Dengue in Travelers: a Review

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Dengue is progressively making its way from being "one of the great neglected diseases of mankind" [1] towards 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 (Fig. 1).[2,3]

Despite all the threats of terrorism, wars and economic crises in recent years, in 2002 the number of international tourist arrivals exceeded the 700 million mark for the first time in history. According to the World Tourism Organization, more than 130 million arrivals were registered in Asia and the Pacific, which many regard as the destination of the future, and 120 million in the Americas.[4] Both are highly endemic areas for dengue viruses.

Both the increase in international air travel and the increasing frequency of dengue in the tropics are responsible for the increased chance that health care providers, including those in Western countries, will be confronted with imported dengue virus infections. In recently performed studies at travel clinics, dengue virus infection was the second most common cause of fever in returning travelers.[5,6]

Furthermore, travelers serve as important vectors of dengue viruses. First, they might introduce more virulent virus strains (subtypes) into areas where only mild disease has been observed before. The occurrence of dengue hemorrhagic fever (DHF) in Sri Lanka in 1989, for example, was found to be related to the appearance of a new DENV-3, subtype III variant; this was then probably imported into the Americas in the mid-1990s, resulting in unexpected outbreaks of DHF.[7] Second, travelers might introduce dengue viruses into nonendemic areas where the mosquito vector *Aedes aegypti* is common. In Queensland, northern Australia, several sporadic outbreaks occurred due to the introduction of dengue viruses via international travelers returning from endemic countries.[8,9]

Since dengue surveillance, if performed at all, is passive, and since dengue virus infection presents either as a short and self-limiting viral disease or even asymptomatically, it is certainly one of the most underdiagnosed tropical infections in travelers.

The Virus, the Host, and the Vector

Dengue virus 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 leads to lifelong immunity to the homologous serotype, but to only a short period of cross-reactive heterotypic immunity. This cross-protection is thought to last for 2 to 12 months.[10]

Dengue viruses are usually transmitted by bites of an infected mosquito vector, mainly *Ae. aegypti*. *Aedes* mosquitoes are effective vectors, and their global distribution matches that of the dengue viruses. For transmission to occur, the female *Aedes* mosquito must bite an infected human during the viremic phase of the illness, which generally lasts for 4 to 5 days but may last for up to 12 days.[11] The incubation period in humans ranges from 3 to 12 days, and is most commonly 5 to 7 days. *Aedes* mosquitoes are highly susceptible to dengue viruses and feed preferentially and frequently on human blood, the only important reservoir besides mosquitoes themselves.[12] Dengue viruses may be trans-ovarially transmitted in some *Aedes* mosquitoes.[11] It has been shown that dengue viruses in mosquitoes cause an infection of the nervous system, leading to prolonged feeding periods with a higher likelihood of being interrupted by the host, which increases the chance that this infected mosquito will probe or feed on additional hosts.[13] *Ae. aegypti* is a highly anthropophilic mosquito and breeds in artificial containers such as pots, tin cans and tires. It mainly bites during the day or early evening, and most biting occurs outdoors in urban areas.

These facts highlight the role of dengue in travelers. First, because of the short incubation period, a high

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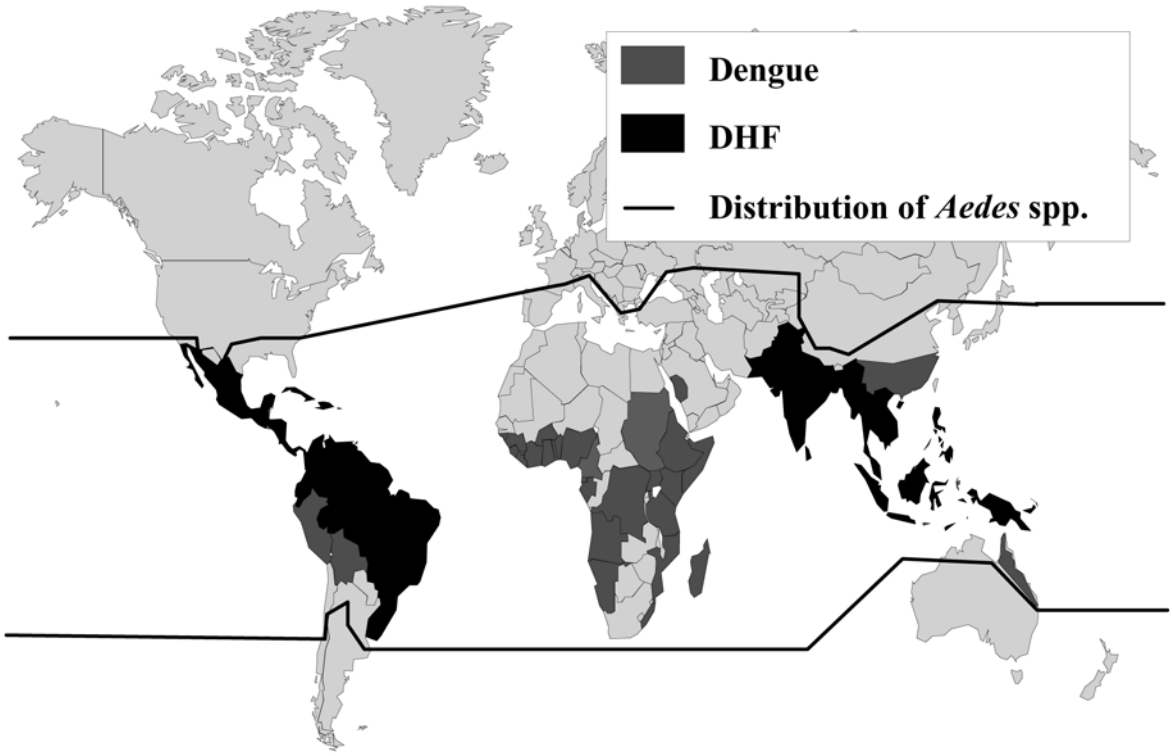

