Tropical Diseases

Definition, Geographic Distribution, Transmission, and Classification

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KEYWORDS

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KEY POINTS

- The term tropical diseases encompasses all communicable and non-communicable diseases that occur principally in the tropics.
- Approximately 15 million people die each year because of tropical infectious and parasitic diseases.
- Tropical diseases are not restricted to the tropics. Increasing migration, international air travel, tourism, and work visits to tropical regions have contributed to an increased incidence of such diseases being seen in the United States, United Kingdom, and Europe.
- Classification of tropical diseases is useful for microbiologists, pathologists, laboratory staff and practicing infectious diseases physicians.
- This article gives an overview of the definition, geographical distribution, transmission and practical classification of tropical infectious diseases.

The term tropical diseases encompasses all diseases that occur principally in the tropics. This term covers all communicable and noncommunicable diseases, genetic disorders, and disease caused by nutritional deficiencies or environmental conditions (such as heat, humidity, and altitude) that are encountered in areas that lie between, and alongside, the Tropic of Cancer and Tropic of Capricorn belts. In tropical countries, apart from noncommunicable diseases, a severe burden of disease is caused by an array of different microorganisms, parasites, land and sea animals, and arthropods. ^{1–3}

Approximately 15 million people die each year because of tropical infectious and parasitic diseases, most living in developing countries.⁴ This wide array of diseases is compounded and made worse by the common issues of poverty, poor living conditions, malnutrition, human immunodeficiency virus (HIV)/acquired immune deficiency

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syndrome (AIDS), and poor health systems (consequential on poverty, mismanagement, and corruption) that afflict a large proportion of developing countries across the tropics. Although, in the past decade, lifestyle issues and changes in diet have led to an increase in the number of noncommunicable disease such as hypertension, diabetes, chronic obstructive airways disease, myocardial infarction, and cerebrovascular accidents in resource-poor tropical countries, tropical infectious diseases remain one of the major causes of preventable morbidity and mortality.⁵ Tuberculosis, HIV/AIDS, and malaria alone are currently responsible for an estimated 6 million deaths annually. 1-4 Schistosomiasis is the second most important parasitic disease after malaria, with 200 million people infected and 779 million at risk in more than 70 countries. In addition to these, leishmaniasis, onchocerciasis, filariasis, Chagas disease, African trypanosomiasis, rickettsioses, enteric fever, helminthiases, viral hemorrhagic fevers, and diarrheal diseases have extremely high public health impacts, and cause significant morbidity and mortality in adults and children. These diseases share population targets, ecological niches, and wide geographic distribution. 1-4 Respiratory tract infections (RTIs) are caused by a variety of bacterial, viral, and fungal pathogens. RTIs remain major causes of morbidity and mortality in adults and children worldwide, causing millions of deaths each year.^{6,7} The identification and diagnosis of acute and chronic bacterial (including tuberculosis), viral, and fungal respiratory infections remain an important challenge in medical inpatient and outpatient practice in Europe, the United States, and developing countries. Respiratory infectious diseases such as severe acute respiratory syndrome (caused by coronavirus) and the avian influenza⁸ are frequently causes of major concern. The Global Surveillance Network of the International Society of Travel Medicine (ISTM) and the Centers for Disease Control (CDC) established a worldwide communications and data collection network of travel/tropical medicine clinics in 1995, and their valuable Web site gives regularly updated information on geographic and temporal trends in disease-associated morbidity among travelers, immigrants, and refugees.9

TROPICAL DISEASES IN THE UNITED KINGDOM, EUROPE, AND THE UNITED STATES

Tropical diseases are not restricted to the tropics. Increasing migration, international air travel, tourism, and work visits to tropical regions have contributed to an increased incidence of such diseases being seen in the United States, United Kingdom, and Europe. 9,10 Climate change and global warming (with a resulting increase in average and nadir temperatures) may be causing tropical diseases and vectors to spread to higher altitudes in mountainous regions, and to higher latitudes that were previously spared, such as the southern United States and the Mediterranean area. The last decade of the twentieth century was marked by a resurgence in tropical diseases being encountered in countries outside the tropics, such as the United States, including Chagas disease, a chronic, systemic, parasitic infection caused by the protozoan Trypanosoma cruzi, and vector-borne viral encephalitides.^{3,9} Other previously rare, but presently emerging, diseases from particular geographic areas include leptospirosis, trypanosomiasis, giardiasis, and viral hemorrhagic fever. Bites from several animal species, including snakes, scorpions, and jellyfish, cause much morbidity and mortality from envenomation and secondary infections. Skin diseases are common in travelers returning from the tropics.3

