Narrative review

Emerging souvenirs—clinical presentation of the returning traveller with imported arbovirus infections in Europe


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ABSTRACT

Background: Arboviruses are an emerging group of viruses that are causing increasing health concerns globally, including in Europe. Clinical presentation usually consists of a nonspecific febrile illness that may be accompanied by rash, arthralgia and arthritis, with or without neurological or haemorrhagic syndromes. The range of differential diagnoses of other infectious and noninfectious aetiologies is broad, presenting a challenge for physicians. While knowledge of the geographical distribution of pathogens and the current epidemiological situation, incubation periods, exposure risk factors and vaccination history can help guide the diagnostic approach, the nonspecific and variable clinical presentation can delay final diagnosis.

Aims and sources: This narrative review aims to summarize the main clinical and laboratory-based findings of the three most common imported arboviruses in Europe. Evidence is extracted from published literature and clinical expertise of European arbovirus experts.

Content: We present three cases that highlight similarities and differences between some of the most common travel-related arboviruses imported to Europe. These include a patient with chikungunya virus infection presenting in Greece, a case of dengue fever in Turkey and a travel-related case of Zika virus infection in Romania.

Implications: Early diagnosis of travel-imported cases is important to reduce the risk of localized outbreaks of tropical arboviruses such as dengue and chikungunya and the risk of local transmission from body fluids or vertical transmission. Given the global relevance of arboviruses and the continuous risk of (re)emerging arbovirus events, clinicians should be aware of the clinical syndromes of arbovirus fevers and the potential pitfalls in diagnosis. I. Eckerle, Clin Microbiol Infect 2018;24:240
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Introduction

With an increase in global travel rising to around 950 million persons per year, physicians are frequently confronted with patients potentially infected with exotic pathogens [1]. Besides malaria, infection with an arbovirus is a common cause of fever in
travellers returning to Europe [2]. Arboviruses are a large group of emerging RNA viruses spanning different virus families and genera that are responsible for human disease worldwide in the range of hundreds of million cases annually [3–5].

In Europe, several endemic arboviruses are of clinical importance such as tick-borne encephalitis, West Nile fever, Crimean-Congo haemorrhagic fever and sand fly fever [6]. However, there is heterogeneity in the surveillance of endemic, well-known arboviruses and uncertainty about the true burden of related illness in Europe [6]. The situation is aggravated by (re)introduction of viraemic patients after travel [5–8]. Limited autochthonous outbreaks have been described for dengue virus (DENV) [9–13] and chikungunya virus (CHIKV) in Europe [14–16]. The endemic areas for DENV and CHIKV are found in tropical and subtropical regions of the world. DENV is the most successful arbovirus in terms of emergence in recent decades, with an estimated 390 million infections per year globally [17]. The main endemic areas are in Asia and South America, with less data in some areas, particularly in Africa. Returning travellers presenting with DENV can serve as sentinels, and a recent study estimated the proportion of cases in Africa to be in the same range as in Latin America [17–19]. CHIKV is mainly found in Asia and Africa, with recent large outbreaks on the Indian Ocean islands, and has spread to the New World, particularly the Caribbean and the Americas [20–22].

Zika virus (ZIKV) was considered to be a flavivirus of low interest until its dramatic emergence in French Polynesia in 2013 and subsequently in South America in 2015. While Zika usually causes mild disease in adults, it can lead to congenital malformations when infecting pregnant women and is also associated with Guillain-Barré syndrome [23]. This has led to increased awareness of the potential risk of other neglected arboviruses [5]. Fortunately, no vector-borne transmission of ZIKV has been recorded in Europe to date [6]. However, sexual transmission of ZIKV has been reported and is an additional source of introduction besides vectors and travellers with disease [24,25].

While dengue, Zika and chikungunya account for the vast majority of travel-imported arbovirus cases in Europe, there is a plethora of other, less well-known arboviruses capable of causing human disease. These include viruses such as Jamestown Canyon, Mayaro, Oropouche, Tahyna and Usutu viruses—and many more which are not known to most clinicians [26–28]. The increasing importance of arboviruses in Australia, such as Kunjin virus, Murray Valley fever and Ross River fever, poses an underrecognized hazard for travellers from Europe [29,30].

