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Chapter 101

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Geography of infectious diseases

INTRODUCTION

Infectious diseases vary by geographic region and population, and they change over time. Increasingly, humans are moving from one region to another, thereby becoming exposed to a variety of potential pathogens and also serving as part of the global dispersal process.[1] Microbes picked up at one time and in one place may manifest in disease far away in time and place. Because many microbes have the capacity of persisting in the human host for months, years or even decades, the relevant time frame for study of exposures becomes a lifetime. Furthermore, microbes also move and change and reach humans via multiple channels.

Caring for patients in today's world requires an understanding of the basic factors that underlie the geography of human diseases and events that cause shifts in the distribution and burden of specific diseases. Current technology contributes to massive population movements and rapid shifts in diseases and their distributions, but it also provides communication channels that can aid clinicians who care for patients with unfamiliar medical problems. This chapter reviews the factors that shape the global distribution of infectious diseases and the forces that are expected to shift distributions in the future. Several examples are used to illustrate the broad range of factors that affect the distribution and expression of infectious diseases.[2]

Many authors have traced the origins and spread of specific infectious diseases through human history. A century and a half ago, John Snow noted that epidemics of cholera followed major routes of commerce and appeared first at seaports when entering a new region. *Yersinia pestis*, the cause of plague, accompanied trade caravans and moved across oceans with rats on ships. Exploration of the New World by Europeans introduced a range of human pathogens that killed one-third or more of the local populations in some areas of the Americas. The plants and animals introduced as a result of this exploration have also had profound and long-lasting consequences for the ecology and economics of the new environment.[3] The speed, reach and volume of today's travel are unprecedented in human history and offer multiple potential routes to move biologic species around the globe. Pathogens of animals and plants are being transported as well, and this can affect global food security.[4] Establishment of arthopod vectors, such as mosquitoes that are competent to transmit human pathogens, in new geographic areas can expand the regions that are vulnerable to outbreaks of some vector-borne infections. This chapter focuses only on pathogens that directly affect human health and on their sources (Table 101.1). When thinking about geography of human infections, it is useful to consider both the origin of the organism and the conveyor or immediate source for the human (Fig. 101.1).

Table 101.1 Origins and conveyors of human pathogens*

Origin or carrier	Conveyor or immediate source	Examples of disease
Humans	Humans	HIV, syphilis, hepatitis B
Humans	Humans (air-borne pathogen)	Measles, tuberculosis
Soil	Soil, air-borne	Coccidioidomycosis
Soil	Food	Botulism
Animals	Water	Leptospirosis
Humans	Mosquitoes	Malaria, dengue
Humans	Soil	Hookworm, strongyloidiasis
Animals	Ticks	Lyme disease
Animals, humans	Sand flies	Leishmaniasis
Animals	Animals	Rabies
Rodents	Rodent excreta	Hantaviruses
Humans	Water, marine life	Cholera
Humans or animals (with snails as essential intermediate host)	Water	Schistosomiasis
Humans	Food, water	Typhoid fever
Animals	Water	Cryptosporidiosis, giardiasis

*Some pathogens have multiple potential sources.

This chapter addresses three key issues:

- factors influencing geographic distribution: why are some infectious diseases found only in focal geographic regions or in isolated populations?
- factors influencing the burden of disease: why does the impact from widely distributed infections vary markedly from one region or one population to another? and
- factors influencing emergence of disease: what allows or facilitates the introduction, persistence and spread of an infection in a new region and what makes a region or population resistant to the introduction of an infection?

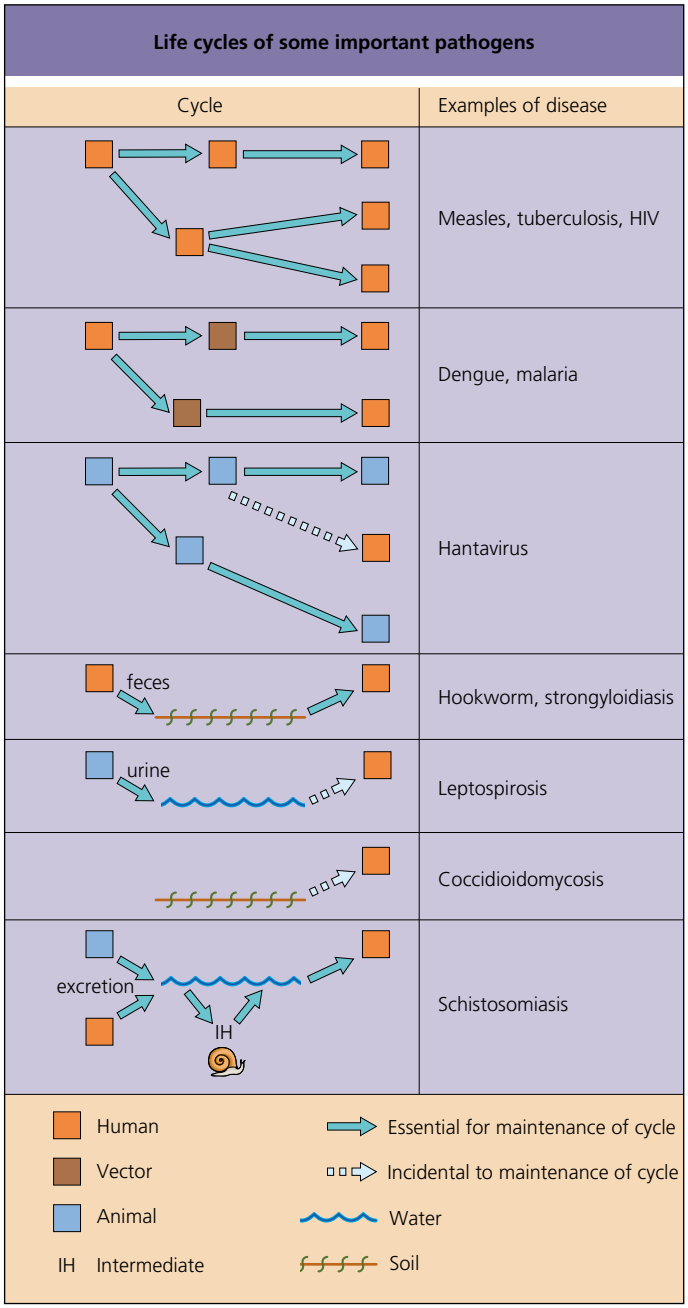

Fig. 101.1 Life cycles of some important pathogens.

