Abstract

First described in 1952, the chikungunya virus may soon spread to warmer parts of the United States as a result of increased globalization. Patients infected by this mosquito-borne virus typically present with arthralgia and may also have fever, headache, nausea, rash, and fatigue; some patients may be asymptomatic while others may require emergency hospitalization. Both Zika and chikungunya viruses have been linked to neurodevelopmental delays in the child, but chikungunya is more readily transmitted from mother to child in the perinatal period rather than in the womb. Although related to Zika, the chikungunya virus is characterized by an acute phase of several days followed by episodic relapses which may go on for months or even years. In rare instances, chikungunya may be fatal. There is currently no vaccine to prevent chikungunya and treatment consists of supportive care in alleviating symptoms, mainly managing arthralgia. Clinicians should be aware of chikungunya and educate patients on preventive strategies, mainly by limiting exposure to mosquitoes.

Keywords: chikungunya, pain, arthralgia

Introduction

The chikungunya virus (CHIKV) is an arbovirus transmitted by the *Aedes* mosquito. Although the virus had been identified over 50 years ago [1], the first significant outbreaks of CHIKV infection occurred only recently, such as in 2006 in Reunion Island and the 2013-2014 Caribbean and American outbreak with an estimated one million cases [2-4]. CHIKV takes its name from the Makonde (Bantu) language of Tanzania, where it was first described in 1952; the term means roughly “contorted” or “one who bends up” because of the severe joint pain that can make normal posture difficult or impossible to maintain [5,6].

CHIKV is endemic to Africa and parts of Asia, and with increased globalization, it has spread to Europe and the Americas [7]. It is thought to pose a particular threat to the warmer portions of the United States where mosquitoes are plentiful [7]. Chikungunya outbreaks have occurred in Africa, Asia, India, Europe and the Caribbean. The Centers for Disease Control and Prevention (CDC) in Atlanta considers the CHIKV to be a rare disease with fewer than 1000 cases per year in the United States [8], but its incidence may increase with time.
A promising new vaccine is in development, but no vaccine is commercially available yet [9]. The best strategies against CHIKV remain education and prevention.

Geographical manifestations

CHIKV has long been known to infectious disease experts, but the earliest clinical experiences with the infection occurred in relatively small, contained outbreaks at geographically circumscribed locations. Outbreaks have grown increasingly larger, more frequent, and in increasingly distant locations. See Table 1. The chikungunya virus was recently detected in Eastern Peru [10] and it is anticipated to become more prevalent in Vietnam [11].

Table 1: Outbreaks of CHIKV have occurred all over the world with notable appearances in over 60 nations in Africa, Asia, Europe, and North America [5,6,8,32,46,54,69-71]

<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>1952</td>
<td>Tanzania</td>
<td>CHIKV first described</td>
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<tr>
<td>1969</td>
<td>Sri Lanka</td>
<td></td>
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<tr>
<td>1975</td>
<td>Vietnam</td>
<td></td>
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<td></td>
<td>Myanmar</td>
<td></td>
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<tr>
<td>1982</td>
<td>Indonesia</td>
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<tr>
<td>1999-2000</td>
<td>Democratic Republic of the Congo</td>
<td></td>
</tr>
<tr>
<td>2005-2007</td>
<td>Reunion Island and other islands in Indian Ocean</td>
<td>Affected about one-third of total population of Reunion Island</td>
</tr>
<tr>
<td>2006-2007</td>
<td>India, Southeast Asia</td>
<td>About 1.4 million affected mostly in Southern India</td>
</tr>
<tr>
<td>2007</td>
<td>Gabon</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Italy and other parts of Europe</td>
<td>197 cases</td>
</tr>
<tr>
<td>2011</td>
<td>West Bengal, India</td>
<td>76 cases</td>
</tr>
<tr>
<td>2013</td>
<td>St. Martin, Caribbean</td>
<td>2 cases</td>
</tr>
<tr>
<td>2014</td>
<td>France</td>
<td>4 cases</td>
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<tr>
<td></td>
<td>Pacific Islands</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Florida, USA</td>
<td>12 locally acquired cases</td>
</tr>
<tr>
<td></td>
<td>Puerto Rico, USA</td>
<td>Sero-surveys found that about 25% of Puerto Rican blood donors had acquired CHIKV infections</td>
</tr>
<tr>
<td></td>
<td>Suriname</td>
<td></td>
</tr>
<tr>
<td>2014-2015</td>
<td>Colombia</td>
<td>Over 1 million suspected cases</td>
</tr>
<tr>
<td>2015</td>
<td>Dakar, Senegal, and Punjab, India</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>Cook Islands, Marshall Islands, American Samoa, French Polynesia, Samoa, Kiribati</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Argentina</td>
<td>First cases reported</td>
</tr>
<tr>
<td></td>
<td>Delhi, India</td>
<td>Over 2600 cases reported</td>
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<tr>
<td></td>
<td>Mandera County, Kenya</td>
<td>260 cases in a small township (population 90,000) reported in 2016</td>
</tr>
<tr>
<td></td>
<td>Cavite, Philippines</td>
<td>About 400 cases in late 2016</td>
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<tr>
<td>2017</td>
<td>Dhaka, Bangladesh</td>
<td>13,176 clinically confirmed cases in 17/64 districts</td>
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<td></td>
<td>Pakistan</td>
<td>More than 30,000 suspected cases</td>
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<tr>
<td></td>
<td>Europe</td>
<td>France and Italy (&lt;20 cases each, not all confirmed) as two distinct events</td>
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<tr>
<td></td>
<td>Brazil</td>
<td>CHIKV identified in 11 of the 13 cities studied</td>
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<tr>
<td></td>
<td>Indonesia</td>
<td>15 confirmed cases in Northern Bali region and 8 confirmed cases in Sumatra</td>
</tr>
</tbody>
</table>

