Chapter 21
Vector-Borne Transmission: Malaria, Dengue, and Yellow Fever

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21.1 Malaria

At least 2 billion people live in malarious areas (Snow et al. 2005). The disease primarily affects poor populations in tropical and subtropical areas, where the temperature and rainfall are most suitable for the development of the malaria-causing *Plasmodium* parasites in *Anopheles* mosquitoes. This limited geographic distribution is no necessity: malaria once occurred widely in temperate areas, including Western Europe and the USA. The infection receded with economic development and public health measures. It was finally eliminated in the USA between 1947 and 1951 through a campaign that included household spraying of the insecticide dichloro-diphenyl-trichloroethane (DDT) . WHO launched the Global Malaria Eradication Program 1955 (WHO 1999). The planning depended on two key tools: chloroquine for treatment and prevention and DDT for vector control. Implementation of the program had substantial impact in some areas, particularly areas with relatively low transmission rates, such as India and Sri Lanka. Despite these successes, lost political will, the emergence of chloroquine-resistant *Plasmodium* parasites, and of DDT-resistant *Anopheles* mosquitoes led to a failure of the campaign. The global eradication of malaria was officially abandoned as a goal in 1972 (Greenwood et al. 2008). Since the Global Malaria Eradication Program ended, the burden of malaria increased substantially in many parts of the world. The resurgence of malaria was sometimes dramatic, including epidemics in Sri Lanka in 1968–1969 and in Madagascar in 1987–1988. However, economic development, improved health infrastructure, and continued anti-vector measures led to a continued decline of transmission in some countries (e.g., Thailand). Recently, good prospects for malaria elimination in some defined epidemiological settings have been emerging (Tanner and de Savigny 2008). This new momentum is supported by the recent demonstration of a dramatic reduction in malaria transmission, morbidity, and mortality in several countries in Africa (Greenwood et al. 2008;

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Tanner and de Savigny 2008), owing to the implementation of effective malaria control measures, such as insecticide-treated bednets (ITNs) , indoor residual spraying (IRS), and artemisinin-based combination therapies (ACTs).

Currently a mixed epidemiological picture is emerging. While malaria transmission is spreading to higher altitudes, probably due to improved climate conditions for the vector, highly endemic areas are reporting a clear decline of cases (Greenwood et al. 2008). A good example for this unclear situation is the Gambia. In a retrospective study on the malaria indices of this country, a clear decrease was evident. From 2003 to 2007, at four sites with complete slide examination records, the proportions of malaria-positive slides decreased by 50–82%. During the same period, the proportions of malaria admissions fell by 27–74% in three sites, while proportions of deaths attributed to malaria in two hospitals decreased by 90–100% (Ceesay et al. 2008). On the other hand, in November 2008, a significant cluster of *falciparum* malaria imported by tourists from the Gambia to Europe and an accompanying increase of local cases indicated a local resurgence of the disease (Promed 2008).

21.1.1 The Parasite and Its Life Cycle

Plasmodium falciparum is the most virulent among the four *Plasmodium* species that cause malaria in humans. It is also distinguished by the particular pathophysiology it causes, in particular through its ability to bind to endothelium during the blood stage of the infection and to sequester in organs, including the brain. This causes the vast majority of deaths from malaria. *Plasmodium vivax* is a far less deadly parasite but highly disabling; it is common in tropical areas outside Africa. The ability of *P. vivax* and also the very similar *Plasmodium ovale* to remain dormant for months as hypnozoites in the liver makes infection with these parasites difficult to eradicate. The fourth plasmodial species that is pathogenic for humans, *Plasmodium malariae*, does not form hypnozoites, but it can persist for decades as an asymptomatic blood stage infection. The *Plasmodium* life cycle leads to numerous transitions and stages of the parasite, all necessitating a specific immune response during this particular part of the cycle. Following inoculation by an *Anopheles* mosquito into the human dermis, motile sporozoites access blood vessels in the skin, are transported to the liver, and then transit through macrophages and hepatocytes to initiate liver stage infection. Subsequently, each sporozoite yields tens of thousands of merozoites. After an incubation period of 1–4 weeks, infected hepatocytes rupture and release merozoites. The clinical disease begins. The merozoites invade erythrocytes. They develop further and multiply within these cells while digesting the hemoglobin. Asexual blood stage parasites produce 8–20 new merozoites every 36–48 h (or 72 h for *P. malariae*), causing parasite numbers to rise rapidly to levels as high as 10^{13} per host. The asexual stages are pathogenic, and infected individuals can present with diverse sequelae affecting different organ systems. The blood stages of infection also include gametocytes (male and female sexual forms) that await ingestion by mosquitoes before developing further. Sexual stage parasites are nonpathogenic