FACTORS INFLUENCING GEOGRAPHIC DISTRIBUTION

In past centuries, lack of interaction with the outside world could allow an infection to remain geographically isolated. Today, most infections that are found only in focal areas have biologic or geoclimatic constraints that prevent them from being introduced into other geographic regions. For example, the fungus *Coccidioides immitis*, which causes coccidioidomycosis, thrives in surface soil in arid and semiarid areas with alkaline soil, hot summers and short, moist winters; it is endemic in parts of south-western USA, Mexico and Central and South America. People become infected when they inhale arthroconidia from soil. An unusual wind storm in 1977 lifted soil from the endemic region and deposited it in northern California, outside the usual endemic region.[5] In general, infection is associated with residence in or travel through the endemic region. However, because the fungus can persist in the human host for years, even decades, after initial infection (which may be mild and unrecognized), disease may be diagnosed far from the endemic regions. Although it is a 'place' disease, coccidioidomycosis has increased in the southwestern USA in recent years, in part attributable to a large influx of susceptible humans into the endemic zone and construction and other activities that disturb the soil. Outbreaks are also linked to climatic and environmental changes.[6]

Vectors

Many microbes require a specific arthropod vector for transmission or an animal reservoir host and hence inhabit circumscribed regions and may be unable to survive in other habitats. Malaria is a vector-borne infection that cannot become established in a region unless a competent vector is present. The presence of a competent vector is a necessary but not sufficient condition for human infection. The mosquito must have a source of malarial parasites (gametocytemic human or rarely other species), appropriate bioclimatic conditions and access to other humans. The ambient temperature influences the human biting rate of the mosquito, the incubation period for the parasite in the mosquito and the daily survival rate of the mosquito. Prevailing temperature and humidity must allow the mosquito to survive long enough for the malarial parasite to undergo maturation to reach an infective state for humans. Competent vectors exist in many areas without malaria transmission, because the other conditions are not met. These areas are at risk of the introduction of malaria, as illustrated by several recent examples in the USA and elsewhere.[7,8]

An estimated 77% of the world population lived in areas with malaria transmission in 1900. Today about 48% live in at-risk areas, but because of population growth and migration the total global population exposed to malaria today has increased by 2 billion since 1900.[9] Malaria was endemic in many parts of the USA into the 20th century (Fig. 101.2), with estimates of more than 600 000 cases in 1914. Even before extensive mosquito control programs were instituted, transmission declined. Demographic factors (population shifts from rural to urban areas), improved housing with screened doors and windows, and the availability of treatment were among the factors that contributed to this decrease.

The distribution of onchocerciasis in Africa is notable for its association with rivers.[10] The reason becomes clear by understanding that the vector of this filarial parasite, the black fly (genus *Simulium*), lays her eggs on vegetation and rocks of rapidly flowing rivers and usually

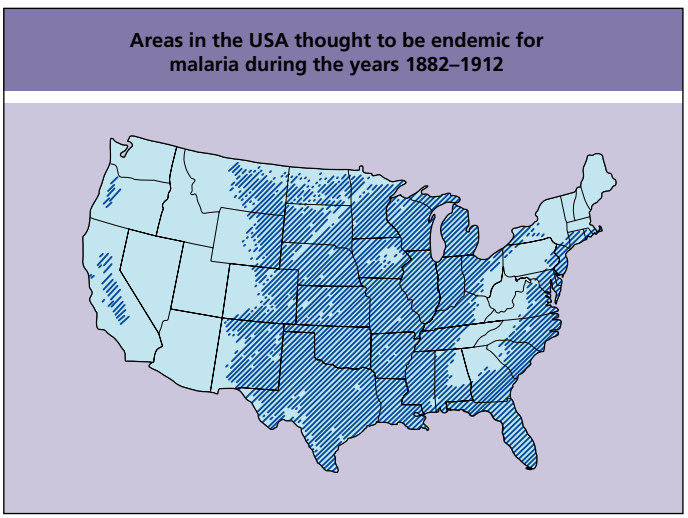

Fig. 101.2 Areas of the USA thought to be endemic for malaria during the years 1882–1912.

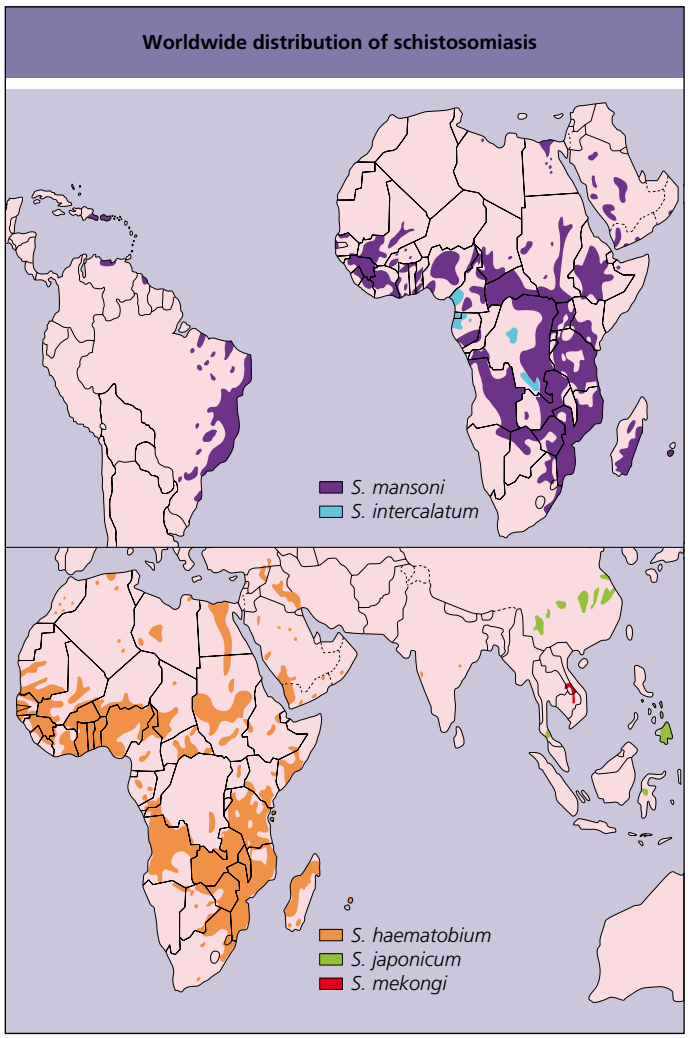

Fig. 101.3 Worldwide distribution of schistosomiasis.

inhabits a region within 5–10 km on either side of a river. Another name for onchocerciasis, river blindness, describes the epidemiology as well as one consequence of infection.

