MAJOR ARTICLE

Epidemiology and Clinical Features of Imported Dengue Fever in Europe: Sentinel Surveillance Data from TropNetEurop

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Travelers have the potential both to acquire and to spread dengue virus infection. The incidence of dengue fever (DF) among European travelers certainly is underestimated, because few centers use standardized diagnostic procedures for febrile patients. In addition, DF is currently not reported in most European public health systems. Surveillance has commenced within the framework of a European Network on Imported Infectious Disease Surveillance (TropNetEurop) to gain information on the quantity and severity of cases of dengue imported into Europe. Descriptions of 294 patients with DF were analyzed for epidemiological information and clinical features. By far the most infections were imported from Asia, which suggests a high risk of DF for travelers to that region. Dengue hemorrhagic fever occurred in 7 patients (2.4%) all of whom recovered. Data reported by member sites of the TropNetEurop can contribute to understanding the epidemiology and clinical characteristics of imported DF.

Dengue fever (DF) is endemic in most tropical parts of the world, many of which are popular tourist destinations. The incidence of epidemic and endemic dengue has increased substantially, notably in the Americas, where, since 1977, various epidemics have occurred [1–4]. It is estimated that the current annual global incidence of dengue infection is 50–100 million patients per year [5]. Among the factors that have been implicated in the current increase in the incidence 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 [6].

Structured data on the epidemiology and clinical course of dengue infection in travelers are rare. Al-

Received 4 March 2002; revised 6 June 2002; electronically published 10 October 2002.

Financial support: Dr. Democh Maurmeier Stiftung and the Förderprogramm für Forschung und Lehre der Medizinischen Fakultät, Ludwig-Maximilians-University, Munich, Germany.

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Clinical Infectious Diseases 2002; 35:1047–52

1058-4838/2002/3509-0004$15.00

though case reports on imported dengue are relatively frequent, they do not allow for an estimation of the risk of illness for travelers. Various case reports regarding dengue infections in international travelers returning from areas of endemicity have been published [2, 4, 7–13]. In a small number of systematic studies on this topic, serological evidence of recent dengue infection was found in 7%–45% of febrile patients after they had returned from areas of endemicity [14–17]. A retrospective study of a small cohort of Swiss travelers showed a surprisingly high prevalence of antibodies to dengue virus (8%) among symptomatic patients [18]. These results were supported further by a prospective study of 130 febrile patients who had returned from areas where dengue is endemic, which found a prevalence of 6.9% [16]. In the latter study, 9 of 10 patients who tested positive for dengue had acquired the infection in Southeast Asia. Similar to the sparse data on the true incidence of DF among travelers, little is known about the clinical spectrum of DF and the proportion of subclinical infections in this group. Studies from areas of endemicity suggest that 14%–87% of all dengue infections manifest few or atypical symptoms [19–21]. Yet the proportion of subclinical dengue infections among travelers is of importance, because it has been suggested that infection with one serotype of dengue virus can predispose for the development of dengue hemorrhagic fever (DHF) and/or dengue shock syndrome on reinfection with another serotype [22].

The lack of surveillance data for imported cases of infectious diseases in Europe prompted the founding in February 1999 of the European Network on Imported Infectious Disease Surveillance (TropNetEurop), which is an electronic network of clinical sites related to imported infectious diseases. The network is designed to effectively detect emerging infections of potential regional, national, or global impact at their point of entry into the European population. Sentinel surveillance reporting is carried out by participating sites by use of a standardized and computerized reporting system. Immediate transmission of anonymous patient and laboratory data to the central database ensures the timely detection of sentinel events. Membership is voluntary and self-selected by participating centers and is monitored by the steering committee of the network. Although the organization of the network does not guarantee that data collected will be representative for Europe, most major referral centers on the continent are represented: there are 37 clinical sites throughout 14 European countries. From the beginning, DF has been one of the major targets for this network. The present article summarizes results from the first years of sentinel surveillance for imported DF.

