Chikungunya
Epidemiology, Pathogenesis, Clinical Features, Management, and Prevention

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- Chikungunya (CHIK) is a disabling and debilitating zoonotic disease of humans caused by the Chikungunya virus (CHIKV); it is transmitted by infected Aedes spp mosquitoes, which sustain sylvatic and human rural and urban CHIK cycles.
- Chikungunya is listed on the WHO Blueprint priority pathogens because in the past 5 years an alarming and unprecedented increase in spread to over 100 countries across Asia, Africa, Europe, and the Americas.
- The incubation period of between 1 and 12 days is followed by symptoms similar to dengue, Zika, parvovirus, enterovirus, malaria, with an abrupt onset of high fever, nausea, polyarthralgia, myalgia, widespread skin rash, and conjunctivitis.
- Serious complications include myocarditis, uveitis, retinitis, hepatitis, acute renal disease, severe bullous lesions, meningoencephalitis, Guillain-Barre´ syndrome, myelitis, and cranial nerve palsies. Severe disease occurs in neonates exposed during pregnancy, the elderly, and those with comorbid diabetes, renal, liver, and heart disease.
- Treatment is supportive and there is no specific antiviral treatment and no effective vaccines.

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INTRODUCTION

Chikungunya (CHIK) is a disabling and debilitating zoonotic disease of humans caused by the Chikungunya virus (CHIKV), which is transmitted by CHIKV-infected *Aedes* spp mosquitoes (Fig 1). The primary CHIKV reservoir hosts are nonhuman primates.[1] Chikungunya is listed on the WHO Blueprint priority pathogens (https://www.who.int/blueprint/en/) because in the past 5 years, an alarming and unprecedented increase in spread has occurred with cases reported from more than 100 countries across the Americas, Africa, Europe, and Asia, affecting millions of people (Fig. 2).

HISTORICAL

CHIKV most likely originated in East and central Africa where the virus is endemic to a sylvatic cycle between mosquitoes and nonhuman primates living in forests. In 1952, CHIK was described during an outbreak on the Makonde plateau in southern Tanzania on the border with Mozambique.[2] CHIKV was isolated from the serum of a febrile patient during an outbreak of an exanthematous febrile disease. Soon after in 1953, CHIKV was isolated in mosquitoes of the *Aedes aegypti* (*Ae aegypti*), and the virus was placed in arbovirus group A.[3] There are remarkable similarities between the clinical syndromes caused by dengue virus and CHIKV.[4] Before the discovery of CHIKV, cases were mostly diagnosed and treated as malaria or dengue. The actual name Chikungunya is derived from the Makonde tribe (Kimakonde language) meaning "that which bends up" or “to become contorted,” which describes the stooped bent posture of patients with CHIKV who develop joint pain (Virusnet.com). The virus is maintained in a complex sylvatic and rural cycle, progressing to an urban cycle every 5 to 20 years, causing global pandemics (Fig. 3). Following discovery of CHIK in Tanzania, it was identified in Uganda and subsequently in many other sub-Saharan African countries[5] with global spread in the ensuing years (see Fig. 2). These CHIKV strains were grouped in a single lineage and named after the geographic location as East, Central and South Africa (ECSA) CHIKV lineage. A different monophyletic group was identified during outbreaks in Asia from 1958 to 1973 and called Asian CHIKV lineage.[6,7] These different geographic genotypes exhibit differences in their transmission cycles. In Asia, the CHIKV seems to be maintained in an urban cycle with *Ae aegypti* mosquito vectors, whereas CHIKV transmission in Africa involves a sylvatic cycle, primarily with *Ae furcifer* and *Ae africanus* mosquitoes. A distinct CHIKV clade, the West Africa lineage, was isolated from West Africa, and this

Fig. 1. Mosquito vector of CHIKV: female *Aedes aegypti* mosquito. A close-up lateral view of the female *Aedes aegypti* mosquito from a left lateral perspective, feeding on the human host with distended abdomen filled with host blood. (*Courtesy of* US-CDC, Public Health Image Library (PHIL) https://phil.cdc.gov/Details.aspx?pid59260.)