but are transmissible to the *Anopheles* vector, where they recombine and generate genetically distinct sporozoites. The mosquito becomes infectious to its next blood meal donor 1–2 weeks after ingesting gametocytes, a time frame that is influenced by the external temperature. Development of *P. vivax* within the mosquito can occur at a lower environmental temperature than that required for the development of *P. falciparum*, explaining the preponderance of *P. vivax* infections outside tropical and subtropical regions.

21.1.2 Course of Disease and Diagnosis

Uncomplicated malaria usually presents with fever and nonspecific symptoms, such as vomiting and/or diarrhea while severe malaria caused by *P. falciparum* is characterized by multiorgan damage, including renal failure. The clinical picture is different in children, who present with prostration, respiratory distress, severe anemia, and cerebral malaria. Additional complications, such as hypoglycemia and acidosis, can occur. The determinants of severe malaria in an individual case are not fully understood. Genetic factors are important (Kwiatkowski 2005). Also, both the age of the patient and the intensity of transmission in the community influence the susceptibility to complicated malaria (Reyburn et al. 2005). Cerebral malaria is a more common presentation of severe malaria where transmission intensity is low, whereas severe anemia predominates where transmission intensity is high. Malaria can interact with other infectious diseases to modify the susceptibility and/or severity of either disease. Solid evidence now indicates that infection with HIV increases the risk of uncomplicated and severe malaria (Korenromp et al. 2005). Conversely, malaria causes a transitory increase in viral load, and this could promote HIV transmission. An important percentage of patients with severe malaria have associated bacteremia, and these patients show increased mortality (Berkley et al. 1999). Microscopy of thin and thick blood films remains the central tool for diagnosis. However, laboratory diagnosis has now become possible through the development of rapid diagnostic tests (Moody 2002). Following initial problems with sensitivity after their introduction, the immunochromatographic tests have become quite reliable.

21.1.3 Global Distribution and Surveillance

Considerable progress has been made in defining the global distribution of malaria and its burden. Since the clinical diagnosis of malaria is imprecise, estimates of the burden of malaria that rely upon clinical data without laboratory support are unreliable. Improved regional and global estimates of the malaria burden have used accurate data collected at selected areas with well-defined geographical, entomological, and population characteristics. Results are then extrapolated to other areas with similar characteristics and known populations. Studies of this kind suggest that

malaria directly causes just under 1 million deaths and at least 500 million clinical cases each year (Snow et al. 2005; Greenwood et al. 2008; Rowe et al. 2006). Furthermore, malaria in pregnancy contributes to a substantial number of maternal deaths as well as infant deaths resulting from low birth weight. However, overall data are still hard to collect. Most malaria-endemic countries, particularly those in sub-Saharan Africa, have weak health information systems and civil registries. Since the consequences of a malaria infection vary, many indicators are used to measure the impact of an intervention. Malaria-specific mortality is very difficult to document because most deaths from malaria occur at home. Data collection on malaria morbidity requires either the use of health facilities as sentinel sites or regularly conducted community-based surveys.

Most important factors that determine the epidemiology of malaria:

• Presence of *Anopheles* mosquitoes and humans: There is no real animal reservoir for the four plasmodial species that cause disease in humans, nor does epidemiologically relevant transmission outside of mosquitoes occur. One of the most indices of malaria transmission intensity is the vectorial capacity, the number of infectious bites that would arise from all bites on a single infected human on a single day (Garret-Jones 1964).

• Climatic factors are a key determinant: Rainfall creates water collections where *Anopheles* can breed. Such breeding sites may dry up prematurely in the absence of further rainfall, or conversely they can be flushed and destroyed by excessive rains. Once adult mosquitoes have emerged, ambient temperature, humidity, and rains will determine their chances of survival. To transmit malaria successfully, female *Anopheles* must survive long enough after they have become infected through a blood meal on an infected human. The parasite development inside the mosquito lasts 9–21 days at 25°C. Warmer ambient temperatures shorten the duration of the extrinsic cycle, thus increasing the chances of transmission. Conversely, below a minimum ambient temperature of 15°C for *P. vivax* and of 20°C for *P. falciparum*, malaria cannot be transmitted. Current trends of global warming may increase the geographic range of malaria and may be responsible for future malaria epidemics.

