Tropical Diseases in Travelers

EDITED BY

Eli Schwartz MD DTMH

Chaim Sheba Medical Center
Tel Hashomer, Israel
and
Sackler School of Medicine
Tel Aviv University
Tel Aviv, Israel

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Dedicated with love
to my wife Carmela and our children, Miriam, Aviad, and Naama

Contents

Contributors

Henry Abramovitch PhD
Department of Medical Education,
Sackler School of Medicine,
Tel Aviv University,
Tel Aviv, Israel

Elizabeth D. Barnett MD
Maxwell Finland Laboratory for Infectious Diseases,
Boston Medical Center,
Boston, Massachusetts, USA

Johannes A. Blum MD
Swiss Tropical Institute,
Basel, Switzerland

Enrico Brunetti MD
University of Pavia
and
IRCCS S. Matteo Hospital Foundation,
Pavia, Italy

Eric Caumes MD
Département des Maladies Infectieuses et Tropicales,
Hôpital Pitié-Salpêtrière,
University Pierre et Marie Curie,
Paris, France

Peter L. Chiodini MD
Department of Parasitology,
Hospital for Tropical Diseases
and
London School of Hygiene and Tropical Medicine,
London, UK

Michal Chowers MD
Sakler School of Medicine,
Tel Aviv University,
Tel Aviv, Israel
and
Infectious Disease Unit,
Meir Medical Center,
Kfar Saba, Israel

Bradley A. Connor MD
Division of Gastroenterology and Hepatology,
Weill Medical College of Cornell University,
New York, USA

Herbert L. DuPont MD
The University of Texas–Houston School of Public Health and Medical School,
and
Baylor College of Medicine
and
St. Luke's Episcopal Hospital,
Houston, Texas, USA

Michael Ehrenfeld MD
Chaim Sheba Medical Center,
Tel-Hashomer
and
Tel Aviv University Faculty of Medicine,
Tel Aviv, Israel

David O. Freedman MD
Division of Infectious Diseases,
University of Alabama at Birmingham,
Birmingham, Alabama, USA

Thiravat Hemachudha MD
Faculty of Medicine,
Chulalongkorn University,
Bangkok, Thailand

Joanna S. Herman MD
Department of Parasitology,
Hospital for Tropical Diseases,
London, UK

Nancy Piper Jenks CFNP
Hudson River Healthcare,
Peekskill, New York, USA

Mogens Jensenius MD
Ullevål University Hospital,
Oslo, Norway

Jay S. Keystone MD
Division of Infectious Disease,
Toronto General Hospital,
University of Toronto,
Toronto, Ontario, Canada

Phyllis E. Kozarsky MD
Division of Infectious Diseases,
Emory University School of Medicine,
Atlanta, Georgia, USA

Karin Leder MD
Royal Melbourne Hospital,
University of Melbourne
and
Monash University,
Victoria, Australia

Eyal Leshem MD
Chaim Sheba Medical Center,
Tel Hashomer, Israel
and
Sackler School of Medicine,
Tel Aviv University,
Tel Aviv, Israel

Eyal Meltzer MD
Chaim Sheba Medical Center,
Tel Hashomer, Israel
and
Sackler School of Medicine,
Tel Aviv University,
Tel Aviv, Israel

R. Scott Miller
Walter Reed Army Institute of Research,
Silver Spring, Maryland, USA

Thomas B. Nutman MD
Laboratory of Parasitic Diseases,
National Institutes of Health,
Bethesda, Maryland, USA

Philippe Parola MD
Hôpital d'Instruction des Armées, Laveran
and
Institut de Médecine Tropicale de Service de
Sante des Armées, Le Pharo,
Marseille, France

Pamela Rendi-Wagner MD
Department of Epidemiology and
Preventive Medicine,
Tel Aviv University,
Tel Aviv, Israel
and
Department of Specific Prophylaxis and
Tropical Medicine,
Medical University Vienna,
Vienna, Austria

Eli Schwartz MD
Chaim Sheba Medical Center,
Tel Hashomer, Israel
and
Sackler School of Medicine,
Tel Aviv University,
Tel Aviv, Israel

Michael J. Segel MD
Chaim Sheba Medical Center,
Tel Hashomer, Israel

Gil Sidi MD
Department of Infectious Diseases,
Memorial Sloan Kettering Cancer Center,
New York, USA

Fabrice Simon MD
Hôpital d'Instruction des Armées, Laveran
and
Institut de Médecine Tropicale du Service de
Santé des Armées, Le Pharo,
Marseille, France

John Simon MD
University of Hong Kong,
Hong Kong, China

Joseph Torresi MD
Department of Infectious Diseases,
Austin Hospital,
The University of Melbourne,
Heidelberg, Victoria, Australia

Elodie Vivier MD
Hôpital d'Instruction des Armées Laveran,
Marseille, France

Henry Wilde MD
Faculty of Medicine,
Chulalongkorn University,
Bangkok, Thailand

Annelies Wilder-Smith MD
Division of Infectious Diseases,
National University of Singapore
and
Duke-NUS,
Singapore

Einar P. Wilder-Smith MD
Division of Neurology,
National University of Singapore
Singapore

Foreword

It is with great pleasure that I write this preface to a new and valuable book, *Tropical Diseases in Travelers*, edited by Professor Eli Schwartz. Professor Schwartz has assembled a diverse, international, and very talented team of contributors to address an important, yet underappreciated, concept in tropical and travel medicine. The clinical presentations of infectious disease may be different in the non-immune, infrequently exposed traveler than the immune and multiply exposed inhabitant in a tropical environment.

The classic descriptions of the great tropical diseases began to appear in the 1800s as the Western powers began their imperial era in the Indian subcontinent, China, Southeast Asia, and, finally, in Sub-Saharan Africa. Suddenly, soldiers, businessmen, missionaries, and settlers needed to run the Western empires became casualties of infectious diseases of the tropics. Even in those early days, clinicians recognized that clinical presentations in otherwise healthy, non-immune, well-nourished adults were different from those seen in the native populations. The reasons for this difference included the size and frequency of the infectious inoculum, the lack of any prior immunity from past exposures or maternal immunity, and the fact that local populations often had a complex background of malnutrition, multiple co-infections, and far advanced diseases.

Symptoms in travelers are caused by far fewer organisms, leading to acute presentations with exuberant immune reactions in the non-immune. Symptoms in local populations may be manifest after years of multiple infections, with a large organism burden, organ system damage from years of inflammation, and chronic disability. Finally, the genetic background of travelers is distinctly different than the local population that have co-evolved with infections, such as malaria.

Acute and chronic schistosomiasis are excellent examples. The acute syndrome can be seen following a single exposure to fresh water and is caused by only a few adult worms, leading to an immune-mediated acute syndrome (Katayama fever). In travelers, subsequent clinical disease is often related to sporadic ectopic egg deposition that leads to catastrophic neurologic involvement, dermatologic presentations, or other bizarre syndromes. Chronic schistosomiasis occurs after years of exposure, the presence of hundreds of adult worms, and the near continuous deposition of eggs into the portal circulation leading to cirrhosis and portal hypertension. These are two very different diseases that occur in the local population or the returning traveler.

This book also includes historically important diseases such as typhoid fever, which used to be more common in the developed world, and leptospirosis, which has a cosmopolitan distribution, but is more commonly encountered in the developing world. Providers of travel medicine may be the first to encounter these patients.

Information on how tropical diseases present in travelers has never before been captured in a single, easy-to-access publication. Professor Schwartz, as book editor and co-author of numerous chapters, is eminently qualified for this task. He has been an original thinker in travel medicine, always pushing the discipline to question dogma and to consider new approaches. The other contributors are also all experts in their field.

Travel medicine is a relatively new discipline that has focused on the pre-travel aspect of traveler needs. This new book is the first to summarize the knowledge of post-travel presentations in the otherwise non-immune and non-endemic population. With such focus, this book will be useful to all practitioners, including primary care and infectious disease clinicians, who encounter the post-travel patient. .

Tropical Diseases in Travelers is presented in four sections. Following a useful general introduction is a detailed discussion of multiple viral, bacterial, and parasitic infections. The third clinically relevant section on the syndromic approach to patients will be useful in evaluating

returning travelers with symptoms. The book concludes with two helpful appendixes.

In the globally connected world of the twenty-first century, the lines of travel and tropical medicine are blurred. Immigrants and refugees, displaced and discarded in their own world, may turn up at your first-world doorstep as tropical medicine patients, whereas soldiers and humanitarian workers may present with clinical presentations in the developing world, confusing those used to caring for local populations. The same infectious agent can lead to dramatically different diseases, depending on the background immunity of the host, access to timely care, and the pathogen load in the body. This book will help us all to see the differences.

Alan Magill MD, FACP, FIDSA
Director, Division of Experimental Therapeutics,
Walter Reed Army Institute of Research
President, International Society of Travel Medicine
(ISTM), 2009–2011

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I would like to begin by thanking the publisher, Blackwell-Wiley, for recognizing the value of a special volume on tropical diseases in travelers and for helping to bring this book to fruition. Special thanks go to Robin Bonner and Eleanor Umali of Aptara, for their dedication to the book's production and their commitment to meeting our target date for publication.

My gratitude goes to all of the contributors for their efforts and for sharing their experience and expertise to produce such high-quality chapters. My special thanks to Nancy Piper-Jenks for her invaluable assistance during the writing of this book. I would also like to thank my colleagues at the Center of Geographic Medicine and at the Department of Medicine C at Sheba Medical Center, Tel Hashomer, for engaging in constant dialogue with me over the years concerning these topics and for their support during the writing of *Tropical Diseases in Travelers*.

I end with our ancient verse: "Much have I learnt from my masters, more from my colleagues, but the most from my own students" [*Talmud of Babylon*, Tractate Taanit, 6].

By the same token, I would like to thank all of my teachers and colleagues, in Israel and abroad, from whom I have learned a great deal. However, a special thanks is dedicated to my patients, from whom I have learned the most.

Tropical Diseases in Travelers—General Aspects

1 Introduction

Eli Schwartz

Chaim Sheba Medical Center, Tel Hashomer, Israel and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

The explosion of global travel during recent decades has been well documented, and it has become common to see travelers from the developed world venturing to more and more remote corners of our planet. Exotic travel exposes people to exotic diseases, which they subsequently take with them to other places. The SARS (severe acute respiratory syndrome) epidemic illustrates how one person, who journeyed from an endemic area of China to Hong Kong, was able to infect several people at a hotel, who themselves became infected transporters of SARS, allowing its worldwide spread. A more recent example is the Chikungunia outbreak that began in the regions of the Indian Ocean and spread to Africa and India. Travelers then carried the disease into Europe, thus causing its documented autochthonous outbreak in Italy. Therefore, tropical diseases are no longer confined to the tropics.

The term *tropical diseases* is not limited to ailments acquired from a particular tropical geographic area of the world. Indeed, tropical diseases such as yellow fever and malaria were once a very important cause of morbidity and mortality in regions as far north as Boston, USA. Instead, we are referring to diseases acquired in the developing world, where public health standards are lower and hygiene and sanitation are not customary. For this reason, we are encountering numerous infectious diseases that were at one point endemic worldwide and had been controlled or eradicated in industrialized countries during the twentieth century.