Fig. 2. World map showing countries and territories reporting CHIKV. (*Data from* The Centers for Disease Control: https://www.cdc.gov/chikungunya/geo/index.html.)

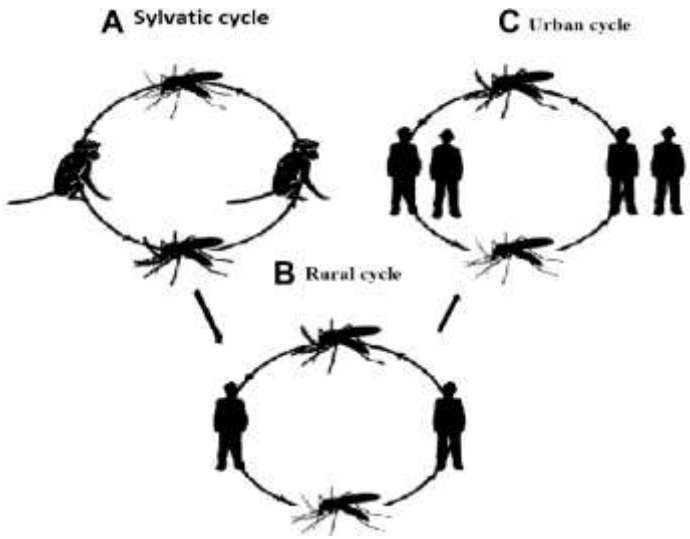

Fig. 3. The transmission cycles of Chikungunya virus as described in Althouse et al (2018). A) The sylvatic cycles of Chikungunya virus exists primarily in Africa between non-human primates, rodents and possibly in bats and forest-dwelling *Aedes species* (*Ae. albopictus*, *Ae. furcifer*, *Ae africanus, Ae. taylori*). B) The rural transmission occur when rural population bitten by infected forest-dwelling mosquitoes, especially by *Ae albopictus*. C) Movement of infected humans can result in establishment of a large urban transmission through urban *Aedes mosquitoes* (*Ae. aegypti and Ae. albopictus*), where a human-mosquito-human cycle is established. *Ae. albopictus* feeds on a range of hosts including humans and wild mammals whereas *Ae. aegypti* primarily feeds on human, and most forest dwelling *Aedes species* (*Ae. furcifer*, *Ae africanus, Ae. taylori*) feeds primarily on animals. (*Date from* Althouse, B. M. *et al.* Role of monkeys in the sylvatic cycle of chikungunya virus in Senegal. *Nat. Commun.* (2018); and adapted from Petersen, L. R., Stramer, S. L. & Powers, A. M. Chikungunya Virus: Possible Impact on Transfusion Medicine. *Transfus. Med. Rev.* (2010); with permission.)

has been circulating in the past 30 years. The 2 major enzootic CHIKV lineages in Africa were introduced from eastern Africa into Asia between 1920 and 1950. The more recent Indian Ocean and Indian epidemic CHIKV strains emerged independently from the mainland of East Africa.[8] This lineage has been called the Indian Ocean Lineage (IOL) and has been repeatedly associated with outbreaks from 2005 to 2014.[8,9]

