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Dengue fever in travellers: A challenge for European physicians

Uditha Bulugahapitiya a, Sajith Siyambalapitiya a, Suranjith L. Seneviratne b, Devaka J.S. Fernando a,⁎

a Sherwood Forest Hospitals NHS Trust & University of Sheffield, United Kingdom
b Queens Medical Centre Nottingham, United Kingdom

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Abstract

Dengue fever (DF) is one of the world’s emerging infectious diseases. The steady increase in European tourists, as well as soldiers serving on peacekeeping duties, in endemic areas, coupled with the present resurgence of dengue, raises the risk of exposure for a large number of European travellers. Significant numbers of travellers have, in fact, developed DF. There is a risk of dengue haemorrhagic fever (DHF) in travellers who revisit the same place, and they have the potential not only to acquire, but also to spread, the dengue viral infection. Of concern is the potential for a dengue outbreak in a previously dengue-free country through imported cases. Another major concern is the potential area of dengue transmission, due to spread of its vectors through sizeable parts of southern Europe. In addition to the risk of haemorrhagic fever in returning tourists, the introduction of DF by returning travellers, whether they have symptoms or are unaffected by signs and symptoms of the disease, poses a threat to health systems in Europe.

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Keywords: Dengue fever; Dengue haemorrhagic fever; Haemorrhagic fever; Fever in travellers

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1. Introduction

Dengue fever (DF) is one of the world’s emerging infectious diseases, with a recorded prevalence in 101 countries [1,2]. Approximately 100 million cases of DF
occur annually, together with an estimated 250,000 hospi-
talized cases of dengue haemorrhagic fever and dengue
shock syndrome (DHF/DSS) officially noted, and a mortality
rate of 25,000 per year [3]. DF is endemic in most countries
of Southern and Southeast Asia, the Western Pacific regions,
Central and South America, the Caribbean and Africa
(Fig. 1). The incidence of epidemic and endemic dengue has
increased substantially, notably in the Americas, since 1977
and various epidemics have occurred [4–6]. In Latin
America, DHF was a rare disease before 1981. The 1980s
and 1990s saw a dramatic geographic expansion of epidemic
DF and DHF from Southeast Asia to the South Pacific
Islands, the Caribbean and Latin America, with regions
changing from non-endemic to hypo-endemic or hyper-
endemic [3]. Many of these endemic areas are popular tourist
destinations. The steadily increasing number of tourists
visiting endemic areas, coupled with the present resurgence
of dengue, has raised the risk of exposure for large number of
travellers [7]. DF is also an emerging problem for troops
deployed in dengue-endemic tropical countries [8].

2. Vector and organism

The disease is principally transmitted by the mosquitoes
*Aedes aegypti* and *Aedes albopictus*, both vectors that have
shown remarkable compliance to environmental changes by
human habitat [4]. *A. aegypti* is the principal vector, found
worldwide in the tropics and sub-tropics [3] (Fig. 1). The vector mosquitoes are daytime feeders, well adapted to an
urban environment. They breed in tires, cans and water jars
near human dwellings, and the females transmit the disease
readily because of their predilection for human blood and
habit of multiple interrupted feedings [9]. In many areas
where DF is endemic, policies for mosquito control are non-
existent or far from successful [1].

Among the factors that have been implicated in the
current extent of dengue are unplanned and uncontrolled
urbanization, overpopulation, crowding, poverty, a weak-
ened public health infrastructure and international journeys
that introduce new serotypes, genotypes and new strains to
different parts of the world [10].

DF is caused by a single-stranded, non-segmented
ribonucleic acid (RNA) virus of the family *Flaviviridae*
and genus *Flavivirus*. Humans are the main reservoir for the
dengue virus, although non-human primates in Asia and
Africa may also be infected [3]. Four distinct serotypes are
recognized: DEN-1, DEN-2, DEN-3 and DEN-4. Infection
with any of these viruses may be asymptomatic, may cause
self-limited febrile illness known as DF or, in a small
percentage of cases, may result in a life-threatening
syndrome, the so-called DHF/DSS [11]. Infection with one
serotype provides lifelong homologous immunity but only
transient cross-protection against other serotypes, thus
allowing a sequential infection with possible progression to
DHF/DSS. The pathogenesis of DHF/DSS is only partially
understood. Today, the majority view is that antibody-
dependent viral infection enhancement is the main mechanism responsible for inducing DHF/DSS associated with secondary dengue virus infection [11,12].

