoans. In Alaskan indigenous children, hospitalization rates for diarrheal diseases are comparable to those of US children, but outpatient visit rates are higher [64]. Of identified causes, most are rotavirus or unspecified virus, followed by unspecified bacterial and parasitic agents [64].

Frequently found microorganisms	Rare microorganisms and conditions
Rotavirus	<i>Escherichia coli</i>
Norovirus	Shigella
Helminths (<i>Echinococcus</i> , anisachiasis, angiostrongyliasis, <i>Diphyllobotrium</i> , <i>Trichinella</i>)	Campylobacter
<i>Enterobius vermicularis</i>	Protozoans (<i>Giardia</i> , <i>Entamoeba</i> , <i>Cryptosporidium</i> , <i>Blastocystis hominis</i>)

Frequently found microorganisms	Rare microorganisms and conditions
<i>Clostridium difficile</i> Salmonella	<i>Ascaris lumbricoides</i> Opisthorchiasis Yersinia Botulism

Gastrointestinal infections with more than four weeks of symptoms

Helicobacter pylori is prevalent in Arctic populations with age-specific seroprevalence patterns intermediate between developed and developing countries. *Helicobacter pylori* (HP) may lead to chronic gastritis, peptic ulcer disease, and gastric cancer [65]. The risk of gastric cancer is substantially higher among indigenous people than in their nonindigenous counterparts [66]. The rate is increasing in most Arctic areas and is especially high in Siberia. Rates of HP reinfection are elevated in Alaska (16% two years post eradication) [67]. Current guidelines for diagnosis and management of HP infection, including the “test and treat” strategy for persons with dyspepsia, have been developed in Western low-incidence countries. These guidelines may not be applicable to high-prevalence countries like Arctic areas, and instead an expert panel has suggested that treatment of persons with *H. pylori* infection should be limited only to instances where there is strong evidence of reduction of morbidity and mortality, for example associated peptic ulcer disease and MALT lymphoma [68].

Infections of liver, spleen, and peritoneum

Acute infections of liver, spleen, and peritoneum with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions
Gastrointestinal bacteria (including <i>E. coli</i> , <i>C. perfringens</i>)	Klebsiella
Hepatitis B	<i>Pseudomonas aeruginosa</i>
Streptococci, including <i>S. pneumoniae</i>	<i>Haemophilus influenzae</i>
Staphylococci	Candida
<i>Mycobacterium tuberculosis</i>	Hepatitis A
Hepatitis D	Hepatitis C
	Hepatitis E
	<i>Echinococcus granulosus</i> and <i>E. multilocularis</i>

Chronic infections of liver, spleen, and peritoneum with more than four weeks of symptoms

The main causes of chronic infections of the liver, spleen, and peritoneum include hepatitis B, and to a lesser degree with regional differences hepatitis C and *Echinococcus*. Infections of the peritoneum and mesenteric glands are rather frequent manifestations of tuberculosis.

Genitourinary infections

Cystitis, pyelonephritis, and nephritis with less than four weeks of symptoms

Frequently found microorganisms	Rare microorganisms and conditions
<i>Escherichia coli</i> Enterococci <i>Klebsiella pneumoniae</i>	<i>Mycobacterium tuberculosis</i>

Sexually transmitted infections with less than four weeks of symptoms

The most frequent sexually transmitted infections are gonorrhea and chlamydia, but a number of other infections are also prevalent. Syphilis occurs in epidemics.

Frequently found microorganisms	Rare microorganisms and conditions
Chlamydia spp. <i>Neisseria gonorrhoeae</i> Herpes simplex virus Human papillomavirus <i>Trichomonas vaginalis</i> Bacterial vaginosis <i>Mycoplasma genitalium</i> HIV	<i>Treponema pallidum</i>

Joint, muscle, and soft tissue infections

Joint, muscle, and soft tissue infections in Arctic populations are caused by many of the same bacterial pathogens as in northern America and Europe, i.e. *S. aureus*, *S. pneumoniae*, *H. influenzae*, and group A streptococci (GAS). Tuberculosis is frequent and may also cause such infections, both in immunocompromised and immunocompetent persons. An unusual soft tissue infection is “seal finger,” an infection caused by accidental cutting with knives used for butchering seals that progresses from a cellulitis to arthritis with eventual joint dissolution and healing by joint stiffness. The infection is believed to be caused by *Mycoplasma* spp. [69].

Skin infections

Skin infections of less than four weeks’ duration such as cellulitis are frequent in Arctic indigenous populations [70] and may be caused by group A and group B streptococci and *S. aureus*. Methicillin-resistant *Staphylococcus aureus* (MRSA) and nonresistant *S. aureus* have caused skin abscesses (boils) in Alaskan indigenous peoples. Group A streptococci may in more rare cases cause necrotizing fasciitis.

Adenopathy

Adenopathy of less than four weeks' duration

Frequently found microorganisms	Rare microorganisms and conditions
Epstein–Barr virus Cytomegalovirus HIV <i>Mycobacterium tuberculosis</i> Adenovirus	Tularemia <i>Treponema pallidum</i> <i>Toxoplasma gondii</i>

Fever without focal symptoms

A range of bacteria may cause septicemia without known focus in Arctic populations, including *S. pneumoniae*, hemolytic streptococci, *S. aureus*, coagulase-negative staphylococci, *Haemophilus influenzae*, *Neisseria meningitidis*, and gastrointestinal bacteria (*E. coli*, enterococci). In newborns group B streptococci and *E. coli* may cause bacteremia.

Fever of unknown origin

Frequently found microorganisms	Rare microorganisms
Epstein–Barr virus Cytomegalovirus HIV	<i>Coxiella burnetii</i> <i>Mycobacterium tuberculosis</i> <i>Toxoplasma gondii</i> Brucella

Eosinophilia and elevated IgE

The main causes of eosinophilia include allergic and parasitic diseases, mainly helminthic infections, although these are rarely found in Greenland.

Helminthic infections

Diphyllobotriasis	<i>Toxocara</i> spp.
<i>Trichinella nativa</i> * Anisachidae (<i>Anisakis simplex</i> (herring worm) and <i>Pseudoterranova decipiens</i> (cod worm)) <i>Echinococcus granulosus</i> and <i>E. multilocularis</i>	Opisthorchiasis <i>Strongyloides</i> (in immunocompromised host)
*Freeze resistant	

Antibiotic resistance

Antimicrobial resistance patterns vary slightly in different Arctic areas. In Alaska, the percentage of invasive penicillin-resistant pneumococcal isolates increased from 0 in 1993 to almost 15% in 2000, but diminished after the introduction of pneumococcal vaccination in the routine childhood immunization program in 2001 [1]. In Canada and Greenland, rates are lower, around 3% and <1%. There has been considerable concern in Greenland over possible penicillin-resistant pneumococci due to high consumption of broad-spectrum antibiotics, but so far this has not occurred.

In Alaska and Canada, outbreaks of community-acquired MRSA occur in indigenous communities [1,71]. Across the US, rates of MRSA increased from 1996–8 to 2003–05 to reach an age-adjusted rate of 58.8 hospitalizations per 100000 among American Indians/Alaska natives, compared with the 84.7 hospitalizations per 100000 in the general US population [72]. In Greenland, MRSA still only occurs sporadically.

High rates of antimicrobial resistance towards clarithromycin, metronidazole, and levofloxacin are found in *H. pylori* isolates from Alaska [73–75] and towards metronidazole in Greenland.

A rapid increase in resistance to ciprofloxacin in *N. gonorrhoea* isolates from Greenland [76] and a high rate of macrolide resistance in *Mycoplasma genitalium* isolates from Greenland [77] have been observed.

Vaccine-preventable diseases in children

Childhood immunization programs in Alaska, Canada, and Greenland are fairly similar. In all countries, the program includes diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type b (Hib), PCV13 (13-valent pneumococcal conjugate vaccine), hepatitis B, human papillomavirus (HPV), measles, mumps and rubella (MMR), besides varicella in Alaska and Canada. *Meningococcus C* vaccine is given in Canada and a quadrivalent meningococcal vaccine is given in Alaska, but none in Greenland. Hepatitis A vaccination is given in Alaska and in some provinces in Canada, but not in Greenland. Rotavirus vaccine is given in Alaska. In Greenland, neonatal BCG vaccination (tuberculosis) was reinstated in 1997 after having been halted in 1991.

On a national level, 76% of US children and 85–90% of Canadian children at age two years are fully vaccinated (see chapter on Northern America). In Greenland, overall vaccine coverage is >80% with vaccinations at ages three and five months given to more than 90% of children in this age group [78]. In Alaska, vaccination coverage is greater than 85% for school-aged children, and greater than 90% among Alaskan indigenous children.

Vaccine introductions have had markedly beneficial effects in reducing targeted infections, with few side effects. Hepatitis B vaccination has greatly reduced the incidence of clinical hepatitis B in Alaskan native people; 7-valent pneumococcal vaccination has reduced the incidence of targeted vaccine serotypes in both Canada and Alaska, and Hib vaccination has eradicated Hib in Greenland and reduced the incidence substantially in Alaska and Canada. However, replacement of vaccine serotypes with nonvaccine serotypes involved in invasive pneumococcal disease has been substantial in Alaska (129%) after HPV7 introduction [2], although such replacement has not been seen in the post-PCV13 period [5], and both in Alaska and Canada epidemics of invasive disease caused by non-B *Haemophilus influenzae* have been documented [6].

Basic economic and demographic data.* No separate figures for Antarctica

	GNI per capita (USD)	Life expectancy at birth (total, years)	School enrollment, primary (% net)
Greenland [†]	19290	71	>95
Alaska ^{**}	53470	79	98
Canada North ^{††}	52210	81	98
Siberia [§]	15850	71	>95

*World Bank.

[†]Last available World Bank GNI per capita figure for Greenland 2009.

^{**}No separate figures for Alaska, USA figures given.

^{††}No separate figures for northern Canada, Canadian figures given. (On average, life expectancy figures five years lower in northern communities).

[§]No separate figures for Siberia, figures for Russian Federation given. In 10 of 15 northern regions, Gross Regional Product higher than national average, but great disparity between indigenous peoples and migrants. GNI, gross national income.

Most common causes of deaths all ages in Greenland, Canada, and Alaska

	% of Deaths		
	Greenland*	Canada [†]	Alaska ^{**}
Malignant neoplasms	25	30	25
Diseases of the heart	22	20	18
Unintentional injuries	4	4	9
Chronic lower respiratory diseases	3	5	5
Cerebrovascular diseases	NS	6	5
Intentional self-harm (suicide)	16	2	4
Diabetes	NS	3	3
Alzheimer's disease	NS	3	2
Chronic liver disease and cirrhosis	NS	NS	2
Influenza and pneumonia	NS	2	2
Infectious diseases	2	NS	NS
Other causes	27	25	25

*Chief Medical Officer of Greenland, national figures 2011.

[†]Statistics Canada, national figures 2011.

^{**}Alaska Bureau of Vital Statistics, statewide figures 2013.

NS, not stated.

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Chapter 28

The immunosuppressed patient

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Immunocompromised patients present unique challenges for clinicians diagnosing and managing infectious diseases. A systematic approach to these patients is key to making a timely and accurate diagnosis. It requires assessment of the level of immune compromise, review of the use of prophylactic medications, a detailed history of potential exposures and a thorough review of known endemic risks. Given the atypical presentation and rapid progression of infections that occur in this unique patient population, early microbiological diagnosis, when feasible, is important to guide treatment. Where microbiological diagnosis is not possible, knowledge of the patient's level of immune compromise and the epidemic and endemic risks is critical for empiric therapy.

Introduction

Patients with immune deficiencies, whether primary or acquired, experience a spectrum of illness broader than that observed in immunocompetent persons within any given region. Disease that occurs in the context of immunosuppression may result from either new infections or reactivation of a prior latent infection. The influence of immunosuppression on infection can occur at multiple levels. Immunocompromised patients may have a **higher susceptibility to infection**, leading to an increase in the incidence and/or prevalence of disease. Secondly, immunocompromised persons may present with **higher burdens of the pathogenic organism**, leading to increased transmissibility. Finally, the inability to mount an effective immune response may lead to **impaired clearance** of infection with subsequent increases in both morbidity and mortality of disease.

Although some geographic localization of opportunistic infections has been described, many opportunistic infections are caused by agents that are ubiquitous and therefore represent important health concerns for immunocompromised patients across all regions of the world. This chapter describes the types and levels of immune deficiency and discusses ubiquitous and geographically localized infections affecting persons with immune deficiencies.

Approach to the patient

Reaching a timely and accurate diagnosis of infection in an immunocompromised hosts can be challenging given the broad differential diagnosis [1]. For this reason, a systematic approach to diagnosis based on timing of travel and disease incubation periods is critical and may prompt empiric treatment (Table 28.1).

Table 28.1 Approach to assessing the immunocompromised patient.

- 1 Assess levels of cellular and humoral immunosuppression
- 2 Review antibiotic prophylaxis history and prior vaccination status
- 3 Review epidemiology of region and exposure history
- 4 Clinical assessment and targeted testing based upon both clinical syndrome and assessed risks

Table 28.2 Categories of immunodeficiency and conferred disease susceptibility.

Functional deficiency	Disease susceptibility	Predisposing condition
Immunoglobulin deficiency	Increased susceptibility to certain bacterial infections	Hereditary, lymphoma, leukemia
Dysregulated B-cell function	Increased susceptibility to certain bacterial infections	HIV, leukemia, lymphoma, medications
Defects in cell-mediated immunity	Increased risk of viral, fungal, and protozoan infections	HIV, lymphoma, leukemia, immunosuppressive medications
Inability to opsonize/ complement deficiency	Increased risk of infections by encapsulated organisms	Asplenia, sickle cell disease, hereditary
Phagocytosis defects and disrupted white blood cell chemotaxis	Increased susceptibility to disease caused by catalase-positive bacterial pathogens, <i>Aspergillus</i> species, intracellular organisms	Diabetes mellitus (hyperglycemia), hereditary, neutropenia
Circulatory dysfunction	Increased susceptibility to multiple infections, impaired wound healing	Diabetes mellitus
Loss of immunoregulatory and immune system effector proteins	Increased susceptibility to multiple infections	Cirrhosis, nephrotic syndrome

The general differential diagnosis of newly returned ill travelers, depending on their area of travel, may include malaria, for which urgent evaluation is required, as well as typhoid fever, dengue fever, zika, chikungunya, rickettsial diseases, leptospirosis, influenza, acute HIV, legionellosis, arboviral encephalitis, region-specific schistosomiasis, leishmaniasis, amebic liver abscesses, and tuberculosis [2]. Tuberculosis risk should be considered in all compromised hosts.

Assess levels of cellular and humoral immunosuppression

The immune response represents the coordinated activity of multiple humoral and cytological factors. Specific deficiencies, both primary and acquired, have been described at all levels as described in Table 28.2, each conferring increased risks of different classes of diseases. Enumeration of the many types of primary immune deficiencies is beyond the scope of this chapter but for more details, the reader is referred to the most recent classification publication from the International Union of Immunological Societies [3]. Drug-induced immunodeficiencies comprise the greatest category of risk, and the list of immune-modifying agents continues to increase. Monitoring for potential interactions between immune suppressing medications and other medications an individual may be taking is important as these may either increase or mitigate the level of immune suppression and impact the individuals risk for infection. Patients with cancer have unique risks associated with both their disease state and the medications used in treatment [4]. Pregnancy induces a state of relative immune suppression. Higher rates of severe malaria and tuberculosis in pregnant women are well documented with risk of adverse fetal outcomes. Pretravel counseling for pregnant patients regarding the potential risk of exposure with travel is important [5].

Though the pathophysiology of immune dysfunction related to many of these factors has been well described, no adequate assays exist to assess the degree of immune dysfunction associated with each. The risk is assessed principally through the sum experience of clinical infections seen associated with each risk factor, combined with the impact of these factors on the serological response to immunizations. Assessment of white blood cell and CD4 cell counts as well as therapeutic drug monitoring for those on immunosuppressive medications may be useful, depending on the type of immune deficiency. The level of immunosuppression can be broadly categorized as **minimal** (no significant excess risk), **limited** (some excess risk of infection requiring consideration of vaccines and other preventive measures), and **severe** (high risk of infection and for severe sequelae of infection) as described in Table 28.3 [6].

Review antibiotic prophylaxis history and prior vaccination status

Well-defined protocols exist for immunization of persons with immune compromise and antibiotic prophylaxis against opportunistic infections for people with significant immunocompromise. Polyvalent immunoglobulin replacement therapy may be used for patients with humoral deficiencies. In addition to standard vaccine recommendations, pretravel vaccines are recommended for persons traveling to areas of endemic disease, including vaccines for hepatitis A and B for those without immunity, typhoid, and in some cases *Meningococcus*, yellow fever, rabies, and Japanese encephalitis. Yellow fever vaccine is contraindicated in persons on immunosuppressive therapy and with uncontrolled HIV with low CD4 count, though it may be given to HIV-infected persons with suppressed virus on antiretroviral therapy (ART) and well-preserved CD4 counts [7–9]. For yellow fever and pneumococcal vaccines, additional vaccine doses may be required and response rates to vaccines may be lower in persons with immune compromise. Serological testing to confirm antibody response may be useful [7,9–11]. If the recommended immunizations have not been received or prophylactic regimens have not been maintained, the targeted diseases should become key considerations in constructing a differential diagnosis [12–14].

Review of epidemiology of region and exposure history

When evaluating an ill compromised traveler, one must consider the risk for opportunistic infections and the epidemiology of disease in the regions visited, including both typical infections and opportunistic infections. A detailed travel and exposure history should be collected, including exposures based on current and prior places of residence as well as travel and occupational history. Particular attention should be given to exposures to insects, animals, and sick contacts as well as specific ingestions of undercooked foods, untreated drinking water, milk, cheese, and exotic foods. Environmental exposures such as swimming or wading in fresh water, exposures to soil, caves, farm animals, animal bites, and sexual contacts should also be assessed [15]. Full pretravel counseling recommendations for persons with immune compromise are discussed in depth elsewhere but avoidance of molds, construction and renovation settings as well as drinking bottled water is recommended [2,13,16–18].

Clinical assessment and targeted testing based on clinical syndrome and assessed risks

As part of the clinical evaluation, a focused assessment for common symptoms should be performed with prompt attention given to fever, diarrhea, and skin lesions. Initial testing should include complete blood counts, liver function tests, urinalysis, cultures of blood, stool, and urine, and chest X-rays [2]. Targeted specific testing should be performed based on the clinical syndrome. Signs and symptoms of infection may be diminished in immunosuppressed patients, and early microbial diagnosis that may require invasive diagnostic procedures is often essential for guiding treatment [2,19].

Organ transplantation

The importance of organ transplantation as a consideration in medical care is increasing worldwide. Transplant centers are active within all settled continents and patients from resource-limited countries with means are increasingly traveling abroad to receive transplants in other countries. They face risks

Table 28.3 Levels of immune compromise.

