Dengue and chikungunya infections in travelers

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Purpose of review

Dengue and chikungunya are arboviruses that have caused major outbreaks and infected travelers, and both can be associated with fever and rash. We review the recent epidemiology of dengue and chikungunya infections and discuss their clinical presentations, diagnosis, treatment, and prevention. We highlight the findings in travelers.

Recent findings

Globally dengue is one of the most common infections associated with travel, and incidence has increased in the Americas in recent years, especially in Brazil. Chikungunya has caused dramatic outbreaks in the Indian Ocean islands since 2004, and has spread to south and south-east Asia. Dengue virus and chikungunya virus also possess the potential to cause autochthonous transmission in temperate regions of developed countries due to the presence of the vector mosquito, *Aedes albopictus*. Such an outbreak (chikungunya infection) did occur in 2007 in Italy. A mutation in chikungunya virus (A226V) appears to improve virus survival in *Aedes albopictus* and also increase its virulence.

Summary

The findings assist in differentiating dengue and chikungunya from other acute febrile illnesses and from each other. The findings also illustrate potential outbreaks in nonendemic countries, important toward developing control and prevention strategies.

Keywords

alphavirus, chikungunya, dengue, flavivirus, travelers

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Introduction

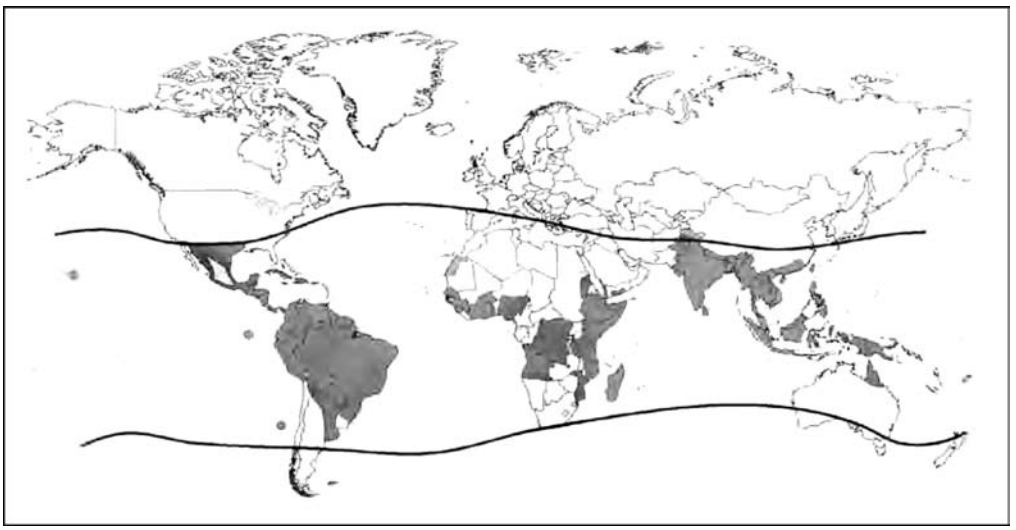
Fever is a common reason for seeking medical care after travel. Because some infections in returned travelers can progress rapidly and require urgent interventions, it is important to have a working knowledge of the more common causes in fevers, especially those that are treatable and can be severe. Among 25 000 returned ill travelers seen at GeoSentinel clinics around the world between 1997 and 2006, 28% sought medical care for fever [1,2]. Dengue fever was the second most common specific infection, after malaria. Another GeoSentinel analysis showed that the spectrum of illness after travel varied depending on the place of exposure [3]. Dengue fever was the top specific etiologic agent in travelers returning from south-east Asia and among the top three diagnoses in travelers from all other regions except sub-Saharan Africa and Central America. Because of extensive overlap in the regions with risk of exposure to dengue and malaria, it is essential to always evaluate a febrile returned traveler promptly for malaria. Rarely coinfection with malaria parasites and dengue virus (DENV) has been reported.

Additional infections that cause undifferentiated fever in returned travelers include rickettsial infections, enteric fever, viruses that cause mononucleosis-illnesses [Epstein–Barr virus, cytomegalovirus, and acute HIV], toxoplasmosis, and amebic liver abscesses. Common cosmopolitan infections and noninfectious diseases should also be considered in returned travelers with fever. Because of the relatively short incubation periods of dengue and chikungunya fevers, these diagnoses should be suspected only in travelers whose symptoms begin within 2 weeks of their last exposure.

