

## SPECIAL SECTION: TRAVEL MEDICINE

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**Dengue Fever in International Travelers**

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**Dengue virus infection is becoming increasingly recognized as one of the world's major emerging infectious diseases. Although only a few systematic studies have been conducted to assess the incidence and clinical course of dengue fever in travelers, it is now possible to estimate risk factors for travelers to areas of endemicity. Dengue virus and its vector, *Aedes* mosquitoes, benefit from human habitation and travel-related aspects of human behavior. Thus, travelers serve an important double role as potential victims of the disease and as vehicles for further spread of dengue.**

**The Disease and Its Symptoms**

Dengue fever is progressively making its way from being “one of the great neglected diseases of mankind” [1] toward becoming acknowledged as one of the world's major emerging infectious diseases. In fact, the infection is now rightly seen as a global pandemic, with recorded prevalence in 101 countries (figure 1) [2, 3]. Principally transmitted by *Aedes aegypti* and *Aedes albopictus*, both vectors that have shown remarkable compliance to environmental changes by human habitation [4], dengue has spread with the increasing sprawl of unregulated housing areas in many tropical cities. The vector mosquitoes are well adapted to an urban environment: they breed in tires, cans, and water jars near human dwellings, and the females transmit dengue readily because of their predilection for human blood and habit of multiple, interrupted feedings [5]. In many areas where dengue fever is endemic, policies for mosquito control are nonexistent or far from being successful [2].

Dengue infection is caused by any of 4 different serotypes of the virus (DEN-1, DEN-2, DEN-3, and DEN-4). After an incubation period of 2–8 days after an infective mosquito bite, the disease usually begins with sudden onset of fever and headache, typically accompanied by any of the following: chilliness, retro-orbicular pain, photophobia, backache, severe muscle ache (one synonym of dengue is “break-bone fever”), and joint ache. High fever may be sustained over 5–6 days. Other signs

and symptoms include a generalized maculopapular rash, lymph node enlargement, a positive tourniquet test, petechiae, and other hemorrhagic manifestations, such as epistaxis and gastrointestinal bleeding. In general, convalescence occurs spontaneously and abruptly, but it might be prolonged, sometimes taking several weeks, and may be accompanied by pronounced asthenia and depression.

Dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), 2 serious variants of the disease, occur in 250–500,000 patients each year, mainly in Southeast Asia [2]. The case-fatality rate among hospitalized patients may vary from <1% to 5% for DHF [6] and from 12% to 44% for DSS [3]. In 1998, a total of 558,000 infections and 15,000 deaths due to dengue fever were reported by member states of the World Health Organization, which translates to a case-fatality rate of 2.7% [7]. However, it must be made clear that dengue fever is not a notifiable disease in most countries. Consequently, actual numbers of both cases of disease and deaths due to dengue virus are most certainly much higher than those reported to the World Health Organization.

Diagnosis of dengue fever or its complications is established by culture of the virus itself, by detection of viral DNA with use of PCR, or by serological methods. Although detection of specific IgM indicates fresh infection, a significant increase in IgG titer in paired serum samples is also sufficient for diagnosing dengue fever. Currently employed methods include capture ELISAs, immunofluorescence tests, and hemagglutination assays. The limitations of laboratory testing are an important consideration in interpreting the results. Isolation of virus in acute-phase tissue culture is only 50% sensitive, and antibody testing might fail at that early stage [3]. Therefore, convalescent samples need to be taken in order to ascertain diagnosis.

Likewise, cross-reactions with other flaviviruses might interfere with serological testing, of which the ELISA method is particularly vulnerable. Yellow fever vaccination especially may play a crucial role here, since many travelers to areas where

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Received 7 February 2000; revised 18 April 2000; electronically published 26 July 2000.

Financial support: Dr. Democh Maurmeier Foundation, Friedrich Baur Foundation, and “Förderprogramm für Forschung und Lehre” of Ludwig Maximilians University, Munich, Germany.