Immune compromise	Category	Condition
Minimal	Age	Persons >60 years of age
	Disease	HIV CD4 >500 Bone marrow transplant patients >2y post transplant off medication, without graft-versus-host disease Autoimmune disease not treated with immunosuppressive therapy
Limited immunosuppression	Medications	Low-dose corticosteroids (<20mg prednisone daily or every other day dosing, steroid inhalers, topical or intraarticular injections) or duration since last dose >1 month Chemotherapy last use 3 months ago or greater Immunosuppressive medications last use 1 month ago or greater
	Disease	Asplenia (encapsulated organisms, malaria, babesia, capnocytophaga) Chronic renal disease, chronic liver disease (including chronic hepatitis C): due to loss of immunoregulatory and immune system effector proteins Diabetes mellitus: skin and soft tissue infection risk: circulatory dysfunction due to microvascular and macrovascular disease, hyperglycemia-induced phagocytic defense and disruption of white blood cell chemotaxis Complement deficiencies (meningococcal infection)
Severe immune deficiency	Disease	Active leukemia or lymphoma Generalized malignancy Aplastic anemia Neutropenia Graft-versus-host disease Congenital immunodeficiency HIV, CD4 count less than 200 Persons who have received current or recent radiation therapy or bone marrow transplant recipients within 2 years of transplantation
	Medications	High-dose corticosteroids (either >2mg/kg of body weight or ≥20mg/day of prednisone or equivalent in persons who weigh >10kg, when administered for ≥2weeks) Alkylating agents (e.g. cyclophosphamide) Antimetabolites (e.g. azathioprine, 6-mercaptopurine) Transplant-related immunosuppressive drugs (e.g. cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil) and mitoxantrone (used in multiple sclerosis) Cancer chemotherapeutic agents (excluding tamoxifen) Methotrexate, including low-dose weekly regimens, is classified as severely immunosuppressive Tumor necrosis factor (TNF)-blocking agents, IL-6 antagonists (intracellular microorganisms, fungi) and other rheumatological disease-modifying agents

related both to exposures preceding transplantation and based on new exposures they may have after returning home post transplant [20]. Regardless of the country of origin, persons who have received organ transplants incur risks of infection as they travel to other regions and countries [4].

The use of potent immunosuppressive medications, while dramatically reducing the incidence of rejection of transplanted organs, simultaneously increases patients' susceptibility to opportunistic infections [21,22]. In addition to contracting infections through **receipt of blood products**, organ transplant recipients may acquire significant tropical diseases in four ways: **transmission with the graft** (e.g. HTLV-1), **de novo infection** (e.g. visceral leishmaniasis), **reactivation of dormant infection** (e.g. tuberculosis, histoplasmosis), and **reinfection/reactivation in an otherwise healthy graft** (e.g. Chagas' disease) [23]. Clinicians assess infection risk by considering the intensity of immunosuppression, the use of prophylactic medications, and the recipients' likely exposures based on results of both donor and recipient serological testing and epidemiological history.

The intensity of immunosuppression is determined by both dose and duration of immunosuppressive therapies. Immunosuppression is highest in the immediate posttransplant period. Induction of immunosuppression requires highly potent antilymphocyte medications such as the antithymocyte globulins ATG, OKT3, and alemtuzumab. These medications lead to depletion of T-cells and their effects persist for several months following treatment. These medications may also be used post treatment to manage episodes of rejection. ATG and OKT3 have been associated with increased rate of CMV infection (if CMV prophylaxis is not used) and fungal infections, as well as posttransplant lymphoproliferative disorder (PTLD) [24]. ATG is also associated with increased risk for nephritis caused by BK virus [25]. Non-T lymphocyte-depleting agents such as the interleukin-2 receptor antagonists (daclizumab, basiliximab) seem to have a lower rate of infectious complications compared with the other induction therapies. Rituximab is a humanized chimeric monoclonal antibody directed against CD20, a transmembrane protein located on pre-B and mature B-cells used in treatment of B-cell dyscrasias, autoimmune syndromes, and antibody-mediated rejection. Skin and soft tissue infections as well as bloodstream infections may increase with its use [26]. Interactions between immunosuppressive medications and drugs used for malaria prophylaxis may occur and monitoring for toxicity is warranted. Other medications may alter the levels of immunosuppressant medications and either increase the risk of infection or of rejection. Reviewing for potential drug interactions is critical before prescribing any new medications to these patients.

The **typical timeframe for transplant-related infections** relative to initiation of immunosuppression is described in Table 28.4 [21]. The timing of infection risk may be altered by subsequent intensification of immunosuppression. Invasive candidiasis can occur at any time post transplantation and may be associated with high mortality. Use of azole prophylaxis has reduced its incidence. In the **first month** following transplantation, most infections are donor derived, recipient derived or associated with complications from surgery. They include infections with antimicrobial-resistant species such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), *Candida* spp., aspiration-related infections, catheter or wound infections, as well as *Clostridium difficile* colitis. Donor-derived infections, although uncommon, include those caused by herpes simplex virus (HSV), lymphocytic choriomeningitis virus (LCMV), rhabdovirus (rabies), West Nile virus, HIV, and *Trypanosoma cruzi*. Recipient-derived infections, occurring mostly through colonization, include infections with *Aspergillus* spp. and *Pseudomonas* spp. Opportunistic infections are generally absent during the first month as the full effect of immunosuppression is not yet achieved.

In **months 1–6 following transplantation**, viruses account for the majority of infectious episodes. Infections include those caused by herpes viruses (HSV, VZV, CMV, EBV), flares of hepatitis B and C, adenovirus infections, and polyoma virus (BK)-associated nephropathy. Other infectious risks include *Pneumocystis*, *Listeria* spp., *Nocardia* spp., *Toxoplasma gondii*, *Strongyloides* spp., *Leishmania* spp., and *T. cruzi*. This has changed with prophylactic medications. Trimethoprim-sulfamethoxazole generally prevents most urinary tract infections and opportunistic infections such as *Pneumocystis* pneumonia, *Listeria monocytogenes*, *Toxoplasma gondii*, and susceptible *Nocardia* species. Infections due to ubiquitous fungi include *Aspergillus* and *Cryptococcus*. Parasitic infections with *Trypanosoma cruzi* or *Strongyloides stercoralis* may reactivate and overwhelm without prior prophylaxis. Opportunistic

Table 28.4 Timeline of infection after transplantation. Source: Adapted from Fishman and Issa [21].

Time period	Infectious risks
<1 month	Antimicrobial-resistant bacterial species, aspiration, line and wound infections, <i>C. difficile</i> Donor-derived infection (HSV, LCMV, rhabdovirus (rabies), West Nile virus, HIV, <i>Trypanosoma cruzi</i>)* Recipient-derived infection: <i>Aspergillus</i> , <i>Pseudomonas</i> spp.
1–6 months	In persons receiving PCP and antiviral prophylaxis for CMV, HBV: Polyomavirus BK infection, nephropathy <i>Clostridium difficile</i> colitis Hepatitis C virus Adenovirus infection, influenza <i>Cryptococcus neoformans</i> <i>Mycobacterium tuberculosis</i> In persons not receiving PCP and antiviral prophylaxis (CMV, HBV): <i>Pneumocystis</i> pneumonia Infection with herpes viruses (HSV, VZV, CMV, EBV) Hepatitis B virus Listeriosis, nocardiosis, toxoplasmosis, <i>Strongyloides</i> spp., leishmaniasis, <i>T. cruzi</i>
>6 months	Community-acquired pneumonia Urinary tract infection <i>Aspergillus</i> , atypical molds, <i>Mucor</i> species Nocardiosis, <i>Rhodococcus</i> spp. CMV infection (colitis and retinitis) Hepatitis (HBV, HCV) HSV encephalitis Community-acquired viral infections (SARS, West Nile virus infection) JC polyomavirus infection (progressive multifocal leukoencephalopathy) Skin cancer, lymphoma (posttransplant lymphoproliferative disease)

*The risk of certain donor-derived infections such as tuberculosis and strongyloides can extend beyond the first month post transplantation.

infections as causes of diarrhea also become more common during this middle time period following transplant [27,28].

Infectious disease **risk decreases six months following transplantation**, correlating with the tapering of immunosuppressive medications in recipients with good allograft function. Recipients remain at risk, however, for community-acquired pathogens causing pneumonia or urinary tract infections. Some patients, despite immunosuppression reductions, may develop opportunistic infections from *Listeria* or *Nocardia* species, invasive fungal pathogens such as *Aspergillus*, atypical mold or *Mucor* species.

HIV and risk of opportunistic infections

HIV infection is endemic throughout all areas of the world, with the greatest burden of disease in sub-Saharan Africa and southern/south-east Asia. HIV disease causes progressive immune dysfunction associated with dysregulated B-cell function and progressive CD4 T-cell deficiency and a resulting decline in cell-mediated immunity. The specific manifestations of HIV disease vary by CD4 count as described in Table 28.5. The incidence of opportunistic infections is significantly impacted by availability of testing programs to permit the early diagnosis of HIV, the use of prophylactic medications and the availability and clinical practices related to antiretroviral therapy. Sexually transmitted diseases

Table 28.5 Risk of infectious complications of HIV as determined by CD4 blood counts.

CD4 range	Manifestations
>500	Herpes zoster, polydermatomal or disseminated
200–500	<i>Mycobacterium tuberculosis</i> infection and disease Bacterial pneumonia, recurrent Oral hairy leukoplakia (Epstein–Barr virus) <i>Candida</i> pharyngitis (thrush)
100–200	Cervical, anal, oropharyngeal neoplasia (human papillomavirus) <i>Pneumocystis jiroveci</i> pneumonia Systemic mycoses (histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis)
≤100	Progressive multifocal leukoencephalopathy (JC virus) <i>Candida</i> esophagitis Cytomegalovirus retinitis, esophagitis or colitis <i>Mycobacterium avium intracellulare</i> , disseminated <i>Toxoplasma gondii</i> encephalitis <i>Cryptococcus neoformans</i> meningitis <i>Cryptosporidium parvum</i> enteritis Mucocutaneous herpetic ulcers, extensive Lymphoma, CNS (Epstein–Barr virus associated)

(STDs) are frequently reported in persons with HIV and may increase the risk of transmitting HIV to others [29]. Some patients with markedly suppressed immune function (typically CD4 < 100 cells/mm³) prior to the initiation of HAART may experience an inflammatory syndrome known as immune reconstitution inflammatory syndrome (IRIS) with the recovery of their immune function. This is thought to represent the development of an immune response to previously tolerated infections or exogenous antigens and is particularly noted in the context of mycobacterial infections, cryptococcosis and other viral infections such as hepatitis B [30].

Severe, atypical, and disseminated presentations of multiple diseases in persons with HIV have been described. Studies regarding the impact of tropical diseases on HIV progression have shown mixed results. Infections with some agents have the potential to increase HIV viral replication through the release of proinflammatory cytokines and CD4 activation [31]. In settings with a high burden of acute and chronic infections, this process could contribute to an acceleration of HIV disease progression. Clinical studies have, however, provided mixed results depending both on the infection studied and the phase of illness [31–34]. The clinical relevance of these impacts, particularly in the context of acute infections, remains unclear.

Geographic distribution of opportunistic infections

The majority of pathogens associated with opportunistic infections in patients with HIV and other states of immune compromise are thought to be ubiquitous. Only limited surveys exist, however, with regard to the distribution of these infectious agents. Even in regions where the infectious agents are uniformly present, clustering of disease may occur based on other associated risk factors, such as sanitation. This is particularly a concern with regard to infectious diarrhea and parasitic infections transmitted through the fecal–oral route. Our ability to assess the potential for significant geographic localization of disease in persons with immune compromise is further limited by the lack of access to comprehensive medical diagnostic services in the areas most impacted by epidemic HIV infections. The lack of transplant registries in resource-limited settings equally makes assessment of the risk of transplant-related infections much more difficult.

The geographic localization of opportunistic infections based on available case reports and surveys is presented in Table 28.6. The majority of available research regarding the impact of immunosuppression on tropical diseases and geographically localized infections is specific to HIV. Limited but accumulating data are available regarding the impact of immunosuppressive medications and other causes of immune deficiency on these infections. Protozoan and fungal infections comprise the majority of geographically localized opportunistic infections. Though not strictly opportunistic infections, infections such as malaria and schistosomiasis are highly localized and their courses may be impacted by immunocompromise as well.

Bacteria

Increased frequency and severity of typical bacterial infections are noted both in transplant recipients and among persons with HIV and CD4 counts less than 350 cells/mm³. The infections observed correlate with the infections commonly seen in the community with upper respiratory and sinus infections and pneumonias being most common and, less commonly, urinary tract infections. Disease from *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus* infections are commonly described [35,36]. In areas of risk for meningococcal infection, persons with HIV have been estimated to be as much as 10 times more likely to develop meningococcal disease [37]. Necrotizing pneumonia with abscess formation due to *Legionella* has been described in patients with HIV and among transplant recipients. Cases of disseminated disease resembling miliary tuberculosis have also been described [38–40]. Infections with less common pathogens such as *Listeria* spp., *Nocardia* spp., and *Rhodococcus* spp. have been described in immunocompromised patients with high associated levels of morbidity and mortality.

Tuberculosis (acute or reactivation disease; pulmonary or extrapulmonary disease with increased risk of extrapulmonary and disseminated disease among immunocompromised patients)

The co-epidemics of HIV and TB represent the most profound impact of HIV on endemic bacterial infections. Tuberculosis occurs with much greater frequency among persons with HIV, independent of CD4 count, and accounts for a substantial portion of the mortality associated with HIV worldwide [41]. Disseminated and extrapulmonary TB become increasingly common as the CD4 count declines [42]. Though patients typically present with more advanced disease, the impact of HIV on the risk of transmission of tuberculosis has been controversial [43,44]. In particular for individuals with marked immunosuppression, the increased frequency of extrapulmonary and sputum-negative pulmonary tuberculosis may lead to a reduced risk of transmission to close contacts [42]. Tuberculosis, including disseminated disease, has been similarly described among persons on immunosuppressive medications, particularly TNF-alpha antagonists [45,46].

Nontuberculous mycobacteria (acute or reactivation disease; pulmonary or extrapulmonary disease with increased risk of extrapulmonary and disseminated disease among immunocompromised patients)

There are over 150 other species of mycobacteria, formerly described as nontuberculous mycobacteria or atypical mycobacteria. Several of these are of interest in immunocompromised patients, and may have broad geographic distributions and new species of pathogenic potential continue to be identified [47].

Bartonella (acute to subacute; vasoproliferative lesions and other atypical presentations in immunocompromised patients)

Bartonella spp. are associated with abscess formation and regional lymphadenopathy in immunocompetent individuals. Bacteremia with endocarditis has also been described. Persons who are immunocompromised develop vasoproliferative lesions and bacillary angiomatosis, mimicking Kaposi's

sarcoma with reported cases of both cutaneous and visceral involvement [48,49]. Disseminated disease, chorioretinitis, and aortitis have also been described [50–52].

Ehrlichiosis (acute to subacute; fever with multisystem involvement possible, case reports of severe illness among immunosuppressed patients)

Ehrlichiosis can be caused by a number of species of coccobacilli in the genera *Anaplasma* or *Neorickettsia*. Species are found worldwide. Though the spectrum of illness in many series of immunocompromised patients has been similar to that in the general population, case reports of severe and at times fatal ehrlichiosis with multiorgan failure have been described amongst recipients of lung transplant and HIV patients with significantly impaired T-cell function [53–55].

***Rhodococcus equi* (subacute, opportunistic infection; granulomatous pneumonia, rare disseminated disease)**

Infection with *Rhodococcus* spp. results from contact with farm animals and exposure to dry and dusty soils. Rhodococcal disease occurs as an opportunistic infection which has been described in the context of HIV and use of immunosuppressive medications. Most cases present with slowly progressive granulomatous pneumonia but there are case reports of disseminated disease and extrapulmonary involvement (mediastinitis, mastoiditis, skin abscess) [56–62].

Key geographically localized bacterial infections

Borrelliosis (acute, subacute or late presentations; erythema migrans, neural and cardiac manifestations) *Borrelia* spp. are associated with tick-borne disease, of which Lyme disease (*Borrelia burgdorferi*) is the most common. Relapsing fever in Africa has been associated with another *Borrelia* species. Cases of lyme neuroborreliosis with severe presentations have been described but there is no clear information to suggest that these presentations are more common in persons with HIV or other forms of immune suppression [63–66].

Melioidosis (acute to subacute or latent infection with reactivation; sepsis, pneumonia, multifocal abscesses, skin ulcers, osteomyelitis, encephalomyelitis; opportunistic infection) Melioidosis refers to a variety of clinical syndromes resulting from infection with *Burkholderia* spp. and occurring particularly among persons with even mild immune compromise. Syndromes range from local abscesses and pneumonia to sepsis and encephalomyelitis [67–69]. The highest burden of cases is seen in south and south-east Asia and the Western Pacific, with lower incidence of disease found in Central and South America, Puerto Rico and the Caribbean islands, the Middle East, and parts of sub-Saharan Africa [70–73].

Parasites and protozoa Information regarding the influence of immunosuppression and HIV on parasitic infections is more limited. Among patients with neurocysticercosis, cyst sizes in one series were shown to be greater in patients with HIV [74]. Travelers' diarrhea may be more severe or may have a chronic course in patients with HIV due to usual enteropathogens including *Entamoeba histolytica* or from less frequent parasites such as *Cryptosporidium parvum*, *C. cayetanensis*, or *Isospora belli* [75,76].

Babesiosis (acute to subacute; febrile illness with severe complications including multiorgan failure in immunocompromised patients) The majority of cases of human disease are attributable to the blood-borne parasite *Babesia divergens* or *B. microti* species complex. Infections may be subclinical or more severe, with fever and anorexia progressing to the acute respiratory distress syndrome, disseminated intravascular coagulation, congestive heart failure, and renal failure. More severe forms of the disease with prolonged courses have been reported in patients with HIV and on immunosuppressive medications, including a malaria-like syndrome caused by temperate species of *Babesia* [32,77]. Prolonged and fatal cases of babesiosis have been documented in asplenic patients associated with high levels of parasitemia [78,79].

Filariasis (subclinical, acute or chronic; fever, lymphangitis, lymphedema) Lymphatic filariasis has also been shown to be more common in patients with HIV, but the clinical course of infection has not been shown to be significantly altered [80,81].

Free-living amebae (acute; meningoencephalitis with high mortality, conjunctivitis, skin lesions and disseminated disease in immunosuppressed patients)

Acanthamoeba and *Balamuthia* species appear to be rare water-borne causes of opportunistic encephalitis, sinusitis, and cutaneous disease in patients with late-stage AIDS or immunosuppression [82–88]. Most case reports have been from the United States, but the worldwide distribution of these ubiquitous protozoa suggests that underdiagnosis is widespread in the tropics. Granulomatous amebic encephalitis is a subacute to chronic disease of immunocompromised hosts, generally causing death in weeks to months [32]. In patients with AIDS and granulomatous amebic encephalitis, the course may be more rapid and pathology often shows a paucity of well-formed granulomas. Patients with cerebral disease usually present with fever, headache, focal neurological deficits, and mental status changes. Disseminated disease has been described in recipients of solid organ transplants [85,89].