3. Symptoms and signs

In endemic areas, most patients with DF are either asymptomatic or present with mild febrile illness. The illness ranges from asymptomatic infection, through undifferentiated fever and benign DF, to severe haemorrhagic fever with or without shock syndrome [13].

3.1. Dengue fever

After an incubation period of 2–8 days of the infective mosquito bite, the disease usually begins with the sudden onset of fever and headache, typically accompanied by any of the following: chilliness, retro-orbital pain, photophobia, backache, severe muscle ache and arthralgia. High fever may sustain over 5–6 days. Also, flushed facies, lymph node enlargement, positive tourniquet test, petechiae, epistaxis and gastrointestinal bleeding may be observed. A rash, typically macular or maculopapular and often confluent with the sparing of small islands of normal skin, has been reported in about half of all infected persons and lasts for 2–4 days [14,15] (Fig. 3).

Very rare complications of DF include myocarditis, hepatitis, and encephalopathy and neuropathies [16]. Usually, convalescence occurs abruptly, but sometimes it may be prolonged for several weeks with associated asthenia [17].

Classical DF in travellers, although self-limiting and rarely fatal, can be incapacitating, may prevent one from travelling and may require hospitalization [16].

3.2. Dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS)

Four major clinical manifestations – high fever, haemorrhagic phenomena and often hepatomegaly and circulatory failure [18] – characterize typical cases of DHF. The characteristic haemorrhagic manifestations of DHF are due to capillary leakage. Patients with DHF usually present in a manner similar to that of DF, but plasma leakage develops 4–7 days after the onset of the disease. Abdominal pain, vomiting, restlessness and changing level of consciousness may be the first warning signs of DHF [3]. DSS is characterized by a rapid weak pulse with profound hypotension. The mortality rate of DSS may be as high as 40% [3].

The risk of DHF is higher in immigrants and in persons visiting friends and relatives in areas where the disease is endemic than in general travellers [19]. DSS in travellers is uncommon [17].

4. Diagnosis and differential diagnosis

4.1. Laboratory diagnosis of dengue infections

Methods used for the diagnosis of dengue infections include virus isolation, serology and molecular techniques such as reverse transcriptase-polymerase chain reaction (RT-PCR). These have been extensively reviewed [20].

4.2. Virus isolation

Dengue viruses can be isolated from serum, plasma or leukocytes during the febrile phase and from post-mortem specimens such as liver, lung, spleen, lymph nodes, thymus, cerebrospinal fluid or pleural/ascitic fluid. Blood should be collected during the febrile period before the 5th day of illness because neutralising antibodies appear at that time to form immune complexes. If present in large numbers, as is the case with secondary DF, this may cause interference with virus isolation techniques.

Mosquito cell lines have replaced newborn mice or cell cultures (Vero cell lines or baby hamster kidney cell lines) where traditionally dengue virus isolation was carried out. Currently, inoculation of C636 mosquito cell lines (obtained from A. albopictus) is the method of choice [21]. Virus isolation is done for research purposes only as it may take as long as 2 weeks to provide a result. In the clinical setting, virus isolation is a reliable tool only in acute dengue virus infections, particularly when antibody response of initial serology shows no dengue-specific IgM or IgG reaction. Hence, attempts at virus isolation seem promising when patients are acutely febrile [22].