The increasing success rates of solid organ and hematopoietic stem cell transplantations, with advances in immunosuppression, make transplants an early therapeutic option for many diseases affecting a considerable number of people worldwide. Thus, transplant programs in Western countries, as well as those in developing countries, have started to

face the impact of neglected tropical diseases transmitted via the donor tissue. 11 More posttransplantation respiratory viral, bacterial, protozoal, and fungal infections are being recognized. It is imperative that physicians globally are aware of the wide spectrum of tropical, infectious, and parasitic diseases to which their patients may have been exposed. It is prudent to enquire about travel history and geographic origins early in consultations, to aid early diagnosis and treatment and thereby prevent poor outcomes in many patients. An extensive enquiry into the travel history is prudent because certain tropical infectious diseases can first present years or even decades after the last tropical travel, including malaria (Plasmodium ovale and Plasmodium vivax), trypanosomiases (T cruzi and Trypanosoma brucei gambiense), strongyloidiasis (Strongyloides stercoralis), filariases, and schistosomiasis (any Schistosoma spp). It is imperative to consider the possibility of a tropical disease in cases that are difficult to diagnose, even potentially in those without a suggestive travel history. For example, malaria can occur in patients who have not traveled overseas, being acquired near city airports where mosquitoes imported on aircraft arriving from the tropics can survive and transmit the infection during the summer months. 12 A high degree of clinical awareness of the possibility of a tropical disease enables an early diagnosis to be made and enables effective treatment measures to be initiated, reducing morbidity and mortality.

CLASSIFICATION OF TROPICAL DISEASES

The number and range of tropical and infectious diseases prevalent globally is extremely large and broad ranging.^{1–3} Thus, for practical purposes, specific listings and classifications are useful for streamlining the microbiological and clinical assessment of the patient's illness. Classification of tropical diseases can also serve as aidemémoires or checklists for guiding clinicians, microbiologists, pathologists, and laboratory staff. For the practicing infectious diseases physician, there are several ways in which tropical/infectious diseases are presented in century-old classic tropical diseases textbooks like *Manson's Tropical Diseases* or other major treatises that present the classification of tropical diseases with a combination of clinical and microbiological approaches. The classification of infectious and tropical diseases, and their treatment, control, and prevention, have historically involved the joint efforts of epidemiologists, microbiologists, and clinicians.

Table 1 gives a basic classification of common infectious pathogens for clinical use. Physicians also tend to classify infectious diseases according to the most important organ or organ system to be affected, or the important clinical manifestations of the specific disease (Table 2). 13,14 Microbiologists tend to prefer classifying infectious diseases according to the classic microbiological nomenclature codes of kingdom, phylum, class, order, family, genus, and species and have large standard textbooks that give detailed classification and nomenclature. 15 They relate information according to microscopic appearance after staining or culture characteristics, to advise the clinician on the most appropriate antibiotic therapy and management. However, with advances in molecular technology, microorganisms are frequently being reclassified and renamed. For example Rickettsia tsutsugamushi, the causal agent for scrub typhus, has been reclassified into the genus Orientia. DF-2 is now known as Capnocytophaga canimorsus. 16 Epidemiologists usually describe tropical disease in terms of person, place, time, and exposure, with a view to developing control and prevention strategies to limit the spread of the diseases in the community. They often classify infectious diseases according to their distribution, their means of transmission, and according to their reservoirs in nature. Such classifications use the routes of transmission or acquisition of the infectious disease (Table 3).