As physicians who encounter returning travelers with various tropical diseases, we see a clear picture of these so-called "exotic diseases" presenting in a unique fashion in travelers. In fact, these diseases tend to manifest very differently in nonimmune travelers than in indigenous populations of the tropics. Textbooks focusing on tropical diseases understandably limit their descriptions to the classical presentation of such tropical diseases, with descriptions of these diseases in indigenous populations, not in travelers.

The significant distinctions between travelers to developing countries and local residents are apparent through differences in the types of infections commonly seen in the two populations, as well as in the clinical presentations and management of these diseases.

Epidemiologically, these distinctions reflect differences in the likelihood of exposure to the infections, as well as intensity of exposure, which is typically higher among indigenous populations. For example, melioidosis (caused by the gram-negative soil- and water-associated bacterium *Burkholderia pseudomallei*) is a common cause of community-acquired sepsis in northern Thailand, yet the disease is rarely seen in travelers. The same is true for trypanosomiasis (sleeping sickness), filarial infections, and cholera, which are rarely seen in travelers.

Outbreaks of yellow fever are commonly reported among local residents in endemic regions, but are virtually never seen in travelers—in this case, most likely because of their high uptake of the efficacious yellow fever vaccine.

Disparate *background immunity* also affects the way in which some diseases manifest. For example, malaria in adult populations in endemic countries may not cause life-threatening disease, whereas in traveler populations, even low-grade parasitemia may cause a severe and life-threatening condition.

In many developing countries, hepatitis A is not viewed as an important problem because most children are infected at a young age, when infection is mild and often unrecognized. Older children and adults are therefore immune to the disease. However, the virus regularly contaminates food and water and poses a significant threat to nonimmune travelers who enter the area.

Clinical manifestations are also often different. These manifestations may be based on previous immunity and/or other not-yet-defined immunological causes. Excellent examples are the manifestations of infection with the various species of schistosome worms. This disease,

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which is one of the most common infections in the tropics, is a leading cause of morbidity due to late and chronic stages of infection (i.e., hematuria, urinary retention, in *Schistosoma hematobium* infection, and portal hypertension with *S. mansoni*). These manifestations, however, are rarely seen in travelers. They most commonly present with acute schistosomiasis, which occurs several weeks after exposure and leads to Katayama syndrome, a hypersensitivity reaction to the helminth antigen. Katayama syndrome is in fact the principal presentation of schistosomiasis in travelers, causing significant morbidity, whereas among local residents, it is virtually nonexistent, and therefore barely discussed in tropical disease textbooks.

Malaria is another example, in that it always presents as a significant febrile disease among nonimmune travelers and yet it can often occur without fever among local populations.

Methods of diagnosis may differ. For example, in endemic countries, diagnosing helminth infections among the indigenous population is done by finding ova in the stool. Serology is usually inadequate because it cannot differentiate between current and past infection and, therefore, will almost always be positive.

In the case of travelers, however, the situation is the contrary; due to low worm burden, ova are infrequently found in stool. Moreover, because travelers can present with illness during the helminthic migration phase, detection of ova in stool is biologically unlikely. Therefore, the most important diagnostic tools in travelers are serological methods.

There are also variations in *treatment.* There are common misconceptions that the best available treatments and most knowledgeable approaches to the treatment of tropical diseases are found in endemic countries. In tropical countries, the most accessible drugs are low-cost medicine, rather than the best available. Thus, malaria may still be treated in local populations with older drugs to which resistance has developed; however, for the nonimmune traveler, this treatment may be fatal.

As another example, we have shown that the most effective (albeit expensive) treatment of *Leishmania braziliensis* is liposomal amphotericin B; yet, antimonial drugs, which are older and more toxic drugs, are used in endemic countries because of their lower costs. Thus, choosing the correct drug and dosage should be tailored to nonimmune travelers.

The study of tropical diseases in travelers offers the advantage of exploring the natural history of these diseases in a clearer light. First of all, these tropical diseases present in nonimmune travelers, resulting in a more accurate picture of their natural history. In addition, there are generally fewer confounders or additional infections (e.g., malnutrition, HIV, or other tropical disease infections) that might impact the natural history of the disease.

The fact that there is usually more thorough patient follow-up in industrialized countries offers an opportunity for further assessment of the outcomes of infectious diseases over the long term. For example, assessing the efficacy of malaria prophylaxis for *Plasmodium vivax* infection can hardly be done in an endemic area because late infection cannot be differentiated from re-infection. However, there are opportunities for long-term follow-up in travelers who return to nonendemic countries. Indeed, observing returning travelers from vivax endemic areas has allowed us to conclude that current malaria prophylaxis is actually inadequate for vivax prevention.

The study of infectious diseases in travelers may also elucidate the natural history of many cosmopolitan diseases, such as leptospirosis, that are seen less frequently these days in industrialized countries. Sporadic cases and outbreaks do occur in industrialized countries, although they tend to be missed by clinicians. The understanding of diseases in travelers can contribute to the clinician's knowledge and awareness of disease when it occurs at home.

Practicing travel medicine may also help in managing patients who have not traveled, such as those with diarrheal diseases. The evaluation of patients with diarrheal diseases in the travel clinic is a large part of everyday practice and can teach non-travel-medicine practitioners about differential diagnosis and methods of detection and management, so that lengthy and expensive evaluations may not be necessary.

Travel medicine is a relatively new discipline and is a subspecialty that has continued to evolve over recent years. A number of textbooks that focus on pretravel health issues and the prevention of illness in travelers are now available.

This book is a first attempt at drawing together knowledge accumulated in recent years in the area of "post-travel"—those issues concerning the manifestation of tropical diseases and their diagnosis and treatment in travelers. The traveler, as a sentinel, has given us the opportunity to observe these diseases from another perspective. This knowledge can help us to understand better the morbidity and mortality of these diseases and, more important, to appropriately evaluate and treat the traveler who may be ill upon returning home.

2 The Art of Travel Medicine a Century Ago

Eli Schwartz

Chaim Sheba Medical Center, Tel Hashomer, Israel and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

In a lecture given about one hundred years ago, Sir Patrick Manson addressed an issue that remains highly relevant today. The title of his lecture was "Diagnosis of Fever in Patients from the Tropics."

As a reminder, Dr. Patrick Manson (1844–1922) was a British parasitologist (born in Scotland) and founder of the field of tropical medicine. He was the first to discover (1877–1879) that filariasis (*Filaria bancrofti*) is a mosquito-borne disease; transmission of a disease by an insect was a revolutionary idea at the time. He hypothesized that malaria could also be transmitted by mosquitoes, which was subsequently proven to be correct through the research of Sir Ronald Ross in India.

In 1890, Dr. Manson settled in London, where he organized the London School of Tropical Medicine (1899). He was knighted in 1903 and continued to practice medicine until his death. His fieldwork in several tropical regions of the world led him to his pioneer observations on tropical diseases, which were then also used to treat colonists and soldiers who encountered infectious diseases unknown in the temperate European climate. His book *Tropical Diseases* (1898) became the classic textbook on this subject.

The British Empire at this time ruled over a vast and expansive domain, encompassing about a quarter of Earth's total land area; as was often said, "The sun never sets on the British Empire." From a medical point of view, this meant that repatriating soldiers or other British officials back to the UK took several weeks, which is a long period of time, exceeding the incubation time of many diseases.

Dr. Manson's lecture (Appendix, this chapter), which was published in the *British Medical Journal* in 1909 [1], may shed some light on the common diseases among travelers of that time, as well as highlight some of the changes that have occurred both in the tropics and in industrialized countries since then (Table 2.1).

The major points that I would like to highlight include the following.

The common mistakes among clinicians who see the returned traveler from the tropics

The most important mistake, according to Manson, was the overdiagnosis of "tropical disease" among those who returned to the UK. He called on the diagnostician to "disabuse his mind" of thinking that any fever occurring in a patient from the tropics must be a tropical fever. He was concerned that cosmopolitan diseases, which were the common diseases of his time, would be ignored by physicians. The significant mundane diseases of his time were tuberculosis, syphilis, typhoid, sepsis, and malignant diseases.

In our era, there are two major changes. First and foremost is that the ordinary infectious diseases that Manson mentioned no longer occur routinely in industrialized countries, which corresponds to the changes in epidemiology of diseases throughout the twentieth century. Although, at the beginning of the twentieth century, infectious diseases continued to be the leading cause of morbidity and mortality, with improved hygienic conditions, followed by the introduction of vaccines and antibiotics, there was a progressive decline of infectious diseases [2]. The current situation is that cardiovascular and malignant diseases are the major causes of mortality, whereas infectious diseases account for only about 5% of mortality, in contrast to the current situation in developing countries, where infectious diseases are still the major cause of death (Figures 2.1a and 2.1b) [3].

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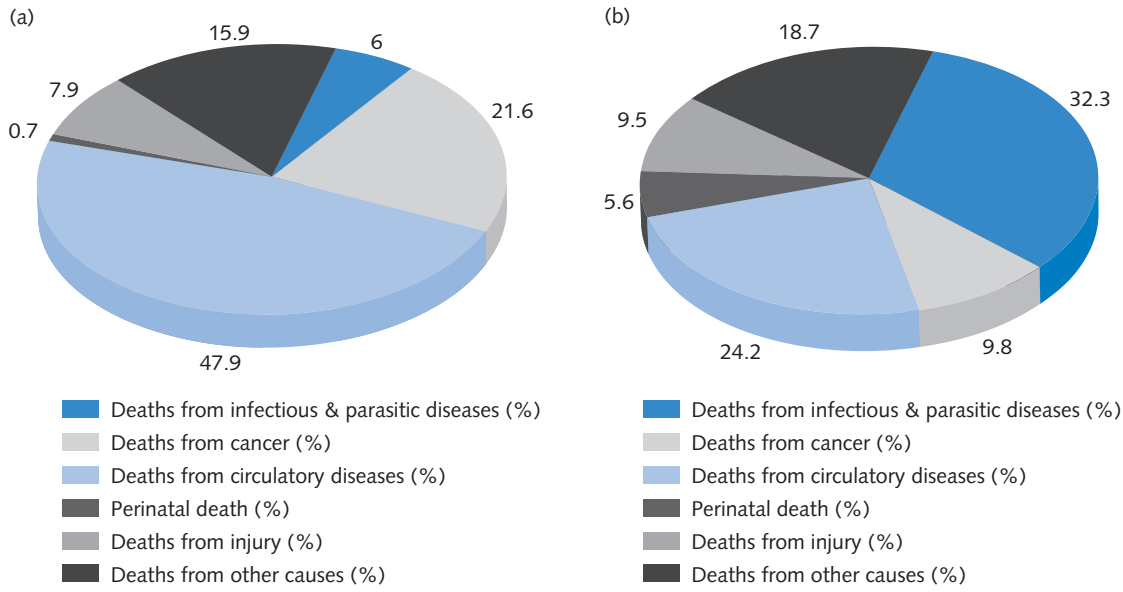

Figure 2.1 Causes of mortality. (a) Developed world. (b) Developing world.

The second development, which followed the first, is that the principal question of differential diagnosis in returning travelers today is not between tropical infectious diseases and ordinary infectious diseases but rather between tropical infectious diseases and chronic, often incurable Western diseases. Our role in dealing with the health of returning travelers therefore is to re-emphasize to physicians who practice medicine in the industrialized world that infectious diseases still exist in the world. Travelers returning from endemic areas may carry with them an infectious disease that could be either life-threatening, or associated with intolerable symptoms, and which, in either case, may have the potential of a simple and rapid cure. An example of the latter is a returned traveler with a few weeks of diarrhea. A Western physician may tend to think about chronic conditions such as inflammatory bowel disease or malignancy and may fail to consider the possibility of parasitic infections such as giardiasis that can be cured within a few days of treatment.

