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Review

Come fly with me: Review of clinically important arboviruses for global travelers

Natalie Cleton[a,b,*], Marion Koopmans[a,b], Johan Reimerink[a], Gert-Jan Godeke[a], Chantal Reusken[a]

[a] Centre for Infectious Disease Control, National Institute for Public Health and the Environment, P.O. Box 1, 3720 BA Bilthoven, The Netherlands
[b] Department of Virology, Erasmus MC, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands

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ABSTRACT

Western tourists are increasingly traveling to exotic locations often located in tropical or subtropical regions of the world. The magnitude of international travel and the constantly changing dynamics of arbovirus diseases across the globe demand up-to-date information about arbovirus threats to travelers and the countries they visit. In this review, the current knowledge on arbovirus threats to global travelers is summarized and prioritized per region. Based on most common clinical syndromes, currently known arboviruses can be grouped to develop diagnostic algorithms to support decision-making in diagnostics. This review systematically combines and structures the current knowledge on medically important travel-related arboviruses and illustrates the necessity of a detailed patient history (travel history, symptoms experienced, vaccination history, engaged activities, tick or mosquito bite and use of repellent and onset of symptoms), to guide the diagnosis.

Contents

* Corresponding author at: Centre for Infectious Disease Control, National Institute for Public Health and the Environment, P.O. Box 1, 3720 BA Bilthoven, The Netherlands. Tel.: +31 30 274 7521; fax: +31 30 274 4418.
E-mail address: natalie.cleton@rivm.nl (N. Cleton).

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1. Introduction

Globally the number of travelers has risen from 450 million in 1990 to nearly 950 million in 2010.[1] Western tourists are increasingly traveling to more exotic medically high-risk locations in developing countries or upcoming economies, like China and India, often located in tropical or subtropical regions of the world.[1] 5–10% of travelers report to a medical care taker after travel.[2] Consequently, doctors are increasingly confronted with travel-related diseases, stressing the need for awareness within the medical profession and general population. The differential diagnosis of fever in travelers is long, including cosmopolitan as well as more exotic infections.[3] The most important syndrome is diarrhea, followed by undifferentiated fever and dermatological problems depending on travel-destination.[2] Although malaria remains the most important cause for systemic febrile disease in travelers, arbovirus infections belong in the differential diagnosis.[3] This is emphasized by the rise in the proportion of travelers being diagnosed with exotic arbovirus infections like chikungunya virus and dengue virus, with dengue currently being the second most important cause for febrile disease in travelers.[4–7]

The magnitude of international travel and the constantly changing dynamics of arbovirus diseases across the globe demand up-to-date information about current arbovirus threats to travelers and the countries they visit.

Establishing a differential diagnosis requires up-to-date knowledge based on evolution of the patient's symptoms, travel history, specific background information on possible exposures and test results. This review focuses on all medically important arboviruses, to facilitate clinicians and clinical laboratories in their differential diagnosis. It summarizes current literature on risk of arbovirus infection in global travelers, and prioritizes them per region.

2. Background on arboviruses (Tables 1 and 2)

Arboviruses use arthropod vectors as their main transmission route and are therefore defined as ARthropod-BOrne viruses. Mosquitoes, ticks, midges and sandflies are known virus-transmitting arthropods. The majority of arboviruses belong to the *Flaviviridae*, *Bunyaviridae* or *Togaviridae* families, but a small number are member of the *Reoviridae*, and *Orthomyxoviridae* families (Tables 1 and 2).[8–10]