For clinicians, the diagnosis of travellers presenting with syndromes of fever, rash (Fig. 1), myalgia, arthralgia and headache is challenging because of their nonspecific nature and the wide range of potential differential diagnoses. Diagnostic test strategies for arboviruses can be complex as a result of the short viraemic period, pitfalls in serology such as high levels of antibody cross-reactivity and patchy access to specialized arbovirus diagnostics. Despite similarities in the disease presentations, there are differences which, together with travel and vaccination history, can help guide identification, sampling and differential diagnosis.

We present three cases to highlight the difficulties which European clinicians face in recognizing travel-related imported arbovirus illnesses, and we discuss similarities and differences in clinical and laboratory findings.

Imported arbovirus infections to Europe

Case 1: Imported chikungunya case in Greece

In spring 2016, a woman in her 20s returned to Greece from Recife, Brazil, where she had stayed since November 2015. During her return travel, she developed myalgia and arthralgia for 9 days, followed by development of high fever (temperature 40 °C) and mild headache upon arriving in Greece. There was no significant medical or surgical history. At physical examination, there was no rash, hepatosplenomegaly or conjunctivitis, but she had swelling of both knees and the left wrist. Her white blood cell count was 3.2 × 10^9/L with 50% neutrophils, 34% lymphocytes and 13% monocytes, haemacrit 39.5%, platelet count 247 × 10^9/L and C-reactive protein 10 mg/dL (normal <5 mg/dL). All other tests were unremarkable. Her fever subsided over the following 72 hours, with normalization of her laboratory tests, and she was discharged after 3 days of hospitalization. She was advised to adopt safe-sex practices until results for ZIKV were received.

Molecular testing for DENV, ZIKV and CHIKV was performed at the National Reference Centre for Arboviruses in Greece on the samples taken on the second day of illness using commercial Real Time RT-PCR kits (Altona Diagnostics, Hamburg, Germany). CHIKV RNA was detected in serum and blood. An in-house nested reverse-transcriptase PCR using generic alphavirus primers [31] obtained RNA was detected in serum and blood. An in-house nested reverse-transcriptase PCR using generic alphavirus primers [31] obtained CHIKV sequence clustering in the ESCA genotype. The sequence showed 100% identity to sequences from Brazil [32]. The presence of CHIKV IgM and IgG antibodies was tested using indirect immunofluorescence test and enzyme-linked immunosorbent assay (ELISA), respectively (Euroimmun, Lübeck, Germany). A weakly positive result was obtained only for CHIKV IgM antibodies in the initial sera, while both IgM and IgG antibodies were detected in a convalescent sample taken on Day 10 of illness. Serology for DENV and ZIKV remained negative. CHIKV was isolated from her blood in Vero E6 cells, with cytopathic effects seen on the second day after inoculation. The patient had an unremarkable recovery, although arthralgia persisted for 3 more months.

Case 2: imported dengue fever case in Turkey

A 24-year-old French national presented in November 2017 at the Koç University Hospital, Istanbul, with a 3-day history of fever, fatigue and malaise, starting 4 days after returning from a 9-month residence in Cambodia.

