Dengue – The Underestimated Risk in Travellers

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Abstract

In recent decades, the incidence, distribution and clinical severity of dengue have increased dramatically in most tropical and subtropical areas worldwide. As a consequence, and due to the expanding international tourism, health care providers in European travel clinics are more and more confronted with dengue, reflecting its global impact.

Based on data of the European Network on Imported Infectious Disease Surveillance (TropNetEurop) and the German Surveillance Network on Imported Infectious Diseases (SIMPID), a total of 483 confirmed and probable cases of dengue fever, including 13 cases of dengue haemorrhagic fever were reported to the networks' coordination centre between January 1999 and December 2002. There was a wide range of epidemiological and clinical features. Non-European travellers (immigrants or foreign visitors) were at 4.3-times higher risk of developing dengue haemorrhagic fever compared to European travellers. Infections were acquired in all endemic regions of the world, with highest frequencies in South-East Asian countries.

Persons travelling to areas where dengue is endemic should avoid exposure to mosquitoes, and health care providers should consider dengue as a differential diagnosis in febrile travellers returning from the tropics after discounting malaria. Surveillance of imported dengue is crucial to monitor the risk of infection for travellers and to strengthen clinical awareness of the disease.

Keywords: Dengue fever, dengue haemorrhagic fever, traveller, Europe.

Introduction

Dengue viruses are members of the *Flaviviridae* and are usually transmitted by the bites of an infected mosquito vector. Four groups of serologically distinct dengue viruses are currently recognized (DEN-1 to 4). Generally, man is the primary vertebrate host and *Aedes* mosquito is the primary vector of infection[1,2].

Dengue occurs principally in the tropical areas of Asia, Oceania, Africa and the Americas. In the past 30 years, there has been a dramatic emergence of epidemic dengue activity in the tropics worldwide[3,4].

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An estimated 2.5 billion people are living at risk of dengue infection, resulting annually in an estimated 50 to 100 million cases of dengue fever (DF) and 250,000 to 500,000 cases of its more severe manifestation, dengue haemorrhagic fever (DHF)[5,6]. In South-East Asia, the mean number of annual cases of dengue haemorrhagic fever has increased from below 10,000 in the 1950s and 1960s to over 200,000 in the 1990s. The same pattern is now unfolding in the Americas[3,6]. At the root of the emergence of dengue are changes in human demography and behaviour, leading to unchecked populations of and increased exposure to the principal domestic mosquito vector[7].

Another factor, which has had a great impact on the emergence of DF/DHF, is the increased air-travel of humans who are incubating the viruses and thus providing ideal mechanisms for transporting pathogens between population centres of the tropics[3]. Therefore, travellers not only have the potential to acquire a dengue infection, but also to spread new and potentially more virulent strains to different parts of the world. One major factor for the increased air-travel is expanding international tourism: in 2002, the number of international tourists, for the first time in history, exceeded the 700 million mark. The preliminary statistics of the World Tourism Organization showed that in that year, more than 130 million international tourist arrivals were registered in Asia and the Pacific, which many regard as the destination of the future, and 120 million in the Americas[8]. Therefore, not surprisingly, supported by higher awareness of physicians in travel clinics and better surveillance systems, reports on dengue infections in travellers became more frequent[9]. Several studies revealed dengue as the second most common tropical disease after malaria causing fever in returned travellers[10,11,12].

This article reviews the current situation – epidemiology, risk and clinical manifestations – of dengue in European travellers in the setting of the global emergence of the disease based on data provided by the European Network on Imported Infectious Disease Surveillance (TropNetEurop) and the German Surveillance Network (SIMPID).

Surveillance of dengue in Europe

Dengue fever is currently not reported in most European public health systems. Our knowledge about the incidence and risk of dengue in travellers is based on a small number of systematic studies.

The European Network on Imported Infectious Disease Surveillance (TropNetEurop) was founded in 1999 in order to detect emerging infections of potential regional, national or global impact at their point of entry into the European population. From the very beginning, dengue has been a disease of concern to the network. This has recently resulted in a publication elsewhere[13]. Briefly, TropNetEurop is the largest network for the surveillance of travel-acquired diseases worldwide and currently consists of 47 clinical member-sites in most West and Central European countries[14]. Although the organization does not guarantee that collected data will be representative for Europe, most major referral centres of the

continent are represented and cover approximately 63,000 patients post-travel and 220,000 pre-travel advices annually. The data on which this article is based were collected by single member sites and submitted by standardized questionnaires to the TropNetEurop coordination centre. The present analysis includes cases of dengue infections reported from January 1999 through December 2002.