Some pathogens have a complex cycle of development that requires one or more intermediate hosts. Distribution may remain relatively fixed, even when infected humans travel widely, if other regions do not supply the right combination and geographic proximity of hosts (Fig. 101.3). Although persons with schistosomiasis visit many regions of the world, the parasite cannot be introduced into a new region unless an appropriate snail host is present, excreted eggs (in urine or feces) are released into water where they reach the snail hosts and humans subsequently have contact with the untreated water.[11] Local ecologic changes and climate change, however, can be associated with expansion of transmission in endemic areas or increased intensity of transmission, as has been projected as a possible consequence of warming temperatures in China.[12]

Many hantaviruses exist worldwide with distributions that are still being defined. Each hantavirus seems to have its specific rodent reservoir with which it has evolved. As with many zoonoses, humans are incidental to the survival of the virus in rodents, yet humans can develop severe and sometimes fatal disease if they enter an environment where they are exposed to the virus. Undoubtedly, other rodent-associated viruses and other pathogens (as well as pathogens associated with other animals or insects) with the capacity to infect humans will be identified as humans enter unexplored environments in the future.

Ebola and Marburg viruses are other viruses that have focal distributions but have caused dramatic human outbreaks with high mortality.

Table 101.2 Biologic attributes of organisms that influence their epidemiology

- Host range
- Duration of survival in host
- Route of exit from host
- Route of entry into human
- Inoculum need to establish infection
- Virulence
- Capacity to survive outside host
- Resistance to antimicrobials and chemicals

They also infect nonhuman primates and threaten the survival of great apes.[13] Recent studies suggest that bats may be the reservoir hosts.[14,15] Because these infections can be spread from person to person, secondary household and nosocomial spread in several instances has amplified what began as an isolated event. Lack of adequate resources in hospitals in many developing regions contributes to the spread of infections within hospitals and to persons receiving outpatient care, such as those receiving injections.

Cultural practices can lead to unusual infections in isolated areas. Residents of the highlands of Papua New Guinea developed kuru after ingestion (or percutaneous inoculation) of human tissue during the preparation of the tissues of dead relatives.

Thus, the presence of a pathogen in a region may reflect the biologic properties of the organism, its need for a certain physicochemical environment or its dependence on specific arthropods, plants or animals to provide the milieu where it can sustain its life cycle (Table 101.2). The presence of a pathogen in a region does not necessarily equate with human disease, because mechanisms must exist for the pathogen to reach a susceptible human host for human disease to occur. Sometimes it is only with exploration of new regions or changes in land use that humans place themselves in an environment where they come into contact with microbes that were previously unidentified or unrecognized as human pathogens. Preferences for specific foods, certain preparation techniques or cultural traditions may place one population at a unique risk for infection.

FACTORS INFLUENCING THE BURDEN OF DISEASE

Among the infectious diseases that impose the greatest burden of death globally, most are widely distributed: respiratory tract infections (e.g. influenza, *Streptococcus pneumoniae* and others), diarrheal infections, tuberculosis, measles, AIDS and hepatitis B.[16] Most of these infections are spread from person to person. The World Health Organization estimated that about 65% of infectious diseases deaths globally in 1995 were due to infections transmitted from person to person (Table 101.3).[16]

Table 101.3 Modes of transmission for major global infectious diseases

Mode of transmission	% of total*
Person-to-person	65
Food-borne, water-borne or soil-borne	22
Insect-borne	13
Animal-borne	0.3

*The figures are based on an estimated 17.3 million deaths due to infectious diseases in 1995, as reported by the World Health Organization.[16]

Burden from these diseases is unevenly distributed across populations and among different countries. Poor sanitation, lack of clean water, crowded living conditions and lack of vaccination contribute to the disproportionate burden from many of these infections in developing regions of the world. In industrialized countries, pockets of high risk persist. Disadvantaged populations have higher rates of tuberculosis, HIV and many other infectious and noninfectious diseases. Rates of reported cases of tuberculosis vary widely by region (Table 101.4).[17] Variation also exists within countries. Figure 101.4 shows the effect of crowded living conditions on rates of tuberculosis in England and Wales in 1992.[18] Among welfare applicants and recipients addicted to drugs or alcohol in New York City, the rate of tuberculosis was 744 per 100 000 person years or more than 70 times the overall rate for the USA.[19] The impact of an infection derives not only from the risk of exposure but also from the access to effective therapy. For example, treatment of a patient with active tuberculosis can cure the individual and eliminate a source of infection for others in the community.

Diphtheria, controlled in many parts of the world through the use of immunization, resurged in new independent states of the former Soviet Union in the 1990s, a reminder of the tenuous control over many infectious diseases. Populations in other countries also felt the impact as cases related to exposures in the Russian Federation were reported in Poland, Finland, Germany and the USA. Serologic studies in America and Europe suggest that up to 60% of adults may be susceptible to diphtheria.

Table 101.4 Rates of reported cases of tuberculosis worldwide by region, 1990 and 2006

Region	INCIDENCE PER 100 000 POPULATION	
	1990	2006
Africa	162	363
Americas	65	37
Eastern Mediterranean	111	105
Europe	37	49
South East Asia	200	180
Western Pacific	127	109

Data from World Health Organization.[17]

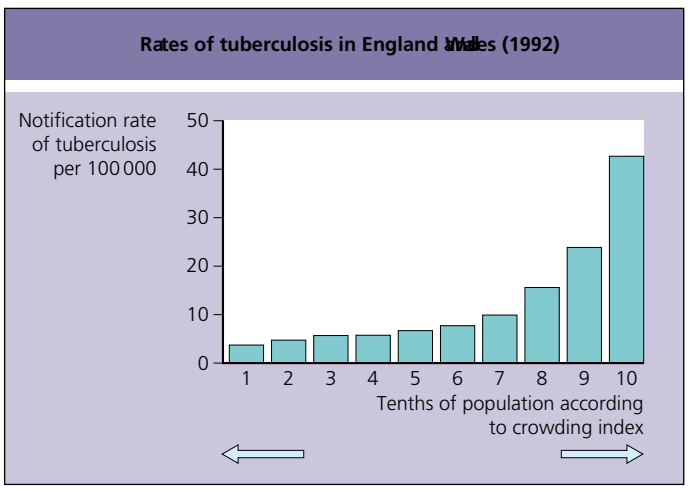

Fig. 101.4 Rates of tuberculosis in England and Wales by crowding index (1992). Adapted from Bhatti *et al.*[18]