At admission, his temperature was 38.9 °C, his blood pressure was 130/70 mm Hg and he had a right subconjunctival haemorrhage. No rash or hepatosplenomegaly was detected, and other physical examination findings were normal. Laboratory tests...
revealed a total white cell count of 3.65 × 10^9/L (reference range, 4.4–11.5 × 10^9/L), platelet count 176 × 10^9/L (reference range, 100–400 × 10^9/L), mildly elevated aspartate aminotransferase with peak level 100 U/L (reference range, 0–31 U/L), alanine aminotransferase peak 67 U/L (reference range, 0–31 U/L), lactate dehydrogenase peak 200 U/L (reference range, 135–225 U/L), γ-glutamyl transferase peak 244 U/L (reference range, 8–61 U/L) and C-reactive protein peak 27.6 mg/L (reference range, 0–5 mg/L). A further tropical diagnostic assessment was requested and blood samples taken on day 2 of hospitalization (day 5 of illness) were sent to the Public Health Institute of Turkey in Ankara. On the third day of hospitalization, he became afebrile, but his temperature increased again 2 days later. Dengue IgG and IgM antibodies (immunofluorescence test; Euroimmun) and multiplex reverse transcriptase PCR were positive, confirming acute dengue infection. He was discharged on day 7 of hospitalization (day 12 of illness), and he made a full recovery, with normalization of blood tests at outpatient review on day 14 of illness. Paired serology remained negative for leptospirosis.

Case 3: imported Zika case in Romania

A man in his 30s presented in summer 2016 at the University Hospital of Infectious Diseases, Cluj-Napoca, Romania, with a 4-day history of fever, headache, fatigue, myalgia and rash spreading from the Cantacuzino Institute in Bucharest. NS1 dengue antigen was negative in the serum samples taken at 6 days after the start of symptoms) were sent to the reference laboratory of the Cantacuzino Institute in Bucharest. NS1 dengue antigen was negative. ELISA testing (Euroimmun) for Zika IgM antibodies showed borderline values on the first two samples (index value, 0.901, with negative <0.8 and positive >1.1) with seroconversion by day 18 of illness (index value, 2.02). ELISA for Zika IgG antibodies was negative in the first two (index, 0.1) and borderline positive in the last serum samples (index, 1.064). Real-time PCR (in-house test) was positive for ZIKV RNA in the urine samples taken 5 and 8 days after symptom onset but negative in the serum samples taken at the same time. Symptomatic treatment was recommended. Counseling was provided regarding sexual transmission and the need for his partner to avoid pregnancy for 6 months. The rash disappeared after 3 days and his platelet count normalized in 1 week. No other signs and symptoms appeared during the 6-month follow-up. His wife was not tested for Zika infection and did not develop clinical illness, but she avoided pregnancy for 6 months.

Discussion

Arboviruses are found worldwide, and more than 150 are documented to cause disease in humans [1,5]. Overall, vector-borne diseases imported to Europe through travel are increasing, among them arbovirus infections such as dengue and chikungunya [2]. The clinical presentation of an acute arbovirus infection can range from asymptomatic or mild disease to severe, life-threatening courses and death, with a high disease burden in endemic countries. As a result of the broad spectrum of differential diagnoses, a rapid and targeted diagnostic approach is necessary.

The clinical syndromes of arbovirus disease can generally be divided in four main syndromes consisting of (a) fever alone or fever with (b) rash and arthralgia, (c) neurologic symptoms and/or (d) haemorrhagic symptoms [1]. Most arboviruses are associated with one or more of these syndrome complexes, with fever as a common feature for all of them, with the exception of Zika, where fever is not always present [33,37]. However, there is significant overlap between the syndromic groups (Fig. 2). Most arboviruses cause a biphasic illness with initial nonspecific symptoms for a few days, followed by improvement, then either resolution or more severe features starting about a week after the onset of symptoms. Common laboratory features of all three arboviruses are decreased white cell counts and platelet counts, which is less pronounced in Zika infection. Tables 1 and 2 show the clinical and laboratory findings in chikungunya, dengue and Zika infections.

Chikungunya infection (case 1) is usually associated with abrupt onset of fever and malaise after an incubation period of 3 to 7 days, although this can extend to 12 days. Most infected patients (>75%) develop symptoms [21]. Distinction from dengue may be difficult, especially in travellers returning from areas where both infections are circulating [38]. Typical symptoms include fever that can exceed 39°C and polyarthralgia. Symmetrical bilateral arthralgia is found in most patients and is usually located in the peripheral joints, appearing shortly after the onset of fever (2–5 days). There may also be visible or palpable swelling. A macular or maculopapular rash is commonly seen, occurring in up to 75% of patients. Other symptoms include pruritus, conjunctivitis, headache, myalgia and gastrointestinal symptoms [39,40]. Laboratory abnormalities that are commonly seen in chikungunya infection include lymphopenia, thrombocytopenia and elevated aminotransferase levels [39,40].