The vectors

Both dengue and chikungunya viruses are transmitted to humans by the bite of an infective mosquito. Transmission by other routes (e.g. transfusion, transplacental, needlestick, or other nosocomial exposures) occurs rarely [4,5]. The most common vector for both viruses is *Aedes aegypti*, a vector that is now widely distributed in tropical and subtropical areas worldwide (Fig. 1) [6••]. Because *Aedes aegypti* can also transmit the yellow fever virus,

Figure 1 Countries/areas at risk of dengue transmission, 2008



The contour lines of the January and July isotherms indicate the potential geographical limits of the northern and southern hemispheres for year-round survival of *Aedes aegypti*, the principal mosquito vector of dengue viruses. Reproduced with permission from [6••].

attempts were made to eradicate the mosquito from the Americas in the mid-20th century. The mosquito was reintroduced largely via ship trade. It is extremely well adapted to today's urban environment and feeds preferentially on humans. It breeds in discarded plastic cups and other trash, flowerpots, used tires, and other sites that are abundant in cities. It enters houses, so exposures can occur indoors. Because it is a nervous feeder, if its blood meal is interrupted, it will resume feeding on another person, sometimes resulting in clusters of infection in a household. It is most active in the hour or two after sunrise and an hour or two before sunset, but its behavior may be altered in a brightly lit urban environment. For example, *Aedes aegypti* mosquitoes in Trinidad did not bite after 19:00 h in rural areas (both indoors and outdoors). In well lit urban areas about 10% of mosquito activity was after 19:00 h [7].

Another mosquito, *Aedes albopictus* – the Asian tiger mosquito, can also transmit both dengue and chikungunya viruses. Originally found in Asia, it has invaded other areas and is now widely distributed in the Americas, Europe, Africa, and the Pacific Islands [8,9]. Many introductions are attributable to air traffic and container ships, especially international shipping of used tires [10]. *Aedes albopictus* can survive cooler temperatures than *Aedes aegypti*, feeds on more different hosts, can breed in natural containers (e.g. water in plants) as well as artificial ones, and can be found in rural, suburban, and forested areas. It was the main vector for dengue outbreak in Hawaii in 2001 and has been an important vector in several of the recent chikungunya fever outbreaks. Strains of *Aedes albopictus* and *Aedes aegypti* collected in Florida [11] and *Aedes albopictus* from southern France [12] have been shown in the laboratory to be susceptible to chikungunya viruses, so future outbreaks are possible if temperatures are sufficiently warm. In Asia, the most important vector is *Aedes aegypti*, but *Aedes albopictus* has been an important and competent vector, particularly in the recent outbreaks in La Reunion and Italy.

The viruses

Although both DENV and chikungunya virus (CHIKV) are RNA viruses transmitted through mosquito bites, they belong to different families. DENV is in the family *Flaviviridae*, genus flavivirus, which includes yellow fever virus, Japanese encephalitis virus, and West Nile virus. There are four serotypes and a number of genotypes with varying virulence. DENV is relatively small, has three structural proteins, and seven nonstructural proteins surrounded by a lipid envelope. Serologic tests used to diagnose DENV cross-react with other flaviviruses.

CHIKV is in the family *Togaviridae*, genus alphavirus, which includes Barmah Forest virus, O'nyong-nyong virus, Mayoro virus, Ross River virus, and Venezuelan equine encephalitis virus. The virion consists of a nucleocapsid core surrounded by a lipid envelope. There are two envelope glycoproteins and four nonstructural proteins [13••]. Phylogenetic analysis of CHIKV has determined three genotypes essentially by geographical distribution: central/east African, Asian, and west African.