EPIDEMIOLOGY

The Chikungunya Virus

Phylogenetic analysis has shown 4 different genotypes of CHIKV based on geographic regions: the west African genotype (Senegal and Nigeria), the ECSA genotype, the Asian genotype, and the IOL genotype.[4,6,7,10] CHIKV is an enveloped, spherical, single-stranded positive-sense RNA alphavirus belonging to the family Togaviridae. It has a genome size of w12 kb, and it consists of 2 open reading frames cleaved into 4 nonstructural proteins (nsP1, nsP2, nsP3, and nsP4)[11] and 5 structural proteins (C, E3, E2, 6K, and E1).[12] E1 and E2 are surface glycoproteins, 439 and 423 amino acids long, respectively.[13] E1 and E2 carry the major viral epitopes and participate in the attachment and the entry of the virus into target cells, where E2 is responsible for receptor binding and E1 for membrane fusion.[14] E3 consists of 64 amino acids that are required for E3-E2-6K-E1 or E3-E2-TF polyprotein translocation into the endo- plasmic reticulum for virus spike formation.[15] The 6K protein is a cation-selective ion channel that causes increased cell permeability to monovalent cations and virion budding during infection.[16] Transframe protein TF is produced as a result of C-terminal extension of 6K protein in the 1 frame.[17] It retains ion-channel activity similar to that of 6K and seems to be important for assembly and release of the virus particle.[17] Although the nonstructural proteins nsP1-nsP4 are primarily associated with the viral replication process,[18,19] they have additional functions during the viral infection, just like in other alphaviruses.[20] Nonstructural proteins are not packaged into the final vi- rions, and hence the structural proteins (mainly surface glycoproteins E2 and E1) are the key targets of the host humoral immune response and of most CHIK vaccines.[21]

Global Distribution, Transmission, and Chikungunya Virus Outbreaks

Human cases of CHIK have been reported from all continents affecting males and females of all age groups. The CHIKV circulates between mosquitoes and naive human hosts in cyclical form similar to dengue viruses. Until 5 years ago, most CHIK cases were reported from Africa, Asia, Europe, and the Indian and Pacific Oceans. International travel led to the spread of CHIKV to Europe and focused global attention.[22] The first local transmission of CHIKV in the Americas was identified in Caribbean countries and territories in 2013 and subsequently spread rapidly throughout the Americas[23] (see Fig. 2). To date, human cases of CHIK have been found in more than 100 countries (Table 1).

Large outbreaks were reported in Comoros in 2005 with approximately 215,000 cases[24] and in Reunion Island between March 2005 and April 2006 with 255,000 cases.[25] The spread of CHIKV to the islands of the Indian Ocean, India, and Southeast Asia after a large outbreak in Kenya in 2004 has been a key factor in focusing global attention. Selected outbreaks in various countries are listed in Table 2. CHIKV subsequently spread beyond its original tropical locations in Africa and the Indian subcontinent, becoming a serious emerging issue in temperate regions of Europe and the Americas with autochthonous small outbreaks occurring as a consequence of spillover from endemic tropical areas in continental Europe: Italy in 2007, and in France in 2010, in 2014, and 2017.[26–29] In 2017, a major outbreak in Italy was concentrated

Table 1
Countries where CHIKV human infections have been reported

Continent	Country	
Africa	• Angola	• Mauritius
	• Benin	• Mayotte
	• Burundi	• Mozambique
	• Cameroon	• Nigeria
	• Central African Republic	• Republic of the Congo
	• Comoros	• Reunion
	• Cote d'Ivoire	• Senegal
	• Democratic Republic of the Congo	• Seychelles
		• Sierra Leone
	• Djibouti	• South Africa
	• Equatorial Guinea	• Somalia
	• Gabon	• Sudan
	• Guinea	• Tanzania
	• Kenya	• Uganda
	• Madagascar	• Zimbabwe
	• Malawi	
Asia	• Bangladesh	• Nepal
	• Bhutan	• Pakistan
	• Cambodia	• Philippines
	• China	• Saudi Arabia
	• India	• Singapore
	• Indonesia	• Sri Lanka
	• Laos	• Thailand
	• Malaysia	• Timor-Leste
	• Maldives	• Vietnam
	• Myanmar (Burma)	• Yemen
Europe	• France	
	• Italy	
	• Spain	
Americas	• Anguilla	• Haiti
	• Antigua and Barbuda	• Honduras Jamaica
	• Argentina	• Martinique
	• Aruba	• Mexico
	• Bahamas	• Montserrat
	• Barbados	• Nicaragua
	• Belize	• Panama
	• Bolivia	• Paraguay
	• Brazil	• Peru
	• British Virgin Islands	• Puerto Rico
	• Cayman Islands	• Saint Barthelemy
	• Colombia	• Saint Kitts and Nevis
	• Costa Rica	• Saint Lucia
	• Cuba	• Saint Martin
	• Curacao	• Saint Vincent and the Grenadines
	• Dominica	
	• Dominican Republic	• Sint Maarten
	• Ecuador	• Suriname
	• El Salvador	• Trinidad and Tobago
	• French Guiana	• Turks and Caicos Islands
	• Grenada	• Venezuela
	• Guadeloupe	• United States
	• Guatemala	• US Virgin Islands
	• Guyana	