PATIENTS, MATERIALS, AND METHODS

Member sites of the imported infectious disease network TropNetEurop treat ~51,000 patients per year. During the 3-year period from January 1999 through December 2001, 294 patients with DF were reported by 24 sites within the network. The final diagnosis was qualified in every patient by the reporting center, which stated the diagnosis as "suspected," "probable," or "confirmed." For a diagnosis of "confirmed" dengue, the virus was detected by isolation or immunohistochemical analysis of necropsy tissue specimens or a type-specific plaque-reduction neutralization test revealed at least a 4-fold increase in antibody titers [23]. A variety of test kits were used by the reporting centers, all of which are established and widely used assays. In-house kits were not used. In all serological methods, cross-reactions with other flaviviruses might have interfered with results, with the ELISA method being particularly vulnerable. Yellow fever vaccination, especially, may play a crucial role here, since many travelers to areas where dengue is endemic also receive that vaccine before departure. Cases for which samples were positive for IgM antibody alone were reported as "probable" dengue infections. "Suspected" infections had the diagnosis established on clinical grounds only. A standardized, anonymous questionnaire was used for data collection. Reported case patients were sorted according to the following 2 categories: (1) patient classification (immigrant/refugee, foreign visitor, European living in Europe, or European living outside Europe) and (2) reason for travel (tourism, business, immigration, military, research/education, missionary/volunteer/humanitarian aid, visiting relatives/friends, or other). Travel and case histories were analyzed for clinical and epidemiological features of the infection. Individual data points were stored in a computerized database (Access; Microsoft) and were analyzed by means of SAS (SAS Institute). Patients with a diagnosis of suspected dengue infection were excluded from the present analyses. Analyses with a clinical end point also excluded patients with multiple infections.

RESULTS

Of the 309 reported patients with DF during the period evaluated, 294 had no other diagnosis reported; 212 (72.1%) had confirmed cases, according to the definition used by the surveillance network. A further 26 patients (8.8%) were classified as having probable cases, and 25 (8.5%) as having suspected cases. The diagnosis status was unknown for 26 patients (8.8%). Patients with suspected dengue and those with unknown diagnostic status were excluded from further analysis. Men constituted the majority (166 patients [56.5%]). The average age of all reported patients was 35.5 years (median, 34 years; range, 1–68 years). The overwhelming majority of patients (252 [85.7%]) were classified as Europeans; 240 patients (81.6%) were living in Europe, and 12 (4.1%) were living elsewhere. Only small proportions of patients were foreign visitors (11 [3.7%]) or immigrants (19 [6.5%]). No classification was pro-

vided for 1 patient (0.3%). Reasons for travel differed for Europeans and immigrants: the former traveled for tourism (77.5% of patients), business reasons (9.2%), missionary work (5.8%), research (3.3%), visits to relatives or friends (2.1%), or other reasons; for the small group of immigrants, reasons for travel were visits to relatives or friends (79% of patients), immigration (15.8%), or tourism (5.2%).

Geographical regions of infection with DF are shown in figure 1. Indonesia and South and Southeast Asia were by far the largest contributors of patients, followed by the Americas. The temporal distribution of cases of dengue imported into Europe is shown in figure 2. The total number of observations increased during the 3-year reporting period, and the proportions of such cases imported from certain areas also changed during that time. The proportion of patients with cases acquired in Southeast Asia increased from 20.7% in 1999 to 35.5% in 2001, and a similar tendency was observed for patients with cases acquired in India (from 17.2% in 1999 to 21.8% in 2001). The proportion of patients with cases acquired in the Americas decreased from 31% in 1999 to 16.2% in 2001. Of the 269 patients reported to have dengue only, 3.3% were reported to be asymptomatic. Symptom information was given for 250 patients; signs and symptoms are presented in table 1. The majority of patients had a combination of fever, headache, fatigue, and musculoskeletal symptoms (arthralgia and myalgia). However, a wide variety of other symptoms were frequently noted. Treatment was symptomatic for all patients; most patients (75.9%) received treatment as outpatients. Those patients who were admitted to a hospital stayed for an average of 5 days (range, 2–11 days). Clinical complications were reported in 8 (3.2%) of 250 patients. Five patients (2%) developed signs of DHF, with petechial bleeding and thrombocytopenia. Two of 10 patients had signs of hepatitis, 1 from an extended fatigue syndrome. All patients recovered.

