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TROPICAL, TRAVEL AND EMERGING INFECTIONS (L CHEN AND A BOGGILD, SECTION EDITORS)

Risk of Dengue in Travelers: Implications for Dengue Vaccination

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Abstract

Purpose of Review Dengue is found in tropics and subtropics that are considered to be popular travel destinations. We set out to review the burden of dengue on international travelers.

Recent Findings GeoSentinel, a global network of travel medicine providers, has seen an increasing trend of dengue in returning travelers over the past decades. In Southeast Asia, annual proportionate morbidity increased from 50 dengue cases per 1000 ill-returned travelers in non-epidemic years to an average of 159 cases per 1000 travelers during epidemic years. Dengue is the leading cause of fever in returning travelers, having overtaken malaria for travelers to Southeast Asia. Most dengue seroconversion studies in travelers report an attack rate of around 5% depending on duration of travel and destination.

Summary Dengue vaccination would be justified for travelers. The first licensed dengue vaccine CYD-TDV is only recommended in seropositive individuals. This review considers preventive measures including how best to use the first licensed dengue vaccine CYD-TDV.

Keywords Dengue · Travelers · Dengue vaccine · Personal protection · Seroconversion · GeoSentinel

Background

Dengue virus has become the world's most frequent *Flavivirus*. Transmitted by mosquitoes of the genus *Aedes*, dengue is found mainly in the tropics and subtropics [1, 2•] that are considered to be popular travel destinations [3]. Understanding the extent of risk of dengue in travelers is important for travelers, clinicians, and travel medicine providers. Pre-travel advice will need to consider the epidemiology of dengue, attack rates in travelers, host factors, and preventive measures. Clinicians caring for ill-returned travelers should be able to recognize dengue and be familiar with its management. Dengue infections exhibit a dynamic risk, with strong geographical heterogeneities, hence we need to improve the accuracy of risk communication combined with appropriate preventive measures [4••].

As surveillance is often just passive with mandatory dengue notifications based on illness clinically compatible with dengue often without laboratory confirmation, the true incidence is not known [5]. Modeling combined with cartographic approaches have estimated the annual incidence of dengue infections to be 400 million infections per year, with clinically apparent cases representing about 25% of all dengue virus infections [6]. However, dengue incidence is cyclical often with a 3–5-year pattern [7] and the incidence is far lower in non-epidemic years. Asia accounts for 75% of the dengue disease burden, followed by Latin America and Africa [6]. In highly endemic areas, approximately 10% of all febrile episodes are due to dengue [8••].

The rapid geographic spread of dengue viruses globally is the result of increasing mobility of people via modern means of transportation [9–12]. Air travel connectivity between dengue-endemic countries and from dengue-endemic countries to non-endemic, but still vulnerable settings has increased exponentially [3]. While imported dengue cases to the USA have resulted in small dengue clusters for many years [13], the first autochthonous sporadic cases in Europe (France and Croatia) were reported only in 2010 [14, 15]. In 2012, the first major European outbreak of dengue occurred in Madeira [16]. Viremic travelers to non-endemic areas where *Aedes*

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mosquitoes exist constitute the source for triggering autochthonous transmission [17••, 18]. About 36% of travelers who acquired dengue during their travel to dengue-endemic countries returned to Europe during the acute phase of the infection (up to 7 days after symptom onset), and 58% of travelers with an acute dengue infection were viremic when seeking medical care, thus highlighting the potential for dengue virus introduction [19]. Fortunately, the seasonal window in Europe when vectorial capacity is sufficient to sustain autochthonous transmission is short [20••]. The risk of dengue importation that will lead to establishment in temperate climates such as those in Europe was modeled to be very low [17••].

The principal vector *Aedes aegypti* is a peri-domiciliary day-biting mosquito capable of biting several people in a short period of time. *Aedes albopictus,* although a less efficient vector compared to *Aedes aegypti*, is continuing its geographic expansion into tropical and temperate climates. Climate change with global warming facilitates a wider geographic distribution of *Aedes* mosquitoes, thereby increasing dengue-epidemic potential in temperate regions. [21] Dengue caused an outbreak in the temperate climate of Japan in 2013 due to increasing importation via travelers from China [22]. Travelers have often served as a sentinel to unmask ongoing dengue transmission in countries before national authorities notified the outbreak [12, 23].