Table 1

Microbiological or Clinical Grouping	Parasitolo	ogic Grouping and Examples
Bacteria	Protozoa	
Morphologic descriptions	Flagellate	S
Cocci, bacilli, vibrios	i.	Trypanosoma spp (T cruzi, T brucei
Gram staining		rhodesiense, T brucei gambiense, T
Gram-positive (high or low GC)		rangeli)
Gram-negative	ii.	Giardia lamblia
Oxygen requirements	iii.	Leishmania spp
Aerobes and anaerobes	iv.	Trichomonas spp
Chlamydia	Ameboids	
Chlamydia pneumoniae	i.	Entamoeba histolytica
Chlamydia trachomatis	ii.	Acanthamoeba spp
Mycoplasma	iii.	Naegleria fowleri
Mycoplasma pneumoniae	Ciliates	5 1 22 2
Mycoplasma arthritidis	i.	Balantidium coli
Mycoplasma genitalium	Sporozoa :	
Spirochetes	i.	Plasmodium spp (Plasmodium
Treponema spp (Treponema		falciparum, Plasmodium malariae,
pallidum, Treponema pertenue,		Plasmodium vivax, Plasmodium
Treponema carateum)	ii.	ovale) Babesia microti
Leptospira spp (Leptospira icterohaemorrhagica, Leptospira	iii.	Toxoplasma gondii
canicola)	iv.	Microsporidium spp
Borrelia spp (Borrelia	1V. V.	Cryptosporium spp
recurrentis, Borrelia burgdorferi)	v. Helminths	• • • • • • • • • • • • • • • • • • • •
Spirillum minus		es (roundworms, pin/threadworms,
Rickettsia		orms, hookworms)
Rickettsia spp	i.	Gut nematodes (<i>Ascaris lumbri-</i>
Spotted fever group		coides, Enterobius vermicularis, Tri-
Typhus group		churis trichiuria, Ancylostoma spp,
Scrub typhus group (now <i>Orientalis</i>)		Necator americanus)
Viruses	ii.	Tissue/muscle nematode (<i>Dracuncu</i> -
DNA viruses		lus medinensis, Trichinella spiralis,
Group 1: double-stranded DNA		Gnathostoma spinigerum, Linguatel-
(pox, herpes, papova, hepadna)		la serrata, Armillifer armillatus)
Group II: single-stranded DNA	iii.	Central nervous system nematodes
(parvo)		(Angiostrongylus cantonensis)
RNA viruses	Trematod	es (flatworms/flukes)
Group III: double-stranded (reo)	i.	Liver flukes (Fasciola hepatica, Fas-
Group IV: single-stranded		ciolopsis buski, Clonorchis sinensis,
(positive sense: orthomyxo,		Opisthorchis spp)
rhabdo, picorna, toga)	ii.	Blood flukes (Schistosoma haema-
Group V: single-stranded		tobium, Schistosoma mansoni, Schis-
(negative sense: Ebola, Marburg)		tosoma japonicum, Schistosoma
Fungi		intercalatum, Schistosoma mekongi)
Ascomycetes (sac fungi)	iii.	Lung flukes (Paragonimus westermani)
Basidiomycetes (club fungi)	Cestodes	(tapeworms)
Zygomycetes (mucor fungi)	i.	Intestinal tapeworms (Taenia solium,
Phycomycetes (algal fungi)		Taenia saginata, Diphyllobothrium
Morphology		latum, Hymenolepis nana)
Unicellular (Candida spp,	ii.	Intestinal tapeworm larval infections
Histoplasma spp)		in organs:
Multicellular (Aspergillus spp,		a. Cysticercosis (Taenia solium
Rhizopus spp, Fusarium spp)		larvae)
Dimorphic (<i>Penicillium marneffei</i>)		b. Echinococcosis (larvae of
		dog tapeworms Echino-
		coccus granulosus, and Echinococcus multilocularis)
		ECHINOCOCCUS MUNICIOCUIARIS)

Basic microbiological classification of common infectious pathogens for clinicians