The importance of malaria

One of the issues that appears to be constant throughout this period of a century is the importance of malaria. Malaria was the commonest of all tropical febrile infections in Manson's time. This remains unchanged in our era and in almost all case series of febrile ill returned travelers, malaria is the leading cause (see Chapter 3).

However, he stated that "there is no disease so easily and so surely recognized as malaria." He made this statement in spite of the fact that a laboratory diagnosis of malaria was not easily made as compared to this day and age. A malaria diagnosis one hundred years ago was based on one of three options, in the following order of importance:

One was the *periodic character of fever*, demonstrating a rise in fever every 2–3 days.

The second option was the result of a *therapeutic trial of quinine*, a successful trial showing a response within 48–72 hours.

Last, diagnosis was made with the use of a *microscope*. To have a reliable microscopic test, the patient could not be under quinine treatment, but just as important, the microscopist "should know his business." According to Manson, extensive training was needed to make an accurate diagnosis and to avoid "comic" mistakes.

Currently, in travelers with malaria who present usually within a few days after the onset of their fever, the synchronous pattern of the fever with a periodicity of 2–3 days (tertian malaria) is rarely seen (see Chapter 21). Thus, diagnosis must be based on the malaria smear. The lack of experience of microscopists continues to be an important issue, particularly because most laboratory technicians have not seen many cases of malaria. Therefore, there are ongoing attempts to find easier, friendlier methods for

Table 2.1 Comparison of the status of diseases during Manson period and our time.

Travel-related diseases in the 1900s	Status of diseases in 1900s	Status of the diseases in the 2000s
Malaria—leading cause	Common	Malaria—leading cause
Hepatitis		Hepatitis is almost never seen in travelers owing to vaccine
		Hepatitis E—on the rise
Liver abscess		Liver abscess—occasionally seen
Brucellosis		Brucellosis—hardly seen
Visceral leishmaniasis (Kala-Azar)	Less common	Seen as co-infection in HIV patients
Trypanosoma		Rarely seen
Filaria		Rarely seen
Relapsing fever		Rarely seen, and mainly from recreational activities in *developed* countries
Dengue fever	Not seen	Very common
Yellow fever		Very rare owing to vaccine effect
Typhoid, tuberculosis, syphilis	Cosmopolitan	Now mostly tropical diseases
Endocarditis, sepsis		Cosmopolitan diseases, but rarely seen
Malignancy		Not a common cause for fever

malaria diagnosis. In recent years the antigen-detection rapid test has become a helpful tool, although it cannot replace malaria smears (see Chapter 22). Further development of the polymerase chain reaction (PCR) method for commercial use may significantly improve our ability to diagnose malaria and more accurately identify the malaria species.

However, the most common and the most important problem we encounter these days in malaria diagnosis in industrialized countries is the lack of physician awareness of the risk of malaria exposure in returning travelers and their failure to consider malaria as a potential cause of fever. The mortality rate from malaria in Western countries is high, reaching about 2–3% of all falciparum cases, and about 10–15% among patients with severe malaria. An important factor in this poor outcome is the delay of diagnosis by physicians [4].

Malaria was a common disease in Dr. Manson's time, but it seemed to be, as it currently is in the hyperendemic countries, a "background" disease. Therefore, another important message he wanted to convey was not to miss other diagnoses due to a self-proclaimed malaria diagnosis. As he described at that time, when the patient came in and told the doctor that he had malaria, the reason for his visit was principally to get treatment for his own diagnosis. Under the name of "malaria fever," the patient might in fact have tuberculosis, endocarditis, a liver abscess, or other illnesses. This is not the case today with returning travelers, but this situation reminds us of scenarios in endemic countries (mainly in Sub-Saharan Africa), where many illnesses are attributed to malaria without a thorough examination and definitive diagnosis, thus missing many other treatable diseases [5].

The incubation time

Although Dr. Manson did not mention the term "incubation period" directly, he clearly mentioned several diseases that were not relevant to the practitioner seeing the returning patient. The two major examples he gave were dengue fever and yellow fever; these diseases "need not to be considered." These diseases belong to the flaviviruses and were well known at that time. Yellow fever was a major killer during the period (e.g., it was one of the major foes during the Panama Canal construction). However, these viral infections have short incubation periods of about 1 week. Transportation during that era was mainly by sea, which meant that the travel time from most areas in the British empire back to London was lengthy, eliminating diseases with short incubation times. (Around the world even in 80 days was an illusion, as illustrated by the classic science fiction novel written by Jules Verne, who lived during the same period.)

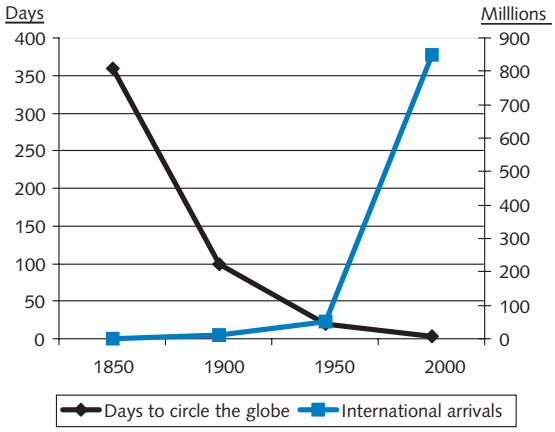

Figure 2.2 Around the world in 80 days?

One of the major changes that began during the second part of the twentieth century was the public aviation service, which today enables us to circumnavigate the globe within 36 hours (Figure 2.2). The idea corresponding to this change, that "the world has become a global village," assumes medical significance in that the incubation time is no longer a barrier in transmitting disease from one side of the globe to the other. Add to this the fact that traveling outside country borders is no longer confined to a select group of people but instead has become a popular trend (approximately 900 million travelers annually), and the public health significance is obvious.

In relation to the diseases mentioned above, dengue is widespread worldwide and has become the most prevalent arbovirus. For travelers, it is a major threat and is seen very often. According to the GeoSentinel data, dengue is now the second most common disease in returning travelers and is the first cause of fever outside Sub-Saharan Africa (see Chapter 7).

Yellow fever is rarely seen in travelers, but this is a result of another change that has occurred since Dr. Manson's time—the development of a highly effective vaccine, which has dramatically changed the morbidity map of the disease.

The vigilance needed for the clinician who sees these patients

In Western medicine, we are taught that we should try to find one disease that will explain or encompass all of the patient's symptoms. In tropical medicine, we should be alert to the possibility of multiple infections. The "zoo phenomenon," which refers to a patient's acquiring several pathogens, is not uncommon, especially in dealing with intestinal infections. Additionally, febrile infections can be caused by simultaneous infections (see Chapter 37).

Manson urges his audience not to fall into the trap of limiting findings to one diagnosis, and if there is just one diagnosis, to be sure that it fully explains the case. During this time, he stated, "In tropical disease, malaria is apt to complicate everything, so that multiple infection is rather the rule rather than the exception." In our time, that might be the rule in the malaria-endemic countries, but it is not the rule among travelers. However, vigilance is needed, and whenever the course of the disease does not correspond with the specific diagnosis, a search for another pathogen should be made.

The shrinking world, a process that has progressed rapidly since the time of Manson, has led to the border crossing of many diseases. Thus, physicians now must be familiar with many diseases, irrespective of their geographic locations and incubation time. In addition, there is a substantial increase in the number of travelers, who are mostly short-term travelers, not the long-term expatriates as seen by Manson, and therefore not immune to diseases from outside of their own environment. These conditions of the twenty-first century have shed new light on and revealed new aspects of the old tropical diseases. Physicians in the West are thus further challenged to understand and manage this vast array of travel and tropical diseases.

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Appendix: "Diagnosis of Fever in Patients from the Tropics," by Sir Patrick Manson (1909) [1]

An Address

ON THE

DIAGNOSIS OF FEVER IN PATIENTS FROM THE TROPICS.

DELIVERED AT A MEETING OF THE WESTMINSTER DIVISION OF THE METROPOLITAN COUNTIES BRANCH.

BY

SIR PATRICK MANSON, K.C.M.G., M.D., LL.D., F.R.S.

I HAVE twenty minutes in which to speak about certain points which have to be attended to in attempting the diagnosis of fevers in patients coming from the tropics. The time is very short. I shall not waste it, therefore, in preliminaries, but proceed at once to my subject.

Sources of Fallacy.

The first point I shall urge is a very important one. It is the necessity for the diagnostician to disabuse his mind of the very natural idea that because a fever has been contracted in or is occurring in a patient from the tropics it must necessarily be a tropical fever, symptomatic of some infection or condition peculiar to the tropics. This in my experience is one of the commonest and most misleading diagnostic fallacies. It so happens that my line of practice lies in great measure among patients from the tropics; but I am bound to say that half the patients from the tropics sent to me for an opinion or who come to me under the idea that they are suffering from tropical disease are not so suffering, although very likely they have fallen sick in the tropics or soon after return from the tropics. When you have dealings with a Scotsman you are apt to be obsessed with the preconceived idea of the national reputation for canniness, forgetting that, in the main, Scotsmen are very like other men, having the same physical, moral, and mental attributes. Just so, and perhaps even more so, in our contemplation of disease from the tropics. The major portion of a Scotsman's attributes is that of other men; only a very minor portion is peculiar. The major portion of disease in and from the tropics is ordinary disease; the minor portion special. Therefore when you encounter a fever in a patient from the tropics, think last and least (unless the diagnosis be glaringly obvious) of a tropical fever. Think first of and carefully test for those great and pandemic conditions—tuberculosis, syphilis, typhoid, malignant disease, and sepsis. If the seat and nature of the disease are not at once obvious, make it an inflexible rule to go over all the organs systematically, one after the other, beginning at the vertex and ending at the soles of the feet. I could tell many a story illustrative of the wisdom and necessity for this precaution—so obvious when stated thus pointedly, but, like so many other obvious things, so frequently overlooked or ignored. This is the first and perhaps the most important point I would make.

The next and equally obvious point I would impress on you is not to be misled by the diagnosis of malaria which

in many instances the patient is nearly sure to volunteer. Patients' statements in this respect are apt to be very positive and correspondingly impressive. Such tropical cases come to you not so much with the idea of your diagnosing their fever as with the idea of getting you to treat them on their own diagnosis. I have seen many cases of tuberculosis, of endocarditis, of liver abscess, of pyelitis, of syphilis overlooked for this reason. It should be an axiom with us never, without a thorough and independent examination, to accept another man's diagnosis, least of all a patient's diagnosis.

Having excluded as far as you can these sources of fallacy, then, and only then, you may conclude that the fever, let us suppose, you are trying to diagnose is probably a tropical one. Your next step should be to put to yourself the question, What are the tropical diseases likely to be brought to this country and which are associated with fever? Of course, we may safely exclude such acute and short fevers as yellow fever, dengue, and so forth; these need not be considered.

Tropical Fevers.