Figure 1 Distribution of dengue and dengue hemorrhagic fever (DHF).

proportion of travelers who acquire a dengue virus infection in the tropics will suffer from disease during their stay abroad. Most of them will not seek medical care when they return to their home countries, and the disease will be underreported in national surveillance systems. Second, dengue is a disease that occurs mainly, but not exclusively, in urbanized areas. These areas are globally much more closely connected to each other than they used to be. With increasing international air travel, new and potentially more virulent viral strains might be introduced to other areas infested with *Aedes* species.[14,15] Therefore, travelers are not only potential victims of infection, but are also important vectors in the global distribution of the viruses. Overcrowding, urbanization, poverty, insufficient water storage systems and insufficient vector control are major causes of the dramatic resurgence of dengue disease.[16]

Epidemiology

Dengue is endemic in most tropical parts of the world, many of which are popular tourist destinations. Worldwide, 2.5 billion people are living in dengue-endemic areas.

The incidence of epidemic and endemic dengue has increased substantially (Fig. 2). This increased epidemic activity, which is caused by all four virus serotypes, is associated with the geographic 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 DHF. Hyperendemicity is the most constant factor associated with the evolution of epidemic DHF in a geographic area.[17]

Today, dengue virus infection has emerged as the most important arboviral disease of humans, with an estimated 50 million to 100 million cases of dengue fever (DF) and several hundred thousand cases of DHF occurring each year, depending on epidemic activity.[18–20] 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.[21,22]

Of major concern is the potential area of dengue transmission due to the spread of its vectors: such areas include sizable parts of the US and Europe, as outlined in Figure 1. Thus, the introduction of dengue by returning travelers to regions as yet unaffected by the disease poses a very real threat to public health systems in the Western world.[23,24] One of the largest dengue epidemics known in history, with approximately 1 million cases and 1,000 deaths,

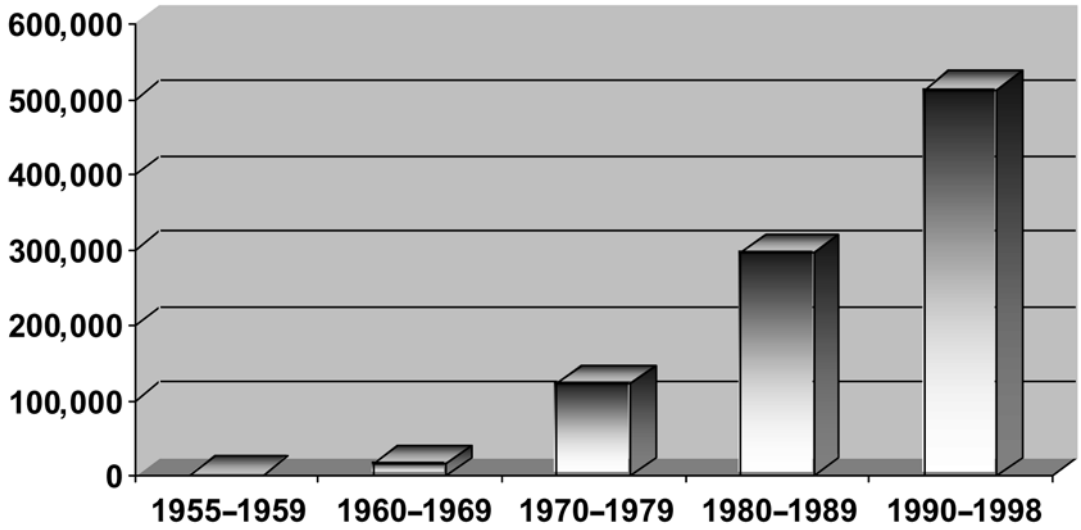

Figure 2 Average numbers of reported DF/DHF cases annually. *Source*: WHO.[105]

occurred in 1927–1928 in Greece. At that time, the vector was the later-eradicated *Ae. aegypti*. In this context, the recent introduction of *Ae. albopictus* to Europe, notably Italy, France and Albania, might serve as a warning of things to come.[2,25,26]

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 have shown 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 increases in the numbers of available containers.[27]

The Risk and Risk Factors for Travelers

Structured data on the risks of dengue virus infection for travelers are rare (Table 1). Though case reports on imported dengue are relatively frequent, they do not allow an estimation of the risk of illness for travelers. In a retrospective study among 323 German expatriate workers and their families after an average stay of 9.8 years in endemic areas, 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 virus infection. However, the majority of people who tested positive for antidengue virus antibodies did not experience any clinical disease suggestive of dengue. It appears that many infections may develop oligo- or asymptomatic courses. In a similar study among 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 antidengue virus IgG were detected in aid workers returning from Thailand (19.4%), Benin (14.8%), and Burkina Faso (9.2%). The latter two countries have not previously been implicated in dengue virus infection in travelers and expatriates. The quality of both studies suffered from their retrospective design and considerable lack of data on exact living standards, housing conditions, and traveling habits of the investigated people.

Of great interest are two prospective studies performed in travelers by collecting serum samples before and after travel. One study was performed in 104 long-term travelers from Israel to various dengue-endemic countries, and revealed dengue seroconversion in 6.7% of all travelers with a median of 5.3 months' stay abroad; three out of seven infections were asymptomatic.[30] The other study was performed in Dutch short-term travelers with destinations in endemic areas in Asia, and demonstrated an incidence rate of 30/1,000 personmonths. The clinical/subclinical infection ratio was 1 : 3.3.[31]

Incidence rates might change in cases of outbreaks. An exceedingly high attack rate of 69% during a dengue virus outbreak among a group of young short-term community aid workers was reported in a Caribbean island with no documented asymptomatic infection.[32]

All results show that dengue virus infection is a real threat, and not only to long-term travelers to Southeast Asia. In outbreaks, high attack rates might occur, with variable clinical/subclinical ratios, possibly reflecting the role of different virulent virus strains, the importance of initial viral load, or host factors (e.g., susceptibility of different ethnic groups). Two prospective studies on dengue seroconversion in travelers showed that a high percentage of infections might occur asymptomatically,