• Behavior of *Anopheles* mosquitoes: Not all *Anopheles* species transmit malaria parasites. In addition, *Anopheles* species differ in selected behavior traits, with important consequences on their abilities as malaria vectors. In some species the females are anthropophilic, in other they are zoophilic. Some species prefer to bite indoors (endophagic), while others prefer outdoor biting (exophagic). All other factors being equal, the anthropophilic, endophagic species will have more frequent contacts with humans and will thus be more effective malaria vectors. Those *Anopheles* that are able to transmit the infection show distinct variations in their breeding habits. For example, *Anopheles gambiae*, the main mosquito host in Africa, prefers to breed in open, savanna-like country. In contrast, the *Anopheles* species of Southeast Asia that transmit malaria are predominantly forest breeders. Thus, malaria decreased significantly in these areas when forests were cut down. Next to all *Anopheles* species prefer fresh, unpolluted water for their breeding sites. This

is developing into a major handicap in important parts of the world since access to clean water is decreasing with the spread of human urban and in particular slum habitation.

- Behavior and biologic characteristics of humans: Genetic and acquired characteristics and behavioral traits can influence an individual's malaria risk and, on a larger scale, the intensity of transmission in a population. For example, the heterozygotic form of sickle cell anemia protects against development of severe malaria.
- Characteristics of the malaria parasite: Occurrence of particular plasmodial species, infection with several strains of the same species and drug resistance influence the impact of malaria on human populations. For example, *P. falciparum* (and to a lesser extent *P. vivax*) have developed strains that are resistant to several antimalarial drugs. Such strains are not uniformly distributed. Constant monitoring of the susceptibility of these two parasite species to drugs used locally is critical to ensure effective treatment and successful control efforts.

As malaria numbers continue to decline in highly endemic areas, patterns of infection and disease will change. An increasing proportion of cases will occur in older children and adults, leading to an increased risk of local outbreaks. The latter will be especially likely to occur if control measures are allowed to lapse in the face of a decreasing burden of infection. Extensive and continuous surveillance will be required to monitor changes and to define optimal and cost-effective strategies for managing the situation. The most effective control programs are those that apply a combination of tools with particular emphasis on mosquito control. Interventions are insufficient to meet the ambitious goal of global eradication. All programs have to be monitored for the efficacy of their interventions since one day they will be lost to a changing parasite or mosquito.

21.2 Dengue Fever

Dengue fever has become acknowledged as one of the world's major emerging infectious diseases. In fact, the infection is by now correctly seen as a global pandemic with recorded prevalence in over 101 countries (WHO 2008b, c). Dengue infection is caused by one of the four serologically distinct dengue virus serotypes (DENV-1, DENV-2, DENV-3, DENV-4) of the family Flaviviridae. Each one is leading to life-long immunity to this homologous serotype, but only to a short period of cross-reactive heterotypic immunity. This cross-protection is thought to last 2–12 months (Kliks et al. 1988).

Dengue viruses are usually transmitted by bites of an infected mosquito vector, mainly *Aedes aegypti*. For transmission to occur, the female *Aedes* mosquito must bite an infected human during the viremic phase of the illness which generally lasts 4–5 days but may last up to 12 days (McBride and Bielefeldt-Ohmann 2000). The incubation period in humans ranges from 3 to 12 days, most common between 5 and 7 days. *Aedes* mosquitoes are efficient vectors and their global distribution goes hand in hand with that of the dengue viruses. *Aedes* are highly susceptible to dengue

viruses and they feed preferentially and frequently on human blood, the only important reservoir besides mosquitoes themselves. In particular *A. aegypti* is a highly domesticated mosquito and breeds in man-made containers such as pots, tin cans, and tyres. It mainly bites during the day or early evening, and most biting occurs out of doors in urban areas. Dengue viruses are transovarially transmitted in some *Aedes* mosquitoes (McBride and Bielefeldt-Ohmann 2000). It has been shown that dengue viruses in mosquitoes cause an infection of the nervous system, consecutively leading to prolonged feeding periods with a higher likelihood to be interrupted by the host, which increases the chance that this infected mosquito will probe or feed on additional hosts.