Table 101.5 Factors that influence the types and abundance of microbes in a community

- Biogeoclimatic conditions
- Socioeconomic conditions
- Public health infrastructure
- Urban versus rural environment
- Density and mobility of population
- Season of the year
- Animal populations

Table 101.6 Factors that influence the probability of exposure to pathogens

- Living accommodation
- Level of sanitation
- Occupational and recreational activities
- Food preparation and preferences
- Sexual activities and other behavior
- Contact with pets, other animals, vectors
- Time spent in the area

Travelers to tropical and developing regions of the world can pick up geographically focal, often vector- or animal-associated infections (such as malaria and dengue),[20] but travelers most often acquire infections with a worldwide distribution that are especially common in areas lacking good sanitation.[21] Food- and water-borne infections are common and lead to travelers' diarrhea, which is caused by multiple agents (including *Escherichia coli*, *Salmonella*, *Shigella* and *Campylobacter* spp., and others), typhoid fever and hepatitis A. Respiratory tract infections may be acquired from other travelers from all over the globe during the crowding that occurs in travel (e.g. in buses, airplanes, terminals and on cruise ships) as well as from persons in the local environment. Tables 101.5 and 101.6 note factors that influence the types and abundance of microbes in a community and the probability of exposure to pathogens.

Hepatitis A virus remains a common cause of infection in developing regions of the world although it is not considered a major cause of morbidity or mortality in those regions where most persons are infected at a young age and become immune for life. The presence and severity of symptoms are related to the age at which a person becomes infected. Infection in young children is typically mild or inapparent. Persons living in areas of high transmission may be unaware of the presence of high levels of transmission, although nonimmune, older people (such as travelers) who enter the environment may develop severe, and occasionally fatal, infection. Some countries with an improving standard of living have noted a paradoxic increase in the incidence of disease from hepatitis A virus as the likelihood of exposure at a young age decreases, shifting upward the age of infection to a time when jaundice and other symptoms are more likely to occur.

Travelers may also contribute to the spread of infectious diseases and influence the global burden of these diseases.[22,23] *Neisseria meningitidis*, a global pathogen, occurs in seasonal epidemics in parts of Africa – the so-called meningitis belt (Fig. 101.5).[24] Irritation of the throat by the dry, dusty air probably contributes to invasion by colonizing bacteria. Pilgrims carried an epidemic strain of group A *N. meningitidis* from southern Asia to Mecca in 1987. Other pilgrims who became colonized with the epidemic strain introduced it into sub-Saharan Africa, where it caused a wave of epidemics in 1988 and 1989. Using molecular markers, investigators were able to trace the spread of the epidemic clone to several other countries.[25] In 1996 in Africa, major outbreaks of meningococcal meningitis occurred

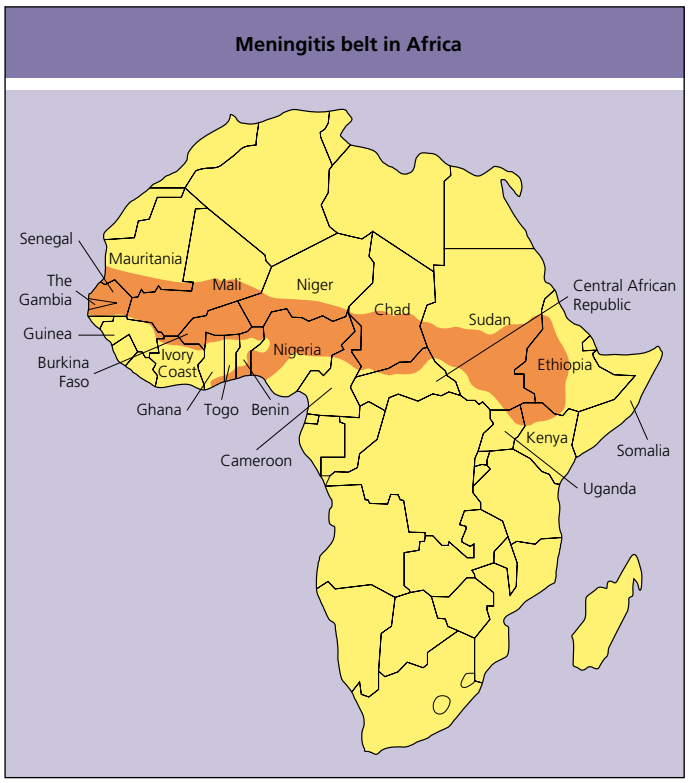

Fig. 101.5 Meningitis belt in Africa.

(>185 000 reported cases with a case fatality rate of ~10%) caused by *N. meningitidis* serogroup A, clone III-1.[26] A virulent group C, ET-15 strain of *N. meningitidis* spread in Canada and was associated with an increased case fatality rate and a higher proportion of cases in persons over the age of 5 years.[27] In these examples, the virulence of the microbe and travel and trade acted synergistically to change the epidemiology and burden of disease. In the spring of 2000 serogroup W135 *N. meningitidis* caused an outbreak of infection in pilgrims to the Hajj and subsequently spread to their contacts and others around the world. Studies using serotyping, multilocus sequence typing, multilocus DNA fingerprints and other techniques found identical W135 isolates in multiple countries. Pilgrims are required to receive a meningococcal vaccine but before this outbreak, pilgrims from many countries received a vaccine that protected against serotype A but not W135. The vaccine reduces risk of disease but does not prevent oropharyngeal carriage of *N. meningitidis*.[28]

FACTORS INFLUENCING EMERGENCE OF DISEASE

Regular, rapid movement of persons from tropical regions to major urban areas throughout the world raises concerns that unusual infections could be introduced into an environment where they could spread to large populations. In order to assess the potential for a pathogen to be introduced into a new population, information is required about the biologic properties of the organism, the region and population being considered and the mechanisms of transmission (see Table 101.1). A key factor that determines whether a pathogen can persist and spread in a new population is its basic reproductive rate, which is the number of secondary infections produced in a susceptible population by a typical infectious individual. To become established in a new host population, a pathogen must have a basic reproductive rate that exceeds one. The concept is simple but invasion and persistence are affected by a range of biologic, social and environmental factors. Also critical in determining how easily an infection can be controlled is the proportion of transmission that occurs before onset of symptoms or during asymptomatic infection.[29]