For a broader overview, we also included data of SIMPID, a similarly designed national surveillance network in Germany for imported infectious diseases. The network is linked to TropNetEurop and currently consists of 51 participating member sites. Data have been collected within this network since May 2001.

Case reports from both networks name the most accurate diagnostic procedure applied to derive the diagnosis, which was used to distinguish "suspected", "probable" and "confirmed" dengue infections according to the WHO classifications[15]. For a diagnosis of "confirmed" dengue, the virus was detected by viral isolation, PCR, or a fourfold or greater change in reciprocal IgM or IgG antibody titres in paired serum samples. The "probable" diagnosis of dengue was supported by a single positive IgM antibody test on a late acute or convalescent-phase serum specimen only. A variety of test kits were used by the reporting centres, all of which are established and widely used assays. "Suspected" cases lacked supportive serology, and diagnosis was based entirely on clinical features and travel history. In the following analysis, only cases of confirmed or probable dengue infection were included.

Epidemiology of dengue in travellers

Between January 1999 and December 2002, an overall 562 cases with a diagnosis of dengue or dengue haemorrhagic fever were reported to the TropNetEurop and SIMPID coordination centre, of which 483 (86%) were assigned either as laboratory-confirmed (n=411) or as probable (n=72). The total number of the annually reported dengue cases in these two networks increased from 39 cases in 1999 to 208 cases in 2002. However, the increase has to be attributed primarily to the increased number of reporting sites of the networks rather than to an increased incidence of dengue infections in travellers.

Figure 1 shows the frequencies of dengue cases reported per month between January 1999 and December 2002. Besides the increase of total numbers of dengue cases, we noted a peak of 38 cases in April 2002. During this month, 70% of all cases were imported from Thailand.

Travel history within two weeks before illness was available in most of the patients. Figure 2 and Table 1 demonstrate frequencies and percentages of imported dengue cases per country or region where the infection had been acquired. A high percentage of dengue cases (45%) was acquired by patients who travelled to countries in South-East Asia, 91 cases (19%) were imported from the South and Central America, 77 cases (16%) from the Indian subcontinent, 56 cases (12%) from the Caribbean and 38 cases (8%) from Africa.

Figure 1. ***Dengue-infections reported within the networks of TropNetEurop and SIMPID between January 1999 and December 2002 (n = 483)***

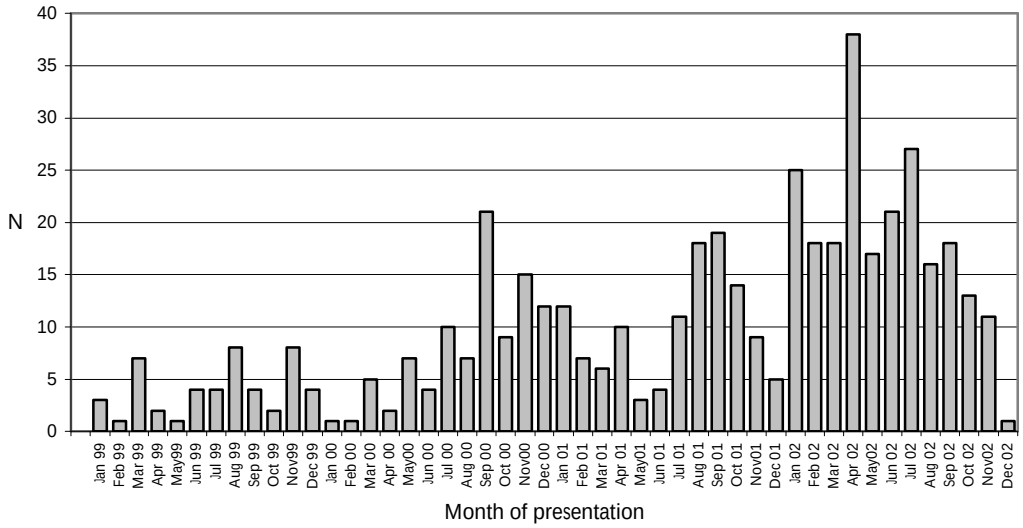

Figure 2. ***Countries in which travellers acquired dengue infection by percentage of total (n = 465) reported cases***