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Table 1
(*continued*)

Continent	Country	
Oceania/Pacific Islands	• American Samoa	• Marshall Islands
	• Cook Islands	• New Caledonia
	• Federal States of Micronesia	• Papua New Guinea
	• Fiji	• Samoa
	• French Polynesia	• Tokelau
	• Kiribati	• Tonga

(*Courtesy of* The Centers for Disease Control: https://www.cdc.gov/chikungunya/geo/index.html.)

around 3 main foci (Anzio, Rome, Guardavalle Marina) in 2 different regions, Lazio (Anzio, Rome) and Calabria (Guardavalle Marina), in Central and Southern Italy.[30] Phylogenetic analysis showed that the CHIKV from the Lazio outbreak belonged to the ECSA clade and clusters within the IOL.[31]

In Africa, CHIKV epidemics have been reported from Central African Republic, Guinea, Burundi, Angola, Uganda, Malawi, Nigeria, Democratic Republic of the Congo, South Africa, and Nigeria. In June 2004 in an outbreak that occurred in Lamu Atoll, Kenya, and spread to Mauritius, Seychelles, Comoros, and Reunion Is- land, almost half a million cases were reported. Several other epidemics occurred in all southwestern Indian Ocean islands except Madagascar from 2005 to 2007. In 2011, a CHIKV epidemic occurred in the Democratic Republic of the Congo (317 cases), Pool (460 cases), and Brazzaville (7014 cases).

Table 2
Major global outbreaks of CHIKV

Year	Country
1954	United Republic of Tanzania
1999–2000	Democratic Republic of Congo
2005 to date	Islands of the Indian Ocean Maldives India Myanmar Thailand
2006–2007	India
2007	Gabon
2007	Italy
2011	Republic of Congo
2013	France
2014	Pacific Islands (Cook, Marshall, and others)
2015	Americas
2016	Pakistan
2017	Italy
2017	Kenya
2019	Republic of Congo
2019	Democratic Republic of Congo

Mosquito Vectors

In Africa, CHIKV circulates in an enzootic cycle between forest-dwelling *Aedes* spp mosquitoes (*Ae furcifer*, *Ae taylori*, *Ae africanus*, *Ae luteocephalus*) and is main- tained in nonhuman primates and other vertebrate reservoirs such as rodents and bats (see Figs. 1 and 3).[1,32,33] The primary CHIKV reservoir hosts are nonhuman primates, and the 5- to 10-year periodicity of CHIKV transmission may depend on oscillations in monkey herd immunity.[1] In Senegal, enzootic strains of CHIKV have been isolated from diverse species of mosquito including *Ae (Dicero- myia) furcifer*, *Ae (Diceromyia) taylori*, *Ae (Stegomyia) luteocephalus*, *Ae (Stegomyia) africanus*, and *Ae (Stegomyia) neoafricanus*.[1] Sporadic spillover of enzootic CHIKV into urban interhuman transmission cycles is amplified by the involvement of anthropophilic mosquito species such as *Ae (Stegomyia) aegypti* and *Ae (Stego- myia) albopictus*.[34]

