Geographic Expansion of Dengue: The Impact of International Travel

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KEYWORDS

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The dengue viruses are among the most widespread geographically of the arboviruses and are found in tropical and subtropical areas where 2.5 to 3 billion people are at risk of infection.[1] Each year an estimated 50 to 100 million dengue infections occur, with several hundred thousand cases of dengue hemorrhagic fever (DHF) and about 20 thousand deaths.[1] Global deaths from DHF already rank with yellow fever in exceeding combined deaths from all other viral hemorrhagic fevers, including Ebola, Marburg, Lassa, and Crimean-Congo. The past 2 decades saw an unprecedented geographic expansion of dengue.[2] This article reviews factors responsible for the worldwide spread of dengue, with a particular focus on the role of travel. International travelers have the potential to acquire and spread dengue virus infection.[3]

BACKGROUND

Dengue viruses belong to the family of Flaviviridae (single-stranded, nonsegmented RNA viruses); there are four serologically distinct dengue virus serotypes (DENV-1, DENV-2, DENV-3, DENV-4).[1] Infection with one serotype confers long-term immunity to that serotype but not to the other types, and individuals may therefore be infected up to four times.[4] Cocirculation of various virus serotypes in a community (hyperendemicity) is the single most common risk factor associated with the emergence of the severe form of disease—DHF—in an area.[5] Dengue virus infection of all four virus serotypes causes a spectrum of illness ranging from asymptomatic or mild febrile illness to classic dengue fever (DF) and to severe and fatal hemorrhagic disease.[2]

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Although the pathogenesis of severe dengue is not fully understood, the main risk factors for developing DHF and dengue shock syndrome (DSS) are believed to be secondary infection with a heterologous serotype and infection with a more virulent strain of virus.[4–8] Cross-reactive but nonneutralizing anti-dengue antibodies from a previous infectious bind to the new infecting virus serotype and enhance viral uptake by monocytes and macrophages. This antibody-dependent enhancement is believed to result in an amplified cascade of cytokines and complement activation causing endothelial dysfunction, platelet destruction, and consumption of coagulation factors, which result in plasma leakage and hemorrhagic manifestations.[4,9–11] T-cell activation accompanied by massive apoptosis has also been proposed as an explanation of the activated cytokine production seen in secondary infection.[12,13]

Dengue viruses are transmitted by mosquitoes of the genus *Aedes*, subgenus *stegomyia* (such as *Aedes aegypti* and *albopticus*).[1] *Ae aegypti* is well established in much of the tropical and subtropical world. It is the principal vector, and is an efficient epidemic vector for several reasons: it is highly susceptible to dengue virus, feeds preferentially on human blood, is a daytime feeder, has an almost imperceptible bite, and is capable of biting several people in a short period for one blood meal.[1,2] As a peri-domiciliary mosquito, it is well adapted to urban life because it typically breeds in clean stagnant water in a wide variety of man-made containers, such as tires, tin cans, pots, and buckets that collect rainwater. The alternative dengue vector, *Ae albopictus*, is continuing its geographic expansion into tropical and temperate climates, but this has had little impact on epidemic dengue transmission.[14]

HISTORY

Dengue virus has a relatively recent evolutionary history; it is estimated that the four serotypes originated approximately 1000 years ago and have established endemic transmission in humans only in the last few hundred years.[15] The geographic origin remains uncertain, however, as does the extent of genetic and phenotypic diversity present in the sylvatic (primate) transmission cycle. Some suggest an African origin, arguing that many of the flaviviruses circulate exclusively in Africa and often infect primates. On the other hand, the presence of all four serotypes in humans and monkeys from Asia, and particularly the phylogenetic position of the Asian sylvatic strains, suggests that the virus has an Asian rather than an African origin.[5] The high prevalence of dengue in this region also supports this hypothesis.[16]

Epidemics that were clinically compatible with DF occurred as early as 1635 and 1699 in the West Indies and Central America, respectively.[17] In 1780, a major epidemic occurred in Philadelphia in the United States and subsequent epidemics were common in the United States into the 1930s, with the last outbreak occurring in New Orleans in 1945.[17]