Let me enumerate what I might designate the important tropical fevers in the approximate order of the frequency with which they present themselves in practice here. First of all, of course, comes malaria; next, perhaps, hepatitis and liver abscess; then Mediterranean or Malta fever; next, and at a long interval, kala-azar, trypanosomiasis and sleeping sickness, relapsing fever, elephantoid fever, and probably other infections about which we as yet know nothing, but only suspect their existence. Each of the fevers I have mentioned has some feature or features by which it may be recognized, or, at all events, suspected.

Tests of Malaria.

Manifestly our first duty is to recognize or to exclude the commonest of them all—namely, malaria. Fortunately, this is easily done. Provided we set about it in the proper way and have a little time allowed us there is no disease so easily and so surely recognizable as malaria, for of this infection we have not one or two, but three absolutely pathognomonic tests. I am in the habit of describing these tests as, *first*, the clinical test of periodicity; *secondly*, the therapeutical test of the action of quinine; and *thirdly*, the microscopical test, the determination of the presence or absence of the malaria parasite or of its product, malarial pigment, in the blood.

There are other indications of malarial infection, such as leucopenia with relative increase of the large mononuclear leucocytes, enlargement of the spleen, and anaemia. These are only of relative value. Their absence is strong evidence against malaria, but their presence, seeing that they occur in other tropical diseases, does not prove the presence of malaria. They are not absolutely diagnostic in the same sense as are the three tests I have just mentioned, and need not be further considered.

The most important clinical test of malaria is *periodicity*—the periodic recurrence of the febrile or other phenomena. Practically all fevers, whether malarial or not, exhibit a periodicity. In tuberculosis, in typhoid, in sepsis, and so forth, there is a regular evening rise and morning fall of temperature, often quite as marked as in malaria. There is very definite quotidian periodicity. Quotidian periodicity is therefore not peculiar to, is no diagnostic mark of, malaria. We do meet with quotidian malarial fevers, especially in malarial countries. But quotidian periodicity, if taken alone, does not justify a diagnosis of malaria. So far from doing so, it is actually misleading. It is perhaps the most frequent cause of erroneous diagnosis in tropical patients. This you can readily understand. A patient from India, for example, comes to you with a story that every afternoon he has a shivering fit followed by a rise of temperature to 103°, and this again after some hours by a drenching sweat. He may mention no other symptoms. You may be in a hurry. You plump for malaria, and you prescribe quinine. The patient does not improve. You make a careful physical examination, and you discover signs of tuberculosis, or of liver abscess, or of some other form of visceral disease.

Quotidian periodicity, therefore, should be absolutely ignored in most cases as an indication of malaria. The periodicity characteristic of malaria, and absolutely diagnostic of that infection, is either a *tertian* or a *quartan periodicity*. These you find in no other condition, and are sure indication of malaria. The only circumstance in which quotidian periodicity may be a help in diagnosis is when the recurring fever sets in very late in the night, say after midnight, or before 12 or 1 o'clock during the day. Such a time for the commencement of a daily fever is almost peculiar to malaria.

The quinine test for malaria has usually been applied more or less intelligently before the case comes under the observation of the consultant. It is reliable if properly applied. Rarely does a malarial fever, in this country at all events, resist adequate dosing with quinine. Ten grains two or three times a day is almost sure in forty-eight to seventy-two hours to tell us whether we are dealing with malaria or not. But in employing this test we must be sure that the quinine is given properly, and that it is absorbed. Very often the quinine is given in adequate dose, but in some insoluble form, as in coated pill, flinty tabloid, or insoluble sulphate. In catarrhal conditions of the stomach given in any of these forms the drug may not be dissolved, much less absorbed, and cannot therefore be regarded as efficiently testing for malaria. When it is of importance that we should be certain of its action, quinine should be given in solution, or, in highly catarrhal or irritable conditions of the stomach, intramuscularly in doses of 7 to 10 grains. If no impression is made on a fever by quinine given in this way, do not blame the drug; revise the diagnosis.

Even more reliable than the clinical or the therapeutical tests of malaria is the microscopical test. If the malaria parasite or its product—haemozoin, or melanin, as it is usually called—is found in the blood, diagnosis is sure. The parasite of malaria is necessarily present at one time or another in the course of all malarial infections; it is always present in the visceral blood, nearly always in the peripheral blood, and, given certain conditions, can be readily demonstrated in the latter. It is necessary, however, to secure these conditions. In the first place the patient must not be under the influence of quinine, in the second place the person who searches for the parasite must know his business. Even a small dose of quinine—one, perhaps, quite insufficient to check the fever—may cause the parasite to disappear temporarily from the peripheral circulation. The possession of a microscope, and even skill in other departments of microscopy, do not always imply ability to recognise the malaria parasite. To do so satisfactorily requires experience—special experience—and long training. It is not a difficult matter, but, as with everything else, you must know how to set about it, and be familiar with the fallacies. It would be a comical list were I to enumerate all the various objects that have been brought to me as specimens of the malaria parasite.

I would warn you, therefore, to be careful about accepting a diagnosis of malaria from an inexperienced microscopist, but I would encourage you to have absolute confidence in the positive diagnosis, and in ninety-nine cases out of a hundred in the negative diagnosis of malaria from an experienced and conscientious microscopist.

Liver Abscess.

Assuming that we have to deal with a tropical fever and that by one or all of the tests I have enumerated we have excluded malaria, the question comes to be, which of the several tropical fevers I have mentioned are we dealing with?

Is the case one of liver abscess? The first and all-important question we put is—has the patient had dysentery or diarrhoea? If so there is, to say the least, strong presumption in favour of such diagnosis. We search, therefore, for local signs, for enlargement of the hepatic area, especially upwards, for local pain, oedema, or even redness. We inquire as to anaemia, progressive emaciation, for irritability and depression of mind; we look for a muddy complexion; we inspect the stools, looking for slime or other indications of a former or an existing dysentery; we inquire for a dorsal or right dorsal decubitis, for shoulder pain, and we make a count for the white corpuscles in the blood—a leucopenia being against, a leucocytosis being in favour of, liver abscess. Finally, if the symptoms are reasonably suggestive we explore the liver under chloroform, being prepared to operate at once if abscess is discovered.

Mediterranean Fever.

We may suspect Mediterranean fever, more especially if the patient has come from Malta, although this disease is by no means unknown elsewhere—as in India, China, and even in Central Africa. The points in favour of a Mediterranean fever diagnosis are an undulant type of the fever, profuse sweats, the occurrence of marked rheumatic pains or of orchitis, and the absence of indications of other disease.

Apart from the symptoms mentioned the evidence for this fever is principally of a negative nature. The fever may assume all sorts of characters. Often it is undulant in type, but as often it is distinctly intermittent and quotidian, often of a low continued type, often a medley of all of these. The serum test is reliable under ideal conditions, but my experience of it in London is the reverse of favourable. When I employ it I usually send the blood to two different laboratories; as often as not I get "positive" from one and "negative" from the other. So I do not trust it here, although, where fresh cultures are obtainable, it is quite as trustworthy as the corresponding test for typhoid, and even more delicate.

Kala-azar.

We have a patient from India, from China, from the Soudan, or from North Africa. He has a chronic fever, his spleen reaches to near his umbilicus, and his liver is very much enlarged. He has been ill for months; he is anaemic; his tongue is clean and his appetite and digestion are good; he has taken quinine by the pound, and he is gradually going downhill. Probably that patient is suffering from kala-azar—the disease produced by the Leishman body. To make sure of the diagnosis we study the fever chart—a four-hourly one; very likely we note that there are two distinct rises of temperature in the twenty-four hours. We examine the blood; there is a very marked leucopenia, more marked even than in malaria, and there is a relative increase in the large mononuclears. Possibly, though this is not likely, we may find a Leishman body or two, if we search long enough, in the white blood corpuscles. In the presence of such a fever and such a history we are entitled to puncture the spleen or liver and to search for the Leishman body in the juice or fragments of pulp so obtained. Such a procedure is not free from risk and must be done carefully, aseptically, and with a dry needle and syringe. I say "dry needle and syringe," for if a trace of moisture be present in these it will, by endosmosis, so distort the parasites that, though present, they may be hard to recognize. Of course, one must be familiar with the technique for their demonstration and also with the details of the structure of the parasite, for it is exceedingly minute and might be mistaken for a micrococcus or a blood platelet.

Trypanosomiasis.

The patient comes from tropical Africa. He complains of irregular fever, of great physical and mental lassitude, headache perhaps, tenderness of the limbs when he knocks them against any hard body. You suspect trypanosomiasis. You strip him and inspect his skin. You see great patches of erythema, many inches in diameter, usually having a ringed appearance and looking slightly puffy; you palpate the glands in his neck, axilla, or groin, and you find that some or all of them are enlarged—perhaps only slightly enlarged. The pulse, as a rule, is abnormally quick, and easily excited. That patient is almost surely the subject of trypanosomiasis, and may die of sleeping sickness. Examine his blood with a sixth objective, examining it especially during one of the recurring attacks of fever, and you are almost sure to find the trypanosome. It will not be found in every field of the microscope, and you may have to return to the hunt several times, but in the end you are almost sure to find it. If you fail to find it in the blood, puncture with a hypodermic needle one of the enlarged cervical glands, and examine the lymph so obtained; in it you have even a better chance of finding the parasite. The blood count is very similar to that of kala-azar.

Relapsing Fever.

The patient comes from India, from tropical Africa, from North Africa, or even from Gibraltar. He tells you that he has attacks of fever, perhaps violent fever, regularly about once a fortnight; that the individual attacks last from three to five or six days, that they subside nearly as suddenly as they begin, and that he is quite free in the interval. He may have had three or four or even eight or nine such attacks. What are they? The blood is negative for malaria; there is no marked leucopenia. Examine the blood during one of the fever paroxysms, and probably you will find the spirochaete of relapsing fever. In the African variety it takes some looking for. If you find it diagnosis is established. Such cases I have seen more than once in recent years in London. They were imported from Africa, from Gibraltar, and from India.

Elephantoid Fever.

Another patient may tell you he has attacks of violent fever coming on at irregular intervals of weeks, months, or years, that the attacks last for two or three days, and may be attended with severe rigor, delirium, high temperature, and be followed by profuse sweating. If he comes from the West Indies, particularly from Barbados, he will call this disease "fever and ague," but it is not fever and ague as we understand it. It is not malaria, but elephantoid fever for the most part, and if we inquire as to the occurrence of inflammation and cellulitis of limb, scrotum, or acute lymphangitis, we are sure to find that such is the case. The patient is suffering from elephantoid fever, and is or has been the subject of filarial invasion.

The possibility of these various and very different infections should always be present to the diagnostician when he is called on to treat a tropical fever in this country.

Multiple Infections.

I began with a word of warning; I shall conclude with another word of warning, and it is this: Do not infer because you have found in your patient's blood or elsewhere the malaria or some other parasite, that you have the complete and full explanation of the case. In tropical disease malaria is apt to complicate everything, so that multiple infection of patients is ra r the rule than the exception.

When you find the malaria parasite the patient has certainly got malaria, but that does not exclude other infections. I have sometimes been "caught" in consequence of ignoring this obvious precaution. Some years ago I was asked to see a patient just returned from Portuguese West Africa. He was said to be suffering from fever and dysentery. He had dysentery sure enough, and his spleen was enormously enlarged. He had taken much quinine; as it seemed to irritate his bowels I stopped it. At my first visit he had no fever. I found nothing in his blood. I left instructions that I was to be sent for should he have an attack of fever.