Table 1 Overview of Studies on Dengue Antibody Prevalence/Seroconversion in Travelers and Expatriates

Study Design	*Study Population*	*Antibody Prevalence (%)*	*S : A*	*Destination*	*Publishing Year*	*Reference*
Prospective	627 expatriates	1	–	Bangkok	1969	104
Retrospective	38 febrile travelers	8	–	Endemic area	1995	48
Prospective	37 symptomatic travelers	64.9	–	Endemic area	1996	47
Prospective	173 febrile travelers	53	–	Asia	1996	103
Prospective	130 symptomatic travelers	6.9	–	Endemic area	1997	49
Retrospective	323 expatriates	4.3	–	Endemic area	1997	28
Retrospective	670 aid workers	7.4	–	Endemic area	1999	29
Prospective	104 long-term travelers	6.7[a]	1.3 : 1	Endemic area	1999	30
Prospective	477 short-term travelers	3[a] per month	1 : 3.3	Asia	2002	31

S : A = symptomatic/asymptomatic ratio.
[a]Seroconversion (= incidence).

a phenomenon that has been described in immune and nonimmune populations—both adults and children—in Thailand and during outbreaks in Cuba.[33,34]

Prospective and retrospective studies have revealed several risk factors that might be associated with dengue virus infection: age, travel duration, travel destination, and season.[31,35–38] However, these risk factors might reflect the travel habits of tourists, the dengue activity in the endemic countries, and the popularity of the country as a tourist destination.

Data from The European Network on Imported Infectious Disease Surveillance (TropNetEurop) and a few case reports give the impression that non-Caucasian travelers have a higher risk of developing DHF than Caucasian travelers.[39–41]

Surveillance of Dengue in Travelers

Even though various case reports on dengue virus infections in international travelers returning from endemic areas have been published,[42–47] the disease was not reported in most European public health systems during the 1990s.

It took until the late 1990s for the Western world to become aware of the increasing problem that dengue also poses to travelers. 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.[48] These results were further underpinned by a prospective study among 130 febrile returnees from endemic areas that showed a prevalence of 6.9%.[49] A small number of systematic studies on this topic were thought to have the effect of awakening calls.

In Germany, for example, a new reporting system for dengue was introduced in 2001 by the Robert Koch Institute. As a consequence of more complete reporting, the numbers of cases within this system rose to 231 in 2002, from 60 the year before.[50] Since surveillance for dengue is passive, only the tip of the iceberg is reported, making DF/DHF one of the most underreported tropical infectious diseases in the past 20 years.[17]

Table 2 Frequencies of Travel-acquired Dengue Virus Infections by Region of Travel in 481 European Travelers between 1999 and 2002.[41]

Region of Infection	*No. (%) of Patients*
Africa	38 (8)
South/Central America	91 (19)
The Caribbean	56 (12)
Indian subcontinent	77 (16)
Southeast Asia and Oceania	219 (48)

TropNetEurop was able to reveal the frequencies of dengue virus infection in various dengue-endemic regions in which 481 European travelers acquired a dengue virus infection between 1999 and 2002 (Table 2). These frequencies mainly reflect worldwide dengue activity, as well as the countries' popularity as tourist destinations. Thailand, Vietnam and Indonesia are not only high-endemic areas for dengue viruses, but also have expanding tourism sectors. Thailand alone was responsible for 134 (28%) of all travel-acquired dengue virus infections over the previous 4 years in this network.[37,41]

Other studies in Europe showed similar distributions, with highest incidences in travelers returning from Southeast Asia.[38] Among 33 US residents who were diagnosed with DF during 1999 and 2000, the disease was acquired most frequently in Asia (13 cases) and the Caribbean islands (12 cases), followed by Central America (seven cases), South America (one case), and Africa (one case).[51]

The Disease and its Symptoms

Dengue virus infection may be asymptomatic or may lead to undifferentiated febrile illness (viral syndrome), DF, or DHF, with or without shock, depending largely on age and immunologic condition.[52]

Table 3 Signs and Symptoms of Travel-acquired Dengue Virus Infections in 465 Europeans and Immigrants.[41]

Symptom	*No. (%) of Patients*
Fever	421 (91)
Headache	295 (63)
Myalgia or arthralgia	241 (52)
Fatigue	197 (42)
Rash	158 (34)
Diarrhea	106 (23)
Vomiting	55 (12)
Lymphadenopathy	31 (7)
Respiratory symptoms	29 (6)
Ear, nose and throat symptoms	28 (6)
Neurologic symptoms	12 (3)
Psychological symptoms	7 (2)
Other symptoms	70 (15)

In DF, the severity of the clinical features increases with the age of the patient.[3] Therefore, classical DF 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 (Table 3). Mild hemorrhagic manifestations, such as epistaxis, petechiae, gingival bleeding and menorrhagia, are accepted as rare aspects of the clinical picture of DF.[52,53] In a study performed in Swedish patients with dengue virus inection after return from travel, 21 of 74 had hemorrhagic manifestations. The disease is self-limiting, and in classical DF no deaths usually occur.