The epidemiology and transmission dynamics of dengue viruses were changed dramatically in Southeast Asia during World War II. The disruption and change in the ecology caused by the war effort expanded the geographic distribution of the viruses and vectors, and increased the densities of *Ae aegypti*, making many countries in this region highly permissive for epidemic transmission. The first recorded epidemic of DHF occurred in Manila, Philippines in 1953 to 1954, followed by Bangkok, Thailand in 1958 and Malaysia, Singapore, and Vietnam in the 1960s.[17] With the economic boom and associated urbanization in Southeast Asia in the postwar years, epidemic DF/DHF spread to the whole region during the 1970s.[17]

In the American tropics, DHF was a rare disease before 1981.[17] A characteristic of dengue in the Americas during these years was that the disease presented as classical

DF usually caused by a single virus serotype. Epidemics were self-limited and transmission disappeared after several months.[5,17] The 1980s and 1990s then saw a dramatic geographic expansion of epidemic DF and DHF from Southeast Asia to the South Pacific Islands, the Caribbean, and the American tropics, with the regions changing from nonendemic (no serotypes) to hypoendemic (one serotype present) or hyperendemic (multiple serotypes present).[17,18]

More than 100 tropical countries now have endemic dengue virus infections, and DHF has been documented in more than 60 of these countries.[1] Global reports of DHF have increased on average by fivefold in the past 20 years.[1] Dengue epidemics vary greatly in magnitude and severity. In 1998, the largest epidemics in history occurred throughout Asia and the Americas, with more than 1.2 million cases of DF/DHF reported to the World Health Organization (WHO). The factors responsible for periodic epidemics in an area are not well understood. They are likely a combination of the increased movement of viruses in people among countries and regions, the level of herd immunity to specific virus serotypes in human populations, and genetic changes in circulating or introduced viruses that give them greater epidemic potential.

At the beginning of the twenty-first century, dengue is the most important arboviral disease of humans.[19] Between 2000 and 2007 alone, at least eight previously dengue-free areas experienced outbreaks, including Hong Kong, Macau, Nepal, Bhutan, Madagascar, Hawaii, Galapagos, and Easter Island (**Fig. 1**).[20] According to the Pan American Health Organization (PAHO), 2007 was the worst year on record since 1985, with 918,495 cases of DF/DHF in the Americas.[20]

REASONS FOR THE GEOGRAPHIC SPREAD OF DENGUE IN THE PAST 30 YEARS

Climate

Global climate change is commonly blamed for the resurgence of dengue.[21] There are no good scientific data to support this conclusion, however.[22] Dengue activity has

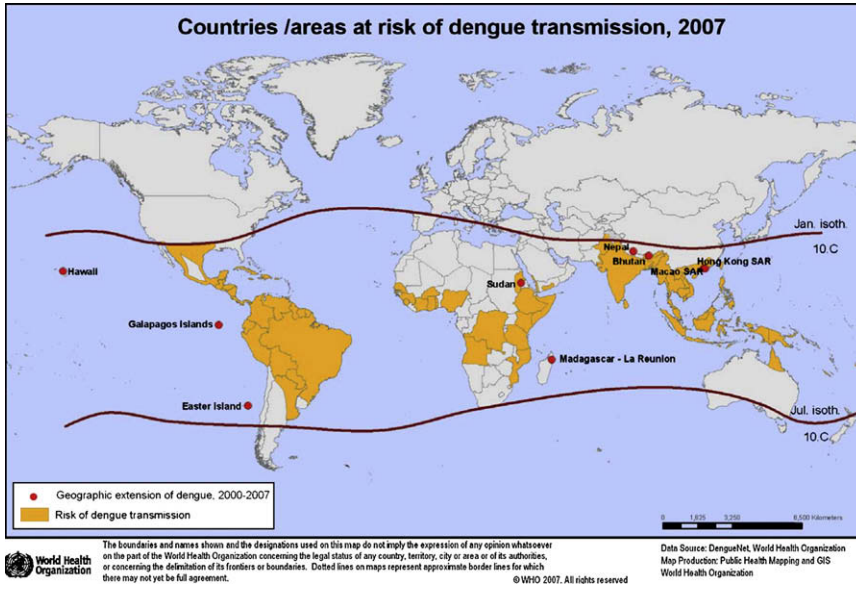

Fig. 1. Countries/areas at risk for dengue transmission, 2007. (*Courtesy of* DengueNet, World Health Organization. Available at: www.who.int/ith (chapter 5). Accessed June 12, 2008; with permission).