The behavior and ecology of *Ae aegypti* makes it an ideal vector during epidemic cycles because of its anthropophilic nature. Moreover, adult females often take several blood meals during a single gonotrophic cycle, and artificial containers are preferred larval sites.[35] *Ae albopictus* mosquitoes are both zoophilic and anthropo- philic and are active throughout the day. In Asia, CHIKV is maintained in an urban transmission cycle vectored by the mosquito *Ae aegypti* and *Ae albopictus*.[8]. *Ae albo- pictus*, the Asian tiger mosquito, was discovered in 1894 in India and is endemic to Southeast Asia. *Ae albopictus* mosquitoes have successfully colonized all 5 conti- nents throughout both temperate and tropical regions.[36] It has successfully spread because of its ability to thrive in arid and cold conditions, undergo periods of adult diapause, and overwinter by laying desiccation-resistant eggs. Although these mosquitoes do not have a specific ecological niche, distinct temperate and tropical populations have arisen. CHIKV circulation typically coincides with periods of heavy rains and increased density of mosquito.[37] The urbanization and human migration from rural to urban areas has led to the introduction of *Ae aegypti* and *Ae albopictus* living around human habitations, sustaining CHIKV transmission in a mosquito-human cycle.

Chikungunya Virus Mutations and Infectivity

The E1-A226V mutation has resulted in a dramatic increase in the infectivity of CHIKV, and the transmission of CHIKV has spread to Europe and the Americas facilitated by widespread distribution of the *Aedes* spp vectors. The nonsynonymous mutation in the E1 glycoprotein of the viral envelope (E1-A226V) was identified in 90% of isolates during the outbreak in Reunion Island in 2006.[38] This mutation is important for viral fitness in *Ae albopictus*, although the mutation does not affect viral replication in *Ae aegypti*.[39,40] This adapted variant was involved in outbreaks in north-eastern Italy in 2007 and in south-eastern France in 2014 and 2017, where *Ae albopictus* is wide-spread.[27,41,42] Thus, although *Ae aegypti* was widely recognized as the main urban vector of CHIKV in tropical areas, *Ae albopictus* is considered able to transmit CHIKV in temperate climate areas too. Mosquito studies highlighted the role of *Ae albopictus* as a CHIKV vector during the European outbreaks [26, 27], and experimental infection confirmed a high susceptibility of local European *Ae albopictus* populations to the mutated ECSA CHIKV strain. Other less widespread mutations are believed to in-crease initial infection in *Ae albopictus* midgut cells, all of them in the IOL lineage. E2-K252Q, E2-K233E, E2/E3-R198Q/S18F, and E2-L210Q affect the initial infection of the *Ae albopictus* midgut cells with major effects on infection of *Ae aegypti*.[43] The same mutations are predicted to affect CHIKV Asian lineages circulating in the

Americas as a result of a so-called founder effect and resultant epistasis. The amino acid mutation A98T in E1 protein in the Asian lineage prevents penetrance for *Ae albopictus* infection.[8,44]

MODES OF CHIKUNGUNYA VIRUS TRANSMISSION

There are several ways in which CHIKV is acquired by humans.[45]

CHIKV is transmitted to people through bites from *Ae aegypti*, *Ae albopictus*, and *Ae polynesienses* mosquitoes, the same mosquitoes that transmit the dengue virus. These mosquitoes breed in or near human habitations and prefer to feed on humans during the daytime in shady areas and early in the evening. Horizontal transmission in *Aedes* spp can occur and contribute to the maintenance of CHIKV cycles.[46] Vertical transmission is rare but has been observed under natural and experimental conditions.[47–49] In Africa, CHIKV circulates primarily in an enzootic cycle, with occasional spillover infections of humans.

Coinfection with dengue virus and CHIKV,[50] and CHIKV with dengue virus, Zika virus, yellow fever virus, and West Nile virus have been described.[51]

Iatrogenic Transmission

To date, no studies on transfusion-transmitted CHIKF from viremic donors to recipients has been published. There is increasing concern that CHIKV might be transmitted by way of transfusions given its high-level viremia attack rate during outbreaks and a significant proportion of asymptomatic infections. Viremic asymp- tomatic[52] CHIKV-infected cases have shown high potential as disseminators of transfusion-associated CHIKF, because CHIKV levels capable of inducing CHIKF were found in the blood of asymptomatic cases during the 2009 epidemic in Songkhla, Thailand.[52] As with other arboviruses, several factors determine the impact of CHIKV on transfusion medicine: (1) prevalence of viremia among blood donors, (2) proportion of components derived from viremic donations that transmit infection to recipients, (3) clinical impact on infected transfusion recipients, (4) availability of measures to reduce transfusion transmission when required, and
(5) the cost and disruption incurred by those measures. Several models have been applied to estimate the risk of transfusion-associated HIKV transmission. Model results from Reunion Island[53] and Thailand[52] indicate a significant short- term risk of transfusion-associated CHIKV transmission during large outbreaks, whereas the Italian model suggests a small, but quantifiable risk that may exceed accepted safety standards during smaller, focal outbreaks[54] that may occur in temperate areas.