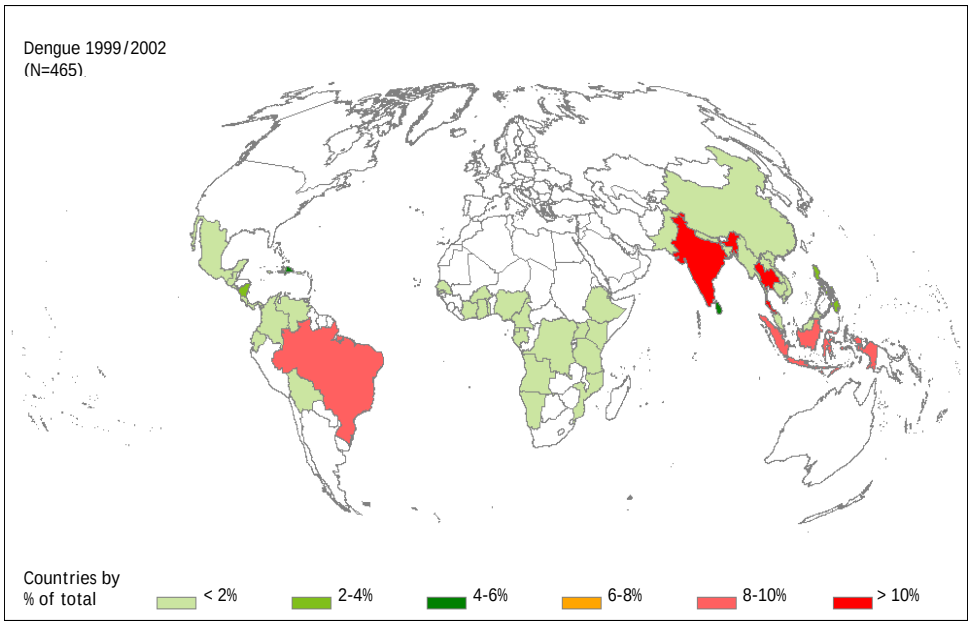

Table 1. *Frequencies of travel-acquired dengue infections by region of travelling (n = 481)*

Region of infection	No. of patients (%)
Africa	38 (8)
South/Central America	91 (19)
The Caribbean	56 (12)
Indian subcontinent	77 (16)
South-East Asia and Oceania	219 (45)

This distribution mainly reflects the global dengue activity which is known to be the highest in South-East Asia, followed by the Americas and the Caribbean islands. The surveillance for dengue in Africa is poor. Therefore, the fact that 8% of all dengue infections are reported in travellers returning from Africa underlines the need that dengue should also be included as a differential diagnosis for fever in travellers returning from this continent.

Furthermore, this distribution also reflects the popularity of the countries as a tourist destination. Thailand, Viet Nam and Indonesia are not only high-endemic areas of dengue viruses, but also the countries with an expanding tourism sector. Thailand alone was responsible for 134 cases (28%) of all travel-acquired dengue infections over the past four years in our networks. In contrast, the surprising decrease of reported dengue infections in travellers returning from India (from 18% in 2001 to 4% in 2002) might reflect, in addition to other factors (such as low epidemicity), its decreased popularity as a tourist destination, as there was a 6.6% decrease in international tourist arrivals reported by the World Tourism Organization for India in 2002[8].

Overall, many confounding factors will have an influence on the epidemiology of travel-acquired dengue: activity and possibly variations in the virulence of dengue viruses, vector activity, both related and seasonally distributed with an irregular occurrence of outbreaks on one side and the activity of travelling on the other.

Only few data are available in literature about the risk in travellers to acquire dengue infection. Several research groups have studied the rates of dengue infections in travellers, but most of them focused on febrile patients presenting with symptoms at a clinical site. A retrospective study performed among a small cohort of Swiss travellers with fever showed a surprisingly high prevalence (8%) of antibodies to dengue virus[16]. A prospective study performed in 130 returned febrile German travellers revealed rising dengue antibodies in 6.9% [17]. Among the 335 febrile travellers presenting at a different German travel clinic, 13 (3.9%) cases of DF were laboratory-confirmed[12].

Incidence rates might change in cases of outbreaks: An extensively 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[18].

Of great interest were two prospective studies performed in travellers by collecting serum samples before and after travel. One study was performed in 104 long-term travellers from Israel to various dengue endemic countries which revealed a dengue seroconversion in 6.7% of all travellers with a median of 5.3 months stay abroad, and three out of seven infections were asymptomatic[19]. The other study was

performed in Dutch short-term travellers with destinations to endemic areas in Asia and demonstrated an incidence rate of 30/1,000 person-month. The clinical-to-subclinical infection ratio was 1:3.3[20].

All results showed that dengue infection is a realistic threat not limited only to long-term travellers to South-East Asia. In outbreaks, high attack rates might occur, with variable clinical to 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) in the disease severity. Two prospective studies on dengue seroconversion in travellers showed that a high percentage of infections might occur asymptomatically, a phenomenon that has been described in immune and non-immune populations – both adults and children – in Thailand and during outbreaks in Cuba[21,22]. Furthermore, in a certain percentage of travellers, the course of the disease will occur entirely during the stay in the endemic country, since the incubation period for dengue infection is relatively short (typically 5 to 7 days) and the disease is self-limiting (typically after 4 to 6 days), and will therefore not be reported to health authorities at home[23,24]. Thus, only the tip of the iceberg is reported, making dengue infection one of the most under-reported tropical diseases in travellers.