Clinical Presentation

The clinical presentation of CHIKV is often benign, but it can also be severe enough to warrant emergency hospitalization [4]. Patients typically experience arthralgia, which can be mild to severe and varies in duration; the associated joint pain, which is typically bilateral and symmetric, can be debilitating [5]. Other symptoms may include fever, headache, nausea, fatigue, and rash [5,12]. About 40% to 75% of CHIKV infected individuals will have
cutaneous symptoms, such as a maculopapular rash on the face, trunk, and limbs as well as on the palms of the hand and the soles of the feet. The rash may or may not be pruritic and typically resolves in about a week. Ocular symptoms may include iridocyclitis, retinitis, and conjunctivitis [13]. Patients may also report fatigue, nausea, muscle pain, and diarrhea. It has been estimated that 3% to 28% of CHIKV infections are asymptomatic [2,14,15], and the rate of asymptomatic infection is even higher in children, estimated at 35% to 40% [16].

In a study of 65 CHIKV-infected patients admitted to an intensive care unit (ICU) during the Caribbean outbreak in 2013-2014, 83% had a preexisting condition (such as chronic hypertension, diabetes mellitus, chronic heart failure or chronic renal failure) [17]. In this population 57% required mechanical ventilation and the hospital crude mortality rate was 27%. Septic shock occurred in about 10% of these patients [17]. Vulnerable populations such as neonates and small children, those ≥ 65 years, and individuals with other medical conditions typically have more severe clinical presentation of CHIKV than older children and adults (<65 years) [16].

The acute phase of CHIKV lasts about seven to ten days followed by a chronic phase with persistent or relapsing arthralgia (particularly of distal extremities) and sometimes morning stiffness [18-20]. One study found that 60% of patients who experienced CHIKV infection experienced episodic relapse and recovery for three years after the initial infection; the arthralgia was described by 77% as incapacitating and 56% reported it was accompanied by depression [19,20]. In a study of 47 CHIKV-infected adults in France, 48% reported symptoms of joint pain six months after infection [21]. Forty-seven percent of Reunion Island patients reported persistent symptoms two years after the initial infection [18]. The risk factors for long-term arthralgia following CHIKV infection include: older age (＞34 years), the presence of arthralgia four months after initial symptoms, and the presence of comorbid conditions [22]. In a study from Colombia (n=152 CHIKV-infected patients), roughly half (54%) experienced chronic rheumatologic sequelae six weeks to six months after the onset of symptoms [23]. In rare instances, CHIKV infection may be fatal with encephalitis, encephalopathy, myocarditis, and hepatitis reported. Multiorgan failure and septic shock have also been reported [24,25].

Infants have different symptoms than older children and adults. In a study of 56 infants with confirmed cases of CHIKV infection (all were under 1 year of age), fever was present in all and the most commonly observed signs were lethargy, irritability, excessive crying, acrocyanosis, and symmetrical superficial vesiculobullous lesions [26]. In some cases, erythematous asymmetrical macules were observed, which progressed to morbilliform rashes but did not spread to the face and oral cavity.