Leishmaniasis (acute or subacute, disseminated disease with visceral involvement in immunosuppressed patients)

After toxoplasmosis, leishmaniasis is the most common tissue protozoan opportunistic infection in persons with AIDS. Though the bulk of the reported data involves visceral leishmaniasis (VL) due to *Leishmania infantum* in the Mediterranean region, there are increasing reports of HIV-related VL due to *Leishmania donovani* in southern Asia and Africa and *Leishmania chagasi* in South America [32]. Limited cases have been reported in the US, occurring primarily in the states near its southern border with single cases reported in other areas [90]. Though most clinical manifestations are the same as those seen in patients without immune compromise, increased peripheral parasitemia and clinically evident ectopic parasites are more common in those with HIV infection. HIV-infected patients can develop the visceral form of this disease, even when infected by nonviscerotropic species, and experience higher mortality [75,91].

Prolonged subclinical courses and delayed diagnoses have been described in case series of recipients of organ transplantation with leishmaniasis, with significant mortality [92–95]. Leishmaniasis can itself result in immunosuppression in otherwise immunocompetent hosts and case reports of coincident opportunistic infections have been described [96].

Malaria (acute; increased frequency of severe malaria in immunosuppressed patients)

Malaria is among the leading causes of morbidity and mortality worldwide. Immunosuppression from HIV appears to lessen the acquired immunity usually seen in persons from endemic areas leading to both increased frequency of disease and increased incidence of severe malaria in these populations [97–99]. Cases of malaria transmission with organ transplantation have been well described and atypical clinical presentations in transplant recipients, including lack of periodicity of fevers and clinical symptoms, have been described [100,101]. More severe disease is seen in asplenic patients due to the inability to clear the parasite.

Schistosomiasis (subacute to chronic; genitourinary or gastrointestinal/hepatic disease, possible increase in risk of HIV transmission with chronic infection)

Schistosomal infection, particularly infection with *Schistosoma haematobium*, may impact HIV transmission through both increased HIV viral activity among HIV-positive persons and immune-modulating effects in the urogenital tract [102,103]. Studies have suggested that HIV may reduce the transmission of schistosomiasis but the epidemiological significance of this is unclear [104–106]. Immunosuppression and HIV have not been shown to significantly alter the clinical course or response to treatment of patients with schistosomiasis [105,107,108]. The possibility of IRIS has been raised, but no definitive cases have been identified [109–111].

Strongyloidiasis (subacute or chronic; abdominal and respiratory symptoms; disseminated disease among immunosuppressed patients) Disease from infection with *Strongyloides* spp. occurs worldwide, with areas of hyperendemicity in areas of South America, West Africa, south-east Asia and emerging disease in China [112]. Though hyperinfection with *Strongyloides* spp. has been described in association with corticosteroids and use of other immunosuppressive agents, there is no clear indication of an increased risk among patients with HIV and, paradoxically, patients with HIV seem to have reduced burden of infectious forms within the gut, decreasing the extent of autoinfection [113–116]. Strongyloidiasis hyperinfection syndrome may be complicated by polymicrobial and gram-negative bacteremia or meningitis and may occur decades after exposure and initial infection [116].

Toxoplasmosis (acute, opportunistic infection; focal CNS lesions or disseminated disease) Toxoplasmosis is a ubiquitous pathogen and a common cause of opportunistic encephalitis in persons with HIV disease. It is typically seen in persons with CD4 counts less than 100. Transmission of toxoplasmosis through organ transplantation has been well described and there have been multiple reported cases of disseminated fatal toxoplasmosis in this context [117–119].

Trypanosomiasis, African (acute to subacute; fever and lymphangitis progressing to meningoencephalitis) It is unclear whether HIV infection alters the epidemiology or clinical course of either West or East African trypanosomiasis [32]. Case series have suggested that mortality from trypanosomiasis may be higher amongst HIV-infected persons. There have additionally been case reports of disease in persons with HIV caused by normally nonpathogenic, lower trypanosomatids. Though risk of transmission of trypanosomiasis with organ transplantation has been described, the impact of immunosuppressive medications on the course of disease is not known.

Trypanosomiasis, American or Chagas' disease (acute, chronic, reactivation disease; cutaneous and CNS lesions, myocarditis in immunosuppressed patients) Reactivation Chagas' disease is a well-documented opportunistic infection amongst persons with AIDS, with CNS lesions being the most common presentation [32,20–122]. Patients typically present with multiple brain lesions, often with necrosis, hemorrhage, and inflammatory infiltrates. Patients may have clinically silent myocarditis or present with arrhythmias or congestive heart failure [123]. Parasite burdens in patients with HIV are significantly higher. Reactivation Chagas' disease has been described among recipients of organ transplantation [124–127].

Fungi

Fungal infections in the immunocompromised can range from invasive disease caused by ubiquitous yeasts such as *Candida albicans*, to tissue invasive disease caused by environmental molds or endemic mycoses. Travel-acquired fungal infections are of particular concern for travelers to tropical or subtropical areas. Inhalation of aerosolized fungi can lead to potentially severe pneumonia and skin inoculation can cause circumscribed cutaneous infections. Both of these localized infections can disseminate in the immunosuppressed and may present as acute or reactivation disease [128].

***Aspergillus* and *Zygomycetes* (acute, subacute, opportunistic infection; sinusitis, pulmonary or cutaneous disease with secondary dissemination described)**

Invasive fungal infections are important causes of morbidity and mortality among transplant patients, with invasive aspergillosis accounting for 19%, non-*Aspergillus* molds 8%, and zygomycosis 2% in a large survey [129]. Invasive aspergillus has been estimated to occur in between 1% and 14% of transplant recipients, with high morbidity and mortality [130]. Though it may occur in association with HIV disease in those with low CD4 counts, the association is much less pronounced [131]. Infections by *Zygomycetes* among those with HIV infection are less common and typically seen in patients with simultaneous neutropenia from other causes [131].

***Cryptococcus* (acute to subacute, opportunistic infection; meningitis and meningoencephalitis, pulmonary disease, myositis, and disseminated disease)**

Cryptococcal infections occur worldwide and are important causes of morbidity and mortality among transplant recipients and persons with HIV infections and low CD4 counts [132,133]. *C. gatti* has emerged as a major opportunistic pathogen and 38–55% affected in a 2011 outbreak were immune compromised [128]. Cryptococcal meningitis and meningoencephalitis are most common, but pulmonary disease, cutaneous infections, myositis, and disseminated infections have also been well described [134–138]. New species are also emerging. *Cryptococcus uzbekistanensis* was described in an elderly Asian man with undiagnosed T-cell lymphoma [139].

***Nocardia* spp. (acute, subacute, chronic; cutaneous, pulmonary, CNS, or disseminated disease in immunosuppressed patients)**

Disease from *Nocardia* spp. includes pulmonary disease which may be complicated by pleural and pericardial effusions, cutaneous lesions or CNS lesions as well as disseminated disease [140–142].

***Rhodotorula* spp. (acute, opportunistic infection; fungemia, meningitis, endophthalmitis, endocarditis, peritonitis)**

Rhodotorula spp. are yeasts with worldwide distribution. Fungemia is common particularly in the context of central venous catheter use. Meningitis, peritonitis, and other invasive manifestations have been described in immunocompromised patients [143–147].

Geographically localized fungal infections

***Coccidioides immitis* (reactivation of latent infection; pulmonary lesions with meningitis, osseous lesions, disseminated disease in immunosuppressed patients)**

Coccidioides immitis is a dimorphic yeast found in semi-arid to arid climate zones, principally in the south-western United States and northern Mexico. It is also found in parts of Argentina, Brazil, Colombia, Guatemala, Honduras, Nicaragua, Paraguay, and Venezuela [33]. During transplantation, possible routes of transmission include (i) reactivation of latent infection, (ii) posttransplant *de novo* infection of recipients who live or travel to areas of endemicity, and (iii) transmission secondary to transplantation of organs from an infected donor. Reactivation disease is most common, although in a few cases, brief visits to areas of endemicity have led to acute infection. Dissemination is common among transplant recipients and persons with uncontrolled HIV [33,148].

***Histoplasmosis* (acute to subacute, reactivation of latent infection, opportunistic infection; fever, hepatosplenomegaly, meningitis, and encephalopathy)**

Histoplasma capsulatum is endemic in the Mississippi and Ohio River valleys, Central America, and certain areas of South-east Asia and the Mediterranean basin. *Histoplasma capsulatum* var. *duboisii* is localized to western and central Africa and to Madagascar where it is common among persons with HIV infection [149–152]. In HIV-uninfected persons, the pathogen tends to cause chronic necrotizing cutaneous and skeletal infections. In patients with HIV, atypical and disseminated cases have been commonly described [153–155]. In transplant-associated cases described in the literature, symptoms started a median of one year after organ transplantation, and the majority of cases occurred in the first 18 months [33]. The majority of infections are thought to be due to new acquisition in an endemic area, though reactivation disease is possible. Rarely, histoplasmosis in transplant patients may be transmitted through an infected allograft from a patient with unrecognized histoplasmosis. Persons on TNF alpha inhibitors are at increased risk for histoplasmosis as well.

***Penicillium marneffei* (acute to subacute, opportunistic infection; cutaneous disease with disseminated disease possible)**

Penicilliosis is an endemic mycosis in south-east Asia and China where it is seen among those with HIV infection. It is typically characterized by papular skin

eruptions but systemic disease has been described and is considered uniformly fatal if left untreated [156]. Cases of disseminated infection have also been described among bone marrow and organ transplant recipients [157,158].

***Paracoccidioides brasiliensis* (acute or subacute with delayed progression; disseminated granulomatous disease)** The adult form of the disease accounts for the vast majority of cases in immunocompetent patients in South America, Latin America, and the Caribbean. A juvenile form occurs and is characterized by a rapid course with disseminated involvement of macrophages and lymphoid tissue associated with severe suppression of cellular immunity. Disseminated disease similar to the juvenile pattern is more common in the immunosuppressed [159–161].

Pheohyphomycoses (acute; fever with respiratory and CNS involvement) Disseminated infections from pigmented, dematiaceous fungi have been described in immunosuppressed patients, termed pheohyphomycoses. Disease resulting from these fungi is characterized by fever, rash, fungemia and often respiratory and CNS involvement, particularly brain abscesses [162–164]. Cases have been described in immunocompromised hosts in patients in the Middle East, India, Pakistan, and Afghanistan.

***Sporothrix* spp. (subacute, cutaneous disease with disseminated disease in context of immunosuppression)** *Sporothrix* spp. are dimorphic fungi found in tropical and subtropical areas of the Americas. Although cutaneous and lymphocutaneous disease types are most common, extracutaneous involvement has been described in both immunocompetent and immunocompromised hosts [165,166]. Disseminated disease with involvement of the joints, heart valves, eyes, and central nervous system also occurs and is more common in persons with an underlying immune deficiency and may result from hematogenous spread following inhalation of yeast forms [167]. IRIS associated with sporotrichosis has been described [168].

Viral infections

Zika (asymptomatic to moderate febrile illness with rash, conjunctivitis, arthralgias; occasional Guillain–Barré syndrome; most concerning for congenital infection/fetuses: microcephaly and other severe destructive neurological disease)

An ongoing epidemic in the Americas and Singapore has prompted appropriate heightened alert for all mosquito-borne viral illnesses worldwide as well as the rapid escalation in development of vaccine and treatment of Zika virus. Adults with severe immunosuppression, including HIV, experience more severe complications of infection in general. It is not known whether immunosuppressed individuals may shed more virus than other individuals but active diagnosis of asymptomatic infection is important in persons who visit Zika-endemic regions who are pregnant or of childbearing age, as well as their male sexual partners. Detectable Zika RNA can persist in semen after it is cleared from other body fluids. For evolving clinical information and recommendations for diagnosis and testing, access www.cdc.gov/zika or www.who.int regarding Zika.

Chikungunya (acute to subacute; febrile illness with rash, myalgias/arthralgias)

There are very few data regarding the impact of immunosuppression on patients with chikungunya. A single case series from Tanzania noted higher rates of leukopenia as a complication but the significance of this is not clear [169]. Atypical presentations without prominent myalgias in immunosuppressed patients have been reported [170].

Dengue (acute; febrile illness with hemorrhagic complications)

Primary infection with dengue virus is most commonly asymptomatic or mildly symptomatic. Dengue fever and its complications, including hemorrhagic manifestations and dengue shock syndrome, occur more frequently in the context of repeat infection and typically cause a self-limited febrile illness characterized by headache, myalgias, and retroorbital pain. A small case-control study from Singapore demonstrated a trend toward more severe dengue virus illness in HIV-infected individuals with advanced immunosuppression (median CD4 count 123 cells/mm³) yet other studies of patients with immunosuppression suggest that the risk of severe dengue complications is not increased by immune suppression and may be decreased in the context of immunosuppressive medications used for transplantation [169,171–175].

Hepatitis

Viral hepatitis occurs worldwide. Hepatitis A is passed through fecal-oral transmission and is associated with acute hepatitis higher risk of fulminant hepatitis among those with immune compromise. Hepatitis A is largely restricted to areas with limited sanitation facilities but may be transmitted in outbreaks through food handling by infected persons in other areas. Hepatitis E is transmitted principally through contaminated drinking water with outbreaks described in many areas of the world. Fulminant cases with increased mortality are seen in pregnant women and the immunosuppressed and prolonged or chronic cases may occur as well. Hepatitis B occurs worldwide but is highly endemic in South-east Asia and sub-Saharan Africa. In adults who are exposed, it typically causes an acute hepatitis with significant morbidity but low rates of chronic infection. Persons with immunosuppression more commonly become chronically infected. Hepatitis C is of highest prevalence in North America, Europe, and the former Soviet Union, principally associated with unsafe injection practices prior to the identification of the virus and among drug users. High rates are also present in areas of Asia and Africa, primarily associated with unsafe medical practices.

Herpes viruses

Recurrent outbreaks of herpetic lesions, including herpes simplex and herpes zoster, are common in persons with immunosuppression with atypical presentations possible with severe immunodeficiency [176,177]. Epstein-Barr virus (EBV) reactivation in the immunocompromised is associated with a number of opportunistic and nonopportunistic malignancies, including primary CNS lymphoma amongst those with HIV, posttransplant lymphoproliferative syndromes, Burkitt's lymphoma, and nasopharyngeal carcinoma [178–182]. Cytomegalovirus (CMV) disease is a common cause of morbidity in the posttransplant population, most commonly colitis and pneumonitis. CMV disease, particularly retinitis, has been similarly described in persons with HIV with extremely low CD4 counts (<50). Because diagnosis requires tissue biopsy and detailed pathological review, CMV disease may go undiagnosed outside specialty referral centers.

Influenza virus (acute; upper and lower respiratory tract infection)

Influenza cases have been documented amongst both transplant recipients and patients with AIDS but there is no clear increased risk of complications in these patients if they are on routine HAART [183,184]. High-dose inactivated influenza vaccine may be helpful but is not proven.

Measles virus (acute; febrile illness with rash, upper respiratory tract symptoms, encephalitis in severe cases)

Measles virus is associated with an annual mortality rate in the tropics that far exceeds the annual mortality rate associated with “traditional” tropical viruses [33]. Measles is itself exacerbated in the presence of HIV co-infection and co-infected patients have a higher risk for developing measles pneumonitis and for having prolonged shedding of measles virus [185]. Failure to develop or maintain protective immunity leading to recurrent infections has also been described in persons with HIV [186].

MERS virus (acute; upper and lower respiratory tract symptoms, respiratory failure and multiorgan failure in severe cases)

Limited data exist regarding the MERS virus in patients who are immunosuppressed. Two cases in renal transplant patients were reported, one of which was fatal [187]. Though the largest number of cases have been geographically linked to the Arabian peninsula, global travel has contributed to the development of incident cases in Europe, North Africa, North America, and East and South-east Asia.

Polyoma viruses

JC virus activation in the central nervous system is associated with the development of progressive multifocal leukoencephalopathy. Though cases have been described in those without clear immunodeficiency states, this condition is most commonly seen in persons with significant immune deficiency, frequently those with HIV and CD4 counts less than 200. BK virus is a cause of hemorrhagic cystitis and renal dysfunction in the transplant population [188]. Similar to JC virus, in patients with HIV and low CD4 counts, BK virus can cause a severe form of meningoencephalitis [189–191].

Other viral infections

Adenovirus is a well-described cause of hemorrhagic cystitis among transplant recipients [192]. Systemic illnesses involving central nervous system, respiratory system, hepatitis, and gastroenteritis have also been described amongst the immunocompromised, with high morbidity and mortality [193,194]. Parvovirus has been well described as a cause of anemia and other hematological abnormalities among transplant patients and parvovirus encephalitis has also been described [195–197].

Geographically localized viral infections

HTLV (chronic; cause of immunosuppression) Human T-cell lymphotropic virus is a viral infection that causes a less severe form of immunosuppression than that seen with HIV. Two strains have been identified: HTLV-1 has been localized to Japan, the Caribbean, and sub-Saharan Africa while HTLV-2 is principally seen among IV drug users and sexual contacts in the Americas, Europe, and Vietnam. Co-infection has been well described and may accelerate HIV disease progression [198,199]. HTLV-3 and HTLV-4 have recently been described in Africa, but clinical data are limited at this time [200].

West Nile virus (acute; CNS involvement with meningitis, encephalitis or flaccid paralysis)

Naturally acquired West Nile virus has been described in patients with HIV as well as in transplant recipients. The spectrum of illness appears to be similar to that seen in immunocompetent patients but some studies have suggested the resulting morbidity may be higher [201–203]. Although the virus originated in Africa, its distribution has spread to include Europe, the Middle East, Asia, Oceania, and North America.

Conclusion

Immunocompromised patients present unique challenges for clinicians diagnosing and managing infectious diseases. A systematic approach to these patients emphasizing assessment of level of immune compromise, review of the use of prophylactic medications, a detailed history of potential exposures, and a thorough review of endemic risks in the region is key to obtaining a timely and accurate diagnosis. Given the atypical presentation and rapid progression of infections that occur in this unique patient population, early microbiological diagnosis, when feasible, may be important to guide treatment. Given the atypical presentation and rapid progression of disease that occurs in this unique patient population, early accurate microbiological diagnosis can guide critical timely treatment. We hope this outline of immunologic and infectious risks in immunocompromised hosts will guide the

clinician to offer directed empiric treatment based on the level of severity of their patient's immunocompromise and comprehensive assessment of their geographic and other exposure risks.

Case study, adapted from Hart et al [204]

A 67-year-old native Australian who was four years post a deceased donor renal transplant for vasculitis on prednisone, mycophenolate, and tacrolimus developed graft failure two weeks after a 10-day trip to South-east Asia. He was given high-dose steroids and increased mycophenolate for one week for what was felt to be a flare of vasculitis. Six weeks later he presented with a three-week history of abdominal pain and diarrhea and was found to have pancytopenia, hepatitis, hypoalbumenia and decompensated with septic shock shortly after presentation. He ultimately required a laparotomy and Hartmann's procedure for a perforated sigmoid diverticulum and the opportunistic fungus *Penicillium marneffe* was isolated from both blood and peritoneal fluid (Figures 28.1, 28.2).