Patients' characteristics

The vast majority of the 483 laboratory-confirmed or probable dengue cases reported to TropNetEurop and SIMPID were Europeans living in Europe (87%). Only 31 infections (6.4%) were reported in immigrants, and 14 cases (2.9%) in foreign visitors. The major purpose of travel for Europeans was tourism (82%), followed by business (5%) and missionary work (4%). Immigrants were mostly infected during visits to their former home country (74%).

The median age in our population was 32 years (range 1–69 years). Males were slightly more frequently affected with a male to female ratio of 1.2:1.

The median duration of travel, during which subjects acquired the dengue infection, decreased from 38 days (range 10–880 days) in 1999 to 23 days (range 3–1,825 days) in 2002.

Since our data were passively collected in symptomatic patients who presented at one of the networks' clinical member sites, we are not able to extrapolate any particular risk factors to acquire dengue infection during travel, but travel destination as well as duration of travel tend to be associated with risk.

One of the two above-mentioned prospective studies on seroconversion was not able to show any association of developing dengue-like illness with age, sex, travel destination and season, but subjects were only included when travelling to Asia[20]. The other study performed among long-term Israeli travellers revealed a trend of higher risk when travelling to South-East Asia, and during the summer season[19].

Clinical manifestations

Dengue virus infection may be asymptomatic as described above or may lead to undifferentiated febrile illness (viral syndrome), dengue fever (DF), or dengue haemorrhagic fever (DHF) with or without shock, depending largely on age and immunological conditions[25,26].

Generally, dengue haemorrhagic fever occurs rarely in travellers, but several cases have been reported[27,28,29,30]. In our population, 470 cases were reported as classical dengue fever and 13 as dengue haemorrhagic fever (incidence rate of DHF-cases/100 dengue infections: 2.7). Out of 465 travellers with dengue infection, 421 (91%) were reported to have fever, 63% suffered from headache, 52% from muscle or joint pain, 42% from fatigue, 23% complained of diarrhoea, and 34% developed a macular or a maculopapular rash (Table 2). The presented clinical manifestations refer mainly to Caucasian adults with DF and therefore differ in several aspects from that in children in endemic countries with DF or DHF[5].

Table 2. *Signs and symptoms of travel-acquired dengue infections in 465 Europeans and immigrants (multiple entries possible)*

Symptom	No. of patients (%)
Fever	421 (91)
Headache	295 (63)
Myalgia or arthralgia	241 (52)
Fatigue	197 (42)
Rash	158 (34)
Diarrhoea	106 (23)
Vomiting	55 (12)
Lymphadenopathy	31 (7)
Respiratory symptoms	29 (6)
ENT symptoms	28 (6)
Neurological symptoms	12 (3)
Psychological symptoms	7 (2)
Other symptoms	70 (15)

In our network, it is optional to report clinical details of complications associated with the notified disease. Therefore, only limited data on this issue were available. Interestingly, there were two reports on dengue infection associated with ocular involvement, one resulting in prolonged visual impairment[31].

In eight cases, the subjects were reported to have dengue infection with hepatic involvement (reported as hepatitis or highly elevated liver enzymes). Most certainly, this manifestation is by far underreported, since liver function abnormalities seem to be quite common in dengue with aspartate aminotranferase (AST) higher than alanine aminotransferase (ALT). In a study of 275 patients with classical dengue fever in Taiwan, it was found that liver enzymes were increased in 93% of the cases, in 11% the elevation was tenfold or higher[32]. Other studies reported that the severity of liver involvement seems to be associated with disease severity[33,34]. In a series of 18 Israeli travellers with dengue, all had liver-function abnormalities[35].

In our population, the disease severity in most cases was mild to moderate. The majority of patients were treated as outpatients (n=355, 74%), while 125 (26%) were hospitalized due to an aggravation of clinical symptoms.

Dengue haemorrhagic fever and fatality in travellers

The pathogenesis of DHF is poorly understood, and several hypotheses have emerged to explain why DHF occurs in some individuals who are infected with dengue virus. The observations that classical dengue fever without complications occurs

in non-indigenous foreigners while DHF occurs in indigenous children, and that most aspects of the disease become prominent only after several days of illness when fever and viremia remit, support an immunological explanation for these phenomena: the so-called antibody-dependent enhancement theory[36,37,38,39,40,41].