Risk of Dengue in Travelers

In parallel with the increasing incidence of dengue globally, the incidence of dengue in travelers has increased exponentially in the past decades [24, 25]. GeoSentinel is a global network of travel medicine providers that see ill-returning travelers [26]. GeoSentinel has seen an increasing trend of dengue in returning travelers over the past decades [27, 28]. In Southeast Asia, annual proportionate morbidity increased from 50 dengue cases per 1000 ill-returned travelers in non-epidemic years to an average of 159 cases per 1000 travelers during epidemic years [29]. Dengue is the leading cause of fever in returning travelers, having overtaken malaria for travelers to Southeast Asia [29]. GeoSentinel also identified the seasonality of dengue transmission [29]. Dengue occurs both in adult [29, 30] and pediatric travelers [31, 32], with one study in expats showing similar attack rates for adults (4.7%) and children (6.3%) [33]. However, as most travelers are adults, the majority of travel-associated dengue cases have been reported in adult travelers.

Prospective studies are better suited to determine the attack rate than sentinel surveillance. A dengue antibody seroconversion study in travelers with a median length of travel of 21 days seen in the Boston Area Travel Medicine Network found a seroconversion rate by either anti-DENV IgM or IgG ELISA between 2.9 and 6.8% [34]. Eighteen percent of those with seroconversion reported dengue-like symptoms. Seroconversion was documented for travel to Africa as well as countries and regions known to be highly dengue endemic (India, Brazil, Southeast Asia) [34]. In Swedish travelers, an increasing trend of dengue infections over time was found for most destinations [35•]. The majority of the dengue cases were acquired in Thailand (492 out of 925 travelers; 53%), with an attack rate of 13.6 (95% CI 12.7, 14.4) per 100,000 travelers. However, the two highest attack rates per 100,000 travelers were found for Sri Lanka (45.3, 95% CI 34.3, 56.4) and Bangladesh (42.6, 95% CI 23.8, 61.5).

Prevalence of dengue virus infection in US travelers who have lived in or traveled to dengue-endemic countries was 19%; 12% had antibodies by PRNT, 85% of whom had no history of dengue [36]. Presence of DENV antibodies was associated with years lived in dengue-endemic countries and self-reported history of dengue [36]. 5.8% of travelers returning to Italy had IgM and/or IgG antibodies specific for dengue [37]. The seroprevalence of dengue infection in one Australian study in travelers to Asia was 4.4% and a greater number of prior trips to Asia was a predictor for dengue seropositivity [38]. Dengue was the most common laboratory-confirmed diagnosis in travelers from Bali, reported in 5% of travelers returning to Australia [39].

Special Sub-Populations of Travelers

Peace Corps Volunteers (and other humanitarian aid workers as well as missionaries) are often long-term travelers at particular risk for dengue. The dengue incidence rate was 1.12 cases per 1000 volunteer-months [40]. The highest rate of dengue among volunteers was reported in the Caribbean region, with a rate of 5.51 cases per 1000 volunteer-months followed by the East Asia/South Asia region (3.34) and Central America (2.55) [40]. Recent or past infection with a DENV was evident in 93% missionaries with available sera, but the sample size was very small to defer such a high prevalence for all missionaries [41]. In a serosurveillance project using predeployment and postdeployment sera collected from US Army Special Operations Forces deployed to South and Central America, Africa, and Southeast Asia showed a 13.2% seropositivity rate [42]. Business travelers are another risk group as discussed in a recent GeoSentinel analysis [43]. Given the fact that dengue is predominantly a disease of urbanized areas [44•], even short-term travel for business in cities may pose a risk. Longer-term expats were shown to be at higher risk than the endemic population [33]. Despite increasing migration to Europe [45] and South-South migration and travel [46–48], little is known about the incidence of dengue in migrants [49, 50]. In Singapore, differences were documented for dengue severity between local and migrant Chinese [42]. In migrants now living in non-endemic countries, returning to dengue-

endemic countries to visit friends and relatives (VFR), a higher risk of severe dengue was documented in a GeoSentinel study [51], which was most likely due to the fact that many of the VFRs already had a primary dengue infection and were hence at a higher risk of a more severe dengue. Travelers visiting friends and relatives (VFRs) often have complex pre-travel needs. Future research should focus on improving the uptake of recommended interventions in VFR travelers [52]. Given the rise of migrants especially to Europe, with importation of dengue and other infectious diseases, clinicians need to be aware of dengue, and surveillance of imported dengue via migrants would be justified especially for migrants from Southeast Asia and Latin America.