been reported to correlate with the El Nino Southern Oscillation (ENSO), in the South Pacific region, where ENSO or southern oscillation indexes correlated with temperature or rainfall anomalies.[23] The ENSO has not been shown to affect periodicity of dengue activity in Southeast Asia or the Americas independent of factors such as herd immunity and infection enhancement.[24] Warm temperature and high moisture may contribute to increased adult survival, however.[25] In addition, warmer temperatures shorten the extrinsic incubation period.[25] The minimum daily temperature, rather than the average temperature, was reported to be the most important determinant of dengue transmission seasonality in Bangkok.[26] One study attempted to analyze a potential association between dengue hemorrhagic fever (DHF) incidence and temperature computed by satellite.[27] Land surface temperature (LST) was chosen as an indicator that combined radiated earth temperature and atmospheric water vapor concentration. Positive association between LST and DHF incidence was significantly correlated in 75% of the cases during nonepidemic months, whereas no correlation was found during epidemic months. The authors concluded that nonclimatic factors are supposed to be at the origin of this discrepancy between seasonality in climate (LST) and DHF incidence during epidemics.[27]

A study in Puerto Rico showed that mosquito density was positively correlated with rainfall.[28] An increase in mosquito populations with the onset of the rainy season was also shown in Bangkok.[29] Dengue outbreaks on the Indian subcontinent frequently occur during the hot, dry season, however, because *Ae aegypti* breeds abundantly in the reservoirs of desert coolers (also known as evaporative coolers).[25] A study in Thailand by the *Aedes* Research Unit showed no fluctuations in adult mosquito production and densities in response to rainfall.[26,30] Instead, there was a seasonal increase in adult survival attributable to temperature and atmospheric moisture indicating that the most likely reason for the association of dengue epidemics with rainfall can be explained by increased adult mosquito survival. In other words, adult abundance varies not so much with temperature or rainfall but with increased humidity and the availability and productivity of water-holding containers.[25] This hypothesis is supported by the fact that *Ae aegypti*–borne viral diseases were widespread in temperate latitudes during the Little Ice Age (1600–1700 AD) because water for human consumption was stored in rain barrels, which supported the populations of mosquitoes needed to transmit viruses that were introduced during summer seasons.[25,31] Dengue and yellow fever caused multiple epidemics in the United States (mainly in the eastern and southern parts) in the eighteenth, nineteenth, and early twentieth centuries, and their control was not attributable to a change in climate but rather to changes in industrialization and modernization that led to a reduction in open water-holding containers and breeding sites and improved screening of houses. It is unlikely that these diseases will cause major epidemics in the United States if the public health infrastructure is maintained and improved.[22] The spread of dengue between Pacific islands seems to be independent of inter-annual climate variations, pointing to the importance of modulating factors in dengue transmission, such as population density and travel.[32] In conclusion, climate has rarely been the principal determinant of the prevalence or range; human activities and their impact on local ecology have generally been much more significant.[31] In the future, models of the impact of climate change must attempt to account for these factors.

Virus Evolution

The evolution of dengue viruses has had a major impact on their virulence for humans and on the epidemiology of dengue disease around the world.[33] Although antigenic and genetic differences in virus strains have become evident, it is mainly the lack of animal