DISCUSSION

DF is progressively making its way from being "one of the great neglected diseases of mankind" [24] toward being acknowledged as one of the world's major emerging infectious diseases. In 1998, a total of 558,000 infections and 15,000 deaths due to DF were reported by member states of the World Health Organization (WHO), which corresponds to a case-fatality rate of 2.7% [25]. Cases of DF are not notified to public health officials in most countries. As a consequence, actual numbers of both deaths and cases of disease due to dengue virus are

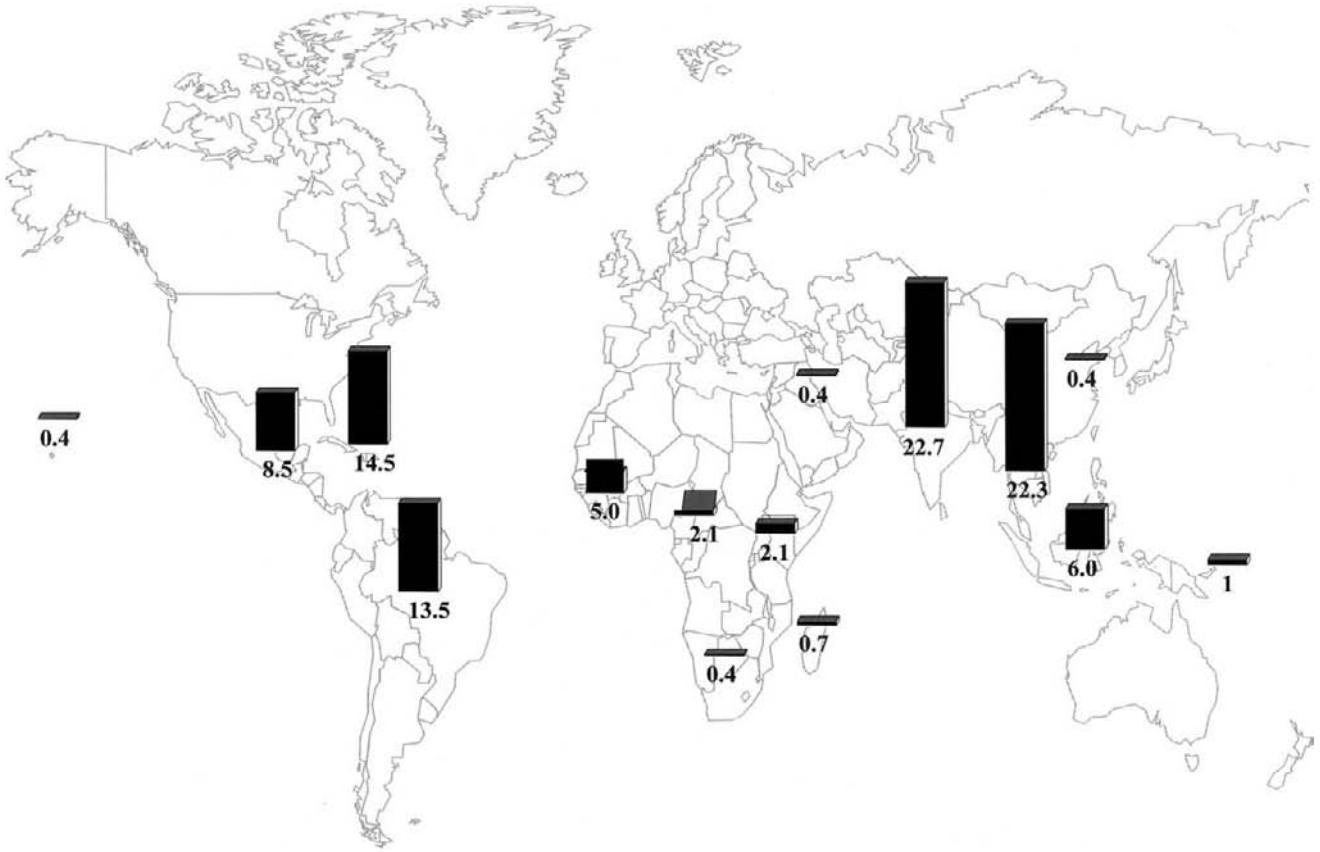

Figure 1. Geographical regions where dengue fever was acquired by 282 travelers living in Europe. Data are percentages.