Few cases of CHIKV infection in solid-organ transplant (SOT) recipients have been reported.[55–57] In a case series from Brazil, 13 SOT recipients (9 kidney, 4 liver) infected with CHIKV showed similar clinical presentation to immunocompetent hosts, including chronic joint symptoms in 46%. However, there were no complications or deaths, and these transplant patients experienced no apparent damage to the graft. In addition, infectious CHIKV can be isolated from corneal grafts from both symptomatic and asymptomatic donors, although no cases transmitted by corneal transplant have been reported to date.[58] SOT recipients who travel to or live in CHIKV endemic areas are at high risk of acquiring the disease.

Maternal-fetal transmission has been reported. Intrapartum contamination without actual placental infection has been well documented for CHIKV virus, which is not able to infect the placenta.[59,60] CHIKV is not transmitted to the fetus in the absence of placental breaches, which allow transfer of maternal blood to the

fetal circulation.[59] A recent meta-analysis[61] estimated a pooled mother-to-child transmission risk across the analyzed cohorts of 15.5%, with the highest risk among infections in the intrapartum period (12 days from delivery). During intra- partum viremia, the vertical transmission rate of CHIKV is reported as 48.7%. Mothers who have a high viral load in their placenta are more likely to transmit the virus.[59] There is no evidence of CHIKV transmission by way of breast milk to infants.[62]

CHIKV has been detected in semen 30 days after symptom's onset,[63] indicating possible sexual transmission. No evidence of sexual transmission between humans has been reported so far.

PATHOGENESIS

During the first week of infection, CHIKV can be found in the blood and can be passed from an infected person to a mosquito through mosquito bites. CHIKV has certain cell types that are particularly susceptible to infection; these include human epithelial and endothelial cells, primary fibroblasts, and monocyte-derived macrophages.[64] Lymphoid and monocytoid cells, primary lym- phocytes and monocytes, and monocyte-derived dendritic cells did not demon- strate CHIKV replication.[65] The human skin is the first site of viral replication, mainly in the dermal fibroblasts. From here, the virus enters the lymph nodes and the circulatory system, disseminating to all organs.[66] During the acute and subacute phases, CHIKV reaches muscle and joint compartments: primary muscle fibroblasts and skeletal muscle fibroblasts, and both have been found to be permissive.[60,67]

Chikungunya clinical syndrome is characterized by arthralgia, which is usually symmetric and affects distal synovial joints more than proximal joints.[68] In patients, during acute and persistent arthralgia CHIKV RNA and proteins have been found in synovial tissue and fluids, with synovial fibroblasts and macrophages susceptible to the infection.[60,68,69] Infected macrophages are the preferred site for viral replication, contributing to viral persistence and chronic symptoms.[68] The presence of increased levels of cartilage bioproducts in urine[70] and low plasma levels of hepa- tocyte growth factor in chronic patients[71] indicate connective tissue alterations and cartilage damage. CHIKV replicates actively and persists in the osteoblasts.[69,72] Bone loss is a characteristic of CHIK-associated arthritis. The pathogenesis of persistent symptoms after CHIK infection is still unclear. CHIKV proteins have been detected in macrophages and muscle cells of patients with relapse of chronic pain, suggesting that low replicative viruses or nonreplicative CHIKV debris may persist. A persistent immune activation has been detected in mouse models.[73,74] Immune and inflammatory responses to CHIKV infection may also contribute to pathogenesis.[75,76]

Neurologic manifestations have often been reported in several outbreaks, with an increasing number of cases with neurologic complications after the reemer- gence of CHIKV in the Indian Ocean in 2005. The virus has frequently been isolated from cerebrospinal fluid (CSF).[77] The target cells for CHIKV in the human brain remain unknown. In vitro infection of human cells have demonstrated the suscep- tibility of neuroblastoma cells,[78] microglial cells,[79] and glial cells, such as astro- cytes,[80] showing signs of apoptosis. Nevertheless, it is still unclear if the pathogenesis of the nervous system is directly connected with the infection of the neurons and glial cells or is indirectly connected triggering the immune- mediated effects.