Interestingly, from a traveller's point of view, cross-reactive heterotypic immunity has been reported to last between two and 12 months[42]. In infants, the dual role of maternal dengue antibodies has been demonstrated *in vivo* and *in vitro*: in the first six months, they protect infants from dengue infection, but at 7-8 months they cause a period of greatest risk to acquire DHF/DSS because of enhancing antibodies. Beyond this critical two-month period, further IgG degradation results in a decrease of infection-enhancing antibodies[39]. This observation would explain why DHF is rare in travellers.

However, a few cases of DHF have also been described in patients with primary dengue infection[27,30,43,44], as well as the absence of DHF despite hyperendemic dengue virus transmission[45,46]. Therefore, other hypotheses suggest that DHF/DSS results from infection by a more virulent serotype or strains within serotypes of the virus[41,47,48]. A third theory proposes cross-reactive T cells to cause tissue damage and cytokine secretion[49].

Over a period of four years, 13 cases of DHF have been reported to our networks (2.7% of all dengue infections). Interestingly, the history of travel revealed that the infection was acquired in all endemic regions: seven in South-East Asia, two in Central America, two in South America, one on the Indian subcontinent, and one in Central Africa.

While nine cases of DHF were found in a total of 437 travellers of European origin (2%), four cases of DHF occurred in a total of 45 foreign visitors or immigrants (9%). Therefore, in our population, immigrants or foreign visitors were 4.3 times at higher risk to present with manifestations of dengue haemorrhagic fever when compared with European travellers (95% CI: 1.4–13.5, p-value 0.025). The median travel duration in patients with DHF was 29 days and was not significantly longer compared with patients who developed DF (26 days, p-value 0.38).

No deaths occurred among the 483 reported patients. Since TropNetEurop is also used as a platform for information exchange and discussions by the e-mail system, three fatal cases of dengue in Europe have been reported to the network from sources outside its immediate membership. The first one occurred in 1997 in the United Kingdom and was not published. The other two patients died of DHF in 2002: a Bangladeshi immigrant living in the United Kingdom who returned after visiting his homeland[30], and a young Finnish journalist travelling in South-East Asia (publication in progress).

Conclusion

Even though there is considerable lack of data regarding the actual frequency of dengue infection in international travellers, increasing reports of travel-acquired dengue and first fatal cases indicate that dengue infection is a real threat also to travellers[50]. The dramatic increase in the number of international travellers to tropical countries and the increased incidence of dengue fever and dengue haemorrhagic fever as well as epidemics of both are two major factors responsible for the increased risk to travellers. The shift in age distribution

towards elderly patients in DHF populations of South-East Asia[51,52] and increasing reports on unusual clinical manifestations[53,54,55,56,57] may reflect variations in the virulence of dengue viruses and will, therefore, also have an impact on the course of travel-acquired dengue.

The development of a live attenuated tetravalent dengue vaccine is currently the best strategy to obtain a vaccine against dengue viruses[58,59,60]. Vaccine trials with several candidates are under way, but the necessity of a durable protective immunity to all four serotypes is posing a difficult challenge to researchers.

As long as a vaccine is commercially not available, the single most effective measure of dengue prevention for travellers is to avoid mosquito bites by using insect repellents and protective clothes. *Aedes* mosquitoes are most active in early mornings and late afternoons.

Health care providers should consider dengue in the differential diagnosis for patients recently returned from endemic areas. Serological techniques provide the tools for screening and confirming the diagnosis, but seroconversion occurs most often after the cessation of clinical symptoms; thus, negative IgM results during the first week of the illness period are inconclusive. Pre-vaccinations in travellers against Japanese encephalitis and yellow fever might decrease the specificity of the IgG assays[12,41,61,62].

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References

1. Rigau-Pérez JG, Clark GG, Gubler DJ, Reiter P, Sanders EJ and Vorndam AV. Dengue and dengue haemorrhagic fever. Lancet, 1998, 352: 971-977.
2. Rico-Hesse R. Molecular evolution and distribution of dengue viruses type 1 and 2 in nature. Virology, 1990, 174: 479-493.
3. Gubler DJ. Epidemic dengue/dengue haemorrhagic fever: A global public health problem in the 21st century. In: World Health Organization, the South-East Asia and Western Pacific Region. Dengue Bulletin, 1997, 21: 1-13.
4. Pinheiro F and Nelson M. Re-emergence of dengue and emergence of dengue haemorrhagic fever in the Americas. In: World Health Organization, the South-East Asia and Western Pacific Regions. Dengue Bulletin, 1997, 21: 16-23.
5. World Health Organization. Dengue haemorrhagic fever. Diagnosis, treatment, prevention and control, 2nd ed. Geneva: WHO, 1997: 12-23.