Some days afterwards I was sent for, his temperature being over 103°. I took a slide of his blood, expecting to find in it the parasite of malaria. Judge, however, of my horror when, instead of the malaria parasite, there was an unquestionable trypanosome staring me in the face! After a few days the fever disappeared, and, with the fever, the trypanosome also.

A fortnight later there was again a return of fever, and I again examined the blood, expecting to find the trypanosome. I found no trypanosome, but I found plenty of tertian malaria parasites. And so the case went on, every now and again a fever spell with trypanosomes in the blood, and every now and again a fever spell with malaria parasites in the blood. By the peristent use of atoxyl and of quinine both infections were finally expelled from the circulation. The patient is now, I believe, quite well.

Last year I had in hospital a patient from an African colony who carried about with him the malaria parasite, the trypanosome, the *Spirochaeta pallida*, the filaria, besides an assortment of intestinal parasites, including *Ascaris lumbricoides*, *Trichiurus trichiurus*, and *Ankylostoma duodenale*—a veritable museum, which, as long as it remained with us, we appreciated very highly at the Tropical School. He could always supply us with a subject for demonstration or for a clinical lecture.

I fear my exposition of the subject has been very sketchy and inadequate; it is necessarily so in consequence of the time limit imposed on me. I trust, however, I have given you the leading points for reliable diagnosis.

3 Epidemiology of Post-Travel Illnesses

Pamela Rendi-Wagner[1] and Eli Schwartz[2]

[1]Tel Aviv University, Tel Aviv, Israel and Medical University Vienna, Vienna, Austria
[2]Chaim Sheba Medical Center, Tel Hashomer, Israel and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Introduction

Disease surveillance is a prerequisite for the assessment of health risks and the evaluation of established preventive measures. It enables us to identify changing epidemiological patterns and groups of high-risk travelers possibly requiring modifications and optimal targeting of existing intervention concepts or the introduction of novel strategies. Moreover, information on the epidemiology of specific infections also provides guidance for differential diagnoses in ill returned travelers, facilitating the assessment and quantification of disease risks.

International travel is becoming increasingly popular. The current estimate of 846 million international arrivals represents an average growth of 4.2% between 1995 and 2006, with Sub-Saharan Africa being one of the major contributors to this rise. The leading travel destination is Europe, with more than 460 million travelers, followed by Asia, the Americas, the Middle East, and Africa. With regard to long-term prospects, the number of international travelers is expected to reach nearly 1.6 billion by the year 2020 (Figure 3.1) [1].

Undoubtedly, travel is related to enhanced health risks, most notably when travelers visit areas where the communicable disease burden is high, sanitation is poor, and the quality of medical care is limited. Each year, about 50 million people travel from industrialized to developing countries [2]. About 20–70% of international travelers report travel-related illnesses, usually dependent on destination and other travel conditions, including season, itinerary, duration, and purpose of travel [3, 4]. However, the majority of health problems reported by travelers are mild conditions, such as diarrhea, respiratory infections, and skin disorders [5].

Traveling to endemic countries has become increasingly popular for all age groups. In recent years, the numbers of senior, pregnant, and pediatric travelers have steadily increased. In a population that visited a travel clinic prior to travel, 14% were above 55 years of age [6]. According to an airport survey, 30% of US travelers were 50 years of age or older. Elderly people represent a growing group of travelers with a considerable rate of comorbidity [7]. Also, Stauffer et al. estimated that 4% of overseas travelers are infants and children [8]. This is confirmed by an Israeli study reporting a proportion of more than 5% for the age group below 18 years of age [9]. This varying demography of travelers increasingly needs to be taken into consideration in dealing with post-travel illness.

This lack of surveillance data for imported cases of infectious diseases prompted the establishment of various travel-related surveillance systems.

The GeoSentinel Surveillance Network started in 1995 through a collaborative agreement between the International Society of Travel Medicine (ISTM) and the Centers for Disease Control and Prevention (CDC) and consists of specialized travel/tropical medicine clinics on six continents recording information on ill travelers [10]. The main aims of the GeoSentinel Surveillance Network are to monitor global trends in disease occurrence among travelers and to ascertain risk factors and morbidity in groups of travelers categorized by travel purpose and type of traveler.

A few years later, in 1999, the European Network on Imported Infectious Disease Surveillance (TropNetEurop) was founded, serving as a European electronic network

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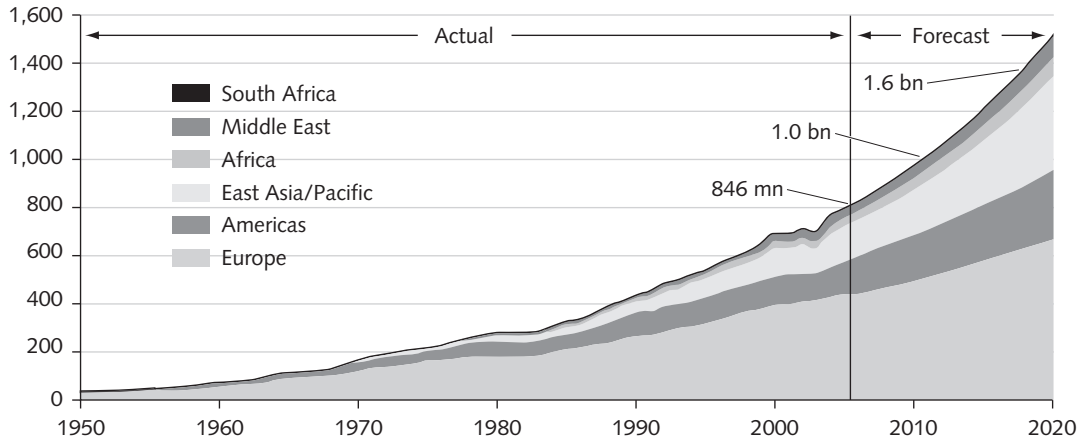

Figure 3.1 Trend of international tourist arrivals, 1950–2020. (From the United Nations World Tourism Organization, http://www.unwto.org/pub/rights.htm.)

of 37 clinical sites related to importation of the major tropical diseases.

For the first time, these novel sentinel surveillance systems allow the identification of temporal and geographic trends in infectious disease occurrence in traveling populations worldwide. Through the global surveillance of infectious diseases in travelers, refugees, and immigrants, valuable persuasive science-based information about important aspects of post-travel morbidity is generated to guide post-travel diagnosis, develop adequate pretravel prevention strategies, and hopefully lead to travelers' improved health.

This chapter summarizes results of available systematic studies investigating the epidemiology of post-travel illnesses, including data on the above-mentioned large-scale surveillance systems. In-depth epidemiology of specific diseases, however, is covered in the specific chapters.

Methods of investigations for post-travel morbidity

Generally, two different categories of post-travel disease epidemiology data exist.

Disease attack rate

Attack rates of specific diseases is calculated by dividing the number of ill travelers (numerator) by the number of all people who traveled to the same destination during the same observation period (denominator). Data of this kind, however, are rare.

Population-based risk

Only a few studies have supplied such specific population-based risk figures, which provide a useful pretravel tool for travelers for assessment and rating of disease-specific geographic risks. The data are limited to selected traveling population groups and/or geographic areas, such as Israeli travelers in Bolivia contracting cutaneous leishmaniasis (attack rate, 1 in 300 travelers) [11] or sufferers from myiasis in the Amazon basin (attack rate 1 in 190 travelers) [12].

In a recent survey, the rabies exposure risk among long-term travelers was estimated to be 2.66 per 1000 travelers per month [13].

Serosurveys

Serosurveys performed pre- and post-travel may likewise provide estimates of disease attack rates. This approach has been used, for instance, to evaluate the incidence of dengue fever in populations traveling to selected geographic regions. Dutch travelers to Asia (with a median stay of 1 month) had a seroconversion rate of 2.9% [14]. An Israeli survey performed among travelers who had spent at least 3 months in a tropical area observed a seroconversion rate of 6.7% [15]. A survey of tuberculin

skin-test conversion among Dutch long-term travelers revealed an overall incidence rate of 3.5 per 1000 person-months of travel [16].

Proportion of morbidity

The majority of available data on the epidemiology of post-travel illness, including the worldwide GeoSentinel database, address the proportion of morbidity, providing information exclusively on ill returned travelers. Proportionate morbidity data pose an adjuvant reference for clinicians in the diagnostic evaluation of ill returned travelers, as well as providing estimates for common diseases that might be seen in returning travelers based on their travel destination.

Until recently, systematic scientific data on the epidemiology of travel-associated diseases and health risks have been rather meager, relying mostly on case reports, case series, or single-center cohort or cross-sectional studies. Today, various approaches are in use.

Case series and chart reviews

Case series and chart reviews collect information on ill travelers who present for medical care to identify the spectrum and relative frequency of particular health problems.

Cross-sectional studies

Cross-sectional studies usually use questionnaires, mostly airport surveys, to investigate both ill and well travelers' attitudes, knowledge, and practices regarding preventive measures to identify potential risk factors.

Cohort studies

Cohort studies usually are based on travelers who seek pretravel health advice; they are then followed up on their return to determine the frequency and types of health outcomes during or after travel. This method provides estimates of disease incidence because the numerator and denominator are given.

Case reports

Case reports are particularly useful for the observation and identification of rare diseases and outcomes in travelers.

Sentinel surveillance networks

Sentinel surveillance networks collect in a prospective and systematic manner data on large samples of ill returned travelers, but are missing external denominator data. This approach enables the calculation of proportionate morbidity, allowing the development of a hierarchy of risk according to travel destination.

Limitations of investigation in ill returned travelers

The major limitations of travel health surveys are retrospective design, bias due to the study population's specific travel habits, and limited post-travel follow-up periods, as well as selection bias because case detection depends on the medical specialization of the reporting physicians (e.g., tropical medicine specialists, dermatologists, pediatricians) or the type of patients (inpatients versus outpatients). Hence, in interpreting study results, one should be aware that most epidemiological data merely reflect a subset of the true number of ill returned travelers. Also, the majority of current studies focus on the epidemiology of travel-associated illness occurring during travel, whereas only a small number investigate the epidemiology of post-travel illness. As a matter of fact, the disease frequency and the spectrum of reported medical conditions originating from these two distinct sources may differ substantially. In a survey analyzing post-travel health problems in a large cohort of American travelers, illness during travel was reported by 64%, including 8% who sought medical care, whereas only 26% of this cohort became ill upon return (during 2 months post-travel), 12% of whom consulted doctors after their trips [17]. One of the pioneer surveys of travelers' morbidity revealed that 15% reported health problems upon return and 8% consulted doctors [3].

Post-travel morbidity data

Generally, data on post-travel morbidity can be divided into outpatient morbidity data in hospitalized ill returned travelers, for whom more information is available. However, these two cohorts must be linked for a clearer understanding of post-travel morbidity.