models for the disease that has made it difficult to detect differences in virulence among dengue viruses. Phylogenetic studies of many different dengue virus samples have led to the association between specific genotypes (within serotypes) and the presentation of more or less severe disease. Currently, dengue viruses can be classified as being of epidemiologically low, medium, or high impact; some viruses may remain in sylvatic cycles of little or low transmissibility to humans, others produce DF only, and some genotypes have been associated with the potential to cause the more severe DHF and DSS in addition to DF.[7,8,33] The American genotypes of DENV-2 and DENV-3, for example, are less virulent with a reduced ability to grow in cell cultures and mosquitoes compared with the Asian genotypes of DENV-2 and DENV-3.[33,34] Phylogenetic studies using envelope protein gene sequences of DENV-1, -2, and -4 suggested that the endemic/epidemic lineages of these three DENV serotypes evolved independently from sylvatic progenitors.[16] Analysis of envelope protein amino acid changes predicted to have accompanied endemic/epidemic emergence suggested a role for domain III in adaptation to new mosquito or human hosts.[16] Although the factors that contribute to dengue virus epidemiology are complex, studies have suggested that specific viral structures may contribute to increased replication in human target cells and to increased transmission by the mosquito vector. Severity of disease also depends on the strain and serotype of the infecting virus, age and genetic background of the patient,[4,5,8] and the degree of viremia.[7,35] As to the question of whether dengue viruses are evolving toward virulence as they continue to spread throughout the world, phylogenetic and epidemiologic analyses suggest that the more virulent genotypes are now displacing those that have lower epidemiologic impact, but there is no evidence for the transmission of antigenically aberrant new strains.[5]

Vector Control

Epidemic dengue was effectively controlled in most of tropical America in the 1950s and 1960s as a side benefit of malaria and yellow fever control programs.[1] Disruption of vector control programs, be it for reasons of political and social unrest or scientific reservations about the safety of DDT, has contributed to the resurgence of dengue around the world. Lack of political will or complacency concerning vector-borne diseases is another factor. Few new and effective mosquito-control methods have been developed in the past 30 years.[36] Vector control strategies are often limited to one approach, such as larvicidal or just adulticidal control. Vector control, however, should be integrated and include source reduction and killing of adult mosquitoes, a combined vertical and horizontal approach that depends on community participation, and possibly the use of predacious copepods of the genus *Mesocyclops* as a biologic control agent.[37]

Societal Factors

The dengue viruses are unique among the arboviruses as the only members of this group that have evolved and fully adapted to the human host and the environment, essentially eliminating the need for maintenance in the primitive enzootic forest cycle.[1] Human population growth is highly correlated with dengue epidemics.[38] Large populations in which viruses circulate may also allow more co-infection of mosquito and human with more than one serotype of virus,[39,40] potentially setting the stage for recombination events that could lead to the emergence of more virulent or transmissible strains. Studies have documented that the number of dengue lineages has been increasing roughly in parallel with the size of the human population over the last two centuries.[41] More urban areas in tropical and subtropical areas have reached the population size, estimated at perhaps 150,000 to 1 million, needed to sustain the ongoing

circulation of dengue virus.[42] The unprecedented global population growth in the past decades, in particular in the developing world, is also the main factor that has driven many of the demographic and societal changes, such as urbanization, deforestation, new dams and irrigation systems, poor housing, sewage and waste management systems, and lack of reliable water systems that make it necessary to collect and store water.[1] Poor garbage disposal associated with poorly controlled urbanization is commonly associated with dengue activity.[43] Nonreturnable containers, such as cans, plastic bottles, and tires, account for almost half of the container habitats found positive for the *Ae aegypti* mosquito in a study in Brazil.[44] Urbanization associated with poor infrastructure contributes to increased mosquito populations and closer contact between humans and mosquito vectors. Population dynamics and viral evolution offer the most parsimonious explanation for the observed epidemic cycles of the disease, far more than climatic factors.[22,27,45]

The reasons for the resurgence of dengue are complex. It is impossible to determine the extent that single factors, such as climate change, virus evolution, deteriorating vector control, and societal changes, play in the expansion of dengue. Our opinion is that population growth associated with rapid uncontrolled urbanization is likely the main factor that has driven the rapid amplification of dengue in the past decades. But the main factors responsible for the geographic spread are movements of populations or individuals by way of travel.[1,5,22]

SPREAD BY WAY OF TRAVEL

Mosquito vectors for dengue were historically spread by sailing ships.[17] The mosquito used the stored water on the ships as a breeding site and could maintain the transmission cycle, even on long journeys.[17] Because of the slow mode of transportation, epidemics were infrequent, with intervals of 10 to 40 years. When a new dengue virus was introduced, however, it frequently resulted in major epidemics that affected numerous countries in that region. Troop movements during WWII accelerated the spread of viruses between population centers in the Asia-Pacific regions, causing major epidemics. By the end of the war, most countries in Southeast Asia were hyperendemic, and a few years later epidemic DHF emerged in the region.[17]