4.3. Serological diagnosis

Dengue-specific IgM and IgG ELISA is a widely used test for serological diagnosis of dengue infection [23]. Most patients have measurable IgM antibodies by the 5th day of infection. On average, they become undetectable 30–60 days after the onset of illness. The sensitivity of IgM ELISAs range from 83.9% to 98.4%, with a specificity of 100% [24]. The serotype of the infecting virus can also be identified using conventional or capture ELISAs [25,26]. Thus, in the
very early acute phase, when differential diagnosis is most desired, an IgM-negative result is inconclusive and, therefore, not good enough for clinical purposes [13].

4.4. Molecular detection

RT-PCR is useful for the detection of dengue infection early in the disease when antibodies are not detected. Its sensitivity, specificity and rapid detection of minute quantities of dengue viral material in the patient’s serum makes RT-PCR more sensitive than virus isolation and allows for rapid detection of dengue infections (results are usually available in 24 h) and easier identification of the circulating serotype [27]. PCR-based diagnosis is useful since it is positive early in the course of the disease and becomes negative towards the end of the febrile period (when IgM becomes positive); thus, the two methods can be complementary [28].

RT-PCR is also useful for epidemiological studies as dengue serotypes can be identified without cross-reactivity with other Flaviviruses. However, molecular techniques have the disadvantages of high cost and the need for expertise.

Cross-reactions with other Flaviviruses interfere with serological testing and this affects the interpretation of test results in travellers exposed to other flavivirus infections, including those previously vaccinated against yellow fever and Japanese encephalitis [13]. The most commonly used test for the diagnosis of DF is the IgM capture ELISA, which should be performed 4–5 days after the onset of symptoms.

Primary dengue infection is characterized by an increase in dengue-specific IgM antibodies in the early stage of the disease and by an increase in IgG antibodies after 7–10 days of the disease [29]. In secondary dengue infection, IgM antibodies are either absent or lower than in primary infection, with high levels of dengue IgG antibodies in the early course of the disease. However, this differentiation may be a false result among persons vaccinated or previously exposed to flavivirus infections [13].

Since the laboratory-based diagnosis of dengue is often unavailable or unreliable at the time of care, a clinical diagnosis should be considered, together with other non-specific laboratory tests, to establish the diagnosis of DF. These non-specific laboratory test findings include marked leucopenia, thrombocytopenia, increased haematocrit and elevation of liver enzymes [20,22].

Malaria, typhoid fever, leptospirosis, West Nile virus infection, Chikungunya, measles, rubella, Epstein–Barr virus infection, viral haemorrhagic fevers, rickettsial disease and early severe acute respiratory syndrome (SARS) should be considered in the differential diagnosis [16]. The diagnosis remains one based on a high index of suspicion in appropriate clinical settings. Pyrexia of unknown origin is a diagnosis considered in patients with fever in whom a cause has not been identified after routine investigation. The diagnosis of pyrexia of unknown origin is often considered after the possibility of self-limiting illness is excluded. It is routine in protocols for managing pyrexias of unknown origin to ask patients about foreign travel. However, in managing acute fevers of short duration, it is not part of current teaching to encourage clinicians to ask patients about foreign travel. Given the likelihood of dengue presenting as an acute febrile illness, patients with acute fevers of short duration should also be asked about recent foreign travel.

Although the symptoms and signs of mild febrile illness, or DF, are non-specific and hard to differentiate from many other undifferentiated febrile syndromes, clinicians tend to treat patients suspected of having DHF before the results from these tests are available [30].

In milder infections in non-endemic areas, as in the case of European travellers, the diagnosis may not be made, the cause of the febrile illness would be labelled “non-specific viral fever” and, therefore, escape notification and recording in public health databases. This, in turn, would lead to underestimation of the prevalence of imported dengue viral infection in European populations.