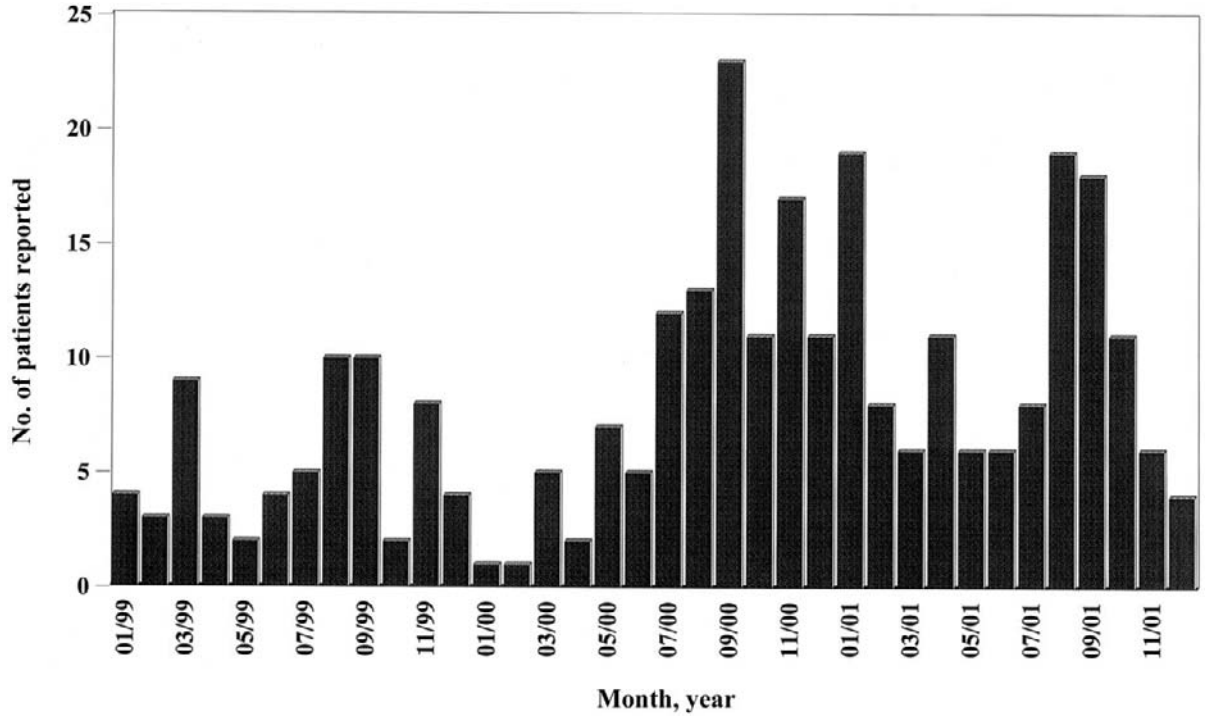

Figure 2. Patients with cases of dengue fever imported into Europe, by month and year reported. Months are indicated as numbers, years as the last 2 digits of the year.

certainly much higher than those reported to the WHO. The marked increase in the problems that dengue epidemics and endemics pose for tropical areas is reflected in travelers' increasing risk of acquiring the infection [26]. There is a considerable lack of data regarding the actual frequency of this infection among international travelers. The data presented here provide some insight into the epidemiology and clinical presentation of DF in travelers.

The overwhelming majority of patients who presented with DF were Europeans who traveled for tourism. Of patients with dengue who presented to TropNetEurop sites, those who had traveled to Asia were by far the highest percentage: 23.3% of patients had visited Southeast Asia, 22.9% had visited the Indian subcontinent, and 6.5% had visited Indonesia (figure 1). The proportion of patients who had acquired infection in the Americas was slightly smaller: 38.2% of all patients. One patient was reported who had acquired infection in Hawaii in 2000; this case heralded the later outbreak of DF on Maui [27]. It is difficult to derive risk estimates from these data. Numbers of patients reported throughout the network lack a true denominator, because no data are available regarding the travel activities of the general population to which the patients belong. A large number of patients returning from Asia with DF may only reflect increased travel activity to that continent and not an increased risk for infection. However, reports from the World Tourism Organization from 1999 and 2000 have shown that 16%–21% of European travelers visited Southeast Asia and only 6%–8% visited India [28, 29]. This suggests a comparatively high relative risk of acquiring DF in latter region, whereas numbers from Southeast Asia appear to reflect the high rate of tourism to that area. The low number of infections that were acquired in Africa is consistent with all previous epidemiological data [2, 4, 7–13]. The 2 African countries contributing the most patients were Ghana and Kenya, which, again, most likely reflects the travel habits of tourists.