6. Gibbons RV and Vaughn DW. Dengue: An escalating problem. British Medical Journal, 2002, 324: 1563-6.
7. Monath TP. Dengue: The risk to developed and developing countries. Proceedings of the National Academy of Science USA, 1994, 91: 2395-2400.
8. World Tourism Organization. Preliminary tourism statistics for 2002. Madrid: 2003. http://www.world-tourism.org (accessed 2nd Feb 2003).
9. Centre of Disease Control, CDC. Imported dengue – United States, 1997 and 1998. Morbidity and Mortality Weekly Report, 2000, 49: 248-253.
10. Suh KN, Kozarsky PE and Keystone JS. Evaluation of fever in the returned traveller. Medical Clinics of North America, 1999, 83: 997-1017.
11. O'Brien D, Tobin S, Brown GV and Torres J. Fever in returned travellers: Review of hospital admissions for a 3-year period. Clinical Infectious Diseases, 2001, 33: 603-609.
12. Stephan C, Allwinn R, Brodt HR, Knupp B, Preiser W and Just-Nübling G. Travel-acquired dengue infection: Clinical spectrum and diagnostic aspects. Infection, 2002, 30: 225-228.
13. Jelinek T, Mühlberger N, Harms G, Corachán MP, Knobloch J, Bronner U, Laferl H, Kapaun A, Bisoffi Z, Clerinx J, Puente S, Fry G, Schulze M, Hellgren U, Grørup I, Chalupa P, Hatz C, Matteelli A, Schmid M, Nielsen LN, da Cunha S, Atouguia J, Myrvang B and Fleischer K for the European Network on Surveillance of Imported Infectious Diseases. Epidemiology and clinical features of imported dengue fever in Europe: Sentinel surveillance data from TropNetEurop. Clinical Infectious Diseases, 2002, 35: 1047-1052.
14. The European Network on Imported Infectious Disease Surveillance (TropNetEurop). http://www.tropnet.net (accessed 15th Feb 2003).
15. World Health Organization. Dengue haemorrhagic fever. Diagnosis, treatment, prevention and control, 2nd ed. Geneva: WHO, 1997: 12-23.
16. Settah SG, Vernazza PL, Morant R and Schultze D. Imported dengue fever in Switzerland – Serological evidence for a hitherto unexpectedly high prevalence. Schweizer Medizinische Wochenschrift, 1995, 125: 1673-1678.
17. Jelinek T, Dobler G, Hölscher M, Löscher T and Nothdurft HD. Prevalence of infection with dengue virus among international travelers. Archives of Internal Medicine, 1997, 157: 2367-2370.
18. Lyerla R, Rigau-Perez JG, Vorndam AV, Reiter P, George AM, Potter IM and Gubler DJ. A dengue outbreak among camp participants in a Caribbean island, 1995. Journal of Travel Medicine, 2000, 7: 59-63.
19. Potasman I, Srugo I and Schwartz E. Dengue seroconversion among Israeli travellers to tropical countries. Emerging Infectious Diseases, 1999, 5: 824-827.
20. Cobelens FGJ, Groen J, Osterhaus ADME, Leentvaar-Kuipers A, Wertheim-van Dillen PME and Kager PA. Incidence and risk factors of probable dengue virus infection among Dutch travellers to Asia. Tropical Medicine and International Health, 2002, 7: 331-338.
21. Burke DS, Nisalak A, Johnson DE and Scott RM. A prospective study of dengue infection in Bangkok. American Journal of Tropical Medicine and Hygiene, 1988, 38: 172-180.
22. Guzman MG, Kouri GP, Bravo J, Soler M, Vazquez S and Morier L. Dengue haemorrhagic fever in Cuba, 1981: A retrospective seroepidemiologic study. American Journal of Tropical Medicine and Hygiene, 1990, 42: 179-184.
23. Schwartz E, Moskovitz A, Potasman I, Peri G, Grossman Z and Alkan ML. Changing epidemiology of dengue fever in travellers to Thailand. European Journal of Clinical Microbiology and Infectious Diseases, 2000, 19: 784-786.
24. Thavara U, Tawatsin A, Phan-Urai P, Ngamsuk W, Chansang C, Mingtuan L and Zhijun L. Dengue vector mosquitoes at a tourist attraction, Ko Samui, in 1995. South-East Asian Journal of Tropical Medicine and Hygiene, 1996, 27: 160-163.
25. 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.
26. Kalayanarooj S, Vaughn DW, Nimmannitya S, Green S, Suntayakorn S, Kunentrasai N, Viramitrachai W, Ratanachu-eke S, Kiatpolpoj S, Innis BL, Rothman AL, Nisalak A and Ennis FA. Early clinical and laboratory indicators of acute dengue illness. Journal of Infectious Diseases, 1997, 176: 313-321.
27. Morens DM, Sather GE, Gubler DJ, Rammohan M and Woodall JP. Dengue shock syndrome in an American traveller with primary dengue 3 infection. American Journal of Tropical Medicine and Hygiene, 1987, 36: 424-426.