5. Treatment and prevention

Classical DF is treated with antipyretic agents, fluid replacement and bed rest since no specific therapeutic agent is available for the treatment of dengue. Prompt and adequate fluid replacement is thought to reduce mortality rates in DSS and DHF [31]. Fluid replacement can be administered orally or parenterally, according to the severity of illness. Aspirin and non-steroidal anti-inflammatory drugs are best avoided due to the increased risk of bleeding. Platelet counts and haematocrit should be repeated at least every 12–24 h in order to recognize the development of DHF. A decrease in platelet counts (<100,000 per mm³) and a rise in haematocrit (>20%) indicates the development of DHF and DSS. Afflicted patients need intensive care management with appropriate fluid replacement (normal saline and Ringer’s lactate). In patients with worsening shock, colloids or crystalloids should be added (10–20 ml/kg body weight per hour) [32]. The critical period is often 4–7 days after the onset of illness and thereafter, once the capillary leakage is stopped, care must be taken to avoid fluid overload and pulmonary oedema.

Considering the risk of exposure for travellers, the risk is highest in rural and urban areas inhabited by lower income groups who lack effective mosquito control. Since the preferred feeding times of these mosquitoes are early morning and late afternoon, preventing mosquito bites is rather difficult. However, protective measures, such as using mosquito repellents and wearing clothes that keep skin exposure to a minimum, are highly recommended [22]. The risk of acquiring infection may be lower in many preferred travel destinations, such as beaches, hotels with well-kept grounds and jungle areas [17]. For soldiers who are expected to travel anywhere at any time, insect repellents and environmental vector control are currently the only line of defence against the mosquito.
An effective, safe and affordable vaccine against dengue virus is not an immediate prospect. Since pre-existing heterotypic antibodies within the host increase the risk of DHF and DSS, an effective vaccine should offer 100% protection against all four serotypes of the vaccine. Attenuated vaccine viruses have been evaluated in the past in Thailand, and a tetravalent formulation of such viruses is currently being tested in repeated trials [2]. Also, a construction of recombinant vaccine is also under evaluation [33].

6. Dengue in European travellers

Dengue is seldom recognized as an important disease in Europe. DF has been diagnosed in increasing proportions of febrile travellers returning from the tropics, ranging from 2% in the early 1990s to 16% more recently [34–38]. Due to the non-specific and self-limiting nature of milder infections, these figures are likely to be an underestimation caused by underreporting.

The epidemiology and clinical manifestation of DF in endemic countries have been extensively described, but few reports exist on serological manifestations among the traveller population. In Europe, the exact extent of travel-acquired or imported dengue infections among travellers is unknown but of growing importance [13,14]. There is a considerable lack of data regarding the actual frequency of this infection in international travellers.

Various case reports have been published that describe dengue infections in international travellers who had visited areas where such infections are endemic [5,6,39]. In a small number of systematic studies of this topic, serological evidence of recent dengue infection was found in 7–45% of patients with fever after they had returned from the areas of endemicity [14,40,41].

As quoted by Jelinek [17], a retrospective study performed among a small cohort of Swiss travellers showed a surprisingly high prevalence of antibodies to dengue virus (8%) in symptomatic patients [42]. A similar result (prevalence of 6.9%) was shown in a prospective study in 130 febrile returnees from endemic areas [41]. In the latter study, 9 of the 10 patients who tested for dengue had acquired the infection in Southeast Asia or Western Indonesia; the other patient had acquired it in Brazil.

In another retrospective study among 323 German expatriate workers and their families staying in areas of endemicity, antibodies to dengue virus were detected in 4.3% [43]. The majority of persons who tested positive did not have any clinical disease suggestive of dengue. It appears that many infections may have oligosymptomatic or asymptomatic courses. In a similar study of 670 German aid workers, seropositivity was detected in 7.4% [44]. IgG antibodies to dengue were detected in 19.4% of aid workers who had returned from Thailand. The quality of both studies suffered from the retrospective design and a considerable lack of data on living standards, housing conditions and travelling habits of these patients. However, these results show clearly that dengue infection is a realistic event in long-term travellers to endemic areas. It appears that this is also true of persons on repeated short journeys [17].

Laboratory-confirmed dengue virus infections among 71 German travellers returning to Berlin were studied retrospectively during 1993–2001 [44]. The majority of patients (77.5%) contracted the disease in South Central and Southeast Asia; the second largest group had been to South and Central America or the Caribbean. Reports of dengue in travellers from Africa or Oceania are less common [45].