Table 101.7 Factors that restrict the introduction and spread of infections

- Geoclimatic factors that cannot support vector or intermediate host
- Genetics of human population, making it genetically resistant or relatively resistant
- Immunity of human population, making it not susceptible because of past infection with same or related microbe or via vaccination
- Demographic factors (e.g. size and density of population will not support sustained transmission of diseases such as measles)
- Social and behavioral factors (e.g. absence of activities such as iv drug use and unprotected sex with multiple partners)
- Food preparation habits and local traditions (e.g. certain dishes not eaten, food always well cooked)
- High-quality housing, sanitation, public health infrastructure, good surveillance
- High standard of living, good nutrition, lack of crowding, access to good medical care
- Biologic characteristics of the microbe

Certain factors restrict the introduction and spread or persistence of infection in a region (Table 101.7); many of these are discussed above. Nutrition is also important in determining susceptibility to and severity of many infections. A substantial proportion of disease burden in developing countries can be attributed to childhood and maternal underweight and micronutrient deficiences.[30] Before measles vaccine was introduced, the epidemiology of measles exhibited marked periodicity in large populations, with peaks typically occurring every 2–3 years.[31] In general, a community size of about 250 000 is necessary to provide a sufficient number of susceptible people to sustain the virus. In small island communities (or other isolated populations), outbreaks typically occur only after periodic introductions from outside. Size and density of a population thus influence the epidemiology of some infections. It has been suggested that measles as it has been known in the 20th century could not have established itself much before 3000 BC because before that time human populations had not achieved sufficient size to sustain the virus. Measles could not have persisted in nomadic, hunting communities.

Examples of emerging pathogens

It is instructive to look at examples of infections that have recently undergone major shifts in distribution and to review the key factors that have influenced their geographic spread. They are a reminder of the complexity of the interactions among host, microbe and environment. A recurring theme is the movement of humans who introduce pathogens into a new region (see also Chapter 4) and human alteration of the landscape or ecology that permits contact with previously unrecognized microbes, often through interaction with animals or animal products. Many infections in humans, in the past and in recent years, have domestic or wild animals as their sources.[32]

Human immunodeficiency virus and other pathogens carried by humans

Organisms that survive primarily or entirely in the human host and are spread from person to person (e.g. by sexual or other close contact or by droplet nuclei) can be carried to any part of the world. The spread of HIV in the past three decades to all parts of the world is a reminder of the rapid and broad reach of travel networks. Although the infection has also spread via blood and shared needles, it has been the human host engaging in sex and reproduction who has been the origin for the majority of the infections worldwide. Person-to-person

spread accounted for the rapid worldwide distribution of severe acute respiratory syndrome (SARS), a coronavirus infection, in the spring of 2003, after the virus emerged from an animal reservoir, most likely bats.[33]

Drugs or vaccines injected by reused inadequately sterilized needles and syringes have been and continue to be an important means of spread of blood-borne infections, such as hepatitis C, hepatitis B and HIV, in some parts of the world.[34]

Multidrug-resistant (MDR) tuberculosis has continued to increase, with World Health Organization estimates of 500 000 new cases of MDR annually (now about 5% of all new TB cases each year).[35] Extensively drug-resistant tuberculosis, which is virtually untreatable, had been reported in 45 countries by 2007. It is not only the pathogens carried by humans that are relevant. Humans also carry resistance and virulence factors that can be transferred to and exchanged with other microbes.[36]

Dengue fever

Dengue fever is a mosquito-borne viral infection that has now spread to most tropical and subtropical regions of the world and continues to increase in incidence and severity. Viremic humans regularly enter regions infested with *Aedes aegypti*, the principal vector of dengue, transporting the virus for new outbreaks. Infection can spread rapidly and outbreaks are sometimes massive, involving >30% of the population. Because four serotypes of dengue virus exist and infection with one serotype does not confer lasting immunity against other serotypes, a person can be infected more than once. The risk of developing severe dengue (e.g. dengue shock syndrome or dengue hemorrhagic fever, DSS or DHF) after repeat infection is 82–103 times greater than after primary infection.[37] In an outbreak in Cuba, 98.5% of cases of DSS or DHF were in persons with a prior dengue infection. The rate of DSS or DHF was 4.2% in persons with prior dengue infection who became infected with a new serotype.[38]

Geographic regions where multiple serotypes are circulating have continued to expand, setting the stage for more severe consequences of infection. Factors that have aided the spread of dengue include increasing (and rapid) travel to and from tropical regions; expansion of the regions infested with *Aedes aegypti*; increasing urbanization, especially in tropical areas, which has provided large, dense populations; the use of nonbiodegradable and other containers that make ideal breeding sites for the mosquito; and lack of support for vector control programs.

Most of the world population growth globally is in urban/peri-urban areas in tropical and developing regions. The expectation is that more urban areas in tropical regions will reach the critical population size, perhaps somewhere between 150 000 and 1 million people, to permit sustained transmission of dengue, and to increase the risk of the severe forms of infection, dengue hemorrhagic fever and dengue shock syndrome.

In 2001 the vector that was implicated in an outbreak of dengue in Hawaii[39] was *Aedes albopictus*, a mosquito species that has been newly introduced into many new regions in recent decades, probably primarily by shipping.[40] On phylogenic analysis the virus responsible for the Hawaii outbreak was similar to dengue, isolates from Tahiti, suggesting that viremic travelers introduced the virus from the South Pacific.

It is instructive to ask not only where dengue occurs but also where it does not. Although large dengue epidemics occurred in the USA in the 20th century, only a handful of cases have been acquired in the USA in recent years, despite the presence of epidemic disease in adjacent areas of Mexico and the presence of a competent vector (*Aedes aegypti*) in south-eastern USA (Fig. 101.6).[24] It is possible that the presence of screened dwellings and air conditioning may make an area relatively resistant to the introduction of infection, even if a competent vector infests a region, though serologic studies have also documented that unrecognized dengue infections are occurring in Texas.[41]

Chikungunya virus

Chikungunya, a mosquito-borne alphavirus originally isolated in Tanzania in 1953, has spread from Africa, causing massive outbreaks in the Indian Ocean islands and India since 2005. Although it has typically been considered an infection of tropical regions, in the summer of 2007 an outbreak caused hundreds of cases (175 laboratory confirmed) in north-eastern Italy. The index case was a visitor from India. Of note, the vector implicated was *Aedes albopictus*, which had been first documented in Italy in 1990 and was postulated to have been introduced via used tires.[42] Mutations in the virus may have enabled it to replicate more efficiently in the mosquito vector. Chikungunya virus can be transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes, which are now both widely distributed, so many regions of the world are vulnerable to introduction of this virus by viremic travelers.