These facts impact the clinical and epidemiological role of dengue: first, because of the short incubation period a high proportion of infected persons will suffer from disease within a short time after infection. For example, travelers being infected in endemic countries will fall ill during their stay abroad. Most of them will not seek medical care in the country of sojourn or when returning to their home country, and the disease will be underreported by far in both national surveillance systems. Second, dengue is a disease which occurs mainly, but not exclusively, in urbanized areas. These areas nowadays are globally much closely connected to each other. Overcrowding, urbanization, poverty, insufficient water storage systems, and insufficient vector control are major causes for the dramatic resurgence of dengue disease (Lifson 1996). With increasing international air travel, new and potentially more virulent viral strains can be introduced to other areas infested with *Aedes* species. Therefore, travelers not only play a role as a potential victim of infection but also as an important transmission vessel in the global distribution of the viruses.

21.2.1 The Disease and Its Symptoms

Dengue virus infection may be asymptomatic or may lead to undifferentiated febrile illness (viral syndrome), dengue fever (DF), or dengue hemorrhagic fever (DHF) with or without shock, depending largely on age and immunological conditions (Jelinek et al. 2002).

In DF, the severity of the clinical features increases with age of the patient (Rigau-Perez et al. 1998). Therefore, classical dengue fever is primarily a disease of older children and adults, characterized by a sudden onset of fever, headache, joint or muscle pain, rash, leukopenia, and thrombocytopenia. Mild hemorrhagic manifestations, such as epistaxis, petechiae, gingival bleeding, and menorrhagia, are accepted as a rare part of the clinical picture of DF. The disease is self-limited, and in classical dengue fever usually no deaths occur. In a study performed in Swedish patients with DF after return from travel, 21 out of 74 had hemorrhagic manifestations but none presented as DHF.

In contrast, dengue hemorrhagic fever (DHF) is primarily a disease in children under 15 years in hyperendemic areas where two or more virus serotypes are circulating simultaneously, but it might also occur in adults. The early clinical features of DHF are indistinguishable from DF (Halstead 1989). Even though

the severity of hemorrhage in DHF tends to be greater than in DF and severe gastrointestinal bleeding may sometimes occur, dengue hemorrhagic fever is somewhat inaptly named, because its central clinical and pathogenetical lesion is not bleeding. The major pathophysiological change that determines the severity of disease in DHF and differentiates it from DF is the leakage of plasma which results into hemoconcentration (manifested as a rise in hematocrit), pleural or other effusions, or hypoalbuminemia or hypoproteinemia. This feature typically occurs simultaneously with a drop in platelet count at the time of defervescence, 2–9 days after the onset of symptoms, and may progress to hypovolemic shock (DSS) and death. Within the European Network on Imported Infectious Disease Surveillance (www.tropnet.eu), 2.7% of all dengue cases (n=483) were reported as DHF (Jelinek et al. 2002). In recent years, there have been an increase in the number of reports on dengue infections with unusual manifestations, mainly with cerebral and hepatic involvement.

21.2.2 Pathogenesis: Current Knowledge and Opinions

The pathogenesis of dengue is not fully understood. There are currently several concepts that try to explain why dengue viruses lead to DHF in some individuals and not in others. The major pathophysiological change, however, that determines the severity of DHF and differentiates it from DF is the acute increased vascular permeability which results in plasma leakage, leading to hypovolemia and shock. Other hallmarks are hemorrhagic diathesis and complement activation.

The observations that classical dengue fever without complications occur in non-indigenous foreigners while DHF occurs in indigenous children, and that most aspects of the disease become prominent only after several days of illness when fever and viremia remit, support an immunological explanation. Fundamental to the immunological events in DHF is the existence in nature of four antigenically related but distinct dengue serotypes that parenterally enter human hosts: Prior infection with a dengue virus of one serotype confers only transient immunity to infections with heterologous serotypes, but does give rise to antibodies broadly cross-reactive with virions of all four serotypes. Several prospective studies demonstrated that the presence of circulating dengue antibodies, acquired actively by prior infection or passively by heterotypic maternal dengue IgG antibodies in infants, is an important risk factor for the development of severe manifestations of infections (Thein et al. 1997).

It has been well documented that higher viral burden is associated with more severe disease. According to the immune enhancement theory cross-reactive non-neutralizing antibodies facilitate virus entry and replication in Fc receptor-bearing cells leading to higher viral loads. These activate precursor cross-reactive memory T cells and lead to the release of chemical mediators that cause plasma leakage.