Fig. 2. Summary of arbovirus syndromes together with fever: central nervous system, fever arthralgia rash and viral haemorrhagic fever. (a) alphavirus, (c) coltivirus, (f) flavivirus, (b) bunyavirus, (n) nairovirus and (p) phlebovirus. CCHF, Crimean Congo haemorrhagic fever; CHIKV, chikungunya; CTFV, Colorado tick fever; DEN, dengue; EEEV, Eastern equine encephalitis; JEV, Japanese encephalitis; LACV, La Crosse virus; MVEV, Murray Valley encephalitis; ONNV, O’nyong-nyong virus; RRV, Ross River fever; RVFV, Rift Valley fever; SLEV, St Louis encephalitis; TBEV, tick-borne encephalitis; VEEV, Venezuelan encephalitis; WEEV, Western equine encephalitis; WN, West Nile fever; YFV, yellow fever; ZIKV, Zika virus. Adapted with permission from Solomon T, chapter 40 in Beeching N, Gill G, eds., Lecture notes: tropical medicine (New York: Wiley, 2014), p. 274.
Patients present with high fever accompanied by headache, vomiting, pain behind the eyes, back pain, and myalgia and arthralgia are usually seen in the febrile phase, which lasts about 2 to 7 days. Other symptoms may include gastrointestinal manifestations such as diarrhea, vomiting, pain and nausea, as well as symptoms such as pruritus and increased capillary permeability and, in severe illness, bleeding and significant plasma leakage. Laboratory findings in this phase include increased haematocrit, thrombocytopenia and leucopenia, particularly neutropenia. The risk of having complications and progressing to severe dengue is highest in this phase. The recovery phase that follows is characterized by fluid resorption and gradual recovery.

In Zika infection (case 3), symptoms are the most nonspecific of all three viruses, and differential diagnosis remains a challenge. A large proportion of infections remain asymptomatic, and only 20% to 25% of infected individuals manifest symptoms [47]. Acute Zika infection is usually characterized by low-grade fever (temperature up to 38.5°C), rash, arthralgia and conjunctivitis. Other symptoms include myalgia, headache, eye pain and asthma [48,49]. A maculopapular rash is seen in approximately 90% of patients, but fever is less pronounced and less common than in chikungunya and dengue infections, affecting 40% to 75% of patients; thrombocytopenia is also much less common. As highlighted in case 3, asymptomatic infections have to be considered in case pregnancy is planned after travel of the patient or his partner to an endemic area. Current recommendations do not recommend testing asymptomatic returning travellers; therefore, emphasis should be placed on providing pretravel advice to couples that are planning pregnancy [50,51].

In the diagnostic approach for the three arboviruses presented here, both serology and direct virus demonstration (such as PCR testing), are useful but several characteristics of the viruses influence time- and cost-effective diagnostic assessment. Serologic testing includes detection of IgG and IgM antibodies, which are usually present by a week after onset of symptoms of all three viruses. DENV and ZIKV are both flaviviruses, so cross-reactivity of antibodies may be a problem. Positive antibody findings may be due to acute infection, but they could also result from previous infection with the same or another flavivirus, or after previous immunization against yellow fever or tick-borne encephalitis [52]. This cross-reactivity can complicate the interpretation of results, and exposure and immunization history should be checked and the information delivered to the laboratory. Frequent travellers who have received immunizations against yellow fever, Japanese encephalitis or tick-borne encephalitis can show a considerable antibody background for flaviviruses that can mimic a wild-type flavivirus infection.