Cholera

Cholera illustrates the complex interactions between microbe, environment and host.[43] Epidemics are seasonal in endemic regions. *Vibrio cholerae* lives in close association with marine life, binding to chitin in crustacean shells and colonizing surfaces of algae, phytoplankton, zooplankton and water plants. *V. cholerae* can persist within the aquatic environment for months or years, often in a viable but dormant state, nonculturable by usual techniques. Environmental factors, including temperature, salinity, pH and sea-water nutrients, affect the persistence, abundance and viability of the organisms, and hence have a striking influence on human epidemics.

Under conditions of population crowding, poor sanitation and lack of clean water, cholera can have a devastating impact, as was shown by the massive outbreak of El Tor cholera in Rwandan refugees in Goma, Zaire, which caused 12 000 deaths in July 1994.[44]

The organism can be carried by humans, who sometimes have few or no symptoms, and introduced into new regions. Trade probably also plays a critical role. Ballast water, picked up by boats in multiple locations and discharged at another time and place, carries a wide range of species, including many that have no direct impact on human health.[45,46] In studies of the ballast and bilge of cargo ships in the USA Gulf of Mexico, researchers were able to identify *V. cholerae* identical to the strains causing epidemic disease in Latin America.[47]

Food-borne disease

The globalization of the food market means pathogens from one region can appear in another; some are common pathogens with a worldwide distribution but others are not. An outbreak of cholera in Maryland, USA, was traced to imported, contaminated commercial frozen coconut milk.[48] Alfalfa sprouts grown from contaminated seed sent to a Dutch shipper caused outbreaks of infections with *Salmonella* spp. on two continents, in at least Arizona and Michigan in the USA and in Finland.[49] Commercial movement of fruits and vegetables redistributes resistance factors along with the microbes. Tracing the source after an infection has been diagnosed can be convoluted and often is not carried out unless disease is severe, lethal or epidemic or involves a highly visible person or population.

Travel and trade are key features in the epidemiology of the infection *Cyclospora*, a cause of gastroenteritis. Recognized for many years in

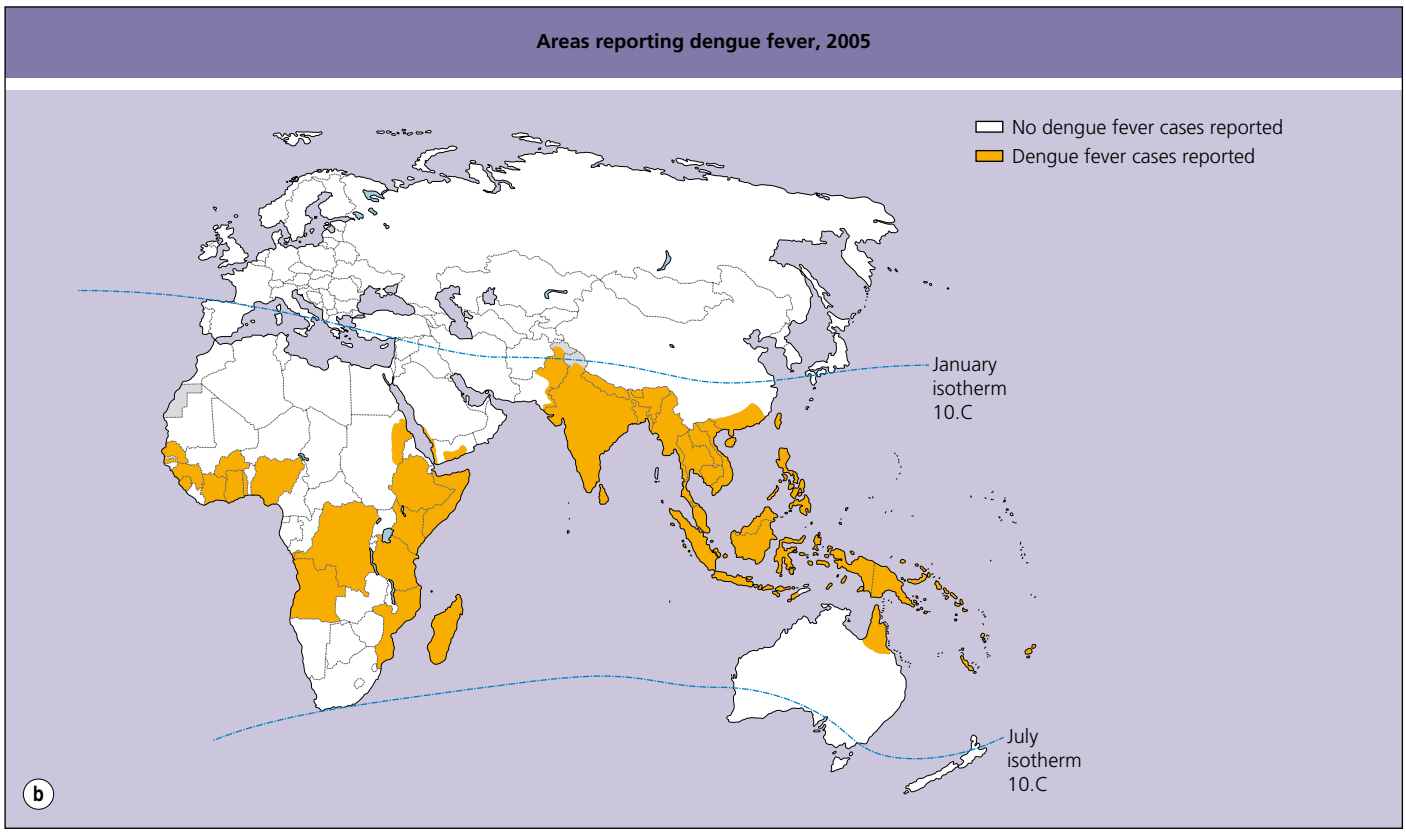

Fig. 101.6 (a, b) Areas reporting dengue fever, 2005. Many areas with a competent vector do not report dengue epidemic activity. Copyright World Health Organization 2008.