In infants it has been shown that maternal dengue antibodies are important in the development of DHF. These antibodies have a dual role: in the first 6 months of life maternal dengue neutralizing antibodies protect infants from dengue infection;

at 7–8 months the neutralizing activity decreases below the protective level and antibody-dependent enhancement activity rises to peak levels causing a period of greatest risk to acquire DHF/DSS. Beyond this critical 2-month period, further IgG degradation results in a decrease of infection-enhancing antibodies. The observation of transient heterotypic immunity followed by a period of highest risk 7–8 months after acquiring dengue antibodies would explain why DHF is rare in travelers. One other recently established explanation for higher viral loads is that cross-reactive T cells (CD8+) activated by original antigenic sin may have lower affinity and be less effective at clearing a secondary infection with dengue viruses.

However, even primary dengue infection can in rare occasions also be associated with fatal dengue hemorrhagic disease and shock. Therefore, the virus itself might play an important role in disease severity. Dengue virus structural differences were shown to correlate with pathogenesis and epidemiological studies showed strong evidence that there are significant differences in disease severity between secondary infections of American and Asian origin (White 1999). Alternatively, there might be differences in the ability of pre-existing dengue antibodies to neutralize or enhance specific viral strains (subtypes). If virus virulence plays an important role in the pathogenesis of dengue, and more virulent strains are widespread, this will also have an effect on dengue morbidity and mortality in travelers.

Since antibodies play a role in enhancing or preventing infection while cellular immunity limits viral infected cells, some of these processes might be under genetic control. Several studies revealed both protective and pathogenic roles in disease severity for specific HLA class genetic variations (Halstead 2002). There is also some epidemiological evidence that there must be genes in blacks that play a major role in restricting severity of dengue infection. Genetic variations might also be an explanation why DHF is rare in Caucasian travelers.

21.2.3 Epidemiology

Dengue is endemic in most tropical parts of the world. Worldwide, 3.5 billion people live in dengue endemic areas. The incidence of epidemic and endemic dengue has increased substantially (Fig. 21.1). This increased epidemic activity, which is caused by all four virus serotypes, is associated with the geographical expansion of both, the mosquito vectors and the viruses, the development of hyperendemicity (the co-circulation of multiple virus serotypes in an area), and the emergence of dengue hemorrhagic fever (DHF) . Hyperendemicity is the most constant factor associated with the evolution of epidemic DHF in a geographical area (Gubler 1997). Today, DF/DHF has emerged as the most important arboviral disease of humans, with an estimated 50–100 million cases of dengue fever and several hundred thousand cases of DHF occurring each year, depending on epidemic activity (Gibbons and Vaughn 2002). DHF is a leading cause of hospitalization and death especially among children in Southeast Asian countries where epidemics first occurred in the 1950s. Epidemic DHF spread out to the South Pacific islands in the 1970s, and reached the American region in the 1980s and 1990s (Pinheiro and Nelson 1997). Of major

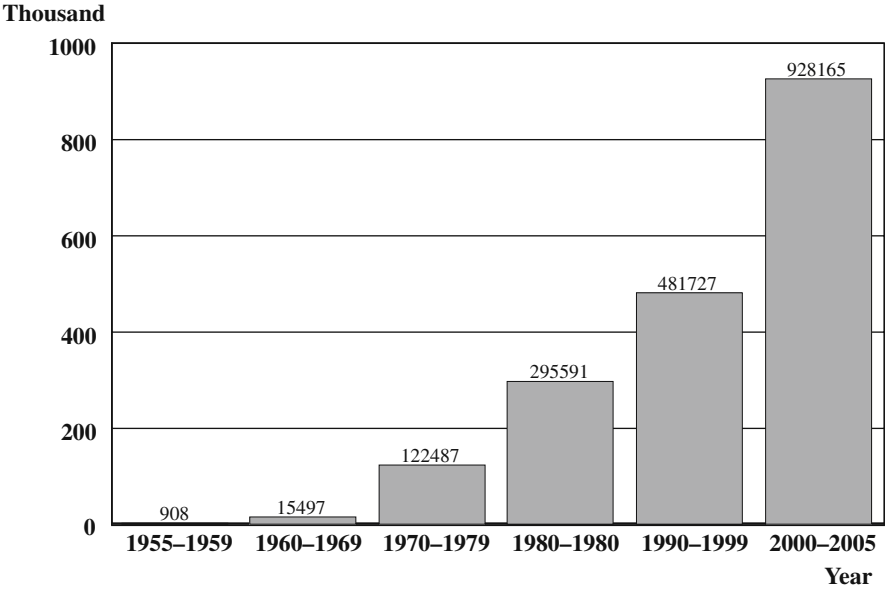

Fig. 21.1 Number of reported cases of dengue per decade, 1950–2005 (Moody 2002; Gibbons and Vaughn 2002)