Penicillium marneffe is a thermally dimorphic fungus that is endemic across south-east Asia, with most clinical cases being described in Thailand, southern China, Hong Kong, Taiwan, and Vietnam. The published literature predominantly describes this infection among the local populations with HIV disease, although about two dozen reports in travelers with HIV and a handful in nontravelers with other forms of immunosuppression, such as a transplanted patient, are also noted by the authors of this case report. The organism is found in several bamboo rat species and inhalation of conidia in

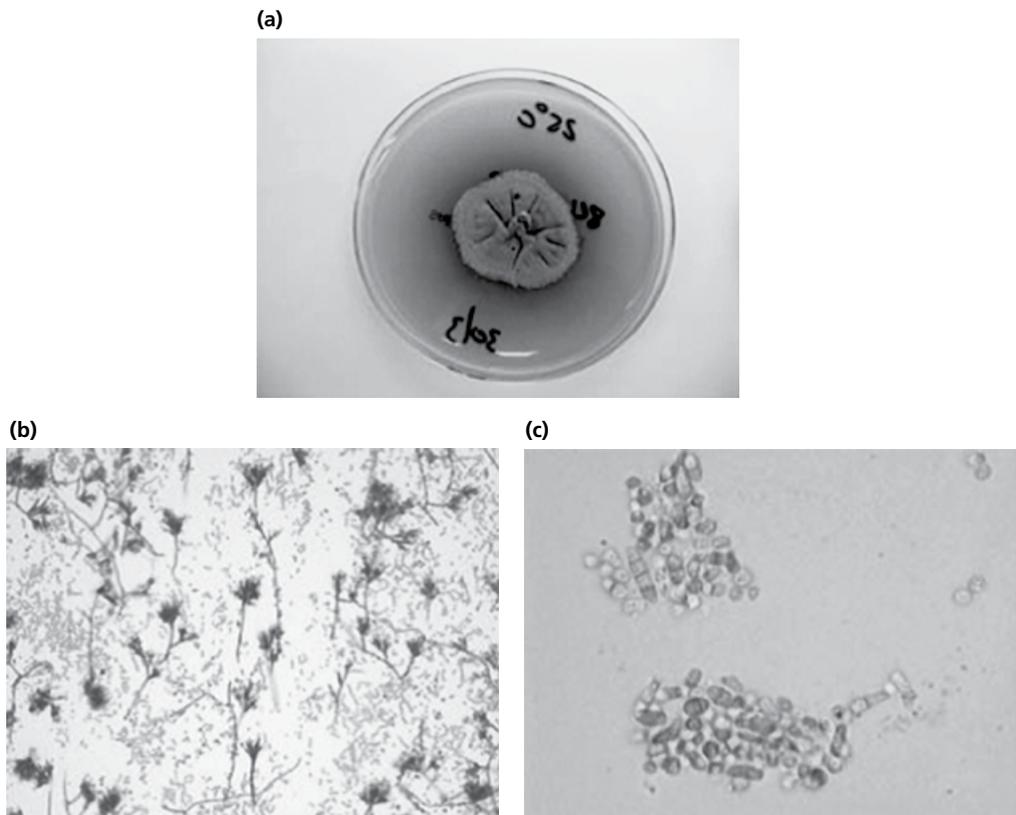


Figure 28.1 (a) Thermal dimorphism of *Penicillium marneffe*: mycelium at 25°C producing red pigment. (b) *P. marneffe* mold form. Lactophenol cotton blue stain. (c) Division by fission of yeast-like form of *P. marneffe* resulting in cross-wall formation. Source: Adapted from Hart et al [204]. Reproduced with permission of John Wiley & Sons.

rat-infested areas is the suspected route of transmission. The reports in travelers highlight that only a short period of exposure – in this case just a 10-day trip – is sufficient for transmission. Also notable is that this patient did not report any element of his trip to be particularly risky (it was the dry season and he did not have high levels of exposure to soil). Additionally, from the case reports in the literature, there can be latency between exposure and infection from months to years, or in some cases, such as this traveler, a burst of high-dose immunosuppression may have served as the trigger for disseminated disease. These features highlight the need for a high clinical index of suspicion and also the need to obtain a thorough and detailed travel history.

The patient eventually recovered with antifungal administration and modification of his immunosuppressive regimen, and his course was also complicated by renal toxicity from one of the antifungal agents used, amphotericin. These complications highlight the need for specialty input by an infectious disease specialist and ideally a transplant infectious disease specialist.

Pretravel assessment and counseling of any, but in particular immunosuppressed, travelers such as this transplant patient is crucial, given the geographically distinct presence of fungal agents in certain areas such as *P. marneffei* in South-east Asia. The new HIV/AIDS opportunistic infection guidelines

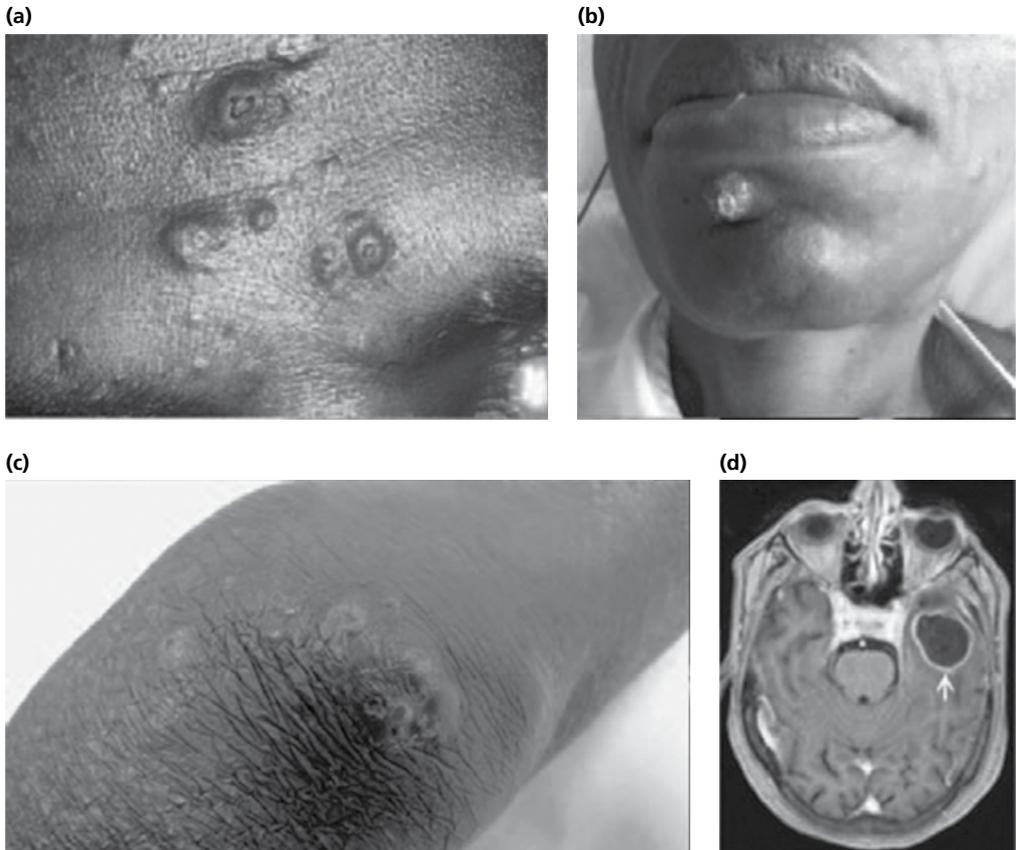


Figure 28.2 Dermatological and neurological findings in cases of tropical invasive fungal infection. (a) Skin lesions during disseminated *Penicillium marneffei* infection in a south-east Asian profoundly immunocompromised patient infected with HIV. (b) Skin lesions during disseminated *Histoplasma capsulatum* var. *capsulatum* infection in a Western African profoundly immunocompromised HIV-infected patient. (c) Skin lesions occurring on the knee during pheohyphomycosis in an African kidney transplant recipient (courtesy of Sarah Guégan, MD, PhD). (d) *Rhinocladiella mackenziei* brain abscess. Postcontrast axial T1-weighted magnetic resonance image showing the rim-enhancing left temporal lobe lesion with a central hypointensity. Source: Adapted from Lortholary et al [128]. Reproduced with permission of Oxford University Press.

support prophylaxis against *P. marneffei* with itraconazole for HIV infected persons with CD4 cell count less than 100 who will travel to or reside in Southeast Asia [205–206]. This approach is also suggested for HIV infected persons traveling to areas of the US endemic for histoplasmosis such as the midwest. Solid organ transplant recipients on immunosuppression require strategies for managing clinically meaningful drug-drug interactions between itraconazole and transplant immunosuppressive medications. [207] Severely immunosuppressed HIV infected travelers to the desert southwestern US also warrant aggressive intentional testing for coccidiomycosis with initiation of early empiric treatment for a new positive test, whether or not they have symptoms.

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Chapter 29

Emerging infections

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Infectious diseases are dynamic and can be expected to continue to change in the foreseeable future. Characteristics of the world today, including extensive interconnections via travel, trade, and migration; human population size, density and location; expansion of food animal populations and increasing contact with wild animal populations; changes in the environment, land use, and climate; and poverty and lack of infrastructure to provide adequate food, clean water, and sanitation, all contribute to the opportunity for new and changed microbes to emerge and spread. Because of their resilience, variety, abundance, short generation time, and capacity to change through a variety of maneuvers, microbes can flourish in new settings. Several disease examples illustrate how multiple factors typically converge to contribute to disease emergence.

Introduction

Infectious diseases in humans are dynamic. Infections have changed in distribution, intensity of transmission, and type in the past and will continue to change in the future. Infectious diseases have shaped human history, and they remain a reason for concern, research, and surveillance. The dynamic nature of human infections means that any attempt to pin down where they exist and display this distribution on a map will never be completely up to date for many diseases. Familiar, extensively studied infections, such as tuberculosis and staphylococcal infection, can change in virulence and resistance patterns. Infections that are new or newly recognized, such those caused by the Nipah, Middle East respiratory syndrome (MERS), and severe acute respiratory syndrome (SARS) viruses, appear and spread, their epidemiology influenced by the biological characteristics of the viruses, their origins, and routes of spread.

The types of changes that can occur in known infections are several and include the following.

- Change in the distribution (expansion, contraction, or appearance in an entirely new area or population); this may be the result of a new route of transmission.
- Increase in resistance to treatment.
- Increase in virulence or transmissibility of a pathogen, leading to infection that is more widespread, more severe, or both.
- Change in clinical expression because of host factors (e.g. Kaposi's sarcoma and other unusual expressions of common infections in individuals with AIDS).

Table 29.1 gives some examples of each of these types of changes and shows the wide range of contributing factors that can lead to change in a disease.

In addition to changes in familiar pathogens, in recent years we have seen the appearance of infections in the human population that were previously absent or not recognized. Many of these infections are zoonoses and have crossed the species barrier from animals to humans, and some

Table 29.1 Examples of the dynamic nature of known infections.

Observation	Infection	Event	Contributors	Consequences
Expansion of distribution	Dengue fever	Increase in number of countries with outbreaks Increase in severity with circulation of multiple serotypes	Increase in international travel Increase in urbanization and population growth, especially in tropical and subtropical areas Inadequate vector control programs Spread of <i>Aedes</i> vector Ecoclimatic conditions	Increase in cases and deaths Economic consequences because of loss of time in school and at work; increase in costs for healthcare
Contraction of distribution	Measles	Elimination of indigenous transmission of measles in the Americas	Availability and wide use of measles vaccine	Decrease in illness and death Infections and small outbreaks occur related to travel Objections to use of vaccine in some groups and pockets of susceptible individuals
Increasing resistance to treatment	Tuberculosis	Appearance of MDR and XDR tuberculosis with spread to multiple countries and populations	Inappropriate use of anti-TB drugs Evolutionary potential of microbes Lack of access to appropriate anti-TB drugs Lack of laboratory capacity to diagnose TB and test drug susceptibility Increased susceptibility because of HIV infection Expanding populations infected with HIV Crowded housing facilities; clinics with patients and HIV and TB Congregate settings that favor transmission (e.g. prisons, hospital, underground mines) Inadequate infection control in many healthcare settings Increase in international travel Inadequate resources invested in TB research and control Lack of highly effective vaccine	Increase in disease and death Marked increased in cost of treatment for infections Need to treat with multiple drugs with significant toxicity No effective drugs available for some infections Increased infections and deaths in healthcare workers

(Continued)

Table 29.1 (Continued)

Observation	Infection	Event	Contributors	Consequences
Increase in virulence or transmissibility	<i>Clostridium difficile</i> colitis	Appearance and spread of strain that produces more toxin	Evolutionary potential of microbes Extensive use of antimicrobials in hospitals and chronic facilities Movement of patients and staff between acute and chronic care facilities Demographic changes with increase in population >80 years old (associated with more severe disease)	Increase in hospitalizations and deaths Appearance of community-acquired <i>Clostridium difficile</i> colitis Change in the epidemiology

are now well adapted to person-to-person spread (e.g. HIV). Among these, viruses, especially RNA viruses, predominate. Many different routes of transmission characterize these infections, including transmission via mosquitoes and other arthropod vectors and via medical procedures.

Many factors can contribute to the emergence of new microbial threats [1], often working synergistically. This chapter will explore some of these major factors and will illustrate them with examples. The main focus will be on infections that are new or newly recognized in the human population. The biological characteristics of microbes (abundant, diverse, ubiquitous, resilient, able to survive in extreme environments (extremophiles), capacity to change rapidly in response to an altered environment (mutation, acquisition of new genetic material, recombination, and other molecular maneuvers), and multiple survival mechanisms (e.g. spores, latency, dormancy)) mean that microbes are well suited to occupying new niches, often created by human activities [2]. They are simply trying to survive.

The factors in emergence defined in the 2003 IOM report remain relevant today [1].

- Microbial adaptation and change
- Human susceptibility to infection
- Climate and weather
- Changing ecosystems
- Economic development and land use
- Human demography and behavior
- Technology and industry
- International travel and commerce
- Breakdown in public health measures
- Poverty and social inequality
- War and famine
- Lack of political will
- Intent to harm

Major global trends

Several major global trends should be highlighted because they provide the milieu in which infections are changing. Key ones include population size, density, location, and mobility [3]. Climate change, which can also influence infectious diseases, is covered in Chapter 31. The size of the human population is larger than ever in human history – a larger substrate for replication events in microbes. The

same can be said for the population of food animals. The increasing affluence in China and other countries and the desire for more animal protein have resulted in major increases in the food animals. In China, for example, between 1968 and 2005, while the number of humans increased less than twofold, the pig population increased more than 100-fold and the poultry population more than 1000-fold [4]. Commercial farms that are raising wild animals for human use (e.g. food, traditional medicines, pets, decoration, souvenirs) have increased dramatically, especially in East and South-east Asia, in the past two decades [5].

Among destinations for the animals are upscale urban wild meat restaurants. Animals raised on the farms are varied, and include sika deer, bears, tigers, crocodiles, turtles, Burmese pythons, field crickets, Chinese cobras, wild pigs, and many species of birds. These farms and the harvesting, preparation, and trade in these animals and their parts serve to expand the wild animal–human interface and allow the juxtaposition of species (microbial and other) that have never before been in contact. Live animals and their parts enter legal and illegal markets and are dispersed widely within and outside the region. In an analysis of 335 emerging infectious disease events reported between 1940 and 2004, researchers found that 60.3% of emerging infections were considered to be zoonoses, the majority (71.8%) originating from wildlife [6].

More than half of the global population now lives in urban areas, and the percentage of the population living in urban areas is expected to continue to increase. This means that more people are living in dense settlements, settings where infections can easily reach large, susceptible populations. Most of the population growth today is occurring in urban areas of developing countries, much of it in areas without adequate infrastructure. Many residents lack clean water and sanitary facilities and live in poorly constructed structures that permit contact with rodents and other animals, mosquito and other arthropod vectors – factors that also place them at risk for infections.

In 2008, the majority of the 25 largest megacities (cities with more than 10 million inhabitants) were located in tropical and subtropical areas; only four were in temperate areas [7]. This is in contrast to the location of the world's largest cities in 1900, when they were located primarily in temperate zones. Most of the recent and projected population growth is also taking place in tropical and subtropical areas. It has been observed that the greatest species diversity (including pathogens) exists at the equator; species diversity declines at higher latitudes, something called the species latitudinal gradient [8]. Many low-latitude cities today have vast slum areas and are poorly equipped to provide diagnosis, treatment, surveillance, and control of infectious diseases. These are areas where new infections may emerge and spread.

Travel, trade and migration

The enormous volume of trade and travel in today's world is a key contributor to the movement of pathogenic microbes around the world – the old and the new [3,9]. In 2014, for example, international tourist arrivals reached 1.138 billion [10]. Infections that are carried by humans and spread from person to person, such as tuberculosis, HIV/AIDS, and influenza, can be easily transported to any part of the world by traveling humans [11]. Humans also transport resistance genes in pathogens and also as part of their commensal flora. Receiving medical care in India, often as part of so-called medical tourism, for example, was identified as a common factor in patients infected with Enterobacteriaceae carrying a resistance gene (New Delhi metallo-beta-lactamase-1) that confers resistance to all or most antimicrobial agents [12]. Bacteria carrying this resistance mechanism have now spread widely.

The ease and speed of spread of an infection vary depending on the characteristics of the pathogen, route of spread, the population groups affected and their travel and behavioral patterns. The H1N1 influenza virus that emerged in 2009, with genes from pigs, humans and avian species, and was easily transmissible from person to person, rapidly spread globally [13]. In contrast, the highly pathogenic avian-origin H5N1 virus that was first recognized in humans almost two decades ago is found widely in avian populations in Asia and has also appeared in Europe and Africa (Figure 29.1), but the majority of human cases have resulted from contact with infected wild or domestic poultry populations,



Figure 29.1 Thai eagles infected with H5N1 smuggled into Brussels in hand luggage and confiscated at the Brussels International Airport. Source: Centers for Disease Control and Prevention.

and multiple chains of person-to-person transmission have not been established to date [14]. The SARS coronavirus that was first identified in humans in 2003 was carried by air travelers to multiple continents. Only because of the characteristics of the pathogen, i.e. fever began before patients transmitted the virus and there was no chronic carrier state, was it possible to halt the spread of this virus with intensive use of quarantine and isolation (see below) [15].

In contrast, the human immunodeficiency virus (HIV) epidemic and pandemic unfolded slowly, over years and decades. Because early symptoms may be mild, nonspecific or absent, and infection is typically followed by a prolonged asymptomatic period during which the virus can be transmitted through sexual activity, needle sharing, from mother to infant, and other exposures to infected fluids or tissues, the virus was able to gain a foothold in all regions of the world before its clinical

course and epidemiology were well understood. The factors that make it more likely that an introduced infection can be controlled are discussed in a paper by Fraser and colleagues who point out the importance of the duration of asymptomatic infection during which transmission can occur [16]. Because influenza has a short incubation period and shedding can start before symptoms begin, spread occurs rapidly.