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**Clinical Infectious Diseases** 2000;31:144–7

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1058-4838/2000/3101-0029\$03.00

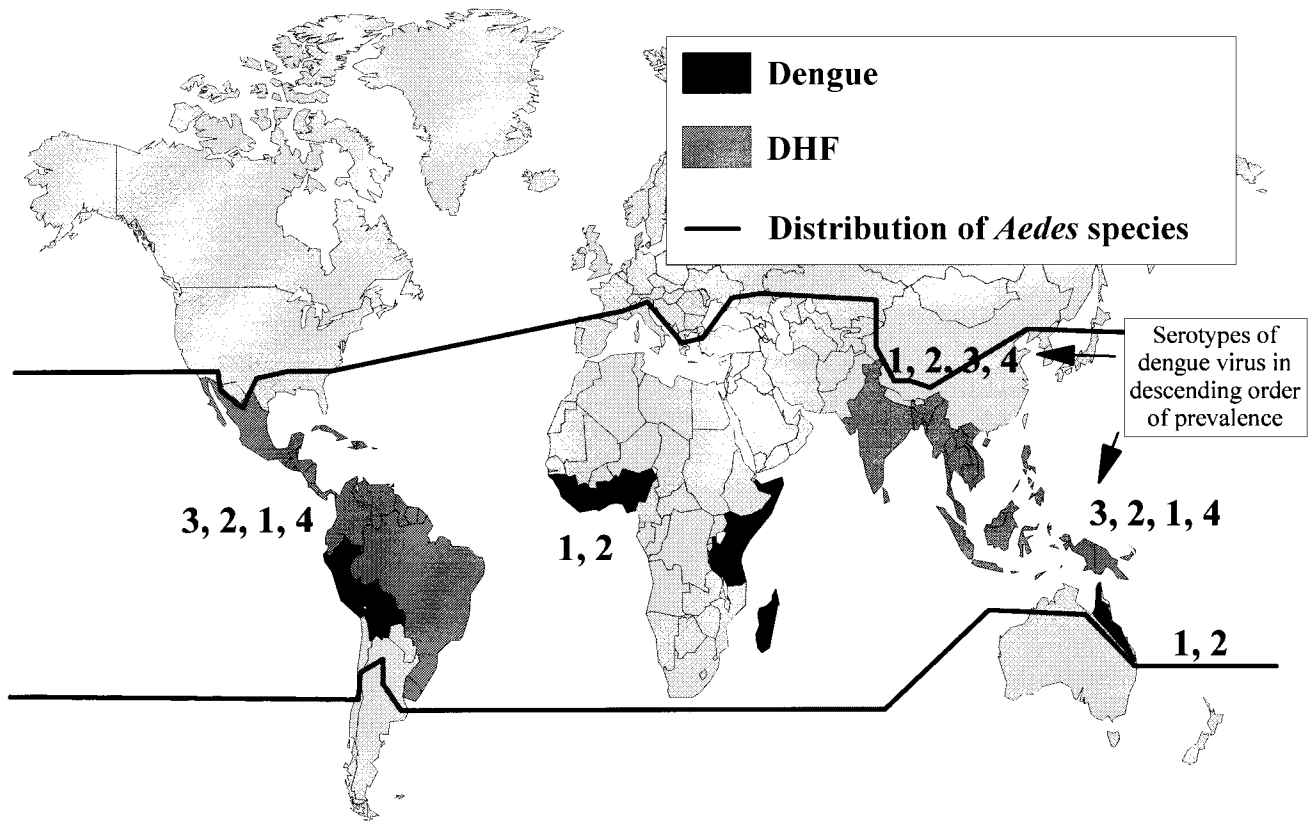


Figure 1. Distribution of dengue and dengue hemorrhagic fever (DHF)

dengue is endemic will also receive that vaccine before departure. For a diagnosis of “confirmed” dengue, the virus should be detected by isolation, by immunohistochemistry in necropsy tissue, or by an increase (at least 4-fold) in antibody titers determined by a type-specific plaque reduction neutralization test [3]. Samples positive for IgM antibody alone should be reported as indicative of only “probable” dengue infections.