The large-scale GeoSentinel database combined these two patient cohorts, although the proportion of each was not precisely known and was not scientifically selected. Yet, the GeoSentinel data provide clear evidence that the major group of post-travel illnesses is gastrointestinal disease, followed by fever, dermatological problems, and respiratory illness (Figure 3.2). Table 3.1 presents a comparison between ill returned in- and outpatients with

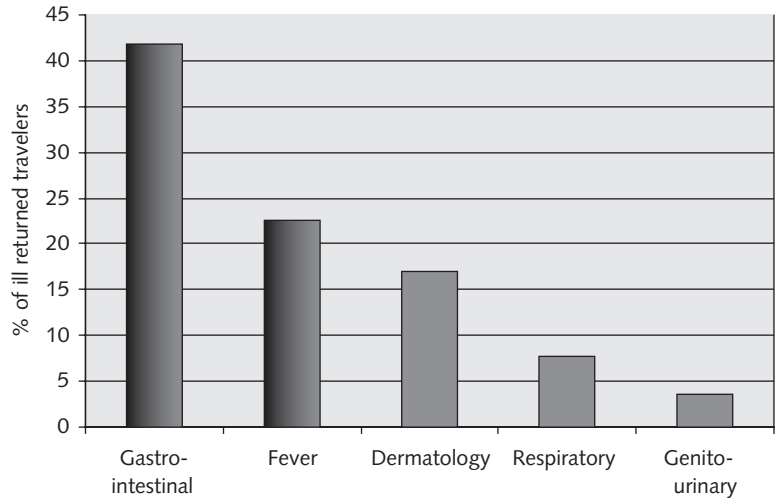

Figure 3.2 The proportion of morbidity per 100 patients (%), in travelers presenting post-travel at GeoSentinel sites. All regions are combined. (Adapted from [32].)

regard to the relative frequencies of the main illness categories.

Post-travel hospitalization data

Hospitalization of ill returned travelers could be due to an acute disease with a potentially severe outcome or to a subacute debilitating condition that could not be resolved in an outpatient setting.

The interval between return from travel and medical evaluation varies widely by diagnosis. Several hurdles constrain surveillance of post-travel hospitalization. Morbidity data on hospitalized patients represent only a very small selection of cases at the severe end of the scale. Moreover, in interpreting disease frequency data, one needs to be aware that in most studies case detection is performed at tertiary care facilities such as highly specialized travel or tropical medicine clinics rather than at primary health care levels. However, it may be assumed that the vast majority of ill travelers consult their family physicians rather than tropical medicine clinics. Another limitation is posed by differing hospitalization practices between various countries, which make comparisons rather difficult.

A study of hospitalized Israeli travelers showed that the majority (77%) were hospitalized due to febrile diseases, with malaria, unidentified febrile diseases, and dengue fever being the most common. The other causes for hospital admission were dermatologic problems, gastrointestinal illnesses, and respiratory diseases [18]. Because fever poses the major challenge of post-travel hospitalization, several studies have focused specifically on febrile patients (Table 3.2).

Table 3.1 Relative frequencies of post-travel health conditions (%), comparing in- and outpatient populations.

	Percentage of patients	
	Outpatients [19]	Inpatients [18]
Gastrointestinal illness	23	11
Dermatologic illness[a]	26	14
Fever	14	59
Respiratory illness	3	4

[a]Including animal bites.

Post-travel outpatient data

The current understanding of the morbidity profile among post-travel outpatients is, with the exception of GeoSentinel data, mostly based on data from single-site studies that examine individual diseases, specific destinations, or defined groups of travelers. Importantly, morbidity rates of ill returned outpatients calculated from present surveillance data constitute a extensive underestimate because case detection misses patients with self-limiting or mild illnesses, who usually consult nonspecialized primary care practices. Hence, in interpreting outpatient data, one has to assume that systemically reported morbidity of ill travelers is only the tip of the iceberg.

Table 3.2 Causes of fever recognized after travel as reported in various published studies (%).

	Doherty et al./ 1995/UK [20]	Klein et al./ 1998/UK [21]	O'Brien et al./2001/ Australia [23]	Casalino et al./ 2002/France [24]	D'Acremont et al./2002/ Switzerland [25]	West et al./ 2003/UK [22]	Antinori et al./ 2004/Italy [26]	Stienlauf et al./ 2005/Israel [18]	Wilson et al./ 2007/ GeoSentinel [27]
Population	Adults/ hospitalized	Children/ hospitalized	Adults/ hospitalized	Adults/ in- and outpatients	Adults/ outpatients	Children/ hospitalized	Adults/ hospitalized	Adults/ hospitalized	All ages/ in- and outpatients
Total number	195	31	232	783	336	153	147	163	6957
%									
Malaria	42	13	27	18.5	29	14	48	33	35
Gastroenteritis	7	3	4	12.5	NA	27	4.8	6	15
Dengue	6	6.4	8	NA	1		3.4	17	6
Typhoid	2	6.4	3.5	NA	2	3	4.1	3	2
Viral hepatitis	3	3.2	3	2.8	2	5	8.8	2	1
Pneumonia bacterial	2.5	3.2	6	9.6	3	8.5	NA		1
Upper respiratory tract infection	3	3.2	12	6.8	8	6	NA	4	9.6
Urinary tract infection	2.5	NA	2	9.6	3	4	1.4	0	2
Rickettiosis	0.5	NA	2	NA	1	0.6	0.7	0 2	
Non-specific/ undiagnosed	24.5	45	9	55.3	32	34	4.8	21	22

NA = not available.

Of 205 ill, New Zealander returned travelers presenting in an outpatient setting, most suffered from diarrheal diseases, followed by dermatologic conditions and febrile illnesses. Tropical diseases were uncommon in this group. As a matter of fact, the specific etiology was not always defined. Usually, one-third of illnesses in returned outpatients remain unspecified [19]. In contrast to the New Zealand study, dermatoses and tropical infections were the chief complaints among a cohort of French post-travel outpatients. This discrepancy clearly reflects the large variety of single-site observations, due mostly to population-specific travel patterns in combination with destination-dependent differences of morbidity profiles. Imported tropical diseases accounted for 36% of the diagnoses in this cohort of ill returned French travelers; malaria, schistosomiasis, intestinal nematodiasis, amebiasis, and dengue fever being the most frequent. This observation is most likely explained by the relatively large number of immigrants among this specific study population.

Generally, the most important difference between in- and outpatient groups in post-travel morbidity profiles is that fever is the major condition in hospitalized patients, whereas in outpatients, gastrointestinal and dermatologic illnesses are the most common causes reported for consulting a doctor.

The four following major syndrome categories of post-travel health problems are discussed in this chapter:

- Systemic febrile diseases
- Gastrointestinal illnesses
- Dermatologic disorders
- Respiratory diseases.

Systemic febrile diseases

Fever is a relatively common cause for seeking medical advice after tropical travel and, because of increasing international mobility, it will be observed even more frequently in the future. Indeed, this may pose a diagnostic challenge to Western physicians, because fever serves as an important marker of potentially serious conditions in persons who have recently traveled.

The majority of ill returned travelers with fever present within 1–2 weeks after their return (Figure 3.3).

Surveys consistently show that the majority of febrile patients who return from Africa present less than a week after return, reflecting the short incubation time of *Plasmodium falciparum* malaria. Immigrants who visited their countries of origin and who traveled to Sub-Saharan Africa, South Central Asia, and Latin America were more likely to experience fever than any other group of travelers.

Whatever the setting or population considered (i.e., tourists or migrants, adults or children), malaria poses by far the most frequent cause of febrile illness in hospitalized patients diagnosed after travel to the tropics, with a prevalence ranging between 13% and 48% (Table 3.2) [18–26]. Moreover, the majority of ill returned malaria patients require inpatient care. Importantly, *P. falciparum*, which causes the most severe form of malaria, was identified in 23–74% of all returned travelers with malaria. In fact, according to reports to the GeoSentinel Surveillance Network, falciparum malaria is listed as a contributory cause in 33% of deaths in febrile travelers [27]. Hence, the presence of malaria in febrile travelers poses a crucial diagnostic consideration, regardless of previous use of antimalarial agents. Of all cases of malaria, persons visiting friends and relatives (VFRs) while traveling are at particular risk and account for approximately 40% of reported cases of malaria in the United States [29].

Similarly, the majority of hospital admissions in Israelis following travel were of febrile diseases [18]. The most common specific diagnosis leading to post-travel hospitalization due to fever for this specific travel population was malaria (26%), followed by dengue fever (13%). In contrast, according to record data for outpatients presenting at travel clinics in New Zealand, febrile illness ranked only third in the list of diagnoses, after diarrheal and dermatologic illnesses [19].

Table 3.2 summarizes the relative frequencies of fever causes in ill returned travelers in several published studies, including in- and outpatient data.

Male ill returned travelers were more likely than female travelers to seek medical care because of fever [26].

Comparison of the travel destinations of the general population and post-travel hospital patients revealed that the risk of contracting severe disease is higher in Sub-Saharan Africa than in any other region. Although malaria, mainly falciparum malaria, was the most common condition in travelers returning from Africa, dengue fever was the most common cause for hospitalization in travelers returning from Asia. Hospitalization due to malaria, as well as dengue fever, showed a clear seasonal pattern, mostly corresponding to the rainy seasons in the respective destinations and to a lesser extent to seasonal travel activity to each region.

Notably, a significant proportion of hospitalized patients have fever that resolves spontaneously without any specific diagnosis or treatment. The proportion of undetermined febrile illness among ill returned inpatients ranges 5–45% (see Table 3.2). Surprisingly, this figure has hardly changed for a long time despite the increased

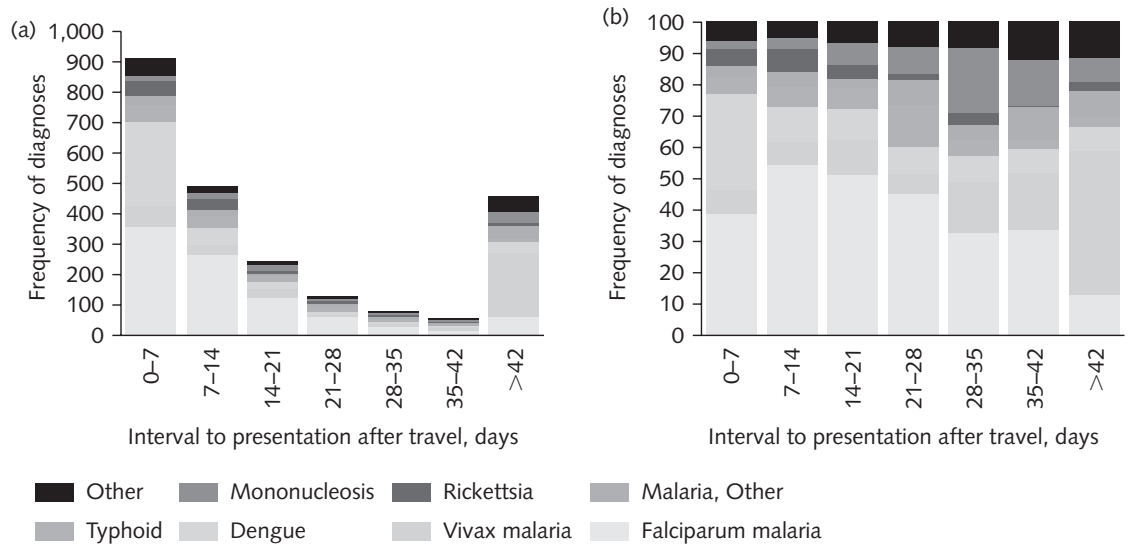

Figure 3.3 Interval from return from travel to clinic presentation for patients who had fevers, by specific febrile illness. (a) Frequency of systemic febrile illnesses based on the duration of the interval to presentation. (b) Proportion of systemic febrile illnesses based on the duration of the interval to presentation. (Reproduced with permission from The University of Chicago Press. Wilson et al. *Clin Infect Dis* 2007;44:1560–8.)

availability of improved diagnostic tools and facilities. According to the worldwide GeoSentinel database, no specific diagnosis could be made in 22% of 4500 febrile travelers (27). However, high hospital admission rates of travelers with systemic febrile illness and a 5-day mean duration of hospitalization suggest that ill returned travelers may consume substantial medical resources [18].