One of the factors that allows certain new infections to be transmitted and to become established in a new geographic area is the presence of competent arthropod vectors. Global trade has played a key role in the establishment of vectors, such as *Aedes albopictus*, in new geographic areas [17]. West Nile virus, which emerged in the United States in 1999, has now swept across the country and into Canada, Mexico, and other parts of Latin America. In this instance, competent mosquito vectors and susceptible avian species were already in place. The introduction of the virus – in a mosquito, animal, or person – allowed the virus to gain a foothold and move across the country over a several year period [18]. The virus is now established in animal/bird and mosquito populations and will not be eliminated.

The following examples demonstrate the range of factors and show that typically several factors act together to allow introduction, establishment, and spread of a new infection.

SARS and MERS

SARS

The severe acute respiratory syndrome was caused by a novel coronavirus (SARS-CoV), first identified in 2003. In retrospect, cases had occurred in China in late 2002. In February 2003, however, the virus spread to multiple countries and gained worldwide attention [19]. The virus, carried by humans, spread to at least 28 countries. In the United States, 97% of cases followed international travel. Collaborative research led to the rapid identification of the virus in 2003, and intensive control efforts globally were successful in interrupting spread. More than 8000 cases were identified, almost 800 of them fatal. The population most affected was healthcare workers and their contacts. In Singapore, for example, 76% of the cases were nosocomial.

The proximate source of the virus was found to be masked palm civets, which were sold in live animal markets in Guangdong Province, China. They were culled after the SARS outbreaks. Researchers subsequently found SARS-like coronaviruses in bats in China. Among groups of bats tested, 28–71% had antibodies to SARS-CoV, and fecal samples were PCR positive for the virus [20]. This established bats as a likely natural reservoir host. Bats can be found in live animal markets in China, where it appears that the virus was able to enter the susceptible civet population, from which humans first acquired infection.

Other features of the SARS epidemic are notable. Marked differences occurred in the number of secondary cases generated by each infected individual. Although overall, the basic reproductive number (number of secondary cases generated by a single infectious case in a susceptible population) for SARS was about 3 [21], some individuals generated dozens of secondary cases. For example, in Singapore, five individuals were the source of infection for 103 of the first 201 cases (Figure 29.2). Superspreading has also been noted as a feature in other emerging infectious diseases [22]. With acute influenza infections, for example, a study found the amount of virus released into the air varied markedly, with a minority of patients emitting up to 32 times more virus than others [23].

Because of the biological characteristics of the SARS Co-V, it was possible to contain the virus [16]. With SARS, fever was virtually always present before the onset of transmissibility. By closely monitoring potentially exposed persons for fever and isolating those with fever, it was possible to interrupt spread. Unfortunately, with other infections, such as influenza and HIV, some or much of the transmission occurs before the onset of symptoms and during asymptomatic infection. Fortunately, with SARS, many of the early cases that spread from China occurred in cities (e.g. Hong Kong, Singapore, Toronto) with excellent medical facilities and strong public health infrastructure, which made it feasible to control transmission.

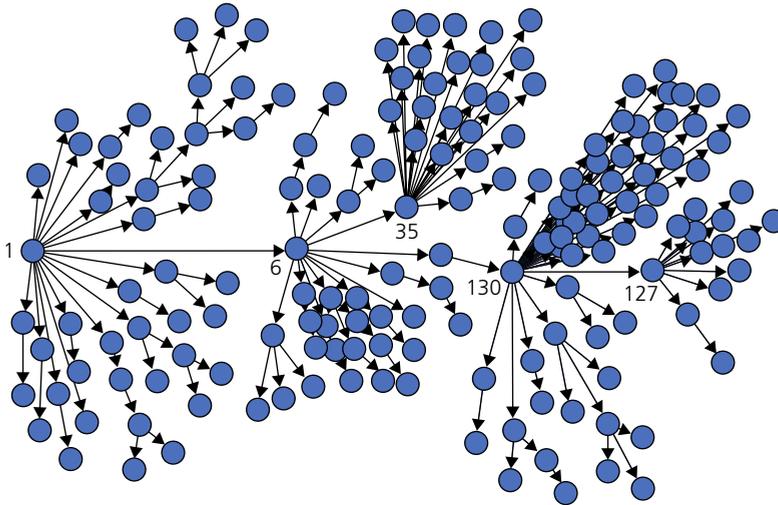


Figure 29.2 Severe acute respiratory syndrome – Singapore, 2003. Source: Centers for Disease Control and Prevention.

Note: Each dot represents one person with SARS. The arrows indicate the direction of transmission.

One dramatic transmission event took place at the Amoy Gardens, an apartment complex in Hong Kong where more than 300 residents became infected in 2003. Investigators concluded that air-borne transmission had occurred within the apartment complex, and the pattern of spread was consistent with virus-laden aerosols (generated from an index case with high concentrations of SARS-Co-V in feces and urine in drainage from a toilet). Spread was consistent with an aerosol carried by a rising plume of warm air in the air shaft between buildings. The contaminated plume entered other apartments through open windows [24].

MERS

Another coronavirus, known as the Middle East respiratory syndrome (MERS) virus, was first recognized in the Middle East in 2012 [25]. It also causes severe respiratory infection and has primarily affected older individuals, with males predominating, and those with chronic medical problems. The majority of the >1600 cases have occurred in Saudi Arabia; mortality among reported infections has been about 40%. A businessman with MERS returning to South Korea from Saudi Arabia in May 2015 sparked an outbreak that involved 186 documented MERS cases (at least 36 deaths) and at least four generations of spread, with much of the person-to-person transmission occurring in healthcare facilities [26]. Among those infected, 26 were healthcare workers. Use of isolation and quarantine and tracing of >16 000 contacts successfully interrupted spread.

The MERS virus has caused multiple nosocomial outbreaks. Recent studies confirm that dromedary camels are an important reservoir for maintenance and diversification of the virus and a source of human infection [27]. The major mode of shedding of the virus is from the respiratory tract of camels. In a survey in Saudi Arabia, 25% of 1309 camels were found to be positive for MERS-CoV by RT-PCR. Persons with close camel contact are more likely to have antibodies to MERS coronavirus than those without such contact [28]. Exposure to persons with unrecognized infection may be a source of infection. Bats can also carry a similar virus.

At present, no specific treatment is available and potential introductions of the virus into the human population remain an ongoing threat, as the outbreak in South Korea demonstrated. Although diagnostic tests are available, knowledge of the infection and resources for appropriate infection control are limited in many parts of the world. One line of research is development of a vaccine for camels that could prevent infection and reduce virus excretion from those infected [29].

Monkeypox

Monkeypox is caused by a zoonotic orthopoxvirus identified in 1970. Cases were first described in remote villages in central and western Africa rainforest countries. The majority of reported cases have been from the Democratic Republic of Congo (DRC). The disease resembles smallpox, though lymphadenopathy is more prominent. Case fatality rates are 1–14% in children not vaccinated against smallpox. The infection, acquired from direct contact with infected animals, can also spread from person to person. The longest chain of transmission was seven generations, but transmission usually does not extend beyond a second generation. A number of African rodents have been implicated as a source of the virus. Smallpox vaccination provides partial protection against infection. In the DRC smallpox vaccination was officially discontinued in 1980.

A study in 2010 documented a major increase in human monkeypox incidence, which has coincided with the end of smallpox vaccination programs and the growing size of the unvaccinated population. Researchers assessed the number of cases of human monkeypox between 2005 and 2007 and compared data with those from population-based surveillance carried out in similar regions from 1981 to 1986 [30]. Overall, they found an average annual cumulative incidence across zones of 5.5 per 10000. Comparison with data from the 1980s suggested a 20-fold increase in human monkeypox incidence. Those who had been vaccinated against smallpox had a 5.2-fold lower risk of infection. As the proportion of the population that is unvaccinated expands, person-to-person transmission may become more common. Also, expansion of the HIV-infected population means that infection in that immunocompromised population may be more severe and duration of viral shedding may be longer, providing opportunity for the virus to acquire mutations that could improve its fitness as a human pathogen.

Although the virus is found in squirrels and several other rodent species, its geographic habitat is Africa. In 2003, however, a human outbreak occurred for the first time in the Western hemisphere, in the mid-western United States. The multistate outbreak was traced to imported African rodents that had been housed with prairie dogs from the US that were being sold as pets [31]. The prairie dogs, which are not normal hosts for the virus, developed disease and were the source of infection in humans who handled them. There was no secondary person-to-person spread. There has been no evidence that new animal populations have become infected with the virus, but many animal species are susceptible to infection, including American ground squirrels. This is a reminder of the importance of wildlife reservoirs for many infections and the multiple routes by which infections can potentially become established in a new geographic region.

Chikungunya virus

Vector-borne infections are also among those that can change rapidly in distribution. A competent vector must be present to allow the introduction of the infection into a new geographic area. One striking example has been the emergence and spread of chikungunya virus infection since 2004 outside its endemic zone in parts of West Africa, where the virus appears to be maintained in a cycle involving humans, *Aedes* mosquitoes, primates, and perhaps other animals [32].

Chikungunya is an RNA virus in the family *Togaviridae*, genus *alphavirus*, and an arbovirus (arthropod-borne virus). The virus was first identified during an outbreak in East Africa in the early 1950s. Lineages defined based on phylogenetic studies include West African enzootic, Asian urban, and east, central, and southern African (ECSA) [32]. A massive outbreak in Lamu, an island off the coast of Kenya, in 2004 was estimated (based on a serosurvey) to have affected 75% of the island's population of 18000. Huge outbreaks followed in the Indian Ocean islands and the virus subsequently spread to India, Sri Lanka, Indonesia, Malaysia, and Thailand. In India, the epidemic was estimated to affect >1.5 million individuals between October 2005 and July 2009, and it spread at least 17 states/union territories [33].

Although chikungunya infection has been considered a tropical disease, in the summer of 2007 an outbreak occurred in two villages in northern Italy with 175 of the cases being laboratory confirmed.

An investigation implicated a visitor from India as the index case [34]. The outbreak took place during the hottest months of the year and transmission stopped with arrival of cooler weather. More recently, local transmission has also been documented in southern France, in 2010 and again in 2014 with an outbreak in Montpellier involving 12 cases (11 confirmed, one probable). In the latter outbreak, the source was a traveler from West Africa [35].

A factor that contributed to the massive outbreaks in the Indian Ocean islands was a mutation in a gene encoding the envelope protein of the chikungunya virus [36, 37]. This mutation has been associated with enhanced susceptibility of *Aedes albopictus* to infection with chikungunya virus and with more rapid viral dissemination to the mosquito salivary glands. This means that a mosquito can become infected when exposed to a lower level of virus in the bloodstream of the host. The mutations enhance viral fitness and have occurred in at least four chikungunya viruses in different geographic locations. The mutations have involved viruses of the ECSA lineage [37].

In October 2013, local transmission of chikungunya virus was documented in the Caribbean; the virus has since spread widely in the Western hemisphere [32]. As of December 2015, 1.7 million suspected or confirmed cases had been reported. The primary genotype circulating in the Americas is the older Asian lineage, which has been found to be genetically constrained in its capacity to adapt to *Aedes albopictus* [32]. However, in 2014 the ECSA lineage was identified in an outbreak in Bahia State, Brazil. Findings suggested that the index case had become infected in Angola. The Asian lineage is also circulating in Brazil. The ECSA lineage in Brazil has not acquired, to date, mutations that allow more efficient transmission by *Ae. albopictus* [38] but careful follow-up is warranted.

***Aedes albopictus* (Asian tiger mosquito)**

The mosquito vector, *Aedes albopictus* (the Asian tiger mosquito), has become widely distributed globally, moved largely by ships and often in used tires which provide an ideal way to transport mosquitoes or their eggs or larvae to new locations [17]. Although *Aedes albopictus* is more cosmopolitan in its feeding habits than *Aedes aegypti* (which has strong preference for human blood), *Aedes albopictus* is able to survive cooler temperatures so can be found in temperate as well as tropical environments. The mosquito is now found in many parts of Europe [39], the Americas, and Africa, having expanded from its original distribution in Asia.

Conditions that must be met for an arbovirus to be introduced into a new area are infected humans who are viremic when they reach an area infested with *Aedes* mosquitoes and environmental temperatures that are sufficiently warm to allow the virus to disseminate to the mosquito salivary glands. The infected mosquito must survive long enough to bite a susceptible human host. Warmer temperatures shorten the extrinsic incubation period of the virus in mosquitoes. The huge volume of global traffic today makes it easy for the chikungunya virus, similar to the dengue virus, to reach new populations. Dengue fever, also spread by *Aedes* mosquitoes, has also increased in number of cases and number of countries affected [40]. Transmission of dengue virus has also been documented in Croatia and south-eastern France [41]. Since 2007 Zika virus, another flavivirus, has caused major outbreaks in Oceania and in 2016 was spread widely in the Americas [42].

Factors that have contributed to the spread of chikungunya and Zika (and intensification of transmission of dengue) include increased air travel, large susceptible populations, urbanization, and abundant mosquito vectors.

Zika virus

The explosive spread of Zika virus in 2015–16 has been followed by recognition of severe sequelae of infection and of nonvector modes of transmission. In north-east Brazil, reports of increased cases of microcephaly appeared in 2015. Subsequent studies have confirmed an association with Zika infection during pregnancy [43]. Reports confirm fetal loss, *in utero* growth restriction, ventricular calcifications,

and other central nervous system lesions. Adverse outcomes have followed infection at any time during pregnancy [44]. The full spectrum of consequences in the developing fetus remains to be defined. A retrospective study of French Polynesia (where an estimated 66% of the general population was infected with Zika virus) also found an increase in microcephaly [45]. Cases of Guillain-Barré syndrome (GBS) have also followed infection with Zika virus, including asymptomatic infections [46]. Recent papers document a broader range of neurological events, including myelitis and acute disseminated encephalomyelitis (ADEM). A few deaths have also been recorded.

Although transmission in the Americas, as elsewhere, has been primarily vector borne, with *Aedes* mosquitoes the primary vector, sexual transmission has been documented multiple times; virus can persist in semen after recovery from acute infection. Transmission can also occur via blood transfusion. Although the virus can be found in saliva and breast milk, transmission via these fluids has not been documented to date.

Speculation about possible reasons for the rapid spread and size and severity of the recent outbreaks has included mutation in the virus to allow more efficient transmission or higher levels of viremia, possible immune enhancement because of prior dengue infections, or other not yet understood co-factors [47]. Recent studies show that the virus is structurally stable even when incubated at 40°C, in contrast to dengue viruses [48].

It remains to be seen whether the virus will become established in nonhuman primates (the way the yellow fever virus has) or other animals that can serve as reservoir hosts for the virus in the Americas [49]. This would influence future epidemiology and prospects for eradication.

Food-borne infections

Unexpected infections appear in unlikely places related to our globalized food supply. The food chain as become very long and has many links – and many potential steps when contamination can occur. Pathogens are primarily viruses, bacteria, and protozoa and affect a wide range of food types, including fresh and processed foods. Because of mass processing and distribution chains, an outbreak may involve persons in different countries or regions of the world.

Meat, chicken, and other foods can be vehicles for the dissemination of resistance genes. The regular use of antibiotics in food animals, including antibiotics critically important in human medicine, has been associated with increasing resistance in human pathogens. The recent identification of plasmid-mediated transferrable colistin resistance in human pathogens in humans, animals, and animal products is of grave concern because colistin is often the antibiotic of last resort in treating multidrug-resistant gram-negative infections. Colistin is currently widely used in agriculture [50].

The availability of molecular techniques makes it possible to identify the precise origin of an outbreak organism. In 2013, 165 hepatitis A cases in 10 states in the US were linked to frozen berries. RNA extraction and genetic sequencing of the virus in outbreak-related cases found it to be genotype IB, a genotype uncommon in the US and common in the Middle East. The frozen berries implicated epidemiologically included five fruits – cherries from the US, strawberries from Argentina, and pomegranate arils from Turkey. The outbreak was linked epidemiologically to the pomegranate arils. In this outbreak, the retailers were able to contact >250 000 consumers who had bought the product, using automated phone calls. They also provided immunoglobulin and hepatitis A vaccine to many who had been exposed [51].

In the US, the largest number of hospitalizations related to food-borne infections are estimated to be from nontyphoidal *Salmonella* spp., noroviruses, and *Campylobacter* [52]. Illnesses due to Shiga toxin-producing *Escherichia coli* have been dramatic because of high rates of hemolytic-uremic syndrome in some, such as the one in Europe in 2011 attributed to contaminated sprouts [53].

The WHO has established the Food-borne Disease Burden Epidemiology Reference Group (FERG) (www.who.int/foodsafety/areas_work/foodborne-diseases/ferg/en/) to measure the burden of food-borne disease regionally and globally. The group estimates that the global burden of food-borne diseases is comparable to major infectious diseases, such as HIV/AIDS, malaria, and tuberculosis. Major causes of food-borne disease deaths include diarrheal agents, such as nontyphoidal *Salmonella enterica*, but also typhoid fever, the parasitic infection *Taenia solium*, and hepatitis A virus [54].

Conclusions

Changes continue to occur in old diseases, such as tuberculosis, which has increasingly become resistant to treatment. Many social factors and interaction with HIV/AIDS have made it a formidable foe. Influenza, another old disease, continues to change in ways that have not been predictable and it remains a serious global threat.

The above examples illustrate the complexity of disease emergence and some of the reasons why the global community must expect and prepare for the continued emergence of old and new microbial threats. The Ebola epidemic in Africa in 2013–14 was a stark reminder of the gaps in global preparation for dealing with an emerging disease. In this case, the virus was already well known because of multiple previous outbreaks in Africa. Despite this knowledge, early signals were missed and the world was unable to mobilize the needed leadership and resources to intervene early in the epidemic, which had profound social, economic, and political consequences.

Recent analyses have tried to identify reforms needed to avert a future disaster [55]. We have more tools available for surveillance, communication, diagnosis, and prevention but at the same time are more vulnerable because of the speed and volume of travel, migration, and trade and profound changes in ecosystems and socioeconomic systems.

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Chapter 30

Migration and the geography of disease

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Around 232 million people are international migrants. While the number of international migrants has increased in absolute terms, the share of international migrants in the world population remains constant at around 3%. Migrants are a heterogeneous population which includes internally displaced persons, temporary migrants and workers, students, conventional travelers, VFR (visiting friends and relatives) travelers, immigrants, refugees and adoptees. Each of these groups will present distinct challenges regarding public health issues and possible interventions and all these groups contribute to changes in the global geography of infectious disease.

Migration and infectious diseases

With 33.3 million people internally displaced and 16.7 million refugees, the number of people displaced by violence and conflict today in the world is the highest since World War II. An unprecedented number of man-made crisis in the world, including in Syria, Iraq, Libya, the Central African Republic and South Sudan, Ebola impacting the economies of West Africa, climate change, and extreme weather events are all factors driving migration [1].