A recently developed rapid test for the detection of IgM and IgG antibodies has shown promising results in early trials [8]. Yet, as with many test kits in which immunochromatographic methods with dipsticks are used, specificity may be a problem [9]. Therapy for dengue fever is symptomatic and involves rest, fluid replacement, analgesics, and antipyretics. With the occurrence of threatening severe sickness, intensive care measures are warranted against complications, such as hypotension, hemorrhagic manifestations, and unconsciousness.

### Epidemiology

Dengue is endemic in most tropical parts of the world (figure 1), many of which are popular tourist destinations. The incidence of epidemic and endemic dengue has increased substantially, notably in the Americas, since 1977, and various epidemics have occurred [4, 10–12]. Current annual global

estimates are that 50–100 million patients now have dengue infection [13]. Of the factors that have been implicated in the current increase of dengue are international travel, which introduces new strains to different parts of the world, urbanization, overpopulation, crowding, poverty, and a weakened public-health infrastructure [5].

Of major concern is the potential area of dengue transmission due to the spread of its vectors: such areas include sizeable parts of the United States and Europe, as outlined in figure 1. The introduction of dengue fever by returning travelers as yet unafflicted by the disease therefore poses a very real threat to public health systems of the western world. One of the largest dengue fever epidemics known in history, involving ~1 million cases and 1000 deaths, occurred in 1927–1928 in Greece. At that time, the vector was the later-eradicated *A. aegypti*. In this context, the recent introduction of *A. albopictus* to Europe, notably Italy and Albania [2], might serve as a warning of things to come.

### Risk Factors for Travelers

Structured data on the risks of dengue infection for travelers are rare. Although case reports of imported dengue are relatively frequent, they do not allow an estimation of the risk of

illness for travelers. Three studies of nontourists have been used as surrogates for estimates of the risk for North American travelers [3]. Of 627 American residents in Bangkok, only 6 (1%) were infected in 1962–1963 with dengue or chikungunya viruses [14]. Among the >30,000 troops deployed in 1993–1994 in Somalia and 20,000 troops in Haiti in 1994, only 59 (0.2%) and 30 (0.1%), respectively, had confirmed dengue fever [15, 16]. However, the use of these studies as indicators for risk of infection in travelers is problematic. Although the data from the first group are clearly outdated because of changes in the epidemiology of dengue, the latter 2 studies were done in the artificial situation of American troops being deployed within areas of endemicity. Surely only few aspects of the behavior of international travelers can be compared with that of soldiers.

Various case reports have been published that described dengue infections in international travelers who had visited areas where such infections are endemic [11, 12, 17–23]. In a small number of systematic studies of this topic, serological evidence of recent dengue infection was found in 7%–45% of patients with fever after they returned from areas of endemicity [24–26]. A retrospective study performed among a small cohort of Swiss travelers showed a surprisingly high prevalence of antibodies to dengue virus (8%) in symptomatic patients [27]. These results were further underpinned by a prospective study of 130 febrile returnees from areas of endemicity that showed a prevalence of 6.9% [26]. In the latter study, 9 of the 10 patients who tested positive for dengue had acquired the infection in Southeast Asia or Western Indonesia, and the other patient acquired dengue in Brazil.

In a retrospective study among 323 German expatriate workers and their families after an average stay of 9.8 years in areas of endemicity, antibodies to dengue virus were detected in 4.3% of patients [28]. Length of stay was clearly correlated with seropositivity. The results of this study show that expatriates may be at substantial risk of acquiring dengue infection. However, the majority of persons who tested positive for antibodies to dengue did not have any clinical disease suggestive of dengue. It appears that many infections may have oligosymptomatic or asymptomatic courses.