28. Lopez-Velez R, Perez-Casas C, Vorndam AV and Rigau J. Dengue in Spanish travelers returning from the tropics. European Journal of Clinical Microbiology and Infectious Diseases, 1996, 15: 823-836.

29. Wittesjo B, Eitrem R and Niklasson B. Dengue fever among Swedish tourists. Scandinavian Journal of Infectious Diseases, 1993, 25: 699-704.

30. Lawn SD, Tilley R, Lloyd G, Finlayson C, Tolley H, Newman P, Rice P and Harrison TS. Dengue haemorrhagic fever with fulminant hepatic failure in an immigrant returning to Bangladesh. Clinical Infectious Diseases, 2003, 37: e1-4.

31. Haritoglou C, Dotse SD, Rudolph G, Stephan CM, Thurau SR and Klauß V. A tourist with dengue fever and visual loss. Lancet, 2002, 360: 1070.

32. Kuo CH, Tai DI, Chang-Chien CS, Lan CK, Chiou SS and Liaw YF. Liver biochemical tests and dengue fever. American Journal of Tropical Medicine and Hygiene, 1992, 47: 265-270.

33. Wahid SF, Sanusi S, Zawawi MM and Ali RA. A Comparison of the pattern of liver involvement in dengue haemorrhagic fever with classic dengue fever. South-East Asian Journal of Tropical Medicine and Public Health, 2000, 31: 259-263.

34. Murgue B, Deparis X, Chungue E, Cassar O and Roche C. Dengue: An evaluation of dengue severity in French Polynesia based on an analysis of 403 laboratory-confirmed cases. Tropical Medicine and International Health, 1999, 4: 765-773.

35. Schwartz E, Mendelson E and Sidi Y. Dengue fever among travelers. American Journal of Medicine, 1996, 101: 516-520.

36. Kliks SC, Nisalak A, Brandt WE, Wahl L and Burke DS. Antibody-dependent enhancement of dengue virus growth in human monocytes as a risk factor for dengue haemorrhagic fever. American Journal of Tropical Medicine and Hygiene, 1989, 40: 444-451.

37. Sangkawibha N, Rojanasuphot S, Ahandrik S, Viriyapongse S, Jatanasen S, Salitul V, Phanthumachinda B and Halstead SB. Risk factors in dengue shock syndrome: A prospective epidemiologic study in Rayong, Thailand. American Journal of Epidemiololy, 1984, 120: 653-669.

38. Thein S, Aung MM, Shwe TN, Aye M, Zaw A, Aye K, Aye KM and Aaskov J. Risk factors in dengue shock syndrome. American Journal of Tropical Medicine and Hygiene, 1997, 56: 566-572.

39. Kliks SC, Nimmanitya S, Nisalak A and Burke DS. Evidence that maternal dengue antibodies are important in the development of dengue haemorrhagic fever in infants. American Journal of Tropical Medicine and Hygiene, 1988, 38: 411-419.

40. Halstead SB. Pathogenesis of dengue: Challenges to molecular biology. Science, 1988, 239: 476-481.

41. Vaughn DW, Green S, Kalajanarooj S, Innis BL, Nimmannitya S, Suntayakorn S, Rothman AL, Ennis FA and Nisalak A. Dengue in the early febrile phase: Viremia and antibody responses. Journal of Infectious Diseases, 1997, 176: 322-330.

42. Nimmannitya S. Dengue fever and dengue haemorrhagic fever. In: Manson´s Tropical Diseases. 20th ed. London, 1996: 721-729.

43. Gubler DJ, Reed D, Rosen L and Hitchcock JC. Epidemiological, clinical, and virologic observations on dengue in the Kingdom of Tonga. American Journal of Tropical Medicine and Hygiene, 1978, 27: 581-589.

44. Barnes WJS and Rosen L. Fatal haemorrhagic disease and shock associated with primary dengue infection on a Pacific island. American Journal of Tropical Medicine and Hygiene, 1974, 23: 495-506.