In the hope of finding better lives for themselves and their families, the number of migrants dying on dangerous journeys is rising: some 5000 migrants lost their lives in 2014 at sea or in remote deserts or mountains. This makes this year the deadliest year on record, with double the number of the previous year's deaths [2].

The health of migrants has social and economic consequences for host countries as well as for individuals and their families. A variety of factors may influence immigrants' health, and these include biological factors, exposure to endemic diseases in their countries of origin, migration routes, overcrowding, and occupational hazards [3].

Most migrants are healthy, young adults, but they often bear a disproportionate burden of infectious diseases [4].

Noncommunicable diseases associated with migration include genetic diseases such as hemoglobinopathies, autoimmune diseases, psychological or psychiatric problems, and nutritional deficiencies. Certain tumors may also be included, such as cervical and hepatocellular carcinoma, associated with higher prevalence of human papillomavirus (HPV) and hepatitis B virus (HBV) infection, respectively, and gastric and esophageal cancer linked to specific dietary habits.

Communicable diseases and infectious diseases in immigrants can be classified as common infections (such as respiratory infections and vaccine-preventable diseases), transmissible infections (HIV, TB, syphilis), and infections which are more typical of tropical areas, such as typhoid fever (more frequent

in immigrants from the Indian subcontinent), malaria (in immigrants from sub-Saharan Africa), schistosomiasis and filariasis (in West Africans), and cysticercosis and Chagas' disease (in Latin Americans) [5,6].

Vaccine-preventable diseases

According to the WHO, immunization averts an estimated 2–3 million deaths every year. However, an estimated 21.8 million infants worldwide are still missing out on basic vaccines [7].

Measles

Measles vaccination has led to a decrease in measles cases and deaths worldwide, with a 75% recorded drop in measles deaths between 2000 and 2013. However, in 2013 there were 145 700 measles deaths globally and measles is still common in many developing countries, especially in Africa and Asia. More than 95% of measles deaths occur in countries with low per capita incomes and weak health infrastructures [8]. Outbreaks have occurred even in developed countries following conventional travel (tourism) and travel for international adoption, in unvaccinated students returning from developing countries, and in specific migrant populations [9].

In areas like the European region, measles elimination remains a challenge. Data from 2013 show that vaccination coverage rates with two doses of measles-containing vaccine in EU/EEA member states are below the 95% target necessary to interrupt circulation of the virus. Several recent outbreaks have been noted, such as the large outbreak that started in October 2014 in Berlin, Germany, where the index case was identified as a child asylum seeker from Bosnia Herzegovina. The outbreak spread to the general population and other European countries including Norway, France, and Austria [10]. Another outbreak, involving the African measles virus B3 genotype, was notified recently in Israel, affecting predominantly unvaccinated migrants of Eritrean and Sudanese origin [11]. Virus importation from other continents where measles is highly endemic may lead to prolonged circulation and spread after introduction into high-risk unvaccinated populations.

Rubella

According to the WHO, rubella vaccine was introduced nationwide in 137 countries by the end of 2013 [7]. Substantial progress has been made in control of this infection and in 2015 the American region was declared free of indigenous rubella transmission. However, adults born before the start of routine immunization may remain susceptible and there are regions where vaccination is still not included in programs, as occurs in most African countries.

Globally, rubella infection therefore remains one of the leading causes of preventable congenital birth defects. A proportion of adult migrants to Western countries may not be immunized and these circumstances may lead to outbreaks, such as occurred in 2004 and 2005 in Madrid, Spain, mainly involving nonvaccinated populations from Latin America as well as Spanish males born before the introduction of universal measles mumps rubella vaccination in the early 1980s [12].

Studies of specific outbreaks are essential in order to obtain accurate data on the distribution of different rubella genotypes worldwide which may allow better management and monitoring of epidemics.

Hepatitis A

Even though hepatitis A virus (HAV) has a worldwide distribution, HAV seroprevalence is highest in less developed countries of Central and South America, Africa, and Asia. As health standards improve in certain areas, a decrease in seroprevalence may be observed. Importation of HAV by immigrant VFR children and subsequent transmission to the general population in the host country has been demonstrated [13]. A study carried out recently in The Netherlands concluded that second-generation migrants, particularly children of Moroccan and other non-Western ethnic backgrounds, may be an important risk group for virus importation [14]. Besides the use of hepatitis A vaccines to control

outbreaks, vaccination of high-risk groups (such as travelers to areas of high endemicity) is recommended in countries with low and very low endemicity and universal vaccination should be considered in countries with intermediate endemicity [15].

Hepatitis B

Although by 2013, hepatitis B vaccination for infants had been introduced nationwide in 183 countries, compared with 31 countries in 1992 [7], prevalence of HBV infection among certain immigrant groups may be high. Although rates may vary according to country/area of origin, observed rates particularly in Asian and sub-Saharan immigrant groups are generally higher than those found in the general population in host countries of the Western world. Further, several studies have shown that low-income immigrant populations may receive insufficient evaluation of their chronic hepatitis B infection and they may be undertreated [16]. Studies have also shown evidence for both vertical/perinatal and horizontal transmission of HBV infection in children born in the Western world to refugee or immigrant parents from countries of high endemicity, as illustrated in studies carried out in US-born children of Hmong refugees [17]. This supports the need for specific surveillance systems in risk groups and systems to ensure adequate vaccination protocols.

Human papillomavirus

Cervical cancer is caused by persistent infection with certain high-risk oncogenic types of HPV. This type of cancer is a major cause of morbidity and mortality worldwide, being more common in low- and medium-resource countries, mainly due to the implementation of screening programs in resource-rich countries. With the recent development of new vaccines for some types of HPV, immunization strategies may need to be developed in the near future to specifically include high-risk groups such as immigrant women from resource-poor countries.

Polio

Polio virus is associated with significant morbidity, and the infection has been targeted for global eradication. Polio remains endemic only in Afghanistan, Pakistan, and Nigeria, but several polio-free countries have reported imported infections in recent years. Many countries, but especially those experiencing armed conflicts where health services have been disrupted, remain at risk until the disease has been fully eradicated.

Pertussis

By 2013, 129 countries had reached at least 90% coverage of DTP3 vaccine [7]. However, the immunity conferred, especially by the newer acellular vaccines, may wane over time. A large epidemic of pertussis was reported in California, USA, in 2014, with reported incidence reaching more than five times baseline levels. The highest burden of disease was observed in infants under 12 months of age, especially Hispanic infants and in non-Hispanic white teenagers (14–16 years of age). Other studies in the USA have noted Hispanic infants to have higher rates of reported disease and pertussis-related deaths than non-Hispanic infants [18, 19]. The causes for these differences have not been established, but specific control strategies such as vaccination of pregnant women during the third trimester to enable transfer of maternal antibodies to the infant would appear to be especially relevant in high-risk populations.

Other infections

Other vaccine-preventable infections such as meningococcal disease, mumps, and influenza have been transmitted and imported into different areas by different types of mobile populations. Practitioners attending special risk groups should be aware of the detailed and updated information regarding the geographic distribution and prevalence of vaccine-preventable diseases in order to implement adequate and targeted control measures.

Tuberculosis

Tuberculosis (TB) remains a leading cause of morbidity and mortality worldwide. In 2013, an estimated 9.0 million people developed TB and 1.5 million died from the disease, 360 000 of whom were HIV positive. Most of the estimated number of cases in 2013 occurred in Asia (56%) and the African region (29%), while significant smaller proportions occurred in the Eastern Mediterranean region (8%), the European region (4%), and the Americas (3%). In terms of absolute incidence of cases of TB in 2013, India, China, Nigeria, Pakistan, Indonesia, South Africa, Bangladesh, Philippines, DRC, and Ethiopia are the top 10 countries (interval 2 000 000 to 200 000 cases). As regards incidence rate per 100 000 population, the top 10 were Swaziland, Lesotho, South Africa, Namibia, Djibouti, Mozambique, Zimbabwe, Timor-Leste, DPR-Korea, and Gabon (interval >1000 cases to 250 cases/100 000 population) [20] (Figure 30.1).

Migration from less developed areas of the world has led to a progressive increase in the number of TB cases amongst the foreign-born population in the Western world. In some countries, these cases now account for the majority of new diagnoses of TB. The risk of developing active TB is greater in patients from highly endemic countries, and reactivation is most common in the first two years following migration [21]. In the United States, the proportion of cases occurring in foreign-born persons has been increasing since 1993, representing 65% of the national case total for 2013. Foreign-born Hispanics and Asians together represented 79% of TB cases in foreign-born persons, and accounted for 51% of the national case total. The top five countries of origin of foreign-born persons with TB were Mexico, the Philippines, India, Vietnam, and China [22].

Tuberculosis cases among foreigners in Western Europe in 2013 represented 28% of the total TB cases reported from EU/EEA countries, mostly in people residing in low-incidence nations. In many countries, TB cases of foreign origin represent a large majority: Luxemburg (94.7%), Sweden (88.7%), Malta (88.0%), Norway (86.0%), Cyprus (85.4%), Israel (82.5%), Netherlands (73.9%), Switzerland (75.3%), and United Kingdom (70.1%). This is also an indication that access to TB diagnosis in these countries is good and that they are committed to the global effort to control TB [4]. The majority of non-EU originating TB cases are from the Eastern Mediterranean region and the South-east Asian region, while the majority of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB cases of non-EU/EEA origin are from the European region (Baltic republics), and higher proportions of TB-HIV co-infection were shown in cases coming from Africa [23].

In recent years, another concern has been the spread of MDR- and XDR-TB, partly as a consequence of the mismanagement of infectious cases and lack of adequate prevention. In 2013, an estimated 480 000 cases of MDR-TB emerged globally, representing 3.5% of new and 20.5% of previously treated TB cases. More than half of these cases were in three countries: India, China, and the Russian Federation. On average, an estimated 9% of patients with MDR-TB had XDR-TB [20]. In the EU/EEA, the countries with the highest prevalence of MDR-TB are Estonia (22.7%), Lithuania (18.9%), and Latvia (11.6%) [23]. Overall treatment success rates for MDR-TB are as low as 48%. Factors related to this unacceptable low cure rate are health system weaknesses, lack of effective regimens, and insufficient funding [20].

Data estimating the impact of the migrant population on MDR-TB in Western countries are scarce, but migration appears to have a clear influence on the spread of MDR-TB. A study of TB cases during 1993–9 found 2.0% of people born outside the UK (mainly from Africa and India) had an MDR-TB isolate compared with 1.0% of those born in the UK (odds ratio (OR) 1.97; $P < 0.001$) [24]. In another study, MDR-TB and XDR-TB among foreign-born patients in California accounted for 84.6% and 83.3%, respectively, of all cases of resistant tuberculosis diagnosed during the period 1993–2006 [25]. Overall data in the USA shows that among people with MDR-TB, the proportion occurring in foreign-born persons increased from 25% (103 of 407) in 1993 to 92% (75 of 82) in 2013 [22].

HIV infection

Since the HIV epidemic was first described in 1981, millions have become infected and have died worldwide. This virus, originating from equatorial Africa, has now spread extensively in all continents. The estimated number of people living with HIV worldwide in 2012 was 35.3 million. This is an

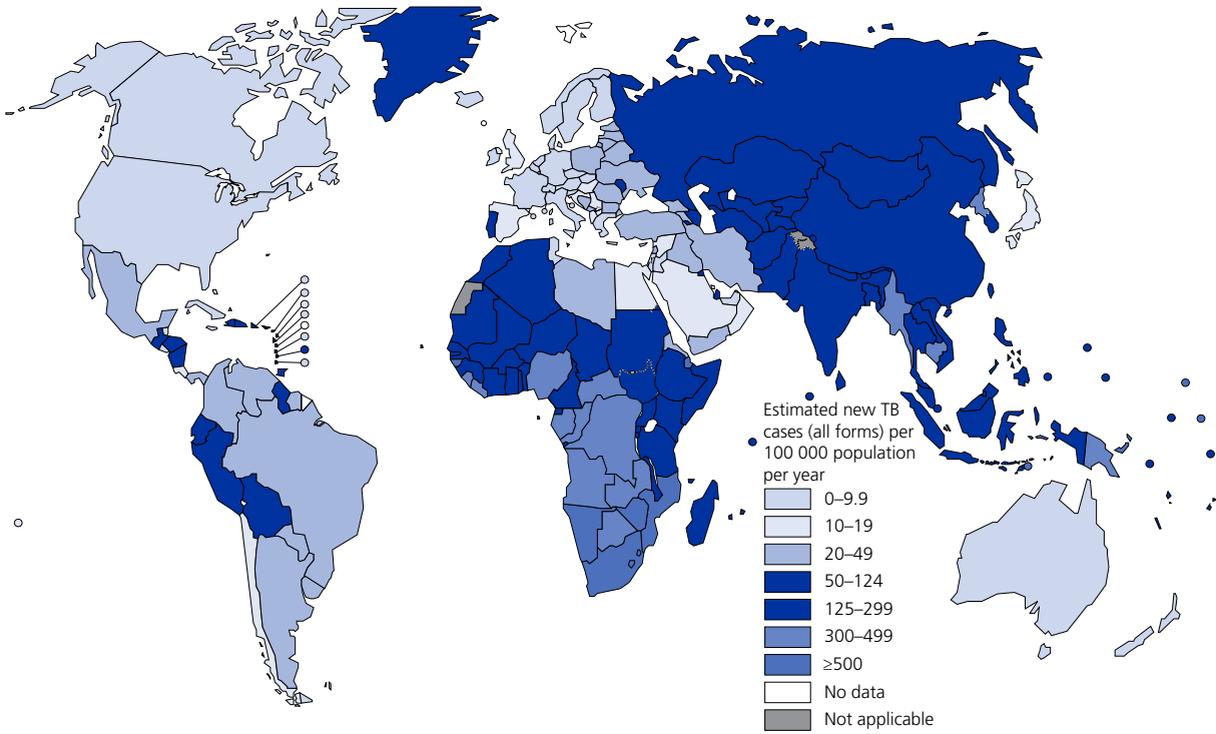


Figure 30.1 Estimated TB incidence rates, 2013. The number of incident TB cases relative to population size (the incidence rate) varies widely among countries. Source: World Health Organization.

increase from previous years as more people are receiving combination antiretroviral therapy (cART). With regard to the number of new HIV infections globally, there has been a 33% decline from the 3.4 million estimated for 2001 to the 2.3 million estimated for 2012. The number of new HIV infections among adults in low- and middle-income countries in 2012 was 1.9 million, which was 30% lower than in 2001. In the same sense, the number of AIDS deaths is also declining, with 1.6 million in 2012, down from 2.3 million in 2005 [26]. These encouraging figures are the consequence of a reduction in sexual transmission and in people who inject drugs, the reduction of mother-to-child transmission, and an increase in the population receiving cART.

However, the epidemic affects the developing world disproportionately and sub-Saharan Africa bears the greatest burden of the disease. In 2012, this region accounted for 71% of HIV infections worldwide, 70% of new HIV infections among adults, 88% of new HIV infections among children, and 75% of the world's AIDS-related deaths [26]. The prevalence rates for adults in South and South-east Asia are much lower than in Africa (0.3% versus 4.7%). However, given that 60% of the world's population lives in this region, this represents a substantial proportion of the HIV-infected population.

In 2012, approximately 159 000 newly diagnosed HIV cases were reported from Europe and Central Asia. Most of them were from Eastern Europe and Central Asia (130 000) where the prevalence of HIV infection is estimated to be 0.7%, compared to 0.2% in Western and Central Europe. For the same year, the number of new cases of HIV infection in North America was 48 000 (0.5% prevalence). In Latin America, the epidemic remains stable with a regional HIV prevalence of 0.4% and 86 000 new cases. Prevalence is higher in the Caribbean area (1.0%) [26].

Migrants from HIV-endemic countries comprise a substantial proportion of all HIV patients in Western countries. Until the mid 2000s, they were typically younger than local HIV-infected individuals, with a greater proportion of females and heterosexual contacts as a mode of transmission, reflecting the large contribution of people from high-endemic countries of sub-Saharan Africa. However, in recent years increasing numbers of males who have sex with males have been reported from other European countries and from Latin America. In the same way, migration from Eastern Europe, where injection drug use has been the main risk factor for HIV infection, could also impact the epidemiology of the HIV epidemic in Europe [27]. For the period 2007–12, 156 817 HIV cases were reported in the EU/EEA, of which 60 446 (38%) were migrants. Of these, 53% were from sub-Saharan Africa, 12% from Latin America, 9% from Western Europe, 7% from Central Europe, 5% from South and South-east Asia, 4% from Eastern Europe, 4% from the Caribbean, 3% from North Africa and Middle East. Late presentation (CD4 lymphocyte count $<350\mu\text{L}$ at diagnosis) was more common among male and female migrants of sub-Saharan and Latin American origin [28].

Most of these HIV diagnoses are made for the first time in Europe, and HIV acquisition is predominantly assumed to have occurred in their countries of origin. Nevertheless, postmigration HIV acquisition is a reality that is not well shaped in the literature. Recent estimates of HIV acquisition post migration range from as low as 2% among sub-Saharan Africans in Switzerland to 62% among black Caribbean men who have sex with men in the UK [29].

In the United States, data regarding HIV infection among the immigrant population are reported as CDC surveillance data according to race and ethnicity, rather than by country of origin. Many come from regions with high rates of HIV infection such as Africa, Asia, and Eastern Europe. Of note, some ethnic groups, such as Hispanics and African Americans, are disproportionately affected [30]. In 2013, the rates of HIV infection per 100 000 inhabitants were 55.9 for blacks/African Americans, 18.7 for Hispanics/Latinos, 12.7 for Native Hawaiians/other Pacific Islanders, 9.4 for American Indians/Alaska Natives, 6.6 for whites, and 6.0 for Asians.

Some migrant and ethnic minority populations are especially vulnerable to the harmful impact of the HIV/AIDS epidemic. Language barriers, social exclusion, and cultural and socioeconomic factors can act as barriers to prompt medical attention and early diagnosis. Moreover, HIV infection in immigrants may present certain features that should be borne in mind by healthcare professionals. These include the higher prevalence of non-B subtypes, different reference ranges for laboratory tests, concomitant imported infections, different AIDS-defining illnesses, different patterns of HBV/HCV co-infection, slower disease progression, differential response to antiretrovirals, and different tolerance

to antiretroviral drug adverse effects and HIV-associated symptoms [31–37]. Additionally, HIV-infected people are not free of restrictions on freedom of movement because of their HIV status. Although since 2010 eight countries or territories have eliminated restrictions on entry, stay and residence for people living with HIV, there are still 44 countries with discriminatory laws. Such restrictions reflect and reinforce the stigma and discrimination that impede an effective AIDS response, and also impose severe hardship on many people living with HIV [26,38].

Chagas' disease (American trypanosomiasis)

Chagas' disease results from infection with the protozoan parasite *Trypanosoma cruzi*. The parasite is mainly transmitted to humans through the infected feces of triatomine bugs (vectorial transmission) and less frequently through vertical transmission, transfusion, or organ transplantation from an infected donor, and more rarely through oral contamination and laboratory accidents.