In a similar study of 670 German aid workers with an average overseas time of 37.7 months, seropositivity was detected in 7.4% [29]. The highest seroprevalence rates of IgG antibodies to dengue were detected in aid workers who had returned from Thailand (19.4%), Benin (14.8%), and Burkina Faso (9.2%). The latter 2 countries have previously not been implicated with regard to dengue infection in travelers and expatriates. The quality of both studies suffered from the retrospective design and considerable lack of precise data on living standards, housing conditions, and traveling habits of the investigated persons. Nevertheless, their results show clearly that dengue infection is a realistic event in long-term travel to areas where it is endemic. It appears most probable that this risk also applies to persons on repeated short journeys.

Similar to the sparseness of data on the true incidence of dengue fever among travelers, little is known about the clinical spectrum of dengue fever and the proportion of subclinical infections in this group. Studies from areas of endemicity suggest that 14%–87% of all dengue infections cause few or atypical symptoms [30–32]. However, the proportion of subclinical dengue infections among travelers is of importance, since it has been suggested that infection with 1 serotype of dengue virus can predispose to development of DHF and/or DSS when reinfection occurs with another serotype [33].

### Preventive Measures

An effective, safe, affordable vaccine against dengue virus is not an immediate prospect [34]. Since preexisting heterotypic antibodies within the host increase the risk for DHF and DSS, an effective vaccine will have to offer ~100% protection against all 4 serotypes of the virus. Attenuated vaccine viruses have been evaluated in the past in Thailand, and a tetravalent formulation of such viruses is currently being tested in repeated trials [3]. Another approach is construction of recombinant vaccines with construction of chimeric viruses by insertion of specific genes of dengue virus into a vaccine candidate virus. Through genetic manipulation, these recombinants may be able to replicate faster, be more immunogenic, and be safer than traditional attenuated strains [35].

The single most effective measure of dengue prevention for travelers to areas where dengue is endemic is taking precautions to avoid mosquito bites, such as using mosquito repellents, protective clothing, and insecticides. The vector of dengue virus, *Aedes* mosquitoes, are frequently found near or inside human habitats. They often rest in dark rooms (e.g., inside bathrooms and under beds) and breed in small water pools that collect in discarded human waste.

The preferred (but by no means exclusive) feeding times of *Aedes* species are the early morning and the late afternoon. The risk of exposure for travelers is highest in rural and urban areas inhabited by low-income groups and that lack effective mosquito control. The risk of acquiring dengue infection may be considerably lower in many preferred travel destinations, such as beaches, hotels with well-kept grounds, and jungle areas.

### Outlook

The marked increase in the magnitude of the problems posed by dengue epidemics and endemicity for tropical areas is reflected in travelers' increasing risk of infection [6]. Serological techniques provide tools for screening and confirming of dengue virus infection [36]. However, there is a considerable lack of data regarding the actual frequency of this infection in international travelers. On the basis of data derived from the few available surveys, infection with dengue fever virus appears to be a realistic threat to travelers to Southeast Asia and, less

frequently, to other areas of endemicity. Symptoms commonly associated with dengue, such as fever, myalgia, arthralgia, and exanthema, can be helpful for diagnosis when present, but missing typical symptoms do not exclude infection. Thus, dengue virus infection should be considered as a diagnosis for all patients who have symptoms compatible with systemic viral infection and who reside in or have recently traveled to regions where such infections are endemic.

The significant lack of knowledge concerning entomological and pathogenetic factors influencing transmission (e.g., how long viremia lasts in asymptomatic travelers and how many carriers of the virus are needed in a given area to make an epidemic possible) makes risk estimates of secondary cases of dengue fever in industrialized countries rather unreliable. Therefore, though of paramount importance from a public health perspective, the risk inherent in introduction of the disease to Western countries by travelers is currently very difficult to calculate.

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