The recent CHIKV outbreaks in La Reunion identified a mutation in the viral gene encoding the envelope protein

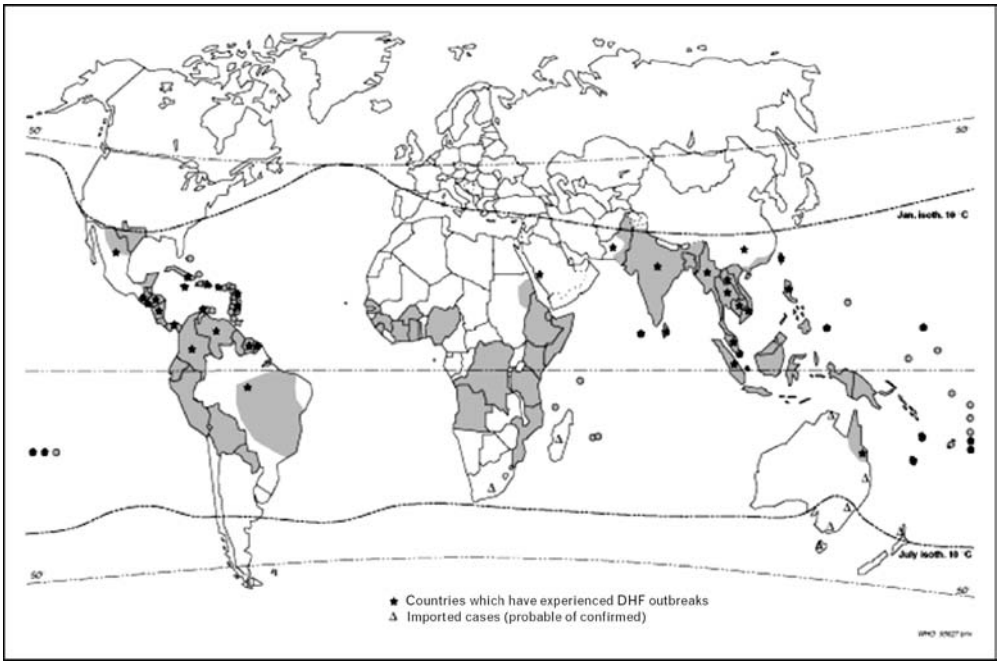
(A226V) that appeared to improve viral survival in *Aedes albopictus* as well as to enhance its virulence [14,15]. One analysis of glycoprotein E1 sequences found that a strain related to the central/east African strain caused outbreaks on La Reunion, Seychelles, Mayotte, Madagascar, and Mauritius islands, and that the A226V strain emerged in La Reunion around September 2005 [14]. Another study found that the E1-A226V mutation significantly increased CHIKV infectivity for *Aedes albopictus* and was more efficient in viral dissemination in mosquitoes and in transmission to mice [15].

Dengue

Dengue fever is widely distributed in tropical and subtropical countries. Although virtually all human cases result from person-to-person transmission by a mosquito vector, DENVs also circulate in a sylvatic (enzootic) cycle involving nonhuman primates; viruses from primates rarely infect humans [16]. Approximately, 2.5 billion humans live in areas with the risk of dengue exposure; an estimated 50–100 million cases of dengue occur annually. Cases have increased in number and severity in recent years. In past decades the heaviest burden from dengue fever was found in south-east Asia and the western Pacific regions, but in the last 3 decades, a dramatic increase has been observed in the Americas [17,18]. Between 1998 and 2008 about 70% of the dengue cases reported in the Americas came from Brazil, where major epidemics have occurred in tropical cities. The average annual incidence in Brazil exceeded 200 of 100 000 during the period 2000–2007 [17] (Fig. 2) [19].

Typical dengue fever is characterized by abrupt onset of fever, headache, severe myalgia ('breakbone' fever), and arthralgia. Gastrointestinal symptoms may also be prominent. A rash is noted in about half the cases. Early generalized erythema may be noted; a maculopapular rash may appear later. Minor bleeding phenomena, such as petechiae and nosebleeds, may also be present. The incubation period is typically 4–7 days (range 3–14). Although clinical manifestations may vary with the specific serotype or genotype, most infections are asymptomatic or mild, and most infections are self-limited, with fever lasting 2–7 days. The ratio of asymptomatic to symptomatic infections ranges from 2 : 1 to 10 : 1. Complicated forms, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), are increasing in number as more populations in larger regions of the world have already been infected with one or more dengue serotypes and are at increased risk for complicated dengue. With increasing urbanization in tropical and developing countries, more urban areas have a sufficiently large population, somewhere between 150 000 and 1 million, to allow the ongoing circulation of one or more dengue serotypes [20]. Infection with a DENV produces transient immunity to all DENV and long-lasting immunity to that serotype but an increased risk for severe dengue after infection with heterotypic DENVs (antibody-dependent enhancement). Presence of preexisting antibodies to

Figure 2 The general distribution of dengue fever and/or dengue haemorrhagic fever, 1975–1996



DHF, dengue haemorrhagic fever. Reproduced with permission from [19].