Fig. 101.7 (a, b) Worldwide distribution of malaria (updated CDC map). Data from Centers for Disease Control and Prevention.[24]

multiple regions of the world, cases were often associated with living in or travel to areas where sanitary facilities were poor. In the summer of 1996, a large US outbreak occurred in persons who had not traveled. Over a period of a few months, 1465 cases of cyclosporiasis were reported from 20 states. The outbreak was linked to eating raspberries imported from Guatemala.[50] During some seasons of the year up to 70% of selected fruits and vegetables sold in the USA come from developing countries.

Visceral leishmaniasis

In the past, visceral leishmaniasis in Brazil was primarily a rural disease. Recently, however, several cities have reported large outbreaks of visceral leishmaniasis.[51] Reasons for the change in epidemiology include geoclimatic and economic factors (drought, lack of farm land, famine), leading to migration of large numbers of persons, who settle in periurban areas where they live in densely crowded shanties, lacking basic sanitation. The presence of domestic animals, such as dogs, chickens and horses, in and adjacent to human dwellings provides ample sources of blood meals for the sand fly, the vector of leishmaniasis. Outbreaks have occurred in many cities in Brazil, including Teresina, São Luis and Natal. Children and young people have been most affected. Malnutrition can also contribute to the severity of the disease.

Disease–disease interactions can also alter the epidemiology of infections. Visceral leishmaniasis has become an important infection in HIV-infected people in Spain and other areas where the two infections coexist.[52] The presence of HIV leads to increased risk of progression of infection; late appearance of disease can occur years to decades after exposure in an endemic region, leading to the appearance of cases of leishmaniasis in regions distant from endemic areas. A common consequence is missed or delayed diagnosis.

Movement of vectors and other species

Movement today involves all forms of life and the movement of nonhuman species can affect infections in humans. Importation of wild animals from Ghana into the United States led to an outbreak of monkeypox, an infection previously known to exist in Africa. Humans became infected by handling prairie dogs (sold as pets) that had been housed with the imported wild animals from Africa.[53] *Aedes albopictus* introduced into the USA via used tires shipped from Asia[54] has since become established in at least 21 contiguous states of the USA and in Hawaii. *Aedes albopictus* can transmit dengue and chikungunya viruses, as described above, and is a competent laboratory vector of La Crosse, yellow fever and other viruses. It is also hardier than many other mosquito species and therefore may spread widely and be extremely difficult to eradicate. Multiple strains of eastern equine encephalitis virus have been isolated from *Aedes albopictus* in Florida.

An example from the past illustrates the potential consequences of the introduction of a mosquito vector into a new region. In March 1930, an entomologist in Natal, Brazil, came upon *Anopheles gambiae* larvae in a small, wet, grassy field between a railway and a river.[55] He was surprised, because the usual habitat for this mosquito was Africa. Investigation revealed that the probable route of entry into South America was via boats that made mail runs between Dakar in Senegal

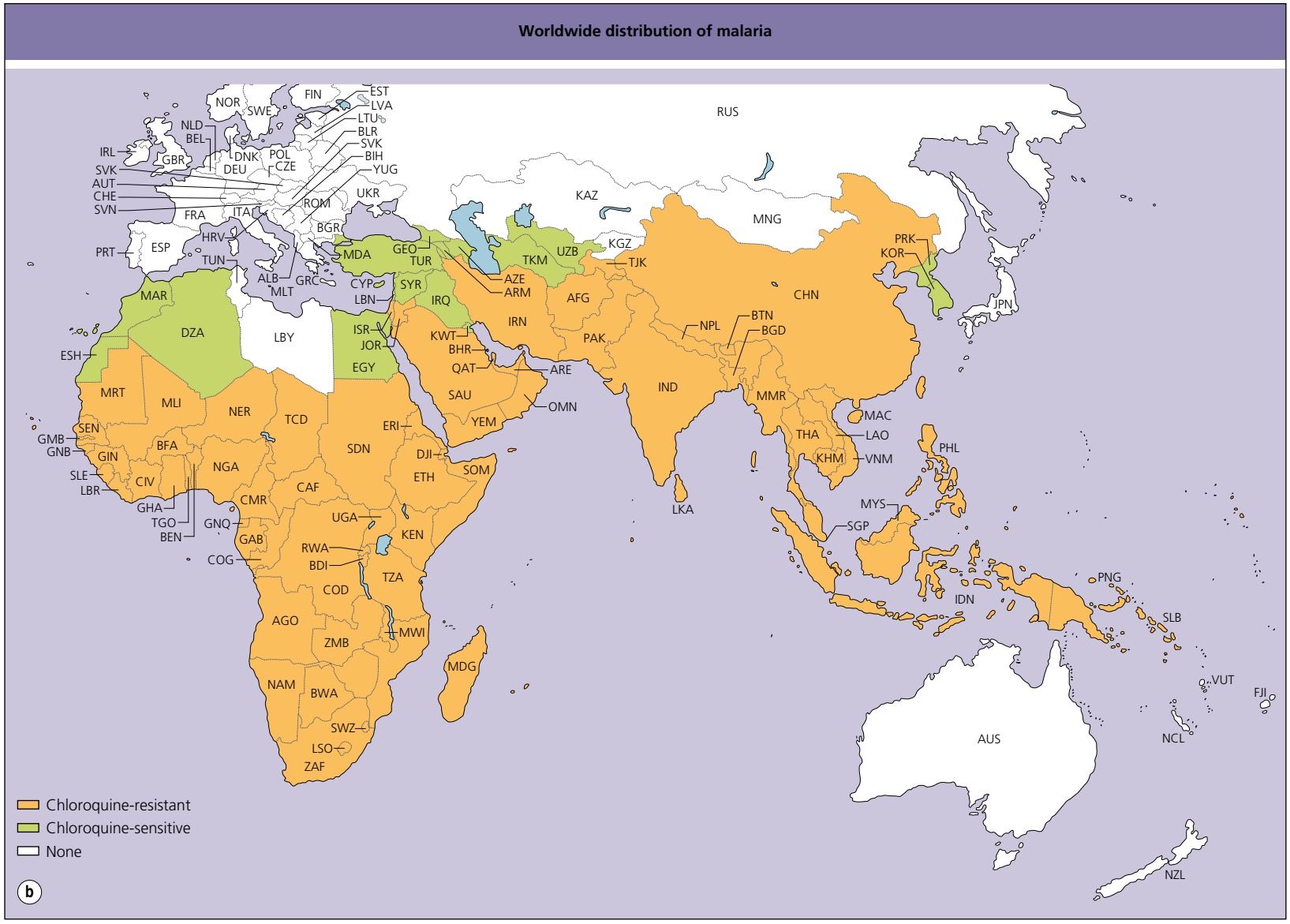

Fig. 101.7—cont'd.