In contrast, DHF is primarily a disease of children under 15 years of age residing in hyperendemic areas where two or more virus serotypes are circulating simultaneously, but it can also occur in adults. The early clinical features of DHF are indistinguishable from those of DF.[54] Even though the severity of hemorrhage in DHF tends to be greater than in DF, and severe gastrointestinal bleeding may sometimes occur, DHF is somewhat inaptly named, because its central clinical and pathogenetic feature is not bleeding.[55] The major pathophysiologic change that determines the severity of disease in DHF and differentiates it from DF is the leakage of plasma, which results in hemoconcentration (manifested as a rise in hematocrit), pleural or other effusions, or hypoalbuminemia or hypoproteinemia.[54] This feature typically occurs simultaneously with a drop in platelet count at the time of defervescence, 2 to 9 days after the onset of symptoms, and may progress to hypovolemic shock (dengue shock syndrome; DSS) and death. The grading of the severity of dengue virus infection is usually performed according to WHO guidelines (Table 4).[56,57]

Generally, DHF occurs rarely in travelers, but several cases have been reported.[35,39,40,47] Within the European Network on Imported Infectious Disease Surveillance, 2.7% of all dengue cases ($n = 483$) were reported as DHF.[58]

In recent years, there have been increasing reports of dengue virus infections with unusual manifestations, mainly with cerebral and hepatic involvement.[59–63] At the same time, reports of unusual clinical manifestations in travelers have also been increasing, including the first fatal case of dengue virus infection accompanied by fulminant hepatic failure imported into the UK in 2002.[39] In the same year, a patient presented at a German travel clinic with DF and visual loss.[64]

Pathogenesis of DHF: Current Knowledge and Opinions

The pathogenesis of dengue is not fully understood. There are currently several hypotheses concerning why dengue viruses lead to DHF in some individuals but not in others. The major pathophysiologic change, however, that determines the severity in DHF and differentiates it from DF is the acute increased vascular permeability, which results in plasma leakage, leading to hypovolemia and shock.[65] Other hallmarks are hemorrhagic diathesis and complement activation.[66]

The observations that classical DF without complications occurs in nonindigenous foreigners and that 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 immunologic explanation.[67] Fundamental to the immunologic events in DHF is the existence in nature of four antigenically related but distinct dengue serotypes that parenterally enter human hosts: recovery from one infection provides lifelong immunity against that serotype but confers only transient protection against the heterologous infections, and sequential infections may increase the risk of more serious disease. In infants, for example, a transient heterotypic immunity due to maternal dengue antibodies was found to be followed by a period of highest risk of acquiring DHF 7 to 8 months after birth.[10] Based on these observations, the immune enhancement theory has been developed.[67–71] According to this hypothesis, non-neutralized antibody–virus complexes bind to monocytes–macrophages, which leads to cytokine production and higher viral loads. It has been well documented that higher viral burden is associated with more severe disease.[72,73] One other recently suggested explanation for the development of DHF is that cross-reactive T cells ($CD8^+$) activated by the original antigenic stimulus may have lower affinity and be less effective at clearing a secondary infection with dengue viruses, resulting in higher viral loads.[74]

However, primary dengue virus infection can also be associated with fatal dengue hemorrhagic disease and

Table 4 Grading of the Severity of Dengue Virus Infection According to WHO Guidelines.[57]

DF/DHF	*Grade*[a]	*Symptoms*	*Laboratory*
DF		Fever with two or more of the following signs: headache, retroorbital pain, myalgia, arthralgia	Leukopenia occasionally Thrombocytopenia may be present. No evidence of plasma loss
DHF	I	Above signs plus positive tourniquet test (as the only bleeding disorder)	Thrombocytopenia $< 100{,}000$ cells/mm^3, Hct rise $\geq 20\%$
DHF	II	Above signs plus spontaneous bleeding	Thrombocytopenia $< 100{,}000$ cells/mm^3, Hct rise $\geq 20\%$
DHF	III	Above signs plus circulatory failure (weak pulse, hypotension, restlessness)	Thrombocytopenia $< 100{,}000$ cells/mm^3, Hct rise $\geq$ 20%
DHF	IV	Profound shock with undetectable blood pressure and pulse	Thrombocytopenia $< 100{,}000$ cells/mm^3, Hct rise $\geq$ 20%

DF, dengue fever; DHF, dengue hemorrhagic fever; Hct, hematocrit.

[a]DHF Grade III and IV are also called dengue shock syndrome (DSS).

shock.[75] Therefore, the virus itself might play an important role in disease severity. Dengue virus structural differences have been shown to correlate with pathogenesis,[76] and epidemiologic studies have provided strong evidence that there are significant differences in disease severity between secondary dengue virus infections of American and Asian origin.[77–79] 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.

Several studies have revealed both protective and pathogenic roles in disease severity for specific HLA class genetic variations.[80,81] There is also some epidemiologic evidence that there must be genes in black people of African origin that play a role in restricting the severity of dengue virus infection.[82]

Diagnosis and Treatment

A definite diagnosis of dengue virus infection is established by culturing the virus itself, by detection of viral DNA by use of PCR, or by serologic methods. Whereas detection of specific IgM indicates acute infection, a significant rise of IgG in paired serum samples is also sufficient for the diagnosis of dengue virus infection.[83] A rapid test for the detection of IgM and IgG antibodies is commercially available.[84]

It is important to consider the limitations of laboratory testing when interpreting the results. Isolation of virus in tissue culture is only 50% sensitive in acute-phase samples, and antibody testing might fail at that early stage.[3] Thus, convalescent samples need to be taken in order to obtain a diagnosis. Likewise, cross-reactions with other flaviviruses might interfere with serologic testing, with the ELISA method being particularly vulnerable to this. In particular, vaccinations against yellow fever and Japanese encephalitis may play a crucial role here, since travelers to dengue-endemic areas might also receive these vaccines before departure. In conclusion, a positive IgG result in a vaccinated traveler as well as negative IgM results in the early phase of the disease need to be interpreted with caution.[85]

For a diagnosis of "confirmed" dengue, one of the following criteria is necessary: the virus should be detected by isolation from serum samples, the dengue virus antigen should be demonstrated by immunohistochemistry in necropsy tissue, the dengue virus genomic sequences should be detected by PCR, or an at least four-fold increase in reciprocal IgG or IgM antibody titers to one or more dengue virus antigens in paired serum samples should be detected.[18] Samples positive for IgM antibody alone should only be reported as "probable" dengue infections.