Modern transportation provides an efficient mechanism to quickly move dengue viruses and mosquitoes to new geographic regions around the globe. In recent decades, used automobile and truck tires have been shown to be carriers for *Ae albopictus* and other exotic species of mosquitoes.[46] *Ae albopictus*, an Asian species, was known outside of that region only in several Pacific islands before the 1980s. In 1979, it was introduced to Albania, most likely from China. In the mid-1980s, it was independently introduced into the United States and Brazil from Japan in used tires.[46] It subsequently spread throughout the Americas and to Italy and Africa. There are no reports that dengue viruses have been introduced in mosquitoes, however. On the other hand, it is well documented that the viruses are spread among countries by way of infected humans incubating the virus.[17]

Viremic humans, whether troops, migrant workers, tourists, business travelers, refugees, or others, carry the virus into new geographic areas, which can lead to outbreaks if a competent vector inhabits the new area. Although a great deal of effort is taken to prevent the spread of dengue viruses in infected mosquitoes by implementing mosquito abatement programs at international airports and spraying adulticides in passenger cabins of arriving aircraft, mosquitoes as agents of spread over long distances (eg, between continents) are probably overrated, and viremic travelers are the most likely source of the importation of dengue viruses.[17,28]

Individual and population movements can lead to epidemic waves. Dengue epidemic waves seem to originate from cities and then move to the rest of the country, causing epidemics in smaller communities.[47] Using the method of empiric mode decomposition to show the existence of a spatial-temporal traveling wave, Cummings and colleagues[48] suggested that the dengue epidemics in Thailand emanated from Bangkok, the largest city in Thailand, moving radially at a speed of 148 km/mo.

Molecular-epidemiologic studies are crucial in determining the transmission patterns of dengue viruses and tracking the spread of dengue around the world.[49] The following section expands on the impact of travel as a mechanism for introducing dengue viruses to new areas, thereby triggering outbreaks and further spread of the disease.

EXAMPLES OF IMPORTATION OF DENGUE

United States

Widespread epidemics of dengue in the continental United States are not likely, despite claims to the contrary.[50] Since its introduction into the United States in 1985, *Ae albopictus* has spread to 36 states, replacing *Ae aegypti* in many areas of the Gulf Coast.[51] Because it is such an inefficient epidemic vector, however, the risk for dengue outbreaks is reduced.[14] The public health infrastructure for vector-borne diseases has deteriorated badly over the past 30 years and became virtually nonexistent in many state and local health departments.[1,50] After an absence of 56 years, dengue caused a small outbreak in Hawaii in 2001,[52] and has appeared with increasing frequency along the Texas-Mexico border from 1980 to the present, usually associated with imported cases from Mexico, but limited local transmission has also occurred.[53] A DENV-2 epidemic causing dengue hemorrhagic fever (DHF) occurred in the contiguous border cities of Matamoros, Tamaulipas (Mexico), and Brownsville, Texas, in 2005.[53] Discarded waste tires and buckets were the two largest categories of *Aedes*-infested containers found in both cities.[53] Dengue has also re-emerged as a major problem in United States tropical territories and commonwealths, such as Puerto Rico, which has experienced increasingly larger and more frequent epidemics caused by all four virus serotypes since the mid-1970s. Because dengue is a common problem in United States travelers,[54,55] more frequent importation events could potentially lead to more autochthonous transmission in the Southern parts of the United States where *Ae aegypti* exists.

The Americas and the Caribbean

The American genotypes of DENV-2 and DENV-3 were present in the 1970s. Dengue serotypes from Asia were introduced into the Americas, most likely by travelers, in 1977 (DENV-1), followed by DENV-2 and DENV-4 in 1981, and DENV-3 in 1994.[17] The Asian genotypes of DENV-2 and DENV-3 were more virulent compared with the American genotypes and resulted in increased epidemics.[33,34] The introduction of DENV-2 in 1981 from Vietnam to Cuba was associated with a major epidemic of DHF and spread throughout the tropical Americas, effectively replacing the American genotype in the region.[4,5,56] The Asian genotype of DENV-3 also spread throughout the Americas causing major epidemics of DHF.[4]