Table 2 Some examples of tropical infectious diseases by main organ system involved				
Main Organ System Involved	Common Pathogens			
Gastrointestinal	Bacterial: all gastroenteritides, tuberculosis Protozoal: Chagas disease, amebiasis, <i>Giardia</i> , coccidia Helminthic: multiple			
Hepatic	Bacterial: leptospirosis, polymicrobial, anaerobes Protozoal: amoebic hepatitis/abscess, malaria, trypanosomiasis Helminthic: schistosomiasis, liver trematodes, hydatidosis Viral: hepatitis A–E, yellow fever, herpes viruses			
Respiratory	Bacterial: tuberculosis, pneumococcal pneumonia, legionnaires, mycoplasma pneumonia Fungal: aspergillosis, histoplasmosis, coccidioidomycosis, blastomycosis Helminthic: paragonimiasis, strongyloides hyperinfection, hydatid, tropical pulmonary eosinophilia Protozoal: Plasmodium falciparum			
Cardiovascular	Bacterial: endocarditis, rheumatic fever, tuberculosis, syphilis Protozoal: Chagas disease Helminthic: schistosomiasis			
Renal tract	Bacterial: poststreptococcal, tuberculosis Helminthic: schistosomiasis Protozoal: <i>Plasmodium falciparum</i>			
Neurologic	Bacterial: Neisseria meningitidis and other bacterial meningitis, leprosy, botulism, diphtheria Protozoal: Naegleria fowleri, Acanthamoebae, trypanosomiasis, Plasmodium falciparum Helminthic: cysticercosis, hydatid, Angiostrongylus cantonensis, gnathostomiasis Viral: HIV, HTLV-1, Japanese encephalitis, enteroviruses, rabies			
Dermatologic	Bacterial: tropical ulcers, syphilis, mycobacteria (eg, leprosy, tuberculosis, <i>Mycobacterium ulcerans</i>), anthrax Fungal: sporotrichosis, mycetoma, <i>Penicillium</i> Protozoal: leishmaniasis Helminthic: acute schistosomiasis, <i>Loa loa, Gnathostoma</i> , onchocerciasis, cutaneous larva migrans, larva currens Arthropods: bites and stings, scabies, myiasis, tungiasis			
Musculoskeletal	Pyomyositis, trichinosis, cysticercosis, tuberculosis, hydatid			

Many tropical infectious diseases are characterized by chronic inflammation as the battle between the host and pathogen becomes protracted. Pathologic reports often describe the presence of a granuloma in biopsy tissue and the tissue may be processed with special stains, molecular methods, or culture to try to identify further. A granuloma $^{17-19}$ is defined as a chronic, compact collection of inflammatory cells in which mononuclear cells predominate, usually formed as a result of an undegradable product, in the case of tropical infectious diseases; examples are given in **Table 4**. Some of the organisms contained within the granuloma remain viable, and these can reactivate to cause active disease when the patient becomes immunosuppressed from HIV or immunosuppressive therapy. Tuberculosis in HIV-infected individuals or in those on anti-TNF- α therapy, and Chagas disease in transplant recipients, are classic examples. Infectious diseases transmitted through medical procedures (eg, transfusion of blood

Route/Mode of Transmission	Disease (Examples)
Mother to child	,
Congenital/vertical	
Transplacental transmission via blood	TORCHES group of infections (toxoplasmosis, rubella, cytomegalovirus, <i>Herpes simplex</i> , syphilis), HIV, hepatitis viruses, malaria, trypanosomiases, bacteria infections
Perinatal	
Vaginal/cervical contact during delivery	Bacterial, viral, fungal infections
Contact via breast milk	Sexually transmitted diseases
Airborne/inhalational	
Inhalation of air, aerosol, fomite contaminated by microbes	RTIs caused by bacteria, viruses, fungi, <i>Chlamydia</i> spp and <i>Mycoplasma</i> spp (eg, lobal pneumonia, influenza, pneumonic plague, tuberculosis)
Contact of skin/mucosa	
Direct (touching, kissing, sex)	Sexually transmitted diseases, mycosis, scabies, MRSA
Indirect (indirect contact with infected fomite, body fluid, secretions, stool, blood, plasma, or pus)	Boils, MRSA, sexually transmitted diseases, respirator infections, <i>C difficile</i> and so forth
Ingestion	
Ingestion of any food or water contaminated with:	
Microorganisms	Infections caused by bacteria (eg, typhoid, cholera, dysentery), viruses (eg, hepatitis A, B, and C), mycobacteria (eg, Mycobacterium xenopi), protozo (eg, Entamoeba histolytica, Cryptosporidium spp)
Toxins	Staphylococcal, botulism, Bacillus cereus, scrombrotoxin, mushroom (Amanita phalloides)
Parasite ova/cysts	Infections caused by nematodes, trematodes, cestode protozoa (Entamoeba histolytica, Cryptosporidium spp)
Insect/arthropod-borne injection thro	ough skin penetration
Mosquitoes and disease transmission	
Anopheles spp	Malaria (all <i>Plasmodium</i> spp), bancroftian filariasis (<i>Wuchereria bancrofti</i>)
Culicine spp	Arbovirus encephalitis (eg, Japanese B encephalitis, St Louis encephalitis, West Nile virus)
Aedes spp	Yellow fever, filariasis (bancroftian)
Sandfly and disease transmission (<i>Phlebotomus</i> spp, <i>Lutzomyia</i> spp)	Leishmaniasis (all forms), sandfly fever (or Pappataci 3 day fever; Toscana, Sicilian, and Naples virus infections), bartenellosis (<i>Bartonella bacciliformis</i>)
Tsetse flies and disease transmission (<i>Glossina</i> spp)	Sleeping sickness (Trypanosoma brucei rhodesiense, T brucei gambiense)
Black flies (Simulium spp)	Onchocerciases (river blindness) (Onchocerca volvulus