After infection, the acute phase is usually asymptomatic and rarely presents with severe disease (myocarditis or encephalomyelitis with 5–10% mortality without treatment). Infected individuals then enter an asymptomatic chronic phase, with positive serology and fluctuating parasitemia. The majority of patients are in this phase and may transmit the disease. After 10–30 years, around 20–35% of patients develop symptoms, mainly characterized by cardiac (20–30%) and/or gastrointestinal (10%) involvement. The estimated annual rate of progression to visceral involvement is 1–2% per year. Clinical follow-up requires chest X-ray, electrocardiogram, echocardiogram, barium enema or barium swallow, and repeated serology and *T. cruzi* PCR. Some patients will require pacemakers, defibrillators, and even heart transplantation [39].

Benznidazole and nifurtimox are the only drugs with proven efficacy. Benznidazole is generally the preferred agent due to its better tolerability profile, tissue penetration, and possible higher efficacy. Treatment with benznidazole has been shown to be effective in infants and in the acute phase of the disease, but the efficacy declines with the duration of infection. Treatment in the late chronic phase remains controversial as tolerance is poor and about 30% abandon treatment due to adverse reactions. Based on nonrandomized trials demonstrating a significant decrease in disease progression and mortality in treated adults, there is an increasing tendency to offer antiparasitic treatment to every patient under age 50–55 years, without severe cardiac involvement, who has not previously received a correct treatment course [40]. A multicenter, randomized, placebo-controlled trial in patients with early Chagas' heart disease is currently under way (BENEFIT study).

Chagas' disease is endemic in countries of the American continent from Mexico to the north of Argentina and Chile. The Pan American Health Organization has certified the interruption of transmission by domestic vectors in several countries in South America and Central America. The estimated global prevalence of *T. cruzi* infection declined from 18 million in 1991 to 5.7 million in 2010. The highest estimated incidence is 4% per year, in the hyperendemic Bolivian Chaco [41]. From the 1960s to the 1980s, there was a large flux of immigrants from Latin America to North America, Australia, and Japan. However, from the 1990s, there has been a dramatic increase in immigration to Western countries. Due to international migration, Chagas' disease is no longer limited to the Latin American continent and has emerged in North America, in the Western Pacific (Australia and Japan), and in Western Europe (mainly in Spain) (Figure 30.2).

Those who migrate seeking work opportunities and wanting to improve their quality of life are usually healthy and younger than the general population. Most Latin Americans will have been infected with *T. cruzi* during childhood and therefore, based on the natural course of the disease, these migrants would now be at an age when the first manifestations of cardiac involvement may be expected to appear. The number of infected immigrants may be inferred from national infection rates for each country of origin. Up to 20% of patients with Chagas' disease will have clinical manifestations and may require health assistance.

More than 44 million Latin Americans (the majority from Mexico) live in the United States. An estimated 325 000 of these immigrants are infected and more than 65 000 may develop symptoms of the infection. In Canada, there are more than 400 000 Latin Americans; around 5500 may be infected

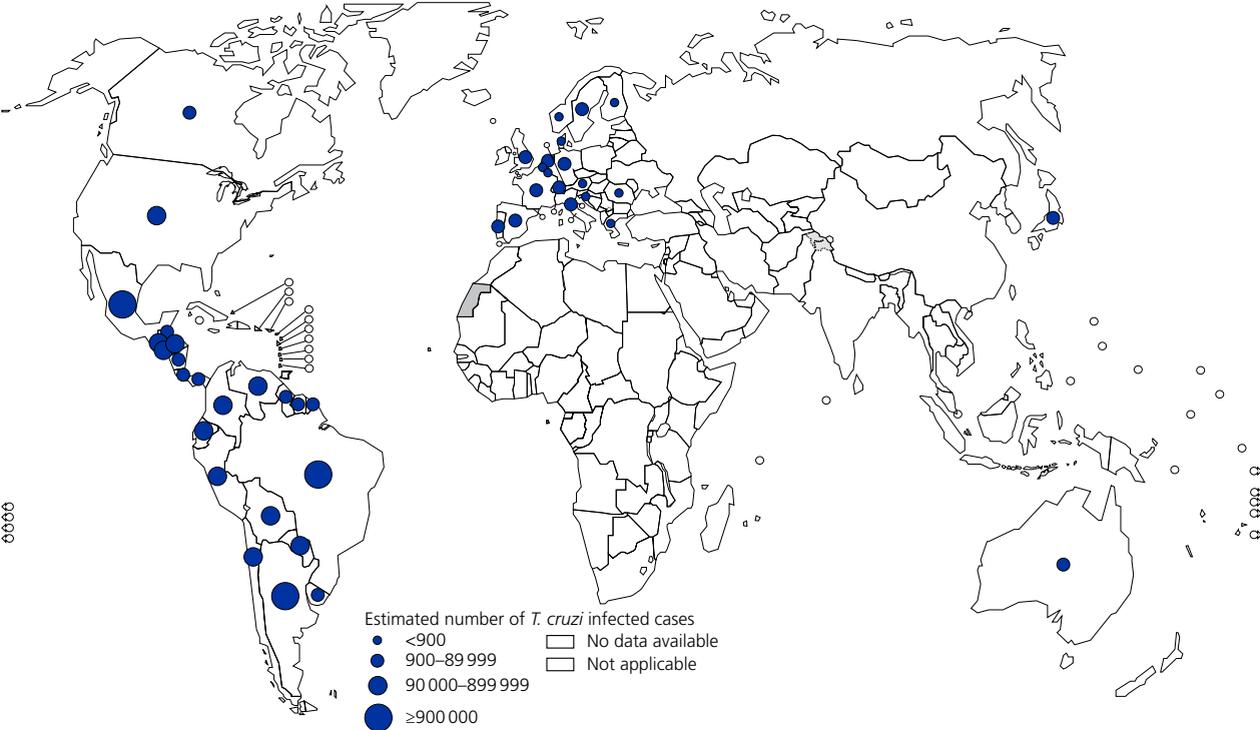


Figure 30.2 Global distribution of cases of Chagas' disease, based on official estimates, 2006–2010. Source: World Health Organization.

and 1100 may be symptomatic. In Japan, there are 116 000 immigrants from endemic areas: 81 000 of these are from Brazil and up to 3500 may be infected. In Australia, around 1400 out of 80 000 immigrants from endemic areas may be infected, and 600 of these may be symptomatic [42].

There are about 2 600 000 Latin American immigrants in the EU15 (2 million in Spain). Conservative estimates indicate there are more than 121 000 infected immigrants in the EU15 countries, and 87 000 of these are living in Spain. In the other EU15 countries, there are approximately 14 000 infected immigrants. However, fewer than 4500 cases had been reported, meaning that 95% of cases remained undiagnosed. Migrants from Bolivia had the highest prevalence of Chagas' disease (18%), followed by those from El Salvador (5.6%), Paraguay (5.5%), Nicaragua (4.6%), Honduras (3.7%), and Argentina (2.2%), and the prevalence amongst migrants from other countries in all studied groups is under 1%. No cases of Chagas' disease were detected in migrants to Europe from Uruguay, Venezuela, Panama, Guatemala or Mexico [43].

An infected pregnant woman may transmit the parasite to the fetus throughout pregnancy and at delivery. In Spain, the majority of infected immigrants are female Bolivians in their 30s, and therefore of child-bearing age. In Spain, seroprevalence in pregnant Latin Americans is 3–4% (18% in Bolivians) and vertical transmission rates vary from 1.3% to 7.3% according to different series. National screening protocols for pregnant women should be established and in an attempt to decrease vertical transmission, chronically infected nonpregnant women of child-bearing age may be offered treatment since women treated before pregnancy are significantly less likely than untreated women to transmit the infection to their offspring. Since the treatment of pregnant women with benznidazole and nifurtimox is currently contraindicated, early detection (by PCR) and treatment of congenital infections are recommended.

The risk of *T. cruzi* transmission from an infected blood transfusion is estimated to be 20%, and this may vary depending on the concentration of parasites in donor blood, the type of blood product transfused (higher risk of transmission with platelet transfusions), or the parasite strain. Cases of *T. cruzi* infection acquired via blood transfusion have been reported in Europe and the United States. Since 2005, screening of at-risk blood donations for *T. cruzi* has been implemented in Spain and the CDC recommends screening of all donated blood in the United States. To avoid transfusion-associated *T. cruzi* infections, all countries should develop strategies to identify and exclude those who may pose a transmission risk and refer them for further management.

Severe and fatal cases of *T. cruzi* infection following organ, tissue, and cell transplantation have been reported outside endemic countries, highlighting the need for screening protocols in all transplantation centers. Cardiac transplantation from a donor with chronic Chagas' disease is contraindicated given the high risk of chagasic myocarditis in the recipient following immunosuppression. There is currently no consensus regarding the use of other organs from infected donors. Severe/fatal reactivation of Chagas' disease has been reported in immigrants with chronic *T. cruzi* infection and immunosuppression (HIV/AIDS associated or drug induced). For the prevention of reactivation, screening and treatment of such patients, if appropriate, is recommended.

Cases of acute Chagas' disease have also been reported in Western citizens returning from endemic countries. This highlights the need for specific pretravel counseling regarding the risk of vector, oral (food-borne), and transfusion-associated transmission of *T. cruzi* in endemic Latin American countries.

Access to specialized clinics for diagnosis and management of chagasic patients and preventive strategies are essential given the burden of the disease and the potential public health repercussions in nonendemic countries [44].

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Chapter 31

Climate change and the geographical distribution of infectious diseases

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Climate and other environmental factors play a fundamental role in the distribution, transmission and survival of microbial pathogens that lead to infectious diseases. Human-induced climate change has and will alter the epidemiology of infectious diseases via interactions with microbes, vectors, and animal hosts and indirectly through higher level tertiary effects related to political, behavioral, and societal impacts. Mosquito-borne, food- and water-borne and respiratory infections are discussed in this chapter as examples of climate-sensitive infections that will have altered geographic epidemiology under climate-changed conditions. Modeling future infectious diseases transmission zones is highly challenging given the complex, nonlinear relationships between the relevant model inputs but is an essential prerequisite of public health planning.

Introduction

Some infectious agents, cytomegalovirus for example, are ubiquitous in human populations, whereas most are limited in their geographical distribution. Some occur all year round, while others are seasonal. Host, agent, and environmental factors determine the distribution of infectious diseases globally. In some cases, smallpox and measles for example, population health programs have dramatically impacted incidence and distribution.

Social, cultural, behavioral, technological, biological, and environmental factors determine where infectious diseases actually occur. A major limiting influence on infectious disease incidence is the climate. Temperature, rainfall, humidity, and consequent physical and ecological characteristics of the environment set spatial and temporal limits on the occurrence of infectious diseases.

A potent variable is now entering the equation: namely, climate change. Determining the extent to which climate change has altered and will alter the distribution of infectious diseases of humans is a new and important challenge.

Human-induced climate change is now regarded, with near-unanimous shared understanding and agreement among climate scientists, as both real and manifestly happening [1]. Global temperatures are projected to rise by between 0.3°C and 4.8°C by 2081–2100 (compared with the baseline period 1986–2005) [1] and “planetary boundaries” for atmospheric carbon dioxide concentration have been recommended to avoid reaching climate thresholds beyond which the globe will become far less hospitable to human societies [2]. Warming and other changes to climate will inevitably affect the geography and temporality of infectious diseases.

†In memoriam

Mechanisms for climate-induced change in infectious disease incidence

Climate influences the biology of all organisms: pathogens, insect vectors, and vertebrates, including humans [3–5]. In this chapter, we consider climate effects on pathogen, host, and vector. Climate impacts on human societies with consequent changes in infectious disease incidence are also discussed [6].

Pathogen

Viruses and bacteria survive and reproduce only under certain conditions with, for each species, limits in terms of temperature, pH, and so on. Within these limits, reproduction and transmission are affected by environmental factors including temperature. Increased temperature often, though not always, increases the likelihood of human disease. Some pathogens (e.g. dengue virus and *Plasmodium*) mature more rapidly at higher temperatures while in the vector organism (mosquito). But temperature variation and mean temperature also influence dengue virus incubation and transmission is reduced above a certain temperature threshold [7–10].

Higher temperatures are associated with increased infection of *Culex* mosquitoes with West Nile virus in Illinois [11]. Temperature also influences colonization of chickens with *Campylobacter* [12]. In contrast, rotavirus and respiratory syncytial virus survive better at low than high temperatures [4] and *Cryptosporidium* oocysts kept at 4°C or 15°C maintain infectivity, but at 20°C or 25°C are completely inactivated after 12 and eight weeks, respectively [13].

Host

Climatic conditions affect many nonhuman hosts of human infectious diseases. For example, the occurrence of mosquito-borne Ross River virus disease in humans is influenced by the relation between rainfall, vegetation and, hence, reproduction in kangaroos – a major reservoir species for this virus [4, 14, 15]. The water snail *Oncomelania hupensis*, an important host for *Schistosoma japonicum* in China [16], is sensitive to temperature, which affects the proportion of snails hibernating and, indeed, surviving during winter [17].

Vector

Temperature influences mosquito populations. For example, in Kenya the abundance of *Anopheles funestus* is increased at higher temperatures, while for another malaria vector, *Anopheles gambiae*, there is a (nonsignificant) negative correlation [18]. Under experimental conditions, *An. gambiae* and its sibling species *Anopheles arabiensis* demonstrate highest larval survival to adulthood at 25°C, with progressively lower survival at 30°C and 35°C, though for *An. arabiensis* the relation of temperature and survival is modified when reared with *An. gambiae* [19]. Temperature (in combination with humidity) also affects mosquito biting rate, and high temperatures limit mosquito longevity and survival.

Other climate influences

Climate and disease research has concentrated on biological effects on pathogen, host, and vector. Butler and Harley proposed a schema in which, in addition to direct biological effects on the human host (primary) and impacts on vectors and pathogens (secondary), a third (tertiary) level of impact is defined [6]. Tertiary climate change effects “operate at the intersection of climate, politics, and ecology, both human and non-human” [6]. Climatic impacts that bring about significant demographic and social changes are considered tertiary; for example, conflicts arising from climate change-induced food scarcity or migration resulting from sea level rise would be considered tertiary. The social determinants of infectious diseases epidemiology have been recognized since Virchow’s research on typhus among cotton mill workers and before [20]. The impact of war on infectious disease epidemiology is well known [21]. Within wealthy countries such as New Zealand, specific ethnic groups and the

socioeconomically disadvantaged are at increased risk for infectious disease [22]. Therefore, it would be naive to assume that tertiary effects, and other societal changes, will not interact with and impact primary and secondary effects of climate change, including infectious diseases.

Implications

Clearly, there are many varied mechanisms whereby climate change can influence the occurrence of infectious diseases. More difficult to determine, though, is whether climate change has altered the distribution of infectious diseases, and how much it may do so in future.

The context: human actions and disease emergence

Human actions

As discussed, the prevalence and geographic distribution of an infectious disease depend on appropriate conditions for growth, survival, and transmission of pathogens. A suitable climate (i.e. providing optimal temperature, humidity, rainfall) plays a critical role, as do human activity, behavior and demographics, population movement, and the nature of the built environment.

There are countless examples of public health measures that have contained or eradicated disease in areas once conducive to infection transmission. These measures include mass vaccination (e.g. polio), vector control (e.g. insecticide spraying), early detection (surveillance) and treatment of index cases, and effective public policy (e.g. food safety standards, quarantine measures). Via combinations of these measures, countries such as Australia (in 1981) could be declared malaria free, despite having a receptive climate in the tropical north and the continuing presence of competent *Anopheles* mosquito vectors [23].

Globalization of travel and trade is an important contributor to infectious disease transmission. The severe acute respiratory syndrome (SARS) epidemic of 2003 [24] and H1N1 influenza (“swine flu”) pandemic of 2009–10 [25] dramatically demonstrated how air travel in particular can quickly disseminate disease that once may have been contained or slowed by geographic or climatic constraints. There have also been prominent examples where infections or vectors have been spread via trade. *Aedes albopictus* (Asian Tiger mosquito), able to transmit alpha- and flaviviruses, is native to South-east Asia but it has been introduced by trade routes to Europe, the Americas, and Africa where it is now endemic [26].

The increasing worldwide trend of urbanization, and the development of “mega-cities” (e.g. Mumbai, Mexico City, Tokyo) can also contribute to disease propagation, particularly where water, sanitation and health infrastructure and services have not kept up with increasing population demand [27]. Destruction of native habitat by human populations and agricultural land intensification result in close proximity between wildlife, domesticated animals, and humans. This ecosystem blending contributes to the emergence of zoonotic infectious diseases, of which the large Nipah virus encephalitis outbreak in Malaysia (1998–9) is a prime example [28]. Additionally, the microclimates within cities, such as the urban “heat island” effect wherein the often dense built environment is warmer than rural surroundings due to heat retention and lack of vegetation, can alter the distribution of infection [29] and make populations more susceptible to infection due to heat stress [30,31].

Disease emergence

The rate of emergence of apparently new human and animal pathogens has increased over the past four decades, with HIV being the most catastrophic for human health [32]. While pathogen evolution and biology is undoubtedly important in such emergence [33], climate and land use change also play a role [34,35]. The phenomenon of disease emergence provides an important stimulus for understanding the relation of climate change, often interacting with other global changes, to infectious disease risk. The complex interplay between climate, social and ecological changes must be understood ecologically and historically if humans are to co-exist, as they must, with microbes [36].

Human-induced climate change

Paleoclimatological records show that over the past 2.6 million years of the current ice age, Earth has fluctuated between glacial (cold) and interglacial (warm) periods. These changes at a global level have occurred gradually, over millennia, and have resulted from natural phenomena, such as alterations in Earth's orbit and axial tilt, varying volcanic and solar activity, and changes to marine life distribution and density [1].

However, a sharp rise in average global surface temperature has been observed in recent decades, the rapidity of which is exceptional in the paleoclimatological record. This coincides with a similarly unprecedented increase in the atmospheric concentration of carbon dioxide (CO₂), resulting from the emissions arising from increasingly intensive human industrial activity. The trapping of solar energy by CO₂ and other greenhouse gases (GHGs) within the lower atmosphere has led to the range of climatic impacts recently observed (Box 31.1).

The Intergovernmental Panel on Climate Change (IPCC) has developed projections for global average surface temperature based on the emissions that would occur under several future development scenarios (i.e. linking demographic, economic, and technological change with likely resultant GHG emissions). Across the range of internationally agreed scenarios, as inputs to global climate models (GCMs), global surface temperatures are projected to rise by between 0.3°C and 4.8°C by 2081–2100 (compared with the baseline period 1986–2005) [1]. The landmark Paris Climate Agreement signed by nearly 200 United Nations member states came into legal force in November 2016 and requires signatories to undertake global greenhouse gas mitigation measures to restrict global temperature rise to less than 2°C (http://unfccc.int/paris_agreement/items/9485.php).