Gastrointestinal illnesses

Gastrointestinal (GI) illnesses pose the most common disorders in travelers [3, 29, 30], with up to 70% of travelers affected by diarrhea during travel [31]. Bacterial diarrhea was reported as the main cause for diarrhea during travel.

GI complaints are also the most common cause for seeking medical advice post-travel, accounting for about 40% of all referrals (Figure 3.2). Diarrheal diseases are still the most common complaint. However, there are differences between the "during" and "post"-travel presentations.

In post-travel referrals, chronic diarrhea is the major reason for seeking medical care. Interestingly, with the exception of Sub-Saharan Africa, where malaria is the predominant pathogen, in all other regions chronic diarrhea is the most common, with a rate of 10–17% of all referrals. The chronic diarrhea group might encompass unrecognized parasitic pathogens or "postinfectious irritable bowel syndrome" (see Chapter 36). The other change between "during" and "post"-travel diarrhea is that bacterial pathogens are the main cause of travelers' diarrhea; whereas parasitic diseases are more common, with giardiasis and amebiasis being the leading identifiable causes, in post-travel diarrhea, even in those who present shortly after travel (Figure 3.4a).

The explanation for this discrepancy is that bacterial diarrhea has a relatively short incubation period and is usually mild and self-limiting, whereas parasitic infections have longer incubation periods and tend to be more chronic. In fact, it is estimated that up to 1.8% of all travelers will develop post-travel chronic diarrhea [3], which is ranked second in causing inability to work among returning travelers [32].

Travelers returning from the Indian subcontinent and from Central America most commonly present with GI illnesses [32].

It should be remembered that infectious GI pathogens may cause nondiarrheal diseases as well, such as viral hepatitis A and E and typhoid and paratyphoid fever.

Between 3% and 14% of adult hospital admissions after travel are reported to be due to febrile gastroenteritis

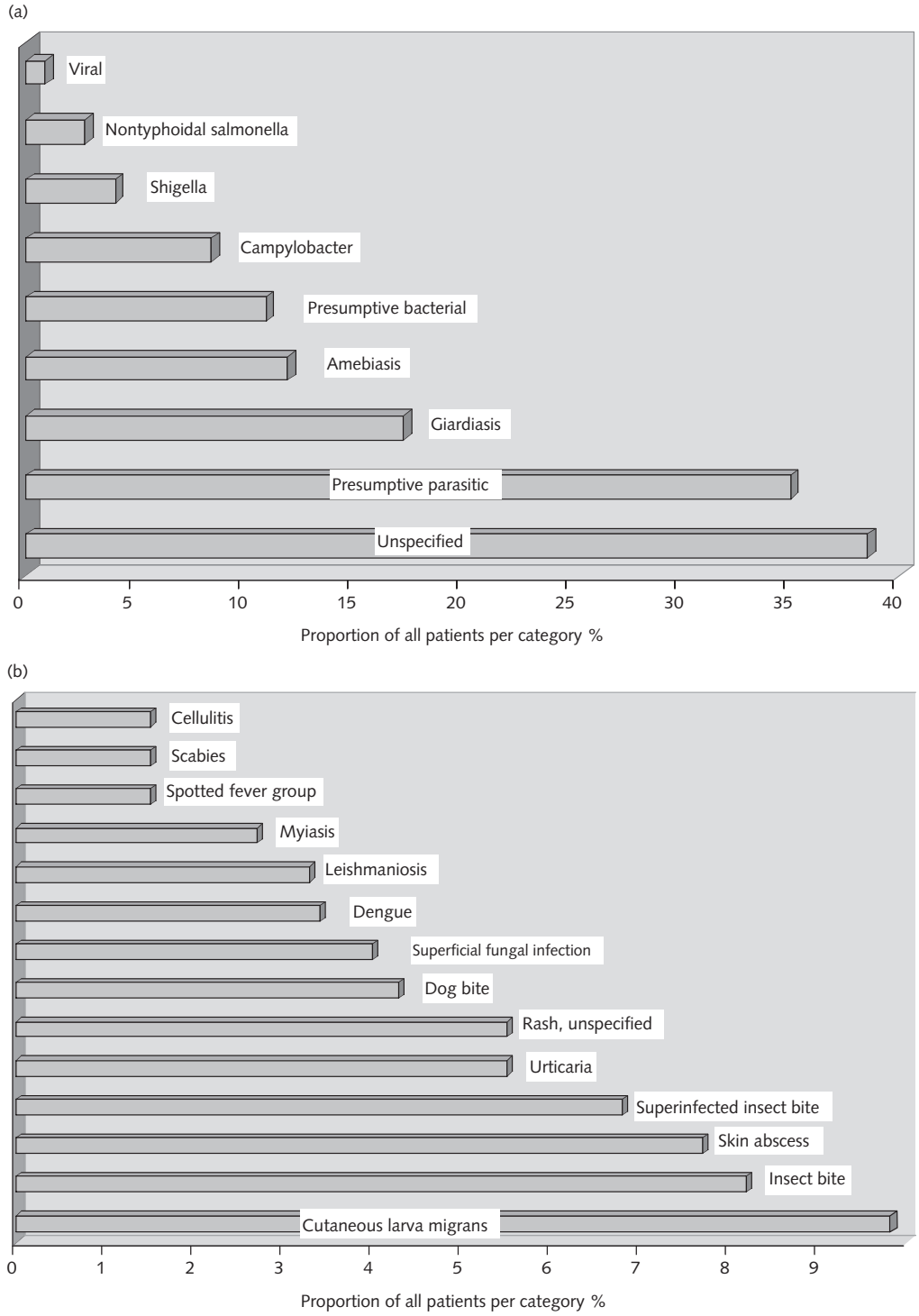

Figure 3.4 Proportions of etiologic diagnoses (%) within selected syndrome categories according to data collected by the GeoSentinel surveillance network. (a) Acute diarrhea (adapted from [32]). (b) Dermatologic disorders (adapted from [33]). (c) Respiratory illnesses (adapted from [39]).

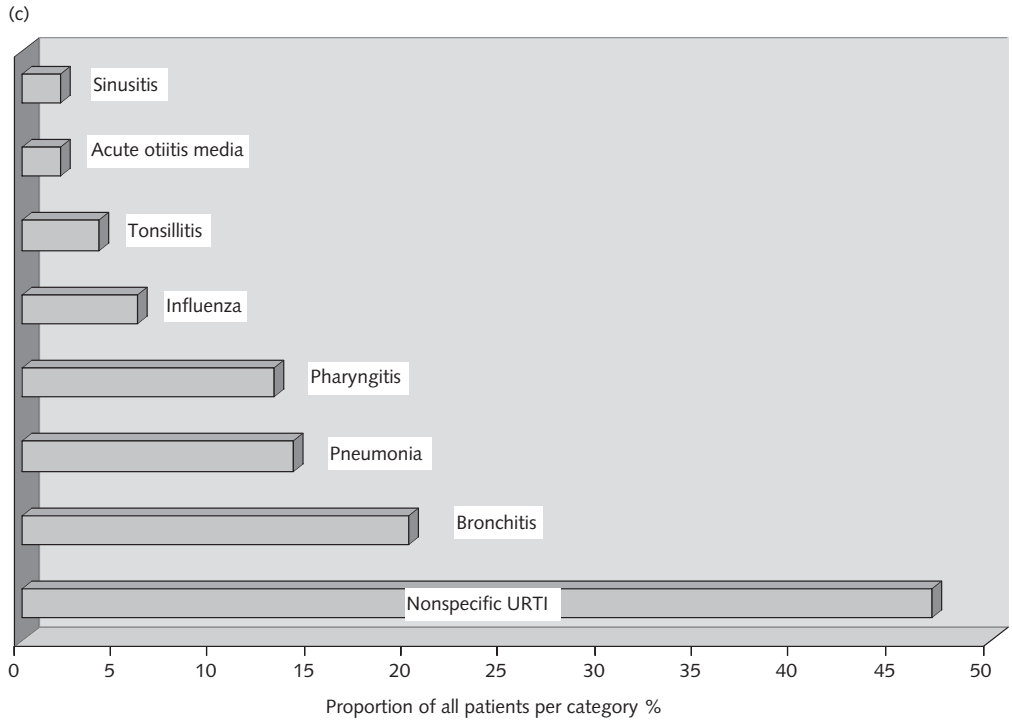

Figure 3.4 (*Continued*)

(Table 3.2). Other causes of hospitalization may be nondiarrheal GI infections presenting as systemic febrile infections. The protracted and sometimes debilitating course of chronic diarrhea may lead to hospitalization as well. Among post-travel hospitalized Israeli travelers, 4% were hospitalized with prolonged, nonfebrile GI diseases [18].

In small children, diarrheal diseases often have a particularly severe and longer lasting course, which explains the higher pediatric post-travel hospitalization rate for diarrhea [21].

In post-travel bacterial diarrhea, the most common isolated pathogens were *Campylobacter* species, followed by *Shigella* and nontyphoidal *Salmonella* [22, 32] (Figure 3.4a).

Dermatologic disorders

Skin disorders are among the six most common reasons for returned travelers to seek medical care [17, 22, 33]. Of all post-travel dermatologic illness self-reported by a cohort of American travelers, 11% needed medical care for their skin problems [17]. The most common complaints are cutaneous larva migrans, arthropod bites, skin abscesses, myiasis, urticaria, tinea, and leishmaniasis [33–35]. Moreover, skin conditions may be associated with the length of stay and environmental risk factors. The frequency of reported skin diseases, however, is highly dependent on the geographical destination, explaining the differences between various traveling populations with different destination preferences. In hospitalized ill returned Israeli travelers, who commonly travel to Latin America, for instance, skin diseases, mostly infections with *Leishmania braziliensis*, account for up to 14% of all diagnoses among hospitalized travelers (due to the need for systemic treatment) and account for the majority of nonfebrile diagnoses [18]. Other studies focusing on febrile inpatients report far lower rates (5%) of skin lesions among ill returned travelers [22, 26].

According to the GeoSentinel database, including in- and outpatients, skin-related diagnoses were reported for 18% of all patients seen in GeoSentinel clinics after travel, mainly imported from the Caribbean. Only 24% of patients had classical tropical skin diseases (e.g., CLM, myiasis, leishmaniasis, dengue); children had a greater likelihood of presenting with dog bites [33]. The GeoSentinel-based proportions of the most common diagnoses within this category are presented in Figure 3.4b.

Respiratory diseases

Respiratory illnesses are among the most common infections affecting human beings, but little information has been published on them in relation to travel. The possible public health significance of imported infections includes the introduction and transmission of new strains of respiratory pathogens into susceptible populations on a traveler's return home.