To determine rates or determinants of viral spread or their directions of movement, a Bayesian method of a coalescent approach was used to assess patterns of strain migration of DENV-2 and DENV-4 after their introduction in 1981.[57] For both viruses there was an initial invasion phase characterized by an exponential increase in the number of DENV lineages, after which levels of genetic diversity remained constant despite reported fluctuations in DENV-2 and DENV-4 activity. Viral lineage numbers

increased far more rapidly for DENV-4 than DENV-2, indicating a more rapid rate of exponential population growth in DENV-4 or a higher rate of geographic dispersal, allowing this virus to move more effectively among localities, most likely reflecting underlying differences in patterns of host immunity.[57] DENV-4 has never caused a major epidemic in Brazil, however.

A total of 4,243,049 dengue cases have been reported in Brazil between 1981 and 2006, with the Northeast and Southeast regions most affected.[58] DENV-1 and DENV-4 were isolated for the first time in the Amazon region of Brazil in 1981 and 1982. The disease became a nationwide public health problem following outbreaks of DENV-1 and DENV-2 in the state of Rio de Janeiro in 1986 and 1990, respectively. The introduction of DENV-3 in 2000, also in the state of Rio de Janeiro, led to a severe epidemic with 288,245 reported dengue cases.[59] Virus strains that were typed during the 2002 epidemic showed that DENV-3 has displaced other dengue virus serotypes and entered new areas.[59]

Europe

Ae albopictus was detected in Albania in 1979 and in Italy in 1990 and has become a threat to many other Mediterranean countries, particularly the southern part of France (French Riviera and Corsica) where climatic conditions are suitable for its establishment.[60] The origin of the infestation in Northern Italy was shown to be related to the importation of used tires.[61] The tolerance exhibited by some natural populations of *Ae albopictus* for low temperatures allows this species to occupy an area much farther north than *Ae aegypti*.[60,62] *Ae albopictus* is now believed to be in at least 12 countries in Europe.[63] An outbreak of chikungunya virus disease affecting more than 200 inhabitants occurred in Northern Italy in 2007 following the importation by a viremic traveler from India.[64] Autochthonous spread was possible because of the susceptibility of *Ae albopictus* for chikungunya virus. Dengue is much more frequently imported than chikungunya,[65] but no autochthonous transmission of dengue has been reported to date. In the past, however, dengue did occur in Europe before the eradication of *Ae aegypti*.[17]

Pacific Islands

Dengue continues to be a threat to Pacific Island countries and territories (PICTs). After an absence of 25 years, all four serotypes were introduced in the 1970s, causing major epidemics, some associated with DHF.[17] The last DENV-1 epidemic affected 16 PICTs and in some of them it affected as much as 20% of the population, having a major public health impact and a massive impact on their fragile economies.[25] The continuing outbreak of dengue in the Pacific has been attributed to multiple, direct introductions of dengue viruses from various locations in Asia followed by local transmission.[66,67]

Australia

Outbreaks of DF have repeatedly occurred in North Queensland following the importation of dengue virus in returned travelers.[68] The successful prevention of widespread local transmission in these circumstances was facilitated by early notification and isolation of cases, and collaboration with local public health authorities in vector control.[68]

DENGUE IN INTERNATIONAL TRAVELERS

The marked increase of dengue over the past 3 decades is in tandem with increasing reports of international travelers suffering from dengue, including long-term

expatriates, aid/development workers, the military stationed in dengue-endemic countries, and immigrants from endemic countries.[3,65,69–89] In some case series, DF now presents the second most frequent cause of hospitalization (after malaria) in travelers returning from the tropics.[71,80] GeoSentinel is a worldwide network of travel medicine providers who see ill returning travelers.[90] Dengue accounted for up to 2% of all morbidity in returned ill travelers visiting GeoSentinel clinics.[91] As part of a broad comprehensive analysis of the spectrum of disease in travelers, the GeoSentinel surveillance network has shown that over the past decade dengue has emerged as a more frequent diagnosis than malaria in ill returned travelers from all tropical regions outside of Africa.[91] Prospective seroconversion studies have estimated the attack rate of dengue virus infection in travelers to the tropics to be 2.9% in Dutch travelers traveling for 1 month to Asia,[76] whereas among Israelis traveling for an average of 5 months the seroconversion rate was 6.7%.[92] The incidence of dengue is now considered to be higher than that of other typical travel-related diseases, such as hepatitis A or typhoid fever.[3] Risk factors for acquiring dengue depend on duration of travel, season, and destination.[76] Most dengue virus infections in travelers are acquired in Asia, followed by the Americas, and only a small proportion in Africa.[69,91]