DENV can promote entry of a different serotype into Fc-receptor-bearing cells and ultimately is associated with increased viral replication. Higher levels of viremia are associated with more severe disease. Investigators have recently identified two mechanisms of immune evasion that are induced by DENV complexed with preexisting antibodies that enter human monocytic cells [21]. This allows the virus to circumvent the normal intracellular antiviral state of the host cell.

Common laboratory abnormalities are leucopenia with a relative lymphocytosis and thrombocytopenia. Liver enzymes may be elevated. In addition to DHF and DSS, other complications reported in patients with dengue infections include myocarditis, hepatitis, and neurologic events. Prolonged fatigue may follow infection.

A study that analyzed 1955 suspected dengue cases in Puerto Rico found 108 laboratory-confirmed cases. The confirmed patients demonstrated five variables that differentiated dengue from other febrile illnesses: retro-orbital pain, rash, platelet count less than 240 000 cells/mm^3, absence of sore throat, and absence of cough [22••].

No specific drugs are available to treat dengue infections, but expert, supportive care can be lifesaving. In some outbreaks mortality has exceeded 20% in DHF/DSS; case fatality rates less than 1% have been reported by institutions experienced in treating complicated dengue infections. The 2009-WHO dengue document contains practical guidance to monitor and manage classic and complicated dengue [6••].

Dengue infection can be confirmed by viral isolation, nucleic acid detection, or antigen detection. Virus can usually be detected for 4–5 days after onset of symptoms. Cell culture using mosquito cell line is most commonly used for viral isolation. Although these tests have the greatest specificity, most clinical laboratories do not have the capacity to grow viruses. Reverse transcription-PCR assays are more widely available and more sensitive than viral isolation, and have more rapid turnaround time.

Studies to detect antibodies are more commonly used, in particular (immunoglobulin M) IgM capture ELISA. Antibodies are detectable in 50% by days 3–5 after onset, 80% by day 5, and 99% by day 10 after initial symptoms [6••]. Patterns of antibody response differ between primary and secondary infections, with primary dengue infections invoking stronger and more specific IgM response than is found in secondary infections, which have stronger and more rapid (immunoglobulin G) IgG response. Prior vaccination against another flavivirus (e.g. JE, YF) or prior infection with nondengue flaviviruses (including West Nile) can potentially influence antibody responses measured in some assays.

Travelers play a critical role in introducing DENV into new areas. Travelers can also serve as sentinels, and diagnosis of dengue in returned travelers has identified regions where dengue transmission is occurring, allowing alerts to the global community, sometimes before a dengue outbreak has been officially reported. Data from the GeoSentinel network showed annual oscillations in reported cases of dengue in returned travelers that reflected the seasonality of infection in dengue-endemic areas [23]. An increase in cases of travelers can herald an epidemic in endemic areas.

Prospective studies that have assessed the likelihood of dengue infection in travelers during visits to dengue-endemic areas found seroconversion of 2.9–6.7% [24,25]. The Boston Area Travel Medicine Network (BATMN) found dengue seropositivity in 19% of travelers who have visited dengue endemic countries; only about 10% of the seropositives gave a history of dengue fever [26].

Vaccines

Development of a well tolerated and effective vaccine against dengue faces major challenges.

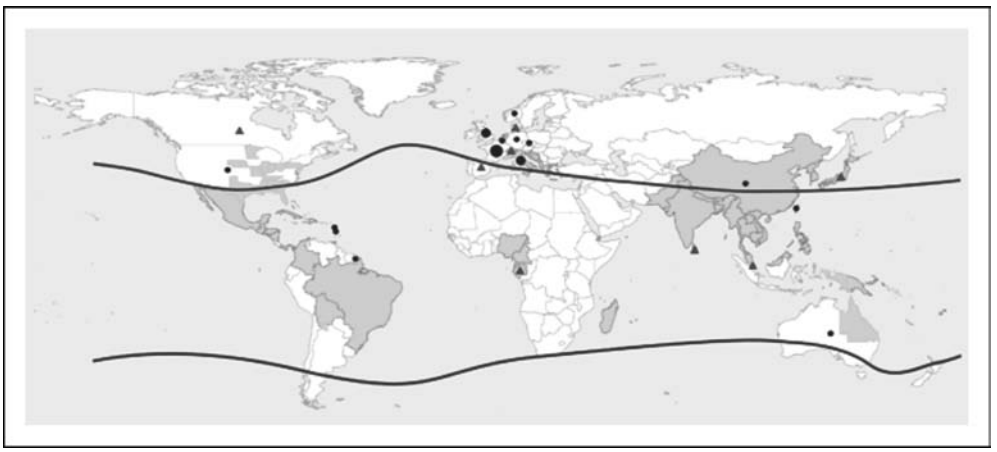
Because the antibodies against the DENV are serotype specific, a vaccine must generate simultaneously long-lasting antibodies against all four serotypes. Another challenge to vaccination in dengue endemic areas is that infants are often born with maternal antibodies to DENV. The window of time may be short between the loss of these antibodies and infection with circulating DENV in highly endemic areas [27].