and Natal in Brazil, covering the 3300 km in less than 100 hours. In Dakar the boats were anchored a distance from the shore within easy flight range of *A. gambiae*. In Brazil, over the ensuing years, the mosquito spread along the coastal region and inland. Natal, as an ocean port, terminus of two railway lines and the hub of truck, car and river transportation, was well suited for dissemination of *A. gambiae* into the region. Although malaria already existed in the region, the local mosquitoes were not efficient vectors. *Anopheles gambiae*, in contrast, lived in close proximity to humans, entered houses, sought human blood and was an efficient biter. In 1938 and 1939, devastating outbreaks of malaria killed more than 20 000 persons. In this instance, the simple introduction of a new vector into a region led to severe problems. Fortunately, an intensive (and expensive) eradication campaign was effective.

Current transportation systems regularly carry all forms of life, including potential vectors, along with people and cargo. In an experiment carried out several years ago, mosquitoes, house flies and beetles in special cages were placed in wheel bays of 747 aircraft and carried on flights lasting up to 7 hours. Temperatures were as low as –62°F (–52°C) outside and ranged from 46°F to 77°F (8–25°C) in the wheel bays. Survival rates were greater than 99% for the beetles, 84% for the mosquitoes and 93% for the flies.[56] Occasional cases of so-called airport malaria – cases of malaria near airports in temperate regions – attest to the occasional transport and survival of a commuter mosquito long enough to take at least one blood meal in the new environment.

In the USA, transportation of raccoons in the late 1970s from Florida to the area between Virginia and West Virginia (in order to stock hunting clubs) unintentionally introduced a rabies virus variant into the animals of the region. From there, the rabies enzootic spread for hundreds of miles, reaching raccoons in suburban and densely populated regions of the north-east USA. Spill-over of the rabies virus variant into cats, dogs and other animal populations and direct raccoon–human interactions have had extremely costly and unpleasant consequences.[57]

Today highly pathogenic avian influenza A (H5N1) is a global concern.[58] It is entrenched in poultry populations in Asia and Africa and has caused outbreaks in Europe and the Middle East. Although the virus causes high mortality in infected humans, thus far H5N1 has not been able to establish sustained transmission from person to person. Most humans appear to have been infected via close contact with poultry or their products. Although the virus can be carried by migratory birds,[59] most introductions appear to have been related to movement of poultry and poultry products. A model designed to map risk in South East Asia found risk was associated with duck abundance, human population and rice cropping intensity.[60]

GEOGRAPHIC INFLUENCES ON DIFFERENTIAL DIAGNOSIS

Geographic exposures influence how one thinks about probable diagnoses in a given patient. In Mexico, for example, more than 50% of patients with late-onset seizures have CT evidence of the parasitic infection, neurocysticercosis.[61] In Peru, 29% of persons born outside Lima who had onset of seizures after 20 years of age had serologic evidence of cysticercosis.[62] In northern Thailand, melioidosis is a common cause of sepsis, accounting for 40% of all deaths from community-acquired sepsis.[63]

In considering the consequences of exposures in other geographic regions, relevant data in assessing the probability of various infections include the duration of visit, activities and living conditions during the stay and the time lapsed since the visit. Among British travelers to West Africa, the relative risk of malaria was 80.3 times higher for persons staying for 6–12 months than among those staying 1 week.[64] In Malawi, the risk of schistosome infection increased directly with duration of stay. Seroprevalence was 11% for those present for 1 year or less, but this increased to 48% among those present for 4 years or longer.[65] In a study of persons with cysticercosis, the average time between acquisition of infection and onset of symptoms was about 7 years.[66]

For malaria, it is necessary to know not only whether infection can be acquired in a specific location but also the specie of parasite present and the patterns of resistance to antimalarial agents. As chloroquine resistance has spread, maps now typically highlight the few remaining areas of chloroquine sensitivity. Because the resistance to antimalarial agents is a dynamic process, with levels of resistance generally increasing over time (involving *Plasmodium vivax* in some areas as well as *P. falciparum*), it is essential to base decisions about chemoprophylaxis and treatment on up-to-date information. Figure 101.7 shows the distribution of malaria and resistance patterns globally as of 2005. Recent analysis of data from a network that uses travelers as a sentinel population found marked differences in the spectrum of disease in relation to the place of exposure.[20]

Expression of disease may vary depending on age of first exposure, immunologic status of the host, genetic factors and the number and timing of subsequent exposures. Temporary residents of endemic regions have different patterns of response to a number of helminths from those of long-term residents. In cases of loiasis, temporary residents have immunologic hyperresponsiveness, high-grade eosinophilia and severe symptoms that are not seen in long-term residents of the same area.[67] Genetic factors can affect susceptibility to infection or expression of disease. Some persons, for example, are genetically resistant to infection with parvovirus because they lack appropriate receptors on their erythrocytes.[68] Persons lacking Duffy factor cannot be infected with the malarial parasite, *P. vivax*.

CONCLUSION

Knowledge about the geographic distribution of diseases is essential for informed evaluation and care of patients, who increasingly have had exposures in multiple geographic regions. Recent travel and trade patterns have led to more frequent contact with populations (human and nonhuman species) from low latitude areas, regions with greater species richness.[69] Infectious diseases are dynamic and will continue to change in distribution. Changes in virulence and shifts in resistance patterns will also require ongoing surveillance and communication to health-care providers. Multiple factors favor even more rapid change, perhaps in unexpected ways, in the future: rapidity and volume of travel, increasing urbanization (especially in developing regions), the globalization of trade, multiple technologic changes that favor mass processing and broad dispersal, and the backdrop of ongoing microbial adaptation and change, which may be hastened by alterations in the physicochemical environment.

REFERENCES

References for this chapter can be found online at http://www.expertconsult.com