Of the over 545 suspected arbovirus species more than 150 are documented to cause disease in humans, and the majority are zoonotic. They are sustained in a transmission cycle between arthropods as vectors and vertebrate animal reservoirs as main amplifying hosts (Table 1). Humans are infected in spill-over events and are often dead-end hosts, as they do not develop the high viremias needed to infect arthropods.[8,11] Only a few viruses like yellow fever, chikungunya and dengue virus have expanded their host range to include humans as an amplifying host. They can lead to mosquito-borne disease outbreaks, often in urban settings, without the need of an animal reservoir. This urban transmission cycle in part explains the 'success' of these viruses.[12] Based on the pattern of occurrence the individual viruses in Table 1 were labeled as endemic (reflecting stable presence in a reservoir), sporadic (reflecting isolated infections), or epidemic (reflecting occurrence during seasons with increased disease activity or outbreaks). Large epidemics can occur for example because of climate variations, like extraordinary rainfall or movement of large populations or viruses into new areas.[13] Arboviruses may also be transmitted through blood from viremic patients, which is a particular concern for the blood supply in endemic areas and when taking care of patients with hemorrhagic fever.[14–17] Cases of human-to-human transmission of West Nile virus through blood transfusions and organ transplantation have been reported,[15,18–20] but all arboviruses that produce viremia in humans are thought to be a potential risk (Table 2).[21,22]

2.1. Bunyaviridae

The genera *Orthobunya*, *Phlebo* and *Nairovirus* within the *Bunyaviridae* family, contain human arboviruses (Tables 1 and 2).[23] *Orthobunyaviruses* use mosquitoes and/or midges as their main vectors.[24] This genus is divided into 18 serogroups, based on cross titrations in haemaglutination inhibition (HI) assays and neutralization assays (NT), and correlating to main vector preferences. Many hold viruses that have been reported to cause disease in humans.[25–27] However, the most clinically important travel-related viruses are found in only two serogroups, the California encephalitis serogroup and the Simbu serogroup.

Nairoviruses use ticks as main vector and comprise 7 serogroups.[28] Only Crimean-Congo hemorrhagic fever virus is considered to be of clinical importance to travelers.[24,29]

The *Phlebovirus* genus contains the phlebotomus fever serogroup (sandfly-borne viruses). The most clinically important are Toscana virus, which is transmitted by sandflies, and Rift Valley fever virus, which is transmitted by mosquitoes.[23] This example also illustrates that taxonomy based on vector preference, and vice versa, may not be consistent.

The clinically important viruses are found across serogroups and in distinct geographical areas, reducing the problems in diagnostic test interpretation due to cross-reactivity when the travel destination is reported (Table 3 and Maps 1–3).

2.2. Flaviviridae

The family *Flaviviridae* is divided into 3 genera. Only the *flavivirus* genus holds arboviruses, some of which are the most clinically important arboviruses world-wide, like dengue, yellow fever and West Nile virus (Tables 1 and 2).[30,31] The human flaviviruses are divided into nine serogroups.[32,33] Five of these contain medically important arboviruses (Tables 1 and 2). Depending on the serological assays used, cross-reactivity between serogroups may complicate interpretation of diagnostic assays. Two main flavivirus transmission routes are recognized: tick-borne and mosquito-borne.[33,34] Inquiring about a history of tick or mosquito-bite during patient evaluation can help focus the differential diagnoses.

2.3. Reoviridae

Three genera of the *Reoviridae* contain arboviruses but only two are considered potentially important travel-related viruses, i.e. Banna virus in the *Seadornvirus* genus and Colorado tick fever virus in the *Coltivirus* genus (Tables 1 and 2).[35–38] These two viruses are found on opposite sides of the world (resp. Old and New World), use different vectors (resp. mosquitoes and ticks) and are not cross-reactive in serology as they differ in genus (Map 1).

2.4. Togaviridae

Arboviruses are found in the *Alphavirus* genus of the *Togaviridae* family.[39] The *Alphavirus* genus is divided into seven serogroups of which six contain clinically important viruses for travelers (Tables 1 and 2).[39,40] Mosquitoes are their main vector.[41] About 50% of the alphaviruses cause disease in humans.[39] Because there is a clear division in New and Old World alphaviruses, the use of travel history of patients can aid substantially in focusing the differential diagnosis (Table 3). Some Old and New World viruses are found in the same cross-reacting groups, like chikungunya and