Classic DF in travelers, although mostly self-limiting and rarely fatal, can be incapacitating, may halt travel, and may require hospitalization and even evacuation and a return home.[3] Severe dengue infections, such as DHF, seem to be less frequent in travelers compared with the indigenous population, however.[93] The low incidence of DHF in these travelers may be attributable to most travelers not having pre-existing antibodies to dengue, given their lack of previous exposure.[94] Another factor that may contribute to the lower incidence of DHF in travelers is that most travelers are adults, and adults are reported to have a lower risk for DHF compared with children.[95]

TRAVELERS AS SENTINEL

As travelers return from any of the countries where dengue is currently endemic, they potentially reflect the evolving epidemiology of dengue. The analysis of DENV isolated from travelers contributes to the global picture of strain distribution and circulation.[96] Properly annotated sequence data for flaviviruses can aid in tracking the spread of dengue. Flavitrack was designed to help identify conserved sequence motifs, interpret mutational and structural data, and track evolution of phenotypic properties, and now contains more than 590 complete flavivirus genome/protein sequences and information on known mutations and literature references.[97] Flavitrack could potentially be used to compare sequences of viruses found in returning travelers and those described worldwide.

Data collected longitudinally over a decade by the GeoSentinel Surveillance Network examined month-by-month morbidity from a sample of 522 cases of dengue as a proportion of all diagnoses in 24,920 ill returned travelers seen at our 33 surveillance sites.[98] The data showed that travel-related dengue reflects defined seasonality for some regions (Southeast Asia, South Central Asia, Caribbean, South America). The natural, year-to-year oscillations of dengue cases in endemic populations were also observed in travelers. In each of the epidemic years of 1998 and 2002 in Southeast Asia, the usual pattern of seasonality changed with an excess of cases throughout the whole year.[98] The outbreak in 1998 in Thailand was reflected in travelers by an excess in cases that preceded the usual increased seasonal activity. When the 1998 pattern in travelers reoccurred in early 2002, it led to the immediate hypothesis that this early transmission would once again herald an epidemic year. In April 2002, GeoSentinel alerted the international community when it posted online the increase in

travel-related dengue from Thailand. Official surveillance data from local populations are often not immediately available to the international community. Data reported later by Thai authorities to the WHO confirmed the observation. The increase in dengue cases in returned travelers from South Central Asia in 2003 was also evident before official surveillance data were available, reinforcing the increasing usefulness of sentinel surveillance in travelers. Because the number of travelers to areas with epidemics may be small and some epidemics may occur in parts of a country that are not visited by travelers, sentinel surveillance in travelers cannot be a definitive and uniquely sensitive tool for detection of all disease outbreaks, but preliminary experience with GeoSentinel show that the traveling population can give additional timely and specific information.[98] Travelers may therefore serve as sentinels rapidly informing the international community about the onset of epidemics in endemic areas. Sentinel surveillance of travelers can provide an additional layer in the international surveillance effort.

SUMMARY

Because of the expanding geographic distribution of the virus and the mosquito vector, increased frequency of epidemics, cocirculation of multiple virus serotypes, and the emergence of DHF in new areas, WHO classifies dengue as a major international public health concern.[1,2] The reasons for this resurgence are complex and include unprecedented urbanization with substandard living conditions, lack of vector control, virus evolution, and international travel.[1,4,5] Of all these factors, urbanization in tropical and subtropical regions has probably had the most impact on the amplification of dengue within a given country, and travel had the most impact for the spread of dengue from country to country and continent to continent. Modern rapid intercontinental transportation has had a major influence on the distribution and transmission dynamics of dengue. Epidemics of dengue, their seasonality, and oscillations over time are reflected by the epidemiology of dengue in travelers. Sentinel surveillance of travelers could augment existing national public health surveillance systems.

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