Chikungunya

Chikungunya fever is an acute febrile illness associated with arthritis and arthralgia, initially identified in Tanzania in the 1950s. CHIKV subsequently caused outbreaks in central, southern, and western Africa, as well as eastern Africa. Since the 1950s, CHIKV outbreaks have occurred in south and south-east Asia, including Thailand, India, and Pakistan [28,29•].

Retrospective assessment determined that the recent CHIKV outbreaks started in 2004 in Lamu, Kenya, where an estimated 13 500 persons (>70% of the population) were infected [30]. CHIKV infections spread to the Indian Ocean islands next, initially in the Comoros and then La Reunion, where 244 000 cases occurred by April 2006 in a population of 766 000; the estimated attack rate was 35% [28]. CHIKV outbreaks spread to Mayotte, Mauritius, Seychelles, and Madagascar, and subsequently to India, Sri Lanka, Indonesia, Malaysia, and Thailand [28,29•] (Fig. 3) [31].

Figure 3 Distribution of imported chikungunya infection



Reproduced with permission from [31].

During the dramatic outbreaks in 2005–2006, imported chikungunya cases were initially reported in European travelers returning from the Indian Ocean islands [32–34]. Subsequently imported CHIKV was reported globally (Fig. 3). In July and August of 2007, an outbreak of autochthonous CHIKV infection occurred in northeastern Italy with 205 confirmed cases associated with an index case from India [35]. This was the first autochthonous transmission in a temperate region, an alarming event because the vector, *Aedes albopictus*, is widespread in many states in the United States and Europe [8,11,36,37].

The incubation period for CHIKV infection is most commonly 3–7 days (range 2–12). Infection is asymptomatic in 3–25% [29•]. Clinical manifestations of chikungunya fever typically include acute onset of high fever, severe joint pain, and rash. The male : female ratio of confirmed cases from La Reunion was 1.24 : 1 [38]. Most patients experienced fever (89%) and polyarthralgia (96%), and some had gastrointestinal symptoms (47%) and rash (40%) [37]. Patients typically had high fever (mean of 38.9°C), symmetrical joint pain (73%) that involved more than one joint – mainly distal and lower limbs [38]. Rash, sometimes bullous, usually spared the face and was accompanied by pruritus in 50%. Some patients had lymphadenopathy (9%), aphthous ulcerations, and dry cough. Hemorrhagic findings occurred in 6%, although some had alternative explanations (oral anticoagulant therapy, pulmonary embolism) [38]. Case fatality rates varied among the affected populations, being about 1 of 1000 population in La Reunion [39].

Persistent arthralgia and arthritis was frequently reported from La Reunion [40,41]. Among 88 adult patients followed, 56 (64%) reported persistent arthralgia 18 months after acute CHIKV infection; 55% reported continuous pain; all were polyarticular, and 40% also had persistent IgM positivity [40].

Unusual manifestations of CHIKV infection include encephalopathy/encephalitis/meningoencephalitis, seizures, neuropathy, Guillain–Barré syndrome, cerebellar syndrome, myocarditis/pericarditis, heart failure, arrhythmias, unstable blood pressure, ischemic heart disease, nephritis, acute renal failure, pigmentation, genital ulcers, bullous dermatosis, optic neuritis, iridocyclitis, episcleritis, retinitis, antepartum fetal deaths, disseminated intravascular coagulation, pneumonia, respiratory failure, hepatitis, pancreatitis, syndrome of inappropriate secretion of antidiuretic hormone, hypoadrenalism [42].