CLINICAL FEATURES

Incubation Period

The incubation period can vary from 1 to 12 days (average, 2–7 days). CHIKV infection causes high levels of viremia, which usually last for 4 to 6 days after the onset of symptoms. CHIKV infection is symptomatic in most children and adults who are infected, with less than 15% having asymptomatic sero-conversion.[53]

Symptoms

The symptoms (Table 3) are similar to those of other arboviruses, such as dengue and other common causes of febrile illnesses in the tropics; thus, accurate diagnosis is challenging.

During the acute phase of illness, the intensity of the clinical symptoms correlates with the viremia during the acute infection, usually lasting 1 week when anti-CHIKV IgM antibodies appear.[81] Following the onset of fever, intense myalgia and arthralgia occur. These symptoms can be severe and disabling, causing much morbidity.

Table 3
Clinical features of Chikungunya: symptoms and signs

Stage	Signs and Symptoms
Acute stage	Common
	Fever
	Macular to maculopapular rash
	edema of the face and extremities
	Benign bleeding (gingival bleeding, epistaxis) in children
	Pruritus
	Myalgia
	Arthralgia
	Periorbital pain
	Headache
	Lymphadenopathy
	Less common
	Diarrhea, vomiting, abdominal pain
	Confusion
	Optical neuritis
	Oral or gingival ulceration
	Conjunctivitis
Post-acute stage	Inflammatory arthralgia, joint stiffness
	Arthritis (synovitis with or without effusion)
	Tenosynovitis, bursitis
	Decompensation of pre-existing degenerative or traumatic arthropathy
	Osteoarthritis or sometimes-calcific tendinitis
	Entrapment syndromes
	Neuropathic pain
	Severe asthenia
	Neuropsychological disorders
Chronic stage	Joints: articular arthritis, synovitis, degenerative osteoarthritis, bursitis
	Tendons: tendinitis, enthesitis, tenosynovitis
	Edema
	Neuropathic pain
	Stiffness
	Loss of physical fitness
	Postural hypotension
	Mood disorders

Disabling polyarthralgia is a key symptom for differential diagnosis with a positive predictive value greater than 80%.[82] The joint pain is usually symmetric in both the arms and legs; the large joints are almost invariably symptomatic. Other common signs are nausea, fatigue, headache, back pain, and skin rash (50% of cases). The skin lesions are characterized by a macular or maculopapular transitory eruption often in the body extremities, palms, soles of the feed, torso, and face.[81,83] Gastrointestinal tract involvement can manifest as nausea, vomiting, and abdominal pain.[84] Ocular manifestations can occur during the acute phase with photophobia, retro-orbital pain, and conjunctivitis.[85]

The acute phase is usually followed by a post-acute stage, usually from the fourth week to the end of the third month.[86] This phase is characterized by persistence of the initial inflammatory events, including inflammatory arthralgia, arthritis (synovitis with or without effusion), tenosynovitis, bursitis, which slowly regress. It is often asso- ciated with decompensation of pre-existing degenerative or traumatic arthropathy (sometimes unknown) such as osteoarthritis or calcific tendinitis, and local events such as reactionary edema, entrapment syndromes, joint stiffness, or neuropathic pain.

The chronic stage (after the third month) is defined by the absence of return to pre-existing condition more than 3 months after the onset of CHIK. The chronic phase can last a few months to several years (more than 6 years for a small group of patients in Reunion Island). The observed clinical symptoms are the same as in the post-acute stage. It is common to observe painful rebounds on joints used too strongly considering their post-CHIK inflammatory condition. The diagnostic approach is to qualify the nosology of each patient according to the presence or absence of inflammatory symptoms (arthritis, enthesitis, tenosynovitis, inflammatory arthralgia) and the number of joints involved (polyarticular if 4 2 joints).