Early in the course of the disease, as described above, serology is usually not helpful in the diagnosis of dengue. PCR would be the investigation of choice to detect virus during the febrile stage,[86] but is rarely available, even in specialized travel clinics. There are some clinical and laboratory indicators of acute dengue illness that might give some clue earlier in the course of the disease. Travel history and the above-described clinical symptoms constitute important information. Well-described laboratory findings are leukopenia, thrombocytopenia, depressed sodium, and liver function impairment.[35,36,54,87] The median time of fever cessation is between the fourth and the sixth day of illness. Around this time, the minimum platelet count is usually found, and the minimum white blood cell count is often found 1 or 2 days before. This is also the time when there is the highest risk that hematocrit will rise and DHF will manifest. The time course relationship between the drop in platelet count and the rapid increase in hematocrit value appears to be unique to DHF.[52] The hematologic changes are thought to be related to bone marrow suppression by dengue virus.[88] Recently, IgM antiplatelet autoantibodies were

demonstrated to be present in dengue patients and to cause platelet lysis.[89]

A positive tourniquet test is incorporated in the WHO clinical case definition of DHF. This is a simple clinical procedure that reflects capillary fragility. However, the test differentiates poorly between DF and DHF and seems to be not very specific.[57,90]

Therapy for DF is symptomatic. For the treatment of DF, oral rehydration therapy for patients with moderate dehydration caused by vomiting and high temperature is recommended, and paracetamol for fever above 39°C. Aspirin should be avoided, as it can cause gastritis and/or bleeding.

The clinical signs plus thrombocytopenia and rise in hematocrit are sufficient to establish a clinical diagnosis of DHF (Table 4). Once this diagnosis is established, patients should be carefully monitored for changes in hematocrit, thrombocytopenia, vital signs and signs of plasma leakage and bleeding. The outcome depends on early recognition of infection and careful monitoring. Early volume replacement when the hematocrit rises sharply as plasma leaks out can modify severity and prevent shock.[91,92]

Preventive Measures

An effective, safe and affordable vaccine against dengue virus is not an immediate prospect.[93] Since preexisting heterotypic antibodies within the host increase the risk for DHF and DSS, an effective vaccine will have to offer nearly 100% protection against all four serotypes of the virus.[94]

Attenuated vaccine viruses have been evaluated in the past in Thailand, and a tetravalent formulation of such viruses is currently being tested in repeat trials.[95,96] With the lots produced in France, a first clinical trial was also performed in the US, using monovalent vaccines and a tetravalent vaccine given in one dose.[97] Another approach consists of the construction of recombinant vaccines, with chimeric viruses being produced by inserting 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.[98]

As long as there is no vaccine commercially available, the single most effective dengue preventive measure for travelers to endemic areas is taking precautions to avoid mosquito bites.

Mosquito repellents, protective (insecticide-impregnated) clothing and (insecticide-impregnated) bed nets are simple measures to reduce biting from various mosquitoes, and therefore also to reduce the risk of acquiring other vector-borne diseases, especially malaria.[99–101]

However, in contrast to the malaria vector, the preferred, but by no means exclusive, feeding times of *Aedes* spp. are the early morning and the late afternoon. Dengue vectors are frequently found near or inside human habitats. Given these factors, the risk of exposure for travelers is highest in urban areas inhabited by low-income groups and without effective mosquito control. The risk of acquiring dengue virus infection may be considerably lower in many preferred travel destinations, such as beaches, hotels with well-kept grounds, and jungle areas.

Pretravel advice should include information about the estimated risk of acquiring a dengue virus infection according to the travel destination, about the symptoms of dengue and DHF, and about where and when there is the highest risk of infection. It is always worth remembering that malaria can resemble the clinical features of dengue and must therefore be excluded first. Personal protection against mosquito bites is the only effective measure for travelers. Homepages of the CDC (www.cdc.gov) or WHO (http://www.who.int/homepage) might be useful for finding information concerning personal protection measures against mosquito bites or the current situation of dengue activity worldwide.

Outlook

The marked increase in the magnitude of the problems that dengue epidemics and endemics are posing in tropical areas is reflected in an increasing risk for travelers of acquiring the infection. Serologic techniques provide tools for screening and confirmation of dengue virus infection.[102] However, there is a considerable lack of data regarding the actual frequency of this infection in international travelers. Judging from data derived from the few available surveys, infection with dengue virus appears to be a real threat to travelers to Southeast Asia, and, less frequently, to other endemic areas. Symptoms commonly associated with dengue, such as fever, myalgia, arthralgia and exanthema, can be helpful for diagnosis when present, but the absence of typical symptoms does not exclude infection. Thus, dengue virus infection should be considered in all patients who have symptoms compatible with systemic viral infection, and who reside in or have recently traveled to endemic regions. The significant lack of knowledge of entomologic and pathogenetic factors influencing transmission (for example, how long does viremia last in the asymptomatic traveler, how many travelers return each month with asymptomatic viremia, and how many carriers of the virus are needed in a given area to make an epidemic possible?) make risk estimates of secondary cases of dengue virus infection in industrialized countries rather unreliable. Therefore, although of paramount importance from a public health perspective, the risk of introduction of the disease to Western countries by travelers is currently very difficult to calculate.