In a retrospective study carried out among Swedish tourists, DF was found to be the most commonly diagnosed imported arbovirus disease in 1989–1990. Out of 24 patients diagnosed with DF, 17 acquired the infection in Thailand during spring and early summer. All patients recovered without sequelae [39].

Another retrospective study among 44 diagnosed cases of DF in French travellers to Southeast Asia, French West Indies, French Guyana and Africa in 1994–1997 showed that, compared to Southeast Asia, French West Indies and French Guyana, fewer patients acquired the infection in Africa [15].

In a prospective study among Spanish tourists who travelled to the tropics in 1989–1994, 14 were diagnosed as having DF; their mean age was 34 years. Some 71% had contracted the disease in Asia, 21% in Central America and the Caribbean islands, while 7% contracted it in Africa [40].

Of the 309 patients with DF reported to the network TropNetEurope (European network on imported infectious disease surveillance) during the period January 1999 to December 2001, 72.1% were confirmed cases according to the definition used by the surveillance network. A further 8.8% were classified as probable cases and 8.5% as suspected cases [15]. The majority was male (56.5%) and of working age (average age 35.5 years). The overwhelming majority of patients (85.7%) were Europeans, 81.6% of whom were living in Europe. Most of these Europeans were travelling as tourists (77.5%). Of the geographical regions infected with DF, Indonesia and South and Southeast Asia were by far the largest contributors of patients, followed by the Americas [15]. Some 23.3% of patients had visited Southeast Asia, 22.9% had visited the Indian subcontinent and 6.5% had visited Indonesia. The proportion of patients who had acquired infection in the Americas was slightly smaller: 38.2% of all patients. 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 in acquiring infection was observed in India (an increase from 17.2% in 1999 to 21.8% in 2001) [15].

DF is also recognized as an emerging health problem for troops deployed in tropical countries. This is mainly because of a lack of effective preventive measures, the high attack rate, the high symptomatic/unapparent infection ratio and the long period that one is unfit for duty after the acute phase of the disease. In a study carried out on Italian troops deployed...
in East Timor from 1999 to 2000, 6.6% of army soldiers contracted probable DF; there were no probable DF cases detected in low-exposure groups, such as navy and air force personnel. Approximately 60% of the troops with supportive serological evidence of recent dengue infection showed the clinical manifestations of classic DF, 20% had milder symptoms and 20% were asymptomatic [8]. The U.S. troops deployed in Somalia in 1993 showed features of classical DF in more than 85% of patients [46]. Performing duties outside the camp was associated with a high risk of infection, probably because vector control activities were regularly carried out only within the compound. The only measure taken for personnel protection was the use of bed nets. However, most of the soldiers were on duty at night and thus slept during the day, when the biting activity of the dengue vector is highest [8]. Moreover, previously infected soldiers redeployed to endemic areas may be at an increased risk of DHF/DSS complications. Therefore, it was suggested that this risk should be taken into account when planning international peacekeeping operations and that the risk of DHF among previously dengue-infected military personnel should be evaluated beforehand [8].

Little is known about the clinical spectrum of DF and the proportion of sub-clinical infection among travellers [17]. Studies from areas of endemicity suggest that 14–87% of all dengue infections cause few or atypical symptoms [47]. The proportion of sub-clinical infections among travellers is of importance. It has been suggested that infection with one serotype of dengue virus can predispose to development of DHF and/or DSS when re-infection occurs with another serotype [48].

Of the 309 patients reported to the network TropNetEurope, most patients with dengue were symptomatic and reported fever, headache, myalgias, fatigue and rashes, as well as diarrhoea [15]. Therefore, 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 travelled 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 [15].