Travelers infected with chikungunya presented commonly with fever, polyarthralgia or polyarthritis, and rash [32,43,44]. The joint involvement is usually bilateral and symmetrical, especially distal joints such as hands, wrists, feet, and ankles. Exanthems resembled those seen in DENV infection, usually widespread macular or maculopapular with islands of sparing. Some have described ulcers and vesiculobullous lesions. Some imported cases of CHIKV have persistent arthralgia beyond 2 years, particularly those infected in La Reunion [44].

The diagnosis of CHIKV infection can be confirmed by viral culture, reverse transcriptase-PCR to detect viral RNA, or antibody tests including ELISAs, immunofluorescence assays, and plaque reduction neutralization test [29•]. ELISAs are more readily available to clinicians.

Patients with persistent symptoms attributed to CHIKV also have a high prevalence of mixed cryoglobulinemia [45]. Among 66 suspected CHIKV cases, 51 had anti-CHIKV IgM. Six were IgM-negative initially when sera

were kept at 4°C, but became positive when the sera were incubated for 2 h at 37°C. 94% of CHIKV-seropositive patients screened for cryoglobulinemia were positive, and more than 90% had concurrent arthralgias and cryoglobulinemia, some persisting for a year. The positivity and level of cryoglobulins declined with time and as patients recovered, and could serve as a prognostic marker [45].

Treatment of CHIKV infection aims to relieve symptoms. Medications include nonsteroidal anti-inflammatory drugs and corticosteroids. Chloroquine has anti-inflammatory properties, but an open-label study was inconclusive [13••]. Quinine inhibits CHIKV replication *in vitro* and targets the nsP1 protein, an important component of pathogenicity in another alphavirus, Sindbis virus [13••]. Other candidates include ribavirin, the combination of interferon and ribavirin, carbodine, small RNA molecules, and some plant compounds [13••]. A recent study of CHIKV immunoglobulins demonstrated in-vitro neutralizing activity and showed efficacy in preventing as well as treating CHIKV infections in mouse models [46••].

CHIKV outbreaks in temperate regions could affect the blood supply. CHIKV infections were associated with high viral titers, around $10^{3.9}$ to $10^{6.8}$ [47]. The CHIKV outbreaks in La Reunion and Italy required a temporary halt to blood donations and importation of blood products [48].

Overlap of dengue and chikungunya and implications in outbreak countries

Singapore exemplifies a country with both *Aedes aegypti* and *Aedes albopictus* mosquitoes, is endemic for dengue, and has had local CHIKV outbreaks. The initial CHIKV outbreak occurred in 2008 with the wild-type central/east African genotype and was primarily transmitted by *Aedes aegypti*. Viruses in subsequent outbreaks had the A226V mutation, and *Aedes albopictus* was the main vector [49]. The discovery of the more aggressive A226V mutant with a preference for *Aedes albopictus* led to an expanded vector control program in Singapore to include *Aedes albopictus* targets [49].

Table 1 Comparison of symptoms and findings in dengue and chikungunya infections

	Dengue	Chikungunya
Fever	++	+++
Rash	++	++
Arthralgia/arthritis	−	+++
Myalgia	++	+
Retro-orbital pain	++	+/−
Hypotension	++	+/−
Bleeding	++	+/−
Neutropenia	+++	+
Thrombocytopenia	+++	+

COID Dengue Chik Table 2010.

The basic reproductive number for CHIKV is considered to be lower than that for DENV. Mathematical models estimated the risk of DENV infection in travelers range from 43 to 1700 per 100 000 travelers who visit Singapore for 1 week [50]. Similar models have also derived the risk of CHIKV infection to be 22% in a local resident but lower (0.31–1.23%) in visiting travelers depending on the duration of stay [51].

Conclusion

Because both DENV and CHIKV can cause fever and exanthems, both diagnoses are frequently considered in febrile patients. Since 2006, cocirculation of DENV and CHIKV has confounded the diagnosis of febrile patients [52,53]. Coinfection with DENV and CHIKV has also occurred in travelers [54]. Table 1 compares some clinical features of DENV and CHIKV. Currently, avoidance of bites and vector control programs are essential to prevent the local transmission of DENV and CHIKV in temperate regions with *Aedes* mosquitoes, if the viruses are introduced into those regions during summer months.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 531).

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