Table 3	
(continued)	
Route/Mode of Transmission	Disease (Examples)
Horse/deer flies (Chrysops spp)	Filariasis (Loa loa), tularemia (Francisella tularensis)
Lice	Pediculosis Trench fever, bacillary angiomatosis and endocarditis (Bartonella quintana), epidemic typhus (Rickettsia prowazekii), louse-borne relapsing fever (Borrelia recurrentis)
Fleas	Plague (Yersinia pestis), endemic/murine typhus (Rickettsia typhi), bartonellosis, and cat scratch disease (Bartonella henselae), dwarf tapeworm (Hymenolepis nana)
Arachnids	
Mites	Chiggers, scrub typhus (<i>Orientia tsutsugamushi</i>) Scabies
Ticks	Lyme disease (Borrelia burgdorferi), tick typhus (Rocky Mountain spotted fever), ehrlichiosis (Anaplasma phagocytophilum), relapsing fever (Borrelia recurrentis), tularemia (Francisella tularensis), arboviruses (eg, Crimean-Congo hemorrhagic fever, Omsk hemorrhagic fever, babesiosis (Babesia microti)
Insect feces rubbed into skin	
Reduvid bugs (<i>Rhodnius</i> spp, <i>Triatoma</i> spp, <i>Panstrongylus</i> spp)	Chagas disease: feces of reduvid bugs with <i>T cruzi</i> spp are rubbed into skin by scratching)
Direct penetration through skin	
Helminth larvae	Helminth larvae penetration into subcutaneous tissue: swimmers itch (<i>Schistosoma</i> spp), hookworm and roundworm larvae
Fly larvae	Fly (bots and warbles) larvae (cutaneous myiases)
Innoculation or injection	
Breach of skin or mucous membrane caused by needles, tattoos, ear piercing, acupuncture, cupping, traditional scarification via blades	Viruses, bacteria, or fungal infections
Animal and human bites	Viruses (rabies, HIV, hepatitis B, hepatitis C, Herpes spp), bacterial infections (anaerobic and aerobic) including tetanus, actinomycosis, rat bite fever (Spirillum minus), Pasteurella multocida, Capnocytophaga canimorsus
Multiple modes of transmission	
Insect bites and airborne	eg, Plague: <i>Y pestis</i> flea bite (bubonic plague), airborne (pneumonic plague)
Direct contact, airborne, and ingestion of contaminated meat	eg, Anthrax: Bacillus anthracis skin contact with animal hides (cutaneous anthrax), airborne (pulmonary anthrax), ingestion of contaminated meat (gastrointestinal anthrax)
Insect bites, blood transfusion, needles, and congenital	eg, Malaria: <i>Plasmodium</i> spp
Skin/mucosa contact, needles, blood transfusion	eg, HIV, hepatitis B