References

1. Halstead S. The XXth century dengue pandemic: need for surveillance and research. World Health Statistics Q WHO Rep 1992; 45:292–298.
2. Kay B. Dengue vector surveillance and control. Curr Opin Infect Dis 1999; 12:425–432.
3. Rigau-Perez J, Clark G, Gubler D, et al. Dengue and dengue haemorrhagic fever. Lancet 1998; 352:971–977.
4. World Tourism Organization. World Tourism in 2002: better than expected. Released Madrid, 27 January 2003. Available at: http://www.worldtourism.org/newsroom/releases/2003/jan/numbers2002.htm (accessed 29 July 2003).
5. Stephan C, Allwinn R, Brodt HR. Travel-aquired dengue infection: clinical spectrum and diagnostic aspects. Infection 2002; 30:225–228.
6. O'Brien D, Tobin S, Brown GV, Torresi J. Fever in returned travellers: review of hospital admissions for a 3-year period. Clin Infect Dis 2001; 33:603–609.
7. Messer WB, Gubler DJ, Harris E, et al. Emergence and global spread of a dengue serotype 3, subtype III virus. Emerg Infect Dis 2003; 9:800–809.
8. Hanna JN, Ritchie SA, Phillips DA. An epidemic of dengue 3 in far north Queensland, 1997–1999. Med J Aust 2001; 174:178–182.
9. Das P. Infectious disease surveillance update. Lancet Infect Dis 2003; 3:267.
10. Kliks SC, Nimmanitya S, Nisalak A, Burke DS. Evidence that maternal dengue antibodies are important in the development of dengue hemorrhagic fever in infants. Am J Trop Med Hyg 1988; 38:411–419.
11. McBride WJ, Bielefeldt-Ohmann H. Dengue viral infections; pathogenesis and epidemiology. Microbes Infect 2000; 2: 1041–1050.
12. Harrington LC, Edman JD, Scott TW. Why do female Aedes aegypti (Diptera: Culicidae) feed preferentially and frequently on human blood? J Med Entomol 2001; 38:411–422.
13. Platt KB, Linthicum KJ, Myint KSA, et al. Impact of dengue virus infection on feeding behaviour of Aedes aegypti. Am J Trop Med Hyg 1997; 57:119–125.
14. Rocco IM, Kavakama BB, Santos CL. First isolation of dengue 3 in Brazil from an imported case. Rev Inst Med Trop Sao Paulo 2001; 43:55–57.
15. Singh UB, Seth P. Use of nucleotide sequencing of the genomic cDNA fragments of the capsid/premembrane junction region for molecular epidemiology of dengue type 2 viruses. Southeast Asian J Trop Med Public Health 2001; 32:326–335.
16. Lifson A. Mosquitos, models, and dengue. Lancet 1996; 347:1201–1202.
17. Gubler DJ. Epidemic dengue/dengue hemorrhagic fever: a global public health problem in the 21st century. Dengue Bull 1997; 21:1–13.
18. World Health Organization. Dengue haemorrhagic fever. Diagnosis, treatment, prevention and control, 2nd edn. Geneva: WHO, 1997.
19. Gibbons RV, Vaughn DW. Dengue: an escalating problem. BMJ 2002; 324:1563–1566.
20. Gubler DJ. Dengue and dengue hemorrhagic fever. Clin Microbiol Rev 1998; 11:480-496.
21. Harris E, Videa E, Pérez L, et al. Clinical, epidemiologic, and virologic features of dengue in the 1998 epidemic in Nicaragua. Am J Trop Med Hyg 2000; 63:5–11.
22. Pinheiro F, Nelson M. Re-emergence of dengue and emergence of dengue haemorrhagic fever in the Americas. Dengue Bull 1997; 21:16–23.
23. Monath TP. Dengue: the risk to developed and developing countries. Proc Natl Acad Sci USA 1994; 91: 2395–2400.
24. Jelinek T. Dengue fever in international travellers. Clin Infect Dis 2000; 31:144–147.
25. Romi R. Aedes albopictus in Italy: an underestimated health problem. Ann Ist Super Sanita 2001; 37:241–247.
26. Schaffner F, Karch S. First report of Aedes albopictus (Skuse, 1984) in metropolitan France. C R Acad Sci III 2000; 323:373–375.
27. Strickman D, Kittayapong P. Dengue and its vectors in Thailand: introduction to the study and seasonal distribution of Aedes larvae. Am J Trop Med Hyg 2002; 67:247–259.
28. Janisch T, Preiser W, Berger A, et al. Emerging viral pathogens in long-term expatriates (II): Dengue virus. Trop Med Int Health 1997; 2:934–940.
29. Eisenhut M, Schwarz TF, Hegenscheid B. Seroprevalence of dengue, chikungunya and Sindbis virus infections in German aid workers. Infection 1999; 27:82–85.
30. Potasman I, Srugo I, Schwartz E. Dengue seroconversion among Israeli travellers to tropical countries. Emerg Infect Dis 1999; 5:824–827.
31. Cobelens FGJ, Groen J, Osterhaus ADME, et al. Incidence and risk factors of probable dengue virus infection among Dutch travellers to Asia. Trop Med Int Health 2002; 7:331–338.
32. Lyerla R, Rigau-Perez JG, Vorndam AV, et al. A dengue outbreak among camp participants in a Caribbean island, 1995. J Travel Med 2000; 7:59–63.
33. Burke DS, Nisalak A, Johnson DE, Scott RM. A prospective study of dengue infection in Bangkok. Am J Trop Med Hyg 1988; 38:172–180.
34. Guzman MG, Kouri GP, Bravo J, et al. Dengue hemorrhagic fever in Cuba, 1981: a retrospective seroepidemiologic study. Am J Trop Med Hyg 1990; 42:179–184.
35. Wittesjö B, Eitrem R, Niklasson B. Dengue fever among Swedish tourists. Scand J Infect Dis 1993; 25:699–704.
36. Schwartz E, Mendelson E, Sidi Y. Dengue fever among travelers. Am J Med 1996; 101:516–520.
37. Jelinek T, Mühlberger N, Harms G, et al. Epidemiology and clinical features of imported dengue fever in Europe: Sentinel surveillance data from TropNetEurop. Clin Infect Dis 2002; 35:1047–1052.
38. Lindbäck H, Lindbäck J, Tegnell A, et al. Dengue fever in travelers to the tropics, 1998 and 1999. Emerg Infect Dis 2003; 9:438–442.
39. Lawn SD, Tilley R, Lloyd G, et al. Dengue hemorrhagic fever with fulminant hepatic failure in an immigrant returning to Bangladesh. Clin Infect Dis 2003; 37:e1–e4.