A study carried out on German travellers with confirmed DF also showed that the most important clinical characteristics were fever, prostration (100%), headache, predominantly frontal or retro-orbital (86%), arthralgia (79%), a measles-like rash (66%) and myalgia (48%). Also, it was shown that the most meaningful laboratory results were marked leucopenia (72%), thrombocytopenia (70–89%), hyponatraemia (41%) and increase hepatic enzymes (45–60%). Fourteen percent had haemorrhagic phenomena. The median duration of fever was 6 days (range 1–11 days) [20]. The majority of patients in a Spanish study (61.5%) had post-dengue syndrome, characterized by marked asthenia [40].

Because of the short incubation period of the disease, it is conceivable that many infected travellers may experience DF while still abroad, leading to an underestimation of the true incidence in the traveller population [7].

Dengue virus infection should be considered if clinical signs, travel history and the possible incubation period of 4–7 days (range 3–14 days) are suggestive [20,22]. Therefore, it is important to suspect DF in every febrile patient returning from the tropics, particularly if thrombocytopenia, elevated serum aminotransferases and/or rash are also present [32]. A diagnosis of dengue should be considered second only to malaria in travellers returning with fever [22]. Whenever it is suspected, a quick and reliable laboratory diagnosis is mandatory to avoid complications [40].

It is also important to keep in mind that both IgM and IgG dengue antibodies may cross-react with other Flaviviruses, such as Japanese B encephalitis, West Nile encephalitis or yellow fever. The rate of IgG cross-reactivity between dengue infection and Japanese encephalitis or yellow fever vaccine may be 17–40%; IgM cross-reactivity has not been found after vaccination [49].

Without a doubt, there is underreporting of dengue cases imported to Europe, either because the patient does not seek medical care or because the physicians fail to establish the correct diagnosis [15]. In an era of pressure on cost effectiveness in medical care and with a diagnosis that, in most cases, requires no further treatment, it is difficult to persuade both patients and doctors to perform follow-up investigations. Therefore, some travellers with symptoms of acute viral fever in whom malaria has been excluded may not come back after they have recovered [20,22]. Another reason for underestimation of DF among European travellers is that few centres use standardised diagnostic procedures for febrile patients. In addition, DF is currently not reported in most European public health systems [15]. Therefore, the voluntarily reported cases in Europe still represent the tip of the iceberg.

Of great concern is the possibility of a dengue outbreak in previously dengue-free countries via imported cases. In Spain, which is considered a non-infected area, several surveys based on non-specific haemagglutination inhibition assay have shown a seroprevalence of Flaviviruses including dengue virus [50]. Another major concern is the potential area of dengue transmission due to the spread of its vectors, notably in sizable parts of the United States and Europe. Thus, the introduction of DF by returning travellers to those not afflicted with the disease poses a very real threat to the public health systems of the western world. One of the largest DF epidemics known in history, involving approximately one million cases and 1000 deaths, occurred in 1927–1928 in Greece. At that time, the vector was the later eradicated A. aegypti. In this context, the recent introduction of A. albopictus to Europe, notably Italy and Albania, may serve as a warning of things to come [1].

7. Conclusion

It can be inferred that travellers have the potential to both acquire and spread dengue virus infection [15]. Dengue


infection should be considered in all febrile patients returning from endemic areas with or without typical symptoms [20]. Dengue can be ruled out if symptoms begin more than 2–3 weeks after the patient has left an endemic area or if the fever lasts more than 2 weeks [2]. Imported dengue in non-immune travellers usually takes a favourable course, but the global expansion of dengue virus and increased international travel have intensified the possibility of sequential infections and the risk of developing DHF and DSS [20]. Nevertheless, DHF and DSS are rare in travellers. Those with a history of dengue should be advised to protect themselves well from mosquitoes when travelling to endemic areas [51]. DF is also an emerging problem for troops deployed in dengue-endemic tropical countries [8].

Box 1

Learning points:

- Travellers have the potential to acquire and spread the dengue viral infection.
- Dengue infection should be considered in all febrile patients returning from endemic areas.
- Increased international travels intensifies the possibility of DHF/DSS, which is rare in travelers.
- Dengue infection is an emerging problem for troops deployed in endemic countries.

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