The chikungunya virus

The CHIKV is a spherical, enveloped, very small (60-70 nm diameter) 12 kb positive-stranded RNA genome of *Alphavirus togaviridae* [6,27]. The ubiquitin proteasome system (UPS) is a major system for protein degradation in eukaryotic cells [28]. Many positive-stranded RNA viruses, including CHIKV, depend on the UPS for replication [29]. A recent study found that CHIKV replication depends in part on μ-calpain (Calpain-1; CAPN1), a type of calcium-dependent non-lysosomal cysteine protease [29]. Although its exact role in cellular biology remains unknown, μ-calpain appears to be involved in cytoskeletal remodelling. It is intriguing to note that replication of the SARS coronarvirus likewise depends on μ-calpain [29,30]. CHIKV replication appears to increase proteasome activity in cells and results in accumulated polyubiquinated proteins. Thus, the proteasome system and μ-calpain may serve as therapeutic targets for drug development to fight CHIKV infection [29].

To date, three lineages of CHIKV have been identified, each with its own distinctive genotype and antigenic characteristics based on genome sequences of the CHKV strain isolated obtained in 2005 to 2007. These three are the West African; the Asian; and the East, Central, and Southern African (ECSA) genotypes. From the ECSA genotype, an unexpected genetic adaptation known as the Indian Ocean lineage evolved, which was associated with the Reunion
Island outbreak in 2007 [31]. It is thought that the CHIKV strains associated with the Reunion Island outbreak in 2007 were mutations that facilitated disease transmission by the Aedes albopictus mosquito in addition to the Aedes aegypti mosquito [32,33]. This mutation also reduced the time from mosquito bite to onset of symptoms from about seven days to two days [32]. The mutation is one of the viral envelope genes (involving the E1 glycoprotein gene or E1-226V), which has made viral transmission more efficient [31,34]. The mutation occurred as an alanine-to-valine substitution occurred at position 226 in the E1 glycoprotein with the result that the CHIKV no longer depended upon the presence of cholesterol for growth and infectivity [31]. It is thought that this mutation improved the ability of the Aedes albopictus mosquito to transmit the disease, adding a major new vector and, in that way, contributing to the re-emergence of the CHIKV [24]. The Aedes albopictus mosquito is thought to be the primary vector for the Indian Ocean lineage as opposed to Aedes aegypti [35].

**CHIKV Transmission**

The CHIKV may be transmitted via a sylvatic cycle or by way of human-to-mosquito-to-human transmission, in which humans (or in some cases birds, rodents or other small animals) can act as reservoirs for the virus [5]. A human with CHIKV infection may transmit the virus to an Aedes mosquito for further transmission; the risk of such a transmission appears to be during the viremic period or roughly two to six days after onset of symptoms [36]. The human-mosquito-human transmission cycle occurs primarily in urban or semi-urban areas and is more likely in epidemic periods (Figure 1) [7].

![Chikungunya virus life-cycle](image)

**Figure 1**: Chikungunya virus life-cycle

The two mosquito vectors for CHIKV of the most interest for the United States (Aedes aegypti and Aedes albopictus) are active primarily during daylight hours. The Aedes aegypti is found in the tropics and subtropics and has been associated with the spread of the CHIKV, Zika virus, and dengue [5]. The Aedes albopictus (“tiger mosquito”) has a broader habitat and can thrive in more inhospitable environments, including urban areas. Other mosquito vectors have been implicated in Africa, including the Aedes furcifertaylori and Aedes luteocephalus.
mosquitoes [5]. In the French Polynesian outbreaks of CHIKV, Aedes polynesiensis was also recognized as a local vector. *Aedes polynesiensis* is more abundant in the remote atolls of this region, while *Aedes aegypti* is more common in the urban and peri-urban regions (Figure 2) [37].

![Mosquito Image]

**Figure 2:** The *Aedes aegypti* mosquito transmits chikungunya, dengue, and the Zika virus

“Vertical transmission” of CHIKV from a mother to a neonate at the time of birth is possible, but this mode of transmission is considered rare [8,38]. However, the CHIKV is more likely to be transmitted from mother to child during the perinatal period than in utero, which is more common with the Zika virus. There are no cases described in the literature of an infant contracting the CHIKV through mother’s milk. It is theoretically possible for the CHIKV to spread through blood transfusions, but there are no known cases on record of such an event [8].

**Diagnosis**

Enzyme-linked immunosorbent assays (ELISA) can be used on blood to confirm the presence of IgM and IgG anti-chikungunya antibodies [5]. IgM antibody levels will be highest three to five weeks after the onset of symptoms and will be present for up to two months. Virologic testing may be required using reverse transcriptase-polymerase chain reaction methods (RT-PCR) if testing is done in the first week after symptoms start, but RT-PCR tests have varying sensitivity. If a genotype of the virus is needed, for example, to compare virus samples of various locations, RT-PCR may be used as well [5]. A real-time RT-PCR is being developed to help differentiate among the Zika, chikungunya, and dengue viruses [39].