40. Morens DM, Sather GE, Gubler DJ, et al. Dengue shock syndrome in an American traveller with primary dengue 3 infection. Am J Trop Med Hyg 1987; 36:424–426.
41. Wichmann O, Mühlberger N, Jelinek T. Dengue—the underestimated risk in travellers. Dengue Bull 2003; 27: 126–137.
42. Lange WR, Beall B, Denny SC. Dengue fever: a resurgent risk for the international traveler. Am Fam Physician 1992; 45:1161–1168.
43. Melissant CF, Kauffmann RH. Infection with dengue virus. Neth J Med 1992; 41:272–274.
44. Chippaux A, Poveda JD. Imported dengue in France (1989–1993). Conditions to be met for assuring an accurate etiological diagnosis. Bull Soc Pathol Exot 1993; 86:402–405.
45. Hasler C, Schnorf H, Enderlin N, Gyr K. Imported dengue fever following a stay in the tropics. Schweiz Med Wochenschr 1993; 123:120–124.
46. Pick N, Potasman I. Dengue fever. Harefuah 1995; 129:30–32.
47. Lopez Velez R, Perez Casas C, Vorndam AV, Rigau J. Dengue in Spanish travelers returning from the tropics. Eur J Clin Microbiol Infect Dis 1996; 15:823–826.
48. Settah SG, Vernazza PL, Morant R, Schultze D. Imported dengue fever in Switzerland—serological evidence for a hitherto unexpectedly high prevalence. Schweiz Med Wochenschr 1995; 125:1673–1678.
49. Jelinek T, Dobler G, Hölscher M, et al. Prevalence of infection with dengue virus among international travelers. Arch Intern Med 1997; 157:2367–2370.
50. ProMED-mailing system: Dengue/DHF update 2003 (28), part [3]. Archive Number 20030714.1736, published 14.07.2003.
51. Clark GG, Rigau-Pérez JG, Vorndam V, Hayes JM. Imported dengue—United States, 1999 and 2000. MMWR 2002; 51:281–283.
52. Nimmannitya S. Clinical manifestations of dengue/dengue haemorrhagic fever. In: World Health Organization, Regional Office for South-East Asia. Monograph on dengue/dengue haemorrhagic fever. Regional Publication No. 22. New Delhi: WHO, 1993:48–54.
53. Hayes EB, Gubler DJ. Dengue and dengue hemorrhagic fever. Pediatr Infect Dis J 1992; 11:311–317.
54. Kalayanarooj S, Vaughn DW, Nimmannitya S, et al. Early clinical and laboratory indicators of acute dengue illness. J Infect Dis 1997; 176:313–321.
55. Halstead SB. Antibody, macrophages, dengue virus infection, shock, and hemorrhage: a pathogenetic cascade. Rev Infect Dis 1989; 11:S830–S839.
56. World Health Organization. Guidelines for treatment of dengue fever/dengue haemorrhagic fever in small hospitals. New Delhi: WHO, 1999.
57. World Health Organization. Prevention and control of dengue and dengue haemorrhagic fever, comprehensive guidelines. New Delhi: WHO, 1999:11–19.
58. Wichmann O, Jelinek T. TropNetEurop: Surveillance of dengue in Europe. Euro Surveill Weekly 2003; 7(32).
59. Nimmannitya S, Thisyakorn U, Hemsrichart V. Dengue hemorrhagic fever with unusual manifestations. Southeast Asian J Trop Med Public Health 1987; 18:398–406.
60. Sirivichayakul C, Sabcharoen A, Chanthavanich P, et al. Dengue infection with unusual manifestation: a case report. J Med Assoc Thai 2000; 83:325–329.
61. Pancharoen C, Kulwichit W, Tantawichien T, et al. Dengue infection: a global concern. J Med Assoc Thai 2002; 85(Suppl 1):25–33.
62. Solomon T, Dung NM, Vaughn DW, et al. Neurological manifestations of dengue infection. Lancet 2000; 355: 1053–1059.
63. Cam BV, Fonsmark L, Hue NB, et al. Prospective case-control study of encephalopathy in children with dengue hemorrhagic fever. Am J Trop Med Hyg 2001; 65:848–851.
64. Haritoglou C, Dotse SD, Rudolph G, et al. A tourist with dengue fever and visual loss. Lancet 2002; 360:1070.
65. Bethell DB, Gamble J, Loc PP, et al. Noninvasive measurement of microvascular leakage in patients with dengue hemorrhagic fever. Clin Infect Dis 2001; 32:243–253.
66. Avirutnan P, Malasit P, Seliger B, et al. Dengue virus infection of human endothelial cells leads to chemokine production, complement activation, and apoptosis. J Immunol 1998; 161:6338–6346.
67. Halstead SB. Pathogenesis of dengue: challenges to molecular biology. Science 1988; 239:476–481.
68. Green S, Vaughn DW, Kalajanarooj S, et al. Early immune activation in acute dengue illness is related to development of plasma leakage and disease severity. J Infect Dis 1999; 179: 755–762.
69. Kliks SC, Nisalak A, Brandt WE, et al. Antibody-dependent enhancement of dengue virus growth in human monocytes as a risk factor for dengue hemorrhagic fever. Am J Trop Med Hyg 1989; 40:444–451.
70. Sangkawibha N, Rojanasuphot S, Ahandrik S, et al. Risk factors in dengue shock syndrome: a prospective epidemiologic study in Rayong, Thailand. Am J Epidemiol 1984; 120: 653–669.
71. Thein S, Aung MM, Shwe TN, et al. Risk factors in dengue shock syndrome. Am J Trop Med Hyg 1997; 56:566–572.
72. Vaughn DW, Green S, Kalayanarooj S, et al. Dengue viremia titer, antibody response pattern, and virus serotype correlate with disease severity. J Infect Dis 2000; 181:2–9.
73. Libraty DH, Endy TP, Houng HS, et al. Differing influences of virus burden and immune activation on disease severity in secondary dengue-3 virus infections. J Infect Dis 2002; 185:1213–1221.
74. Mongkolsapaya J, Dejnirattisai W, Xu X, et al. Original antigenic sin and apoptosis in the pathogenesis of dengue hemorrhagic fever. Nat Med 2003; 9:921–927.
75. Barnes WJS, Rosen L. Fatal hemorrhagic disease and shock associated with primary dengue infection on a Pacific island. Am J Trop Med Hyg 1974; 23:495–506.
76. Leitmeter KC, Vaughn DW, Watts DM, et al. Dengue virus structural differences that correlate with pathogenesis. J Virol 1999; 73:4738–4747.
77. Watts DM, Porter KR, Putvatana P, et al. Failure of secondary infection with American genotype dengue 2 to cause dengue haemorrhagic fever. Lancet 1999; 354:1431–1434.
78. White NJ. Variation in virulence of dengue virus. Lancet 1999; 23:1401–1402.
79. Halstead SB, Streit TG, Lafontant JG, et al. Haiti: absence of dengue hemorrhagic fever despite hyperendemic dengue virus transmission. Am J Trop Med Hyg 2001; 65:180–183.