concern is the potential area of dengue transmission due to the spread of its vectors: such areas include sizeable parts of the USA and Europe. In such a manner, the introduction of dengue fever by returning travelers as yet unafflicted by the disease poses a very real threat to public health systems of the western world, as has already been demonstrated with the introduction of dengue into Australia (Queensland), and the USA (Hawaii and Mississippi) (WHO 2008b,c). One of the largest dengue fever epidemics known in history, with approximately 1 million cases and 1000 deaths, occurred in Greece during 1927–1928. At that time, the vector was the later locally eradicated *A. aegypti*. In this context, the recent introduction of *Aedes albopictus* to Europe, notably Italy, France, and Albania, might serve as a warning of things to come (Romi 2001). In most disease-endemic areas dengue transmission has a definite seasonality, but the reasons for the seasonal patterns are not fully understood. However, studies on the vector showed that the larval index per house increased during the wet season due to a higher proportion of colonized containers at each house, as well as increased number of available containers.

21.3 Yellow Fever

Yellow fever is caused by a flavi virus. The disease is transmitted by infected mosquitoes, in particular *A. aegypti*. The clinical spectrum of yellow fever shows a wide spectrum, ranging from mild symptoms of acute viral infection to severe

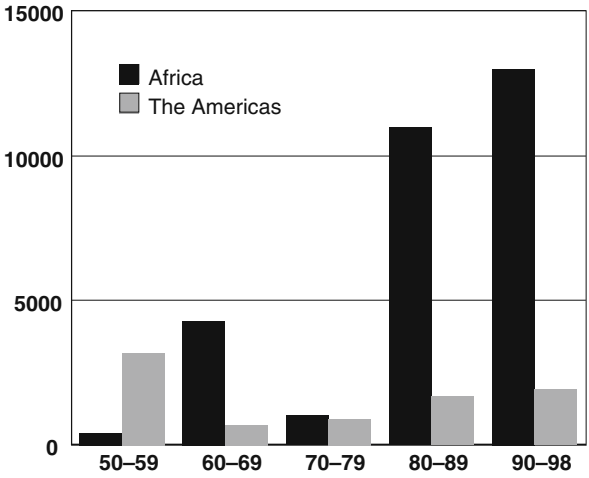

Fig. 21.2 Number of reported cases of yellow fever per decade, 1950–1998 (Gibbons and Vaughn 2002)

disease and death (WHO 2000; Monath 2001). Jaundice caused by hepatitis, kidney failure, and hemorrhagic signs dominate the picture of severe disease; hence the name yellow fever. Case fatality rates during outbreaks tend to be in the range of 15–50%. The disease has caused large epidemics in Africa and the Americas in the past and can be recognized from historic texts stretching back at least 400 years. Following a long period of comparatively low case numbers during the last century, case reports have been increasing for two decades, and yellow fever is now again a serious threat to public health (Fig. 21.2) (WHO 2000; WHO 2005). Yellow fever is one of the diseases that are reportable under the International Health Regulations (IHR) . Reporting began in 1948. Countries are required to report cases and deaths to WHO within 24 h of being notified. As with other diseases under the IHR, it is estimated that only a small fraction of true cases are reported to WHO (1–10%). However, it is also assumed that large outbreaks have not been missed due to the public disturbances they cause.

Important reasons for the re-emergence of yellow fever are an increased presence of vector mosquitoes and the lapse of yellow fever immunization programs in endemic areas (Monath 2001). Although a very effective and safe live-attenuated vaccine is available, large unvaccinated populations are now living at risk of the disease. Another important factor is the increasing urbanization in many developing countries. Since the vector is anthropophilic and breeds in abundance in slum areas, the potential for explosive urban outbreaks is constantly increasing.