However, post-travel data on respiratory illness most likely underestimate the number of travelers who develop respiratory tract infections. Studies have documented that respiratory tract symptoms occur in about 26% of persons during travel, but only in 10% post-travel [36]. Respiratory tract infections accounted for about 8% of all infections in returned travelers reported to GeoSentinel, with nonspecific upper respiratory infection being the most common diagnosis [36]. Figure 3.4c summarizes the major causes of respiratory complaints reported to the GeoSentinel network clinics.

A review of admissions to an Australian tertiary care hospital following travel showed respiratory tract infections to be the second most common cause of febrile illness after malaria [22]. About a quarter of patients with post-travel respiratory illness and fever require hospitalization. Diagnoses of pneumonia (odds ratio [OR], 9.92; 95% confidence interval [CI], 6.77–14.57), influenza (OR, 5.88; 95% CI, 3.60–9.59), and lower respiratory tract infection (OR, 6.49; 95% CI, 4.22–9.99) showed far higher risk for hospital admission compared with other diagnoses such as bronchitis and upper respiratory infections [36].

Among outpatients, between 3% and 12% are diagnosed with respiratory tract infections [19, 36, 37], the majority of which are infections of the upper respiratory tract.

Generally, the most significant predictors for developing specific categories of respiratory infections while abroad were age, sex, season of travel, trip duration, and type of traveler. Long-term travel was associated with an increased risk of influenza and lower respiratory tract infection. Furthermore, increasing age and male sex are associated with a greater risk of lower respiratory tract infection, particularly pneumonia and bronchitis. Importantly, persons visiting friends and relatives are more likely to acquire influenza than any other group of travelers [38]. This is most likely explained by the close contact between these travelers and the local populations. Undoubtedly, this group should be specifically considered for pretravel influenza vaccination, regardless of age, because it may significantly reduce morbidity associated with this infection [39].

Profile of post-travel illness according to destination

The probabilities of specific diagnoses among ill returned travelers are closely associated with travel destination. Based on the worldwide GeoSentinel surveillance data [32], including more than 17,000 reports of a broad range of ill travelers returning from developing regions on all continents, a summary of the proportions of specific diagnoses or diagnosis groups is given in Figure 3.5. Shown is the proportion of morbidity per 100 patients (%), not the incidence rate, of each of the leading five diagnoses among travelers returning from each of these regions.

As can be seen, fever is the most common cause for seeking care after trips to Africa, due to overpresentation of falciparum infection, whereas in the other regions dengue supersedes malaria as a cause of fever in returning travelers presenting at the GeoSentinel sites [32]. Skin diseases are more frequently seen in travelers from Latin America, where tropical skin diseases are common, and the overwhelming majority of leishmaniasis cases are from there. In Sub-Saharan Africa, schistosomiasis is very close in frequency to dermatologic and respiratory diseases.

Rare diagnoses in post-travel illnesses

Rare diagnoses in returning travelers (e.g., Japanese encephalitis, Ebola virus disease, plague, anthrax, or yellow fever) are usually reported in sporadic case reports. It is comforting to know that among more then 17,000 diagnoses of ill returned patients reported to the GeoSentinel surveillance network, no such exotic condition has been reported [32].

However, according to Internet-based disease monitoring and reporting systems such as Program for Monitoring Emerging Diseases (ProMED-mail), established in 1994, or GIDEON, founded in 1992 as a global infectious diseases database, sporadic cases of Japanese encephalitis, yellow fever, Lassa fever, and rabies have been reported in travelers. These reports stress that these often fatal diagnoses may be rare but pose a serious health risk to travelers in areas where they are endemic, and even a large

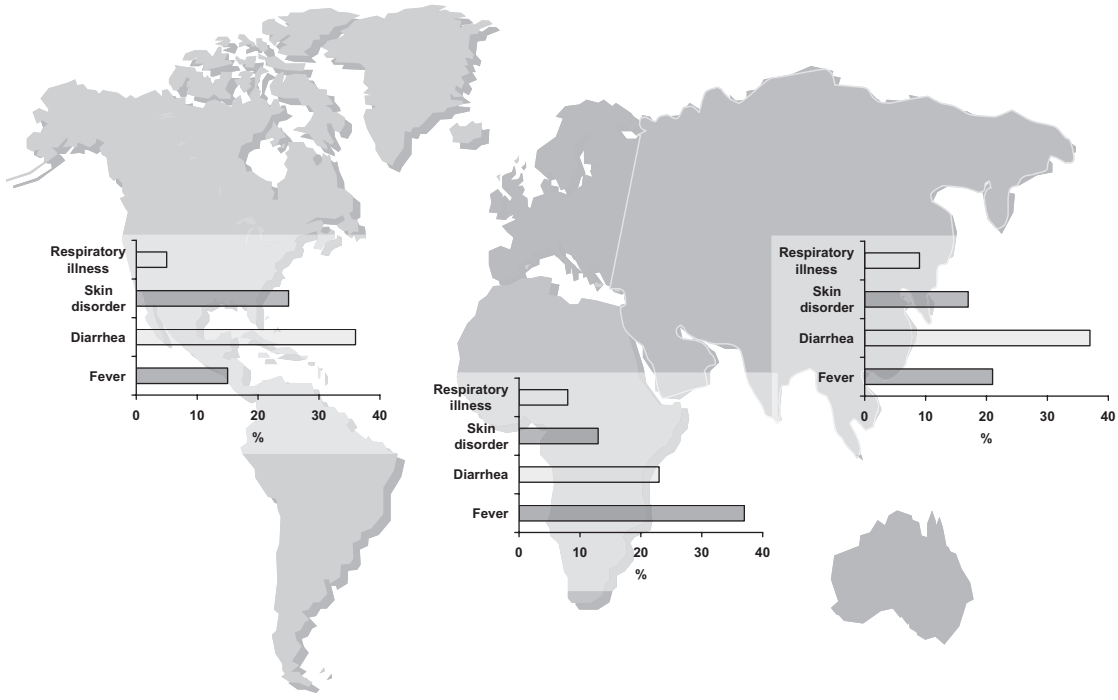

Figure 3.5 Proportion of morbidity among ill returned travelers (%) by continent visited, according to the GeoSentinel database, including in- and outpatients. (Adapted from [32].)

international system such as GeoSentinel may not capture them. Some of these diseases are vaccine-preventable, which emphasizes the role of pretravel consultation.

Risk in special populations

Generally, VFRs, as well as adventure travelers, are at increased risk of becoming ill while traveling because they have an increased risk of exposure, may less perceive travel-associated risks, and may forgo recommended vaccinations and chemoprophylactic measures [39] (see Chapter 5).

Furthermore, both age and travel duration are potential risk factors for post-travel illness and hospitalization and may explain the varying frequencies of illness in different study populations.

Gender-related morbidity

Over the past decade, it has become increasingly apparent that differences in the prevalence and severity of a broad range of diseases, disorders, and conditions exist between genders.

With regard to travel-related morbidity, a higher proportion of males, relative to healthy travelers, experience all major imported diseases. Surveys show clear male preponderance among ill returned outpatients (50% vs 42%) [19], as well as among febrile hospitalized travelers [18, 20, 27].

Males represented 71% of Israeli hospitalized ill returned patients, whereas they represented only 55% of the population of healthy travelers [18]. Data collected by the GeoSentinel surveillance network revealed that one of the most significant predictors for developing specific categories of respiratory infections while abroad was sex. Male sex was associated with a greater risk of lower respiratory tract infection, particularly pneumonia and bronchitis, but a lower risk of upper respiratory tract infection [36]. According to an Indian study, male travelers also revealed a higher rate of attack by hepatitis E virus [40]. The preponderance of men among malaria patients has been documented extensively among both travelers and local populations [41, 42]. Moreover, Canadian male travelers

had a higher risk of dying [71% vs 22%] and were also more likely to be arrested or detained while abroad [42].

Interestingly, no such observation has been made for dengue fever. Studies from various countries showed that the risk of acquiring dengue fever in travelers is not affected by gender [14, 18, 43, 44].

The reasons for gender differences in major illnesses are not yet clear. Some authors have argued that men follow riskier itineraries, or take fewer precautions, thus putting them at higher risk for febrile illnesses, such as malaria. One case-control study, however, did not find any major differences between men and women in terms of compliance with chemoprophylaxis and the use of protective measures. It has been concluded that males are generally more susceptible to malaria or infections [45]. However, to date, the biological causes of the suspected vulnerability of men are poorly understood. X-linked immunoregulatory genes appear to contribute to greater female resistance to infectious diseases [46].

On the other hand, women may have a lower threshold than men for seeking pre- and post-travel advice and may be more likely to present to health care facilities for nonfebrile illnesses [47]. This observation is most likely to be explained by the fact that women worry more than men about travel-related stressors such as infected food, contaminated water, and illness [48].

Post-travel morbidity in children

Over recent years, families with children have traveled increasingly to tropical destinations, exposing themselves to numerous infectious agents and tropical illnesses not encountered at home. However, there exist only a very limited number of published data on the subject of imported infections in children. Generally, it is assumed that children are more at risk of falling ill while traveling than adults. For this reason, traveling to tropical destinations with small children is mostly discouraged by pediatricians. Yet, there is no science-based evidence to support this presumption.

According to a prospective controlled study of 157 Swiss children and their parents, which included reports during as well as after travel, no major differences between children and adults in the incidence of illnesses apart from febrile episodes were observed. Age seems not to be a major determinant of travel-related morbidity. The chief complaint reported during and following travel was diarrhea, followed by febrile illness [49]. Similarly, the primary diagnosis of febrile hospitalized children from the UK who had returned from a tropical country within 4 weeks prior to hospital admission was unspecified fever, self-limiting illnesses of presumed viral origin, followed by malaria, bacillary dysentery, and dengue fever [21].

Like other retrospective reviews of imported malaria [50], most of these cases were reported among children of former immigrants who had visited their families' countries of origin [21]. Many people from this particular group of travelers do not feel that they need prophylaxis when returning home. Hence, the proportion of cases of imported pediatric malaria in children who received any form of malaria chemoprophylaxis was less than 50% [50].

More important, children are particularly at risk from malaria because symptoms may be very severe and usually develop more rapidly than in adult malaria patients. In addition, symptoms may differ from those in adults and, as children often suffer febrile diseases, malaria may not be suspected in the first place. As likewise observed for adults, most cases of officially reported pediatric malaria in travelers are caused by *P. falciparum* [50]. With regard to the time interval between return from travel and medical evaluation, 88% of pediatric cases of falciparum malaria but only 30% of *P. vivax* infections were diagnosed within a month of return [42]. Vivax malaria can occur late because of the dormancy of hypnozoites in the liver, which are not affected by the chemoprophylactic agents commonly used [51].

Air evacuation from abroad

Data on medical repatriation offer a portrait of serious medical problems for travelers while abroad. According to Steffen et al., about 50 per 100,000 travelers require air evacuation [52]. Based on another analysis, male travelers accounted for more than 65% of all medical escorts. In European countries, the majority of evacuations [53] were for medical reasons, mainly cardiovascular; in developing countries trauma and medical conditions accounted for 50%. Interestingly, infectious diseases were the reason for only 7% of all repatriations from developing countries [53].

Death

In terms of the hundreds of millions of international journeys completed annually, international travel is generally a safe undertaking. However, a number of travelers do experience serious injury, illness, and death. In a Canadian study tracking death notification data abroad, male