Direct virus detection by PCR, which is highly specific when positive, is another option for diagnosing flaviviruses. However, the duration of viraemia in flavivirus infections is short, and therefore PCR test positivity is confined to the first few days of illness. This window is often missed in returning travellers, especially if their symptoms start while still abroad. For dengue, direct detection of the virus antigen NS1 in blood can prolong the window up to 7 days [44]. Of wider interest, it has recently been shown that detection of virus RNA in urine can prolong the window for PCR diagnosis for up to several weeks after onset of symptoms of dengue and other arboviruses [53–55]. Diagnostic testing for other, more rare arboviruses beyond the three common ones presented here is mostly limited to specialized laboratories.

Conclusions

The identification and diagnosis of acute arbovirus infections can be challenging and laborious for both physicians and clinical virologists, although the combination of epidemiology, clinical syndromes and findings in basic blood tests such as blood count may provide useful clues. As arboviruses are an emerging group of viruses in Europe and beyond, and as access to highly specified diagnostics is often limited, recognition of suspected arbovirus

### Table 1
Comparison of selected clinical findings in chikungunya, dengue and Zika infections

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Chikungunya</th>
<th>Dengue</th>
<th>Zika</th>
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<tbody>
<tr>
<td>Fever</td>
<td>+++</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Rash</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Myalgia</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Oedema</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Retro-orbital pain</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>+++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

Adapted and modified with permission from [33,34]. ++++, very common; ++, frequently observed; +, sometimes observed; –, not typical.

### Table 2
Comparison of baseline laboratory findings in chikungunya, dengue and Zika infections

<table>
<thead>
<tr>
<th>Laboratory finding</th>
<th>Chikungunya</th>
<th>Dengue</th>
<th>Zika</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>++</td>
<td>++++</td>
<td>–/+</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>++</td>
<td>+</td>
<td>–/+</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>++</td>
<td>+</td>
<td>–/+</td>
</tr>
<tr>
<td>Increased CRP</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>+</td>
<td>++</td>
<td>–</td>
</tr>
</tbody>
</table>

Adapted and modified with permission from [33]; additional data from [35,36]. ALT, alanine aminotransferase; CRP, C-reactive protein; ++++, very common; ++, frequently observed; +, sometimes observed; –, not typical. *If observed, thrombocytopenia is usually mild.

The viraemic period can range from 2 to 10 days, with a total duration of acute illness of approximately 7 to 10 days. Some patients experience persistence or relapse of arthralgia for months, and in a severe course of disease, three phases can be seen that consist of a febrile phase, a critical phase and a recovery phase [44]. Travellers are also reported as long-term sequelae [43].

DENV infection (case 2) is classified by the World Health Organization in the following categories: dengue without warning signs, dengue with warning signs and severe dengue [44]. During the course of disease, three phases can be seen that consist of a febrile phase, a critical phase and a recovery phase [44]. Travellers are usually seen in the febrile phase, which lasts about 2 to 7 days. Patients present with high fever accompanied by headache, vomiting, myalgia, arthralgia and a transient blanching discrete or coalescent macular rash. This rash often has ‘islands of white in a sea of red’ [5]. Pruritus may be present initially. Severe headache, pain behind the eyes, back pain, and myalgia and arthralgia are reported in up to 70% of cases [45], with rash in approximately 50%. Other symptoms may include gastrointestinal manifestations such as diarrhoea, vomiting, pain and nausea, as well as symptoms resembling a respiratory tract infection (cough, running nose, sore throat, injected pharynx). Mild haemorrhagic manifestations like petechiae and mucosal membrane bleeding from the gums or nose can occur [44]. In this phase, clinical features are indistinguishable between severe and nonsevere dengue and are also difficult to distinguish from other nondengue febrile illnesses. The tourniquet (Hess) test is advocated to identify severe disease early: a blood pressure cuff is inflated to between systolic and diastolic pressure for 5 minutes, and the resulting petechiae are counted. However, the specificity and sensitivity of this test is moderate [46]. Laboratory abnormalities include a decreased white blood count, particularly neutropenia. The febrile phase may follow by defervescence around days 3 to 7 of illness and is characterized by...
infections should be addressed both in clinical training and in research on diagnostics and therapeutics.

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Transparency Declaration

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References