Table 4 Infectious causes of granulomas			
Class of Organism	Examples	Clinical Disease and Site of Granulomas	
Mycobacteria spp	Mycobacterium tuberculosis Mycobacterium leprae Mycobacterium kansasii Mycobacterium marinum Mycobacterium bovis	Tuberculosis (any organ) Leprosy (skin and nerves) Pneumonia (lung) Fish tank granuloma (skin) BCGiosis (skin)	
Brucella spp	Brucella abortus, Brucella mellitensis, Brucella suis	Brucellosis (any organ)	
Yersinia spp	Y pestis	Plague (skin, lung)	
Listeria spp	Listeria monocytogenes	Listerioses (brain)	
Spirochetes	Treponema pallidum Treponema carateum	Primary syphilis (skin) Yaws (skin/mucous membranes)	
Fungi	Histoplasma capsulatum Coccidioides immitis Aspergillus fumigatus Cryptococcus neoformans	Histoplasmosis (any organ) Cocciodomycoses (any organ) Pulmonary aspergillosis (lung) Cryptococcosis (any organ)	
Protozoa	Toxoplasma gondii Leishmania spp	Toxoplasmosis (eye or brain) Leishmaniases (skin, mucous membranes, spleen, liver)	
Helminth ova/larvae			
Trematodes	Schistosoma spp Fasciola spp, Opisthorchis spp	Granulomas (any organ) Granulomas (liver, bile duct)	
Cestodes	Clonorchis sinensis Taenia solium	Granuloma around cysticerci (muscle, brain, subcutaneous tissue)	
Helminth larvae	Ascaris lumbricoides, Ancylostoma spp, Necator americanus	Granulomas (cutaneous and visceral) around dead larvae	

or blood-related products²⁰ and via transplantation) can also be classified microbiologically according to the type of microorganism (**Box 1**).

GEOGRAPHIC DISTRIBUTION OF TROPICAL DISEASES

There are geographic differences in the distribution and intensity of tropical infectious diseases and knowledge of these in relation to travel history or country of origin may increase the likelihood of making an accurate and rapid diagnosis. The incidence and prevalence of each disease varies with time, and therefore published World Health Organization data and map resources can rapidly become outdated because of the lag between data collection and publication. The Global Health Observatory (GHO)²¹ is a unique and useful service providing a gallery of global maps illustrating the prevalence of an extensive list of major health topics including tropical diseases, which are updated on a regular basis. These maps are classified by disease themes, including all major infectious and parasitic diseases. Each theme page provides information on the global situation, prevalence, and trends, using core indicators, database views, publications, and links to relevant Web pages. The GHO also issues analytical reports

Box 1

Classification of infections related to transfusion (of blood, platelet, immunoglobulin, clotting factors, or plasma)

Parasites

Plasmodium spp

Babesia microti ssp

Trypanosma cruzi

Trypanosoma brucei ssp

Leishmania donovani

Toxoplasma gondii

Viruses

HIV-1, HIV-2

Human T-lymphotropic virus (HTLV) type I, HTLV type II

Hepatitis A, B, C, D, E

Epstein B virus, cytomegalovirus

Kaposi sarcoma herpesvirus (HHV-8)

Parvovirus

West Nile virus

Severe acute respiratory syndrome

Bacteria

Gram-negative bacteria (eg, Pseudomonas spp, Yersinia spp, Salmonella spp)

Gram-positive bacteria (eq. Staphylococcus spp, Streptococcus spp, Brucella spp)

Spirochetes

Spirochetes (eg, Treponema pallidum, Leptospira spp, Borrelia burgdorferi)

Ehrlichia

Fungi

Candida spp

Other

New variant Creutzfeldt-Jakob disease prion

on the current situation and trends for priority health issues. A key output of the GHO is the annual publication *World Health Statistics*, which compiles statistics for key health indicators and also includes a brief report on progress toward health-related Millennium Development Goals. In addition, the GHO provides analytical reports on cross-cutting topics such as the report on women and health and burden of disease.

SOURCES OF LITERATURE ON TROPICAL DISEASES

Ongoing research and surveillance continues to yield new information. Advances in tropical medicine, as with all clinical specialties, tend to be distributed throughout the general medical and scientific literature, and sole reliance on such sources for specialist tropical medicine information does not usually suffice. There are several major textbooks focusing on clinical and laboratory aspects of tropical and parasitic

diseases.^{1–3} The information they contain is comprehensive, but some details may become outdated rapidly because of new developments, and readers are advised to look up more current sources of literature on each subject area.²² It is important that any comprehensive search encompasses general and specialist sources, including journals, books, databases, and Web sites. Many traditional print resources, such as journals, indexes, and, increasingly, books, are now available online.

This issue of *Infectious Diseases Clinics of North America* on tropical diseases covers the epidemiologic, clinical, laboratory, and management aspects of most of the common tropical infectious and parasitic diseases that may present to the physician in the west. Diseases caused by venomous bites, stings, and poisoning are also described to emphasize that not all tropical diseases are caused by microorganisms.

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