Clinical Manifestations and Complications of Dengue

In most cases, dengue is a self-limiting febrile illness with spontaneous recovery, and no interventions are needed. Clinically relevant complications develop in a proportion of these patients however, with systemic vascular leak syndrome being the predominant complication with or without hemorrhages [53]. This vasculopathy is characterized by increased vascular permeability, plasma leakage, and intravascular volume depletion, which may progress to life-threatening dengue shock syndrome [54, 55]. The 2009 WHO dengue case classification now identifies symptomatic individuals as having "dengue" if they have no major complications, while those who experience complications in any of three categories, (a) plasma leakage severe enough to cause shock or respiratory distress, or (b) severe bleeding, or (c) severe organ impairment, are designated as having "severe dengue" [53]. There is a strong epidemiological association between development of severe complications and secondary infection [56]. Antibody dependent enhancement has been widely used to explain this phenomenon, but was only recently demonstrated in clinical epidemiological studies [57••]: progression to severe dengue appears to require certain antibody-to-virus ratios [57••, 58••]. However, although vascular leakage is the hallmark of severe dengue, other unusual severe complications can also occur. Unusual complications include the hemophagocytic syndrome [59], myocarditis [60], other cardiac problems [60–62], and fulminant hepatitis [63]. Complications in the eye may also occur [64]. Neuro-ophthalmological complications usually involve the posterior segment and include visual disturbance secondary to retinal vasculopathy and optic neuropathy [65]. Dengue can manifest with a wide range of neurological features, which have been noted in 0.5–21% of patients with dengue admitted to hospital [65]. Although the association of Zika with Guillain-Barre syndrome in travelers is much stronger [66•], several cases of Guillain-Barre syndrome have also been reported to be associated with dengue [67–73]. Cases of rhabdomyolysis [74], abducens nerve palsy [75], optic neuritis [76], and strokes, especially hemorrhagic stroke symptoms have been reported because of the coagulopathy associated with dengue fever [77]. Acute encephalopathy is the most common neurological disorder associated with dengue [78]. Encephalitis is secondary to the direct central nervous system invasion of the virus and has also been reported for dengue [78].

Host Factors Relevant for Travelers

Many travelers are older adults, and older travelers may have more comorbidities [79, 80]. Diabetes has been identified as a risk factor for dengue, and so have other comorbidities such as hypertension, cardiovascular disease, and asthma [81, 82]. Travelers with sickle cell disease are thought to be at increased risk of severe dengue [83]. Pregnant women are another group at high risk for severe disease, especially during the third trimester [84, 85], and perinatal transmission to infants is recognized [86].

Dengue Diagnosis in Travelers

The choice of laboratory test depends on the time since onset of fever. Before day 5 of illness, during the febrile period, dengue infections may be diagnosed by virus isolation, by nucleic acid amplification tests such as reverse transcriptase-polymerase chain reaction (RT-PCR), or by detection of viral antigens such as the dengue non-structural protein 1 (NS1) by enzyme-linked immunosorbent assay (ELISA) or rapid diagnostic tests (RDTs). After days 4–5, dengue viruses and antigens disappear from the blood coincident with the appearance of dengue-specific antibodies, hence serological assays should be used [87••]. RT-PCR on specimens other than blood (urine and saliva) [88] can prolong the diagnostic window and is particularly relevant for confirming the diagnosis in returning travelers.

While rapid diagnostic tests are available for NS1 antigen or IgM antibody detection or both simultaneously, the sensitivities and specificities of the available tests are lower than the equivalent laboratory-based ELISA assays [89]. Nevertheless, the combination of NS1 antigen and IgM testing at point of care offers a longer diagnostic window, and RDTs are hence increasingly being used. NS1 antigen testing has been shown to be highly specific in travelers [90]. Diagnostic requests for both Zika virus (ZIKV) and dengue virus (DENV) infections in returning travelers have significantly increased during the recent ZIKV outbreak in the Americás [91]. As these flaviviruses have overlapping clinical syndromes and geographical distribution, diagnostic differentiation is important because of different clinical consequences. As flaviviruses are

known to have a short-viremic period, diagnostics often rely on serological methods, which are challenging due to extensive cross-reactive antibodies. Although the DENV NS1 antigen assay was highly specific for laboratory confirmed ZIKV-infected travelers, high percentages of cross-reactivity of DENV IgM and IgG ELISÁs were found, of which diagnostic laboratories should be aware [91]. An algorithm for ZIKV serodiagnosis based on three simple ELISAs has been proposed to distinguish dengue from Zika [92].