There is no doubt that dengue importation into Europe shows a seasonal pattern (figure 2). Most likely, this reflects the migratory habits of European tourists rather than true variations in disease activity. The increase in the total number of dengue observations per year during the 3-year reporting period may simply reflect an increased awareness of the disease and its signs by the clinicians who are involved in TropNetEurop and who regularly receive its reports. Local changes in the incidence of dengue infection were considerable: the proportion of patients with cases acquired in East Asia increased from 20.7% in 1999 to 35.5% in 2001, and a similar tendency was observed for patients with cases acquired in India (17.2% in 1999 to 21.8% in 2001). The proportion of patients with cases acquired in the Americas decreased from 31% in 1999 to 16.2% in 2001. This may reflect changes in travel patterns, but reports from the World Tourism Organization do not indicate major shifts in the travel activity of Europeans away from the

Table 1. Signs and symptoms in 250 Europeans and immigrants with dengue fever.

Symptom	No. (%) of patients
Fever	215 (86)
Headache	148 (59.2)
Fatigue	108 (43.2)
Myalgia or arthralgia	106 (42.4)
Rash	73 (29.2)
Diarrhea	51 (20.4)
Vomiting	20 (8.0)
Respiratory complaints	15 (60)
Neurological complaints	6 (24)
Psychological complaints	5 (20)
Otitis	22 (8.8)
Genitourinary	3 (1.2)
Other	30 (12.0)

NOTE. Multiple entries are possible.

Americas and toward Asia [28, 29]. More likely, these numbers reflect the activity of dengue in the regions that European travelers frequent. Thus, an increase in the number of reports of DF in patients returning from an area of endemicity can serve as an early indicator of increased disease activity.

Symptoms commonly associated with dengue, such as fever, myalgia, arthralgia, and exanthema, can be helpful in making the diagnosis, when present, but the absence of typical symptoms does not exclude infection (table 1). Most patients with dengue in this study were symptomatic and reported fever and headache. Myalgias, fatigue, and rashes were common, as well as diarrhea. Thus, the diagnosis of dengue virus infection should be considered for patients who present with a broad variety of symptoms and who reside in or have recently traveled to dengue-endemic regions. Dengue has a short incubation period; thus, in this study, symptoms tended to begin before or just after the return from the journey (median, 1 day after return). The course of illness was benign in most patients. However, clinical complications consistent with DHF were reported in 5 patients (2%). These patients were treated on an inpatient basis; therapy included platelet substitution and intensive care management for 4 patients. Fortunately, all patients recovered.

In conclusion, the data reported by member sites of TropNetEurop can contribute to the understanding of the epidemiology and clinical characteristics of imported DF, especially since this infection is not notified to public-health officials in most European countries. It is obvious that the surveillance network cannot guarantee that data collected will be representative for Europe, because membership in the network is self-selected. However, in most European countries, medical services for immigrants and returning travelers are offered primarily at specialized centers. The capacity of the network to detect and report outbreaks within very short time has been demonstrated elsewhere [30]. Also, previous work has shown that the network oversees 10%–12% of all patients with imported infections in Europe [31]. It is also the only clinical network that collects data on imported infectious diseases throughout European. As such, the network has the capacity to provide valuable information for clinical practice and pretravel counseling. Continuous monitoring of reported data will add information on epidemiological changes in affected areas, which is urgently needed because of increasing travel activity and migration.

Acknowledgments

We thank all TropNetEurop site staff, who have been invaluable locally in collecting data. Financial support from Dr. Democh Maurmeier Stiftung and the Förderprogramm für Forschung und Lehre der Medizinischen Fakultät, Ludwig-Maximilians-University, Munich, Germany, is gratefully acknowledged.

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