45. Halstead SB, Streit TG, Lafontant JG, Putvatana R, Russell K, Sun W, Kanesa-Thasan N, Hayes CG and Watts DM. Haiti: Absence of dengue haemorrhagic fever despite hyperendemic dengue virus transmission. American Journal of Tropical Medicine and Hygiene, 2001, 65: 180-183.

46. Watts DM, Porter KR, Putvatana P, Vasquez B, Calampa C, Hayes CG and Halstead SB. Failure of secondary infection with American genotype dengue 2 to cause dengue haemorrhagic fever. Lancet, 1999, 354: 1431-1434.

47. Leitmeter KC, Vaughn DW, Watts DM, Salas R, de Chacon IV, Ramos C and Rico-Hesse R. Dengue virus structural differences that correlate with pathogenesis. Journal of Virology, 1999, 73: 4738-4747.

48. White NJ. Variation in virulence of dengue virus. Lancet, 1999, 23: 1401-1402.

49. Loke H, Bethell DB, Phuong CXT, Dung M, Schneider J, White NJ, Day NP, Farrar J and Hill AVS. Strong HLA Class I-Restricted T cell responses in dengue haemorrhagic fever: A double-edged sword? Journal of Infectious Diseases, 2001, 184: 1369-1373.

50. Jelinek T. Dengue fever in international travelers. Clinical Infectious Diseases, 2000, 31: 144-147.

51. Nimmannitya S. Dengue haemorrhagic fever in Thailand. South-East Asian Journal of Tropical Medicine and Public Health, 1987, 18: 292-294.

52. Hadinegoro SR and Nathin MA. The changing patterns of clinical manifestations in dengue haemorrhagic fever: Ten years observations. South-East Asian Journal of Tropical Medicine and Public Health, 1990, 21: 694.

53. Nimmannitya S, Thisyakorn U and Hemsrichart V. Dengue haemorrhagic fever with unusual manifestations. South-East Asian Journal of Tropical Medicine and Public Health, 1987, 18: 398-406.

54. Sirivichayakul C, Sabcharoen A, Chanthavanich P, Pengsaa K, Chokejindachai W and Prarinyanupharb V. Dengue infection with unusual manifestation: A case report. Journal of the Medical Association of Thailand, 2000, 83: 325-329.

55. Pancharoen C, Kulwichit W, Tantawichien T, Thisyakorn U and Thisyakorn C. Dengue infection: A global concern. Journal of the Medical Association of Thailand, 2002, 85 (Suppl 1): S25-S33.

56. Solomon T, Dung NM, Vaughn DW, Kneen R, Thao LTT, Raengsakulrach B, Loan HT, Day NPJ, Farrar J, Myint KSA, Warrell MJ, James WS, Nisalak A and White NJ. Neurological manifestations of dengue infection. Lancet, 2000, 355: 1053-1059.

57. Cam BV, Fonsmark L, Hue NB, Phuong NT, Poulsen A and Heegaard ED. Prospective case-control study of encephalopathy in children with dengue haemorrhagic fever. American Journal of Tropical Medicine and Hygiene, 2001, 65: 848-851.

58. Bhamarapravati N and Sutee Y. Live attenuated tetravalent dengue vaccine. Vaccine, 2000, 18: 44-47.

59. Kanesa-thasan N, Sun W, Kim-Ahn G, Van Albert S, Putnak JR, King A, Raengsakulsrach B, Christ-Schmidt H, Gilson K, Zahradnik JM, Vaughn DW, Innis BL, Saluzzo JF and Hoke Jr CH. Safety and immunogenicity of attenuated dengue virus vaccines (Aventis Pasteur) in human volunteers. Vaccine, 2001, 19: 3179-3188.

60. Sabchareon A, Lang J, Chanthavanich P, Yoksan S, Forrat R, Attanath P, Sirivichayakul C, Pengsaa K, Pojjaroen-Anant C, Chokejindachai W, Jagsudee A, Saluzzo SF and Bhamarapravati N. Safety and immunogenicity of tetravalent live-attenuated dengue vaccines in Thai adult volunteers: Role of serotype concentration, ratio and multiple doses. American Journal of Tropical Medicine and Hygiene, 2002, 66: 264-272.

61. Schwartz E, Mileguir F, Grossmann Z and Mendelson E. Evaluation of ELISA-based sero-diagnosis of dengue fever in travelers. Journal of Clinical Virology, 2000, 19: 169-173.

62. Innis BL, Nisalak A, Nimmannitya S, Kusalerdchariya S, Chongswasdi V, Suntayakorn S, Puttisri P and Hoke CH. An enzyme-linked immunosorbent assay to characterize dengue infections where dengue and Japanese encephalitis co-circulate. American Journal of Tropical Medicine and Hygiene, 1989, 40: 418-427.