Non-human primates in tropical areas of Africa and the Americas and several *Aedes* spp. form a reservoir for the virus. Thus, eradication of the disease is currently impossible. Close contacts of humans to forested areas and infestation of human habitations by vector mosquitoes form the ground for epidemics. In Africa, 33 countries with a population of 468 million are currently at risk. These inhabit an area ranging from 15°N to 10°S of the equator. In the Americas, yellow fever is

endemic in ten countries and several Caribbean islands. It has recently been spreading south and reached Argentina and Paraguay. It remains unclear why yellow fever is confined to areas in Africa and the Americas, even though the vectors do occur in Asia and are spreading freely into Europe, Central America, and North America (Barros and Boecken 1996). One explanation is the occurrence of dengue in areas free of yellow fever, but this theory no longer holds since dengue has spread rapidly to most tropical and subtropical countries.

Three types of transmission: A variety of species of *Aedes* and *Haemagogus* mosquitoes transmit the yellow fever virus, the latter in South America only. These vectors exhibit domestic, semi-domestic, or wild habits but they are, in general, anthropophilic and day-active. There are three potential transmission cycles of yellow fever: sylvatic, intermediate, and urban.

Sylvatic (or jungle) yellow fever: Monkeys in tropical rainforests are infected by wild mosquitoes. The infected monkeys do not necessarily fall sick and pass the virus to the next mosquito that feeds on them. Thus, a disease reservoir is formed. The infected mosquitoes may bite humans that enter the forest, resulting in sporadic cases of yellow fever. The majority of cases occur in people visiting the forest for their livelihood, e.g., loggers, hunters, but this may also affect visitors to national parks. Occasionally, and increasingly so in the last years, the virus is transported by the infected individual into human dwellings, transmitted to semi-domestic or domestic mosquitoes, and spreads to other persons.

Intermediate yellow fever: Small epidemics can occur in humid or semi-humid areas at the forest fringes. This has been observed particularly in Africa. These village outbreaks behave differently from urban epidemics: usually several villages are affected at the same time, but fewer patients are reported. Semi-domestic mosquitoes in the vicinity infect both monkeys and humans. These areas are classified as "zones of emergence" (WHO 2000), with an increased contact between animal reservoir and humans that may lead to disease. This type of outbreak can easily shift into a more urban epidemic if the virus is carried into a suitable environment.

Urban yellow fever: This type of transmission has a potential for large outbreaks. It occurs when the virus is carried into an urban setting with a high density of human population (frequently slums) that is infested by suitable domestic vectors. In particular *A. aegypti* is a very effective slum breeder. Here the disease is carried by mosquitoes from person to person, no animal reservoir is involved. Outbreaks of this type tend to spread rapidly from single sources and have the potential for many cases.

The potential for large urban epidemics is increasing in many parts of the world. Urbanization and intense mosquito infestation of human settlements go hand in hand in increasing the possibilities of outbreaks. In particular the density of *A. aegypti* has expanded dramatically in rural and urban areas over the last 30 years. The mosquito has re-infested regions where it was previously eradicated and has reached new areas, too. Therefore, areas with *Aedes* populations have to be considered as risk for yellow fever outbreaks, even if the disease has not occurred there yet. This holds for Europe, the Caribbean, Central America, and North America, since these areas

had yellow fever outbreaks in the past, but also for Asia, which has been free of the disease as far as historical records go.

Prevention: The availability of a highly effective and comparatively safe, life-attenuated, single shot vaccine is a great advantage in yellow fever control. Immunity occurs in 95% of vaccines within 1 week. Immunization lasts officially for 10 years with actual protection being much longer, in a considerably amount of vaccinees life-long. Next to mosquito control measures, increasing the vaccine coverage in populations at risk is the most effective measure in preventing outbreaks. Thus immunization with yellow fever vaccine should be part of the routine vaccination campaigns in endemic areas, preferably with administration at the same time as measles vaccine. The vaccine can also be used in mass vaccination campaigns at the beginning of an outbreak in order to block the spread of disease. As this is far less effective than preventive childhood vaccination, the latter is vastly preferable. Current examples of mass vaccination campaigns include those initiated by PAHO and national authorities after the re-introduction of yellow fever in Paraguay (WHO 2008b,c). Another campaign initiated in 2008 was the mass vaccination in 37 districts of Burkina Faso, following deaths by yellow fever (WHO 2008a).

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