Future climate change will not occur uniformly across the globe – there will be significant regional differences. It is likely that developing world populations will be most vulnerable due to both significant exposures to the physical elements of climate change and also a limited economic and social capacity to positively respond and adapt to change.

A framework for understanding the relation of climate and disease

Modes of infectious disease transmission can be classified in two dimensions: anthroponoses and zoonoses, and direct and indirect modes of transmission [4]. To understand and analyze climate–disease relations for these different transmission mechanisms, a theoretical framework for climate

Box 31.1 Observed changes in climate

Increasing global surface temperature – 0.85 (0.65–1.06)°C increase over the period 1880–2012; temperatures have increased most rapidly since the mid-1970s.

The world's oceans absorb the vast majority of excess energy due to global warming. The upper 75 m warmed by 0.11 (0.09–0.13)°C per decade over the period 1971–2010.

Global average sea level rose by 0.19 (0.17–0.21) m over the period 1901–2010 with increases in the rate of sea level rise evident over the most recent decades.

Extreme weather events have changed in frequency and intensity since about 1950, with an increase in heat waves, hot days and nights, heavy precipitation events and a decrease in cold days, nights, and frosts.

Changes have not occurred uniformly around the world – significant regional climate differences have been observed.

Source: Executive Summary, IPCC Fifth Assessment Report (2013) [1].

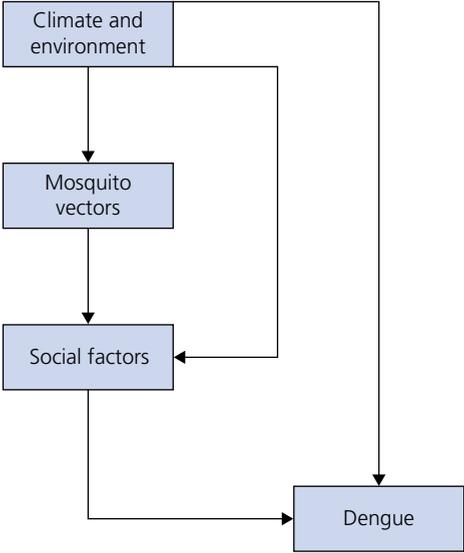


Figure 31.1 Climate and transmission of dengue virus.

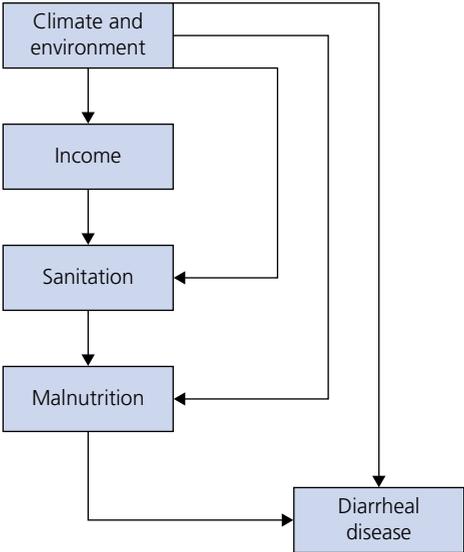


Figure 31.2 Climate and diarrheal disease.

effects encompassing differing modes of transmission is necessary. Such a framework should account for other factors outlined above, including social factors, land use change, pathogen evolution, and so on. Hierarchical conceptual frameworks [37,38] provide a basis for this (Figures 31.1 and 31.2).

Simple models such as those above, while they necessarily omit various lesser influences, are nonetheless sufficiently generalizable to provide a framework for understanding disease causation in different geographical areas and on different timescales.

The present: climate–disease relations

Vector-borne diseases

A key consideration in the theoretical assessment of putative associations between climate change and vector-borne diseases is the basic reproductive number (R_0), which determines the number of cases of a disease that arise from one infected case introduced in a susceptible population [39]. Because arthropods are sensitive to temperature and other climatic variables, and because most of the parameters that determine R_0 for vector-borne diseases are related to vector biology, one would expect changes in climate to influence the incidence of vector-borne diseases [39].

As well as mosquitoes, several other groups of arthropods transmit human diseases [40]. However, the same general principles apply when considering climate–disease relations among diseases transmitted by all arthropods. Only the mosquito-transmitted diseases malaria (the most important human disease transmitted by mosquitoes), dengue (the most significant mosquito-borne arbovirus disease of humans), and Zika are considered here.

Malaria At a global scale, malaria has receded in geographical extent since 1900, though the population at risk has increased in absolute numbers [41, 42]. While maps may display changes in latitude well, they are less able to show changes in altitudinal range. Much of the interest in relation to climate change and malaria is whether the disease will move to higher altitudes – and in some cases impinge on large urban populations currently at low risks (e.g. Nairobi, Harare). Many studies have been done in the eastern African highlands [43], in mountainous regions of South America and in parts of South Asia. There are, as yet, no clear instances of climate-attributable changes in the local geography of malaria. Moreover, observed decreasing global trends in endemicity and geographic extent are occurring concurrent with rising mean temperatures [41].

Particular attention has been paid to parts of eastern Africa [44–47]. No scientific consensus has yet emerged as to how best to model and analyze the data. There has been recurring debate over the relevant scale of analysis, the quality of some data sets, the choice of biologically based versus statistical-empirical models (see also below), and whether or not the seeming absence of clear climate impacts on malaria in the twentieth century provides a basis for projections in the twenty-first century.

Dengue The geographic range for dengue epidemics is expanding [48]. Changes in climatic conditions, patterns of human settlement, movement, and population density, distribution of the two main mosquito vectors, and water management technologies have all influenced the occurrence of dengue outbreaks since the mid-20th century [49]. While Halstead doubts that climate change will increase the incursion of dengue into temperate regions [50], Hales et al, writing in 2002 on the basis of modeling using vapor pressure as a predictor variable for dengue, concluded that “geographical limits of dengue fever transmission are strongly determined by climate” and that climate change will substantially increase the proportion of the global population at risk from dengue [51]. Although in general, the health impacts of climate change will be negative, it is naive to assume a simple relationship between climate and dengue incidence, and incorrect to state that climate warming will uniformly increase dengue transmission [52]. Using a mechanistic virus transmission model to determine whether climate warming would change dengue transmission in Australia, Williams et al calculated future dengue epidemic potential for the period 2046–2064, and found that dengue epidemic potential may decrease under climate warming due to mosquito breeding sites becoming drier and mosquito survivorship declining [52].

The complex dynamics between ecology, environment, and climate involved in dengue transmission are not easily modeled or understood [53]. Moreover, confounding makes it difficult to ascertain the relation between dengue and climatic variables [53]. Epidemiological studies are usually based on an underlying assumption that high temperature or rainfall will increase dengue transmission by influencing the abundance and vectorial capacity of mosquitoes. By using a Bayesian modeling approach incorporating nonlinear relationships between dengue and climate, Sharmin et al found that

mean monthly temperature and rainfall are significantly and positively associated with dengue incidence one month and two months later, respectively, in Dhaka, with values above 26°C and below 29°C associated with high risk and decreasing incidence when mean monthly rainfall increases beyond 15 mm. The nonlinear associations between temperature, rainfall, and dengue detected by this model likely reflect mosquito biology [10].

Zika In 2015, Zika virus (ZIKV) emerged throughout the Americas and in February 2016, the World Health Organization declared ZIKV a public health emergency of international concern. Because of a lack of long-term data on Zika transmission, it is not possible at present to demonstrate a link between Zika and climate. However, as ZIKV is principally transmitted from infected *Aedes aegypti* and *Aedes albopictus* mosquitoes, vectors of dengue and chikungunya viruses, we can expect complex dynamics between ecology, environment, and climate in Zika transmission too.

Food- and water-borne infections

Food- and water-borne diseases, usually manifest by diarrheal syndromes, are very sensitive to climate variability. A changing climate can alter the incidence of enteric infections either directly, via effects of climatic variables (e.g. temperature, precipitation, humidity) on organism proliferation or survival, or indirectly, via effects on sanitation, water and food quality, and outdoor activity patterns (e.g. swimming).

Studies from widely spread geographic locations and including developed and developing world countries have shown a correlation between increasing ambient temperatures and diarrheal disease [54–57]. For example, a European study assessing diarrheal notifications secondary to *Salmonella* spp. infection showed a linear increase in notifications with every 1°C rise in ambient temperature above 6°C, with the maximal effect apparent for temperature one week before the onset of illness [58]. A weaker association has been found with *Campylobacter* spp. infection and raised ambient temperature [59]. The effect of temperature can be negated by improved food safety practices and public health measures [60].

Indirectly, climate can affect rates of diarrheal disease particularly via extreme events (e.g. severe storms, flooding, droughts) which can overload the capacity of sanitation systems, contaminate or reduce availability of safe drinking water, and lead to overcrowded and displaced populations [61]. Increasing sea water temperatures are related to algal blooms which in turn can lead to increased water concentrations of *Vibrio cholerae* and subsequent outbreaks. Outbreaks of cholera have been linked to El Niño events, particularly in South Asia [62].

For the reasons given above, it is likely that morbidity from diarrheal disease resulting via climate change-associated phenomena will be significant, particularly in the developing world. Indeed, the World Health Organization's Global Burden of Disease (2002) report estimated 47 000 diarrhea-related deaths globally were attributable to climate change in 2000 alone [63].

Respiratory infections

In temperate climates, mortality rates exhibit strong seasonal cycles with winter associated with higher rates than summer [64]. Infectious respiratory diseases such as influenza and pneumonia play a significant role in this [65]. Aerosol and droplet transmission of respiratory infectious agents may be facilitated by colder conditions, as individuals are more likely to be in closer proximity indoors or in areas with inadequate ventilation. As temperate regions are projected to experience milder (warmer) winters under future climate change conditions, some predict that respiratory infection incidence will decrease [66]. However, as the relationship between ambient temperature and respiratory infectious disease transmission involves complex host–pathogen–environment interactions, the degree to which future climate change may affect rates of infection-related morbidity has not yet been quantified.

Researchers have shown an association between influenza epidemics and the strongest naturally occurring source of interannual climate variability of global consequence – the El Niño Southern

Oscillation (ENSO) [67, 68]. Zaraket et al demonstrated that peak influenza activity in Japan over the period 1983–2007 occurred earlier in ENSO years than in non-ENSO years [68]. In France and the USA over the period 1971–97, deaths from pneumonia and influenza were significantly higher in those years associated with the cold cycle of the ENSO phenomenon [67].

Other environmentally sensitive respiratory infections may also be affected by climate change. Recent reports from Europe and the US suggest that increased incidence of *Legionella* pneumonia follows humid, warmer weather and heavy precipitation events [69, 70]. Also, in a warming climate, reliance on air-conditioning may lead to increased human exposure to *Legionella*-contaminated cooling towers.

Although the direct effect of climate change on the transmission of respiratory infections may be mild, if not slightly beneficial, there may be increased susceptibility to respiratory infections in regions where climate change contributes to increased air pollution (i.e. ground-level ozone) or exacerbates underlying co-morbidities through increased ambient temperatures [66]. Under more extreme future scenarios of population displacement, due to climate change and its environmental consequences, increased crowding in slums, shanty towns, and temporary settlements would amplify the risk of infection with respiratory, gastrointestinal and, perhaps, sexually transmitted diseases.

The future: projections for infectious disease incidence

Projecting likely climate-related changes in disease incidence is fraught with difficulty, because of uncertainties in predicting future climate variability and the complex interplay between climate and infectious diseases, and the social, ecological, evolutionary and other changes occurring at local, national, and global scales. Nonetheless, projections can provide valuable insights into the likely direction and magnitude of change in infectious disease incidence, which are important for planning future mitigation and adaptation strategies.

Modeling the effect of climate change on infectious disease incidence is a reductionist process – it simulates a highly complex, dynamic process by substitution with simpler, well-elucidated and fundamental relationships. The two principal modeling approaches are the biological (or mechanistic) and the empirical (or statistical).

Biological approaches involve the incorporation of knowledge of biological mechanisms of infectious disease transmission into a mathematical model to make projections. For example, formulas describing mosquito reproductive cycles (with parameters including ambient temperature, humidity, rainfall) have been used to model mosquito population density under various future climate scenarios [71] and transmissibility of mosquito-borne infections by calculation of “vectorial capacity” [65].

Empirical modeling applies the statistical association derived from the current relationship between climatic exposures and disease outcome to the extrapolation of future disease occurrence under varying projected climate conditions. The strength of this method is that it “captures” and incorporates a host of biological, climatic, ecological, and societal processes, although the assumption that the relationship will remain static under future climate scenarios is a major weakness. Examples of this type of modeling include the work of Hales et al who ascertained that the historic geographic distribution of dengue is statistically related to atmospheric water vapor pressure (a surrogate marker for humidity) [51]. Using this knowledge, the investigators projected the potential distribution of dengue under future population and climate change projections. Future malaria incidence under varying climate conditions has also been modeled [72], which may serve as a potential early warning system for disease outbreak.

The main limitation of current models – and the source of much criticism – is that projections of disease incidence do not allow for changes in the climate exposure–disease relationship due to intervention (i.e. vector clearance, public health measures), evolving ecology or changes in host immunity (amongst numerous other factors) [73]. There are valid arguments both for greater sophistication in modeling approaches, on the one hand, and feasible and pragmatic approaches that can provide projections, albeit subject to criticisms, in the present.

Conclusion

All reputable scientists now accept anthropogenic climate change. Uncertainty persists regarding the magnitude of some effects. Debate will continue on current and future impacts on infectious disease incidence and distribution. A nomothetic approach will not suffice in this new, important, and challenging area. While it is implausible that there will be no impacts, determining the magnitude of these is a daunting task, principally because of the difficulty inherent in determining the relation and relative magnitude of climatic and other factors influencing infectious disease epidemiology in the present and the uncertainty in projections for climate futures. This uncertainty is compounded by the complex interaction between climate and other factors outlined in this chapter, including interspecific competition between malaria vector species, emerging infectious diseases, and the changing impact of human interventions, resistance to antimalarials being a prime example. But the challenge to human health and indeed human society is so large that researchers and health professionals must be willing to transgress disciplinary boundaries and become less pertinacious in their adherence to traditional methods.

We must attempt prediction of future disease incidence on the basis of past and current climate–disease associations. Only by making projections can the costs and benefits for mitigation and adaptation strategies be determined. This will allow decisions to be made regarding the relative value of mitigation and adaptation by permitting determination of the opportunity costs for competing health interventions.

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List of abbreviations

ACT	artemisinin combination therapies
ALT	alanine aminotransferase
AR	antibiotic resistance
ARF	acute rheumatic fever
ART	antiretroviral therapy
AST	aspartate aminotransferase
ATBF	African tick bite fever
BSE	bovine spongiform encephalopathy
CCHF	Crimean Congo hemorrhagic fever
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CL	cutaneous leishmaniasis
CLIA	Clinical Laboratory Improvement Amendments
CMV	cytomegalovirus
CNS	central nervous system
CRE	carbapenem-resistant Enterobacteriaceae
CRP	C-reactive protein
CSF	cerebrospinal fluid
CSOM	chronic suppurative otitis media
CT	computed tomography
DHS	drug hypersensitivity syndrome
EBV	Epstein–Barr virus
ECDC	European Centre for Disease Prevention and Control
ENSO	El Niño Southern Oscillation
ENT	ear, nose, and throat
EPI	Expanded Program for Immunization
ESBL	extended-spectrum beta-lactamase
ETEC	enterotoxigenic <i>Escherichia coli</i>
EVD	Ebola virus disease
FAO	Food and Agriculture Organization
FQ	fluoroquinolone
FUO	fever of unknown origin
GAE	granulomatous amebic encephalitis
GAS	group A streptococcus
GHG	greenhouse gas
GN	glomerulonephritis
GPHIN	Global Public Health Information Network
HAART	highly active antiretroviral therapy
HAV	hepatitis A virus
HBV	hepatitis B virus
HCP	healthcare provider

HCV	hepatitis C virus
HF	hemorrhagic fever
HIV	human immunodeficiency virus
HME	human monocytotropic ehrlichiosis
HSV	herpes simplex virus
HTLV	human T-lymphotropic virus
HUS	hemolytic uremic syndrome
ICAO	International Civil Aviation Organization
IPD	invasive pneumococcal disease
IRIS	immune reconstitution inflammatory syndrome
ISTM	International Society of Travel Medicine
JE	Japanese encephalitis
LBRF	louse-borne relapsing fever
LGV	lymphogranuloma venereum
MAI	<i>Mycobacterium avium intracellulare</i>
MDR-TB	multidrug-resistant tuberculosis
MERS-CoV	Middle East respiratory syndrome coronavirus
MIC	minimum inhibitory concentration
MMR	measles, mumps, and rubella
MOTT	mycobacteria other than tuberculosis
MRI	magnetic resonance imaging
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MS	member state
MSF	Mediterranean spotted fever
MSM	men who have sex with men
MVE	Murray Valley encephalitis
NAR	nalidixic acid resistance
NGU	non-gonococcal urethritis
NNRTI	non-nucleoside reverse transcriptase inhibitor
NPV	negative predictive value
NRTI	nucleoside reverse transcriptase inhibitor
NTS	non-typhoidal <i>Salmonella</i>
OIE	Office International des Epizooties (World Organization for Animal Health)
OPV	oral polio vaccine
PAHO	Pan American Health Organization
PAM	pregnancy-associated malaria
PAS	periodic acid–Schiff
PCR	polymerase chain reaction
PCT	procalcitonin
PCV	pneumococcal conjugate vaccine
PET	positron emission tomography
PHEIC	Public Health Emergency of International Concern
PI	protease inhibitor
PJP	<i>Pneumocystis jiroveci</i> pneumonia
PML	progressive multifocal leukoencephalopathy
PNG	Papua New Guinea
PPV	positive predictive value
PVL	Panton-Valentine leukocidin
RDT	rapid diagnostic test
RHD	rheumatic heart disease
ROC	receiver operating characteristic
rRT-PCR	real-time reverse transcription-polymerase chain reaction

RSV	respiratory syncytial virus
RVF	Rift Valley fever
RVGE	rotavirus gastroenteritis
RSV	respiratory syncytial virus
SARPs	Standards and Recommended Practices
SARS	severe acute respiratory syndrome
SEA	South east Asia
SFTS	severe fever with thrombocytopenia syndrome
STEC	Shiga toxin-producing <i>Escherichia coli</i>
STI	sexually transmitted infection
TB	tuberculosis
TBE	tick-borne encephalitis
TBRF	tick-borne relapsing fever
TD	travelers' diarrhea
TEE	transesophageal echocardiography
TST	tuberculin skin test
TTE	transthoracic echocardiography
UTI	urinary tract infection
VFR	visiting friends and relatives
VL	visceral leishmaniasis
VPD	vaccine-preventable disease
VRE	vancomycin-resistant enterococci
VTEC	verocytotoxin-producing <i>Escherichia coli</i>
WAT	West African trypanosomiasis
WBC	white blood cell
WHO	World Health Organization
WNV	West Nile virus
XDR-TB	extensively drug-resistant tuberculosis

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