80. Loke H, Bethell DB, Phuong CXT, et al. Strong HLA class I—restricted T cell responses in dengue hemorrhagic fever: a double-edged sword? J Infect Dis 2001; 184:1369–1373.
81. Zivna I, Green S, Vaughn DW, et al. T cell responses to an HLA-B*07-restricted epitope on the dengue NS3 protein correlate with disease severity. J Immunol 2002; 168:5959–5965.
82. Halstead SB. Dengue. Curr Opin Infect Dis 2002; 15:471–476.
83. Innis BL, Nisalak A, Nimmannitya S, et al. An enzyme-linked immunosorbent assay to characterize dengue infections where dengue and Japanese encephalitis co-circulate. Am J Trop Med Hyg 1989; 40:418–427.
84. Lam SK, Devine PL. Evaluation of capture ELISA and rapid immunochromatographic test for the determination of IgM and IgG antibodies produced during dengue infection. Clin Diagn Virol 1998; 10:75–81.
85. Schwartz E, Mileguir F, Grossman Z, Mendelson E. Evaluation of ELISA-based sero-diagnosis of dengue fever in travelers. J Clin Virol 2000; 19:169–173.
86. Vaughn DW, Green S, Kalajanarooj S, et al. Dengue in the early febrile phase: viremia and antibody responses. J Infect Dis 1997; 176:322–330.
87. Gascon J, Giner V, Vidal J, et al. Dengue: a re-emerging disease. A clinical and epidemiological study in 57 Spanish travelers. Med Clin (Barc) 1998; 111:583–586.
88. LaRussa VF, Innis BL. Mechanisms of dengue virus-induced bone marrow suppression. Baillieres Clin Haematol 1995; 8:249–270.
89. Lin CF, Lei HY, Liu CC, et al. Generation of IgM anti-platelet autoantibody in dengue patients. J Med Virol 2001; 63:143–149.
90. Phuong CXT, Nhan NT, Wills B, et al. Evaluation of the World Health Organization standard tourniquet test and a modified tourniquet test in the diagnosis of dengue infection in Viet Nam. Trop Med Int Health 2002; 7:125–132.
91. Nimmannitya S. Clinical spectrum and management of dengue haemorrhagic fever. Southeast Asian J Trop Med Public Health 1987; 18:392–397.
92. Nhan NT, Phuong CXT, Kneen R, et al. Acute management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. Clin Infect Dis 2001; 32:204–213.
93. Chambers T, Tsai T, Pervokov Y, Monath T. Vaccine development against dengue and Japanese encephalitis: report of a World Health Organization meeting. Vaccine 1997; 15:1494–1502.
94. Morens DM. Antibody-dependent enhancement of infection and the pathogenesis of viral disease. Clin Infect Dis 1994; 19:500–512.
95. Sabchareon A, Lang J, Chanthavanich P, et al. Safety and immunogenicity of tetravalent live-attenuated dengue vaccines in Thai adult volunteers: role of serotype concentration, ratio, and multiple doses. Am J Trop Med Hyg 2002; 66:264–272.
96. Bhamarapravati N, Sutee Y. Live attenuated tetravalent dengue vaccine. Vaccine 2000; 18:44–47.
97. Kanesa-thasan N, Sun W, Kim-Ahn G, et al. Safety and immunogenicity of attenuated dengue virus vaccines (Aventis Pasteur) in human volunteers. Vaccine 2001; 19:3179–3188.
98. Kinney R, Butrapet S, Chang G, et al. Construction of infectious cDNA for dengue 2 virus: strain 16681 and its attenuated vaccine derivative, strain PDK-53. Virology 1997; 230:300–308.
99. Schoepke A, Steffen R, Gratz N. Effectiveness of personal protection measures against mosquito bites for malaria prophylaxis in travellers. J Travel Med 1998; 5:188–192.
100. Fradin MS, Day JF. Comparative efficacy of insect repellents against mosquito bites. N Engl J Med 2002; 347:13–18.
101. Nentwig G. Use of repellents as prophylactic agents. Parasitol Res 2003; 90:S40–S48.
102. Gubler D, Kuno G, Sather G, et al. Mosquito cell cultures and specific monoclonal antibodies in surveillance for dengue viruses. Am J Trop Med Hyg 1984; 33:156–165.
103. Yabe S, Nakayama M, Yamada K, et al. Laboratory virological diagnosis of imported dengue cases. Kansenshogaku Zasshi 1996; 70:1160–1169.
104. Halstead S, Udomsakdi S, Singharaj P, Nissalakk A. Dengue and Chinkungunya virus infection in man in Thailand, 1962–64 III: clinical, epidemiologic, and virologic observations on disease in non-indigenous white persons. Am J Trop Med Hyg 1969; 18:984–996.
105. Gratz NG, Knudsen AB. The rise and spread of dengue, dengue haemorrhagic fever and its vectors—a historical review (CTD/FIL (DEN) 96.7). Geneva: World Health Organisation, 1996.