In the acute phase, CHIKV infection must be differentiated from dengue, another related condition which also commences with fever and typically lasts five to seven days. Dengue fever is frequently accompanied by headache, retro-orbital pain, severe myalgia, and adenopathy. A key differentiation is that CHIKV infection more likely involves severe, symmetric, and migratory polyarthritis, whereas dengue typically involves myalgia rather than joint pain. Rash is more common with CHIKV infection than dengue [40-42].

In the chronic phase, the rheumatic symptoms associated with CHIKV infection may mimic seronegative rheumatoid arthritis (RA) because of the joint distribution patterns, severity of pain, and duration of symptoms. Without distinctive radiological or clinical features to persistent CHIKV, it can be difficult to differentiate between RA and CHIKV [24].

**Pediatric chikungunya**

In infants, the clinical presentation of CHIKV infection includes fever, polyarthralgia (may be severe), myalgia, and erythema with sepsis-like symptoms, central nervous system disorders, and bullous dermatitis also
reported [16]. In the event that standard diagnostic tests are not available, pediatric diagnostic criteria have been published [43], which have been criticized in the literature as in need of modification [44].

Risk factors

In a study of patients infected with the CHIKV in Kerala, South India, in 2006-2007, the most affected age group were people aged 15 to 59 years (73.4%), followed by patients over age 60 (15.6%), and 11% of cases occurring in patients under the age of 15 [45]. Similar age distributions were found in other outbreaks [42,46-48]. Thus, while vulnerable populations such as young children and seniors may experience the most severe forms of the disorder, teenagers and adults (15-59) appear to be the most likely to contract the virus. Males and females appear to be affected about equally by CHIKV infection [24]. Entomology plays a role in virus outbreaks, as do mutations and virus-vector assemblages [49].

Perinatal exposure

With considerable concern and publicity surrounding the association of the Zika virus with microcephaly [50,51], scientists are exploring the potential risks of both prenatal and perinatal exposure to CHIKV. Although much remains to be elucidated, it appears that the CHIKV is not typically transmitted to the fetus in the womb, but rather that the main risk to the baby was CHIKV infection during the intrapartum phase [38,52]. This contrasts markedly to the Zika virus, which can be readily transmitted by a pregnant woman to her fetus with potentially severe adverse consequences [53]. Perinatal mother-to-child transmission of the CHIKV typically occurs in the time period ranging from four days before and one day following birth and may result in morbidity to the neonate [38]. Infants infected with CHIKV in this way are typically asymptomatic at birth but in the subsequent days after birth develop fever, pain, rash, and peripheral edema. About half of neonates (53%) infected in this way develop severe neurological conditions that may result in permanent disability, such as but not limited to, meningoencephalitis and/or seizures [26,38,52]. Cardiac complications including myocardial hypertrophy, pericarditis, and ventricular dysfunction may also occur [26,38,52].

In a cohort study (CHIMERE), neurocognitive function in 33 CHIKV-infected children was compared to 135 uninfected children, finding that developmental quotients (DQ) were significantly lower in CHIKV-infected children, rated as 86.3 (95% confidence interval [CI], 81.0 to 91.5) compared to the uninfected children at 100.2 (95% CI, 98.0 to 10.25), p<0.001 [54]. Moreover, CHIKV infection was associated with global neurodevelopmental delay [54].

Treatment and prevention

There is currently no commercial vaccine to prevent chikungunya nor are there antiviral drugs that can treat it [5]. Several experimental vaccines are currently being evaluated in early-stage clinical trials [55,56]. The ideal vaccine would induce high levels of antibodies against the CHIKV but must also be inexpensive enough for widespread use in economically disadvantaged regions where the infection is prevalent [6].

Treatment of CHIKV infection is focused mainly on alleviating symptoms. Patients may be treated with antipyretics and fluids, mainly aimed at managing arthralgia [5]. Supportive treatment for CHIKV infection must also include pain management, possibly with acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs). In the event of severe joint symptoms and chronic arthritis, rheumatic therapy, including methotrexate, may be considered [57].

Current containment strategies for the CHIKV must focus on prevention. The main preventive strategy is to reduce the mosquito vector, as by far the greatest risk factor for CHIKV infection is proximity to a mosquito-breeding area [5]. Communities must begin mosquito control programs, an important component of which is educating citizens to drain standing water that might be in or near their homes [5]. In the United States, recent rainfall and
flood events in the warmer Gulf Coast states may result in massive mosquito outbreaks which can put the public health at risk.

Clinicians should proactively discuss the chikungunya and Zika viruses with their patients, in particular, educating them about ways to minimize their exposure to mosquitoes. Since these mosquito vectors are primarily active during daylight hours, patients should try to avoid prolonged outdoor activities (if possible) and wear clothing that limits exposed skin [5]. Mosquito repellents should be used, ideally those that contain DEET (N, N-diethyl-3-methylbenzamide), IR3535 (3-[N-acetyl-N-butyl]aminopropionic acid ethyl ester) or picaridin (1-piperidinecarboxylic acid, 2-(2-hydroxyethyl)-1-methylpropylester) [5]. Many patients may prefer “natural” mosquito repellents but should be advised that the most effective products are those listed above. Clinicians can be important sources of information on mosquito repellents and other strategies to reduce potential exposure to CHIKV.

In certain areas where mosquito exposure cannot be entirely reduced, mosquito netting might be considered, especially for those who sleep during daytime hours or may be bedbound. Although *Aedes aegypti* primarily is active outdoors, *Aedes albopictus* has been known to be active in indoor environments as well. If necessary, mosquito coils or other devices may be used to reduce insect activity in the house [5].

**Late Neurological Complications**

The neurological complications following CHIKV infection have recently begun to be chronicled and include encephalitis, optic neuritis, myeloradiculois, and Guillian-Barre syndrome and range from mild to severe and potentially disabling (blindness, paralysis) [4,58-63] and represent a major cause of CHIKV-associated mortality [64]. These symptoms have been described as “Neuro-Chikungunya” in the literature [65]. A retrospective study of Neuro-Chikungunya identified a bimodal age distribution for these symptoms with peaks in middle-aged and pediatric patients [65]. Infants born to perinatally infected women were at elevated risk for neurological complications [38,52,54]. It has been theorized some patients with neurological symptoms from the CHIKV may have an autoimmune response triggered by the virus in that there is a latency between initial signs and symptoms of the CHIKV infection and neurological symptoms [65].

**CHIKV Infection Sequelae**

CHIKV infection is associated with chronic symptoms which may remit completely, persist over time, or occur episodically. Mortality is low with CHIKV infection and individuals who contract the disease typically make a full recovery, which confers on them lifelong immunity [5]. Yet a large subset of patients may experience joint pain for months or even years after the infection. Other complaints may include neurological complications, eye problems, cardiac complications, and gastrointestinal (GI) symptoms [5]. The majority of patients (80% to 93%) experience symptoms up to three months after initial infection [18] and about half (48%) still report symptoms six months later [21]. Although it has not been extensively studied, many patients have certain symptoms two years after the initial infection (47%) [18]. Among these symptoms are polyarthritis, myalgia, chronic neuropathic pain, Raynaud syndrome, fatigue, depression and weakness. Hyperpigmentation of the skin may occur during the acute phase and persist for months after the infection remits [21,66].

**Discussion**

It is likely that the CHIKV along with related arboviruses, such as Zika and dengue, will establish themselves in the Americas, including many portions of the United States. Widespread infection is possible because there is a lack of immunity among Americans and certain parts of this region may be vulnerable to hosting very large mosquito populations in the warmer months [24]. In a Veterans Health Administration (VHA) 2014 study of 180 confirmed
CHIKV infections in the United States, 82.2% were diagnosed in Puerto Rico and the remainder diagnosed among travelers returning from outside the United States [67]. This is likely to change as CHIKV approaches the mainland.

The emergence of the *Aedes albopictus* as a new vector is troubling. The so-called “tiger mosquito” is an invasive species that has expanded its geographic presence throughout the U.S. as well as in other parts of the world [68]. It is more adaptive to challenging urban environments and can survive indoors. Increased globalization and travel can result in increased exposure to CHIKV and other viruses with the result that these viral infections spread to new parts of the world. The current pattern of CHIKV transmission shows increasingly larger outbreaks at increasingly longer distances from the origin of the virus.

Vaccines, antiviral drugs, and more effective therapeutic interventions may be on the horizon, but they are not in the clinics for this coming season. As such, clinicians must provide education, support, and care and become advocates for prevention through mosquito control.

**Conclusion**

The CHIKV is a mosquito-borne arbovirus associated with infection and possibly severe associated symptoms and potential sequelae. Unlike the related Zika virus, CHIKV appears to be more readily transmitted from mother to child in the perinatal period rather than in the womb although both viruses have been linked to neurodevelopmental delays and disorders in the child. A vaccine and antiviral treatments are urgently needed but until then, mosquito prevention and patient education are the best weapons to reducing these major public health threats.

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**References**