In infected newborns, symptoms generally develop on days 3 to 7 of life with fever, rash, and peripheral edema. Pathology typically reveals a bicytopenia, increased prothrombin time, and aspartate aminotransferase level. The presentation in infants is subsequently complicated by seizures, hemorrhagic syndrome, hemodynamic disorders, and myocardial dysfunction.[59,87] Neonatal symptoms range from mild presentation (43%) to severe infection with encephalitis (53%)[59] that requires intensive care. Fever and acute respiratory distress have also been reported.[88] Neurologic complications can have severe effects on postnatal neurologic development, such as lower development quotient at age of 2 years, and moderate to severe global neurodevelopmental delay.[89]

Atypical Features and Complications

Complications of the cardiovascular, renal, respiratory, hepatic gastrointestinal, and adrenal systems are associated with the infection and referred to as atypical features (Table 4). As reported during the Reunion Island outbreak in 2005, the proportion of atypical cases was 0.3%. Atypical cases were defined as patients with clinical presentation of fever, arthralgia, and other atypical signs. The median age of the cases was 70 years. Of the 610 atypical cases, 546 (89%) had underlying medical conditions, 479 (78%) were on medication before hospitalization. However, the involvement of the central nervous system is the most common complication of CHIK infection. Neurologic disease after CHIKV infection was first reported during an outbreak in 1964 in Madras, India.[90] In 2 studies investigating manifestations of CHIKV in patients requiring intensive care, a neurologic disorder was the primary issue in 61%[91] and 79%.[92] Given the large spectrum of neurologic disease and scarce epidemiologic data, estimating the incidence of neurologic disease among all systemically

Table 4
Clinical features of CHIKV: complications

Organ/System	Complication(s)
Nervous system	Frequent
	Encephalopathy and meningitis
	Myelopathy and myelitis
	Encephalomyelopathy
	Myeloneuropathy
	Encephalomyeloneuropathy
	Guillain-Barré syndrome
	Acute disseminated encephalomyelitis
	Neonatal hypotonia
	Optic neuritis
	Less frequent
	Seizures
	Sensorineural hearing loss
	Stroke
	Cerebellitis
	Third nerve palsy
	Encephalopathy
	Behavioral changes
	Carpal tunnel syndrome
	Bilateral ophthalmoplegia
Cardiovascular system	Heart failure
	Arrhythmias
	Myocarditis/pericarditis
	Blood pressure instability
	Acute myocardial infarction
Ocular	Conjunctivitis, episcleritis, nongranulomatous anterior uveitis, granulomatous anterior uveitis
	Keratitis, retinitis with vitritis, bilateral retinitis
	Multifocal choroiditis, optic neuritis, retrobulbar neuritis
	Exudative retinal detachment, pan-uveitis
Other organ involvement	Pre-renal failure
	Exacerbation of chronic renal failure
	Pneumonia and respiratory failure
	Hepatic insufficiency, subacute hepatitis
	Bullous dermatosis
	Pancreatitis
	Syndrome of inappropriate antidiuretic hormone secretion
	Hypoadrenalism

symptomatic CHIKV infections is difficult. In 1 study from the 2006 Indian outbreak, 18 (4.4%) of 405 suspected cases of CHIKV attending the recruiting hospital over 3 months developed neurologic complications.[90] An epidemiologic study of the 2005 to 2006 Reunion Island outbreak found approximately 0.3% of all CHIKV infec- tions resulted in atypical cases,[93] of which 24.1% of the adults presented with abnormal neurology. Thus, approximately 0.1% (1 case per 1000) of all CHIKV infec- tions developed neurologic disease. It has been observed that severe complications of CHIKV typically arise in patients with comorbidities. Studies from Reunion Island and from India show that underlying diseases play a role in neurologic