The most urgent need is to identify biomarkers that can help discriminate patients who will progress to a more severe dengue. However, no single biomarker or combination of biomarkers have been identified to date, despite substantial efforts to this end [93].

Clinical Management

The mainstay of clinical management is prompt and appropriate rehydration therapy, avoiding both too little as well as too much fluid. A state-of-the-art review was recently published in the Lancet Clinical Seminar series [94]. The case fatality rates under good case management should be below 1% for symptomatic dengue. Travel medicine providers caring for dengue patients need to be familiar with the clinical management through specialized training [95], and training in travel and tropical medicine needs to be increasingly incorporated into undergraduate curricula [96].

Preventive Measures and Vaccination

Personal protective measures for travelers include measures taken mainly during the day to avoid mosquito bites such as repellents, long-sleeves and light clothing, and coils or other vapors [24]. Picaridin-containing repellents appears to be as effective as DEET (at 30%), but at > 50% DEET seems to be more effective [97]. However, compliance with such measures have been found to be low in travelers [98]. Bed nets are of limited use as *Aedes* mosquitoes mainly bite during the day. Impregnated clothing has been suggested to be effective [99, 100], but this was not proven in a community-based trial [101]. Wolbachia as a novel vector control strategy was found to reduce outbreaks as a result of dengue importation in Northern Australia [102].

Given the overall lack of effective preventive measures, combined with the relatively high incidence of dengue in travelers, dengue vaccination would be indicated [103]. In 2015, the first dengue vaccine was licensed. CYD-TDV is a live attenuated tetravalent vaccine with yellow fever 17D virus as backbone. In the age group of 9 years and above, efficacy against hospitalized dengue and severe dengue was high, 83 and 91% respectively [104]. Subsequently, in the year 2017, new long-term safety data were released which showed that the vaccine had a different performance depending on serostatus [105]. The analyses stratified by serostatus showed an increased risk of severe dengue in those seronegative at baseline, a risk that emerged about 30 months after the first dose regardless of age. The most plausible hypothesis is that the live attenuated CYD-TDV initiates a first immune response to dengue in seronegative persons that predisposes them to a higher risk of severe disease when they experience their next natural dengue infection [106]. The revised WHO recommendations in 2018 state that CYD-TDV vaccination is only recommended in seropositive individuals where the vaccine is efficacious and safe [87••]. Serostatus, reflecting whether or not the individual has experienced a dengue infection in the past, is determined by a serological assay. As travelers with previous travel to dengue-endemic countries will be more likely seropositive; screening will therefore need to be prioritized for travelers according to the extent of previous exposure to dengue [107••]. The specificity of a serological assay will depend on the extent of exposure to other flaviviruses such as Zika, West Nile, tick-borne Encephalitis (TBE), Japanese encephalitis, (JE) yellow fever (YF) viruses, and others, or vaccination with *Flavivirus* vaccines [108]. The efficacy trials were done with a three-dose schedule, 6 months apart, which will make completion of the primary schedule prior to travel unfeasible. However, the vaccine efficacy between the first and second dose and second and third doses was similar to the vaccine efficacy after the third dose, in the overall trial population in the multi-center phase 3 trials [109]. Although no long-term efficacy data for one or two dose schedules exist because the completion rate of three doses was very high in the trials, it could be argued that a single dose prior to travel may suffice in those traveling for less than 6 months [107••].

Besides CYD-TDV, two other chimeric live attenuated dengue vaccines are now in the phase 3 trials. Whether these second-generation dengue vaccines will encounter the same safety issue in seronegative vaccines is unknown. The first read-outs of the trials will most likely be available by mid-2019.

Concluding Remarks

Dengue infection in international travelers is not infrequent and may be associated with substantial morbidity and undesired interruption of travel. Given widespread risk of dengue, travel medicine counseling should include information on the risk of dengue in endemic areas and advice on preventing insect bites and seeking prompt medical attention for febrile illness. The first licensed dengue vaccine CYD-TDV could be considered in laboratory-confirmed seropositive travelers; however, it is not yet licensed in most countries. Good risk

maps are needed to provide evidence-informed advice on at risk destinations, such as those published by the Centers for Disease Control, USA [4••]. Graded evidence for best practices [110] will be needed for both pre-travel advice and clinical management of travelers with dengue.

Compliance with Ethical Standards

Conflict of Interest The author declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Disclaimer AWS is consultant to the World Health Organization. The author alone is responsible for the views expressed in this publication, and her views do not necessarily represent the decisions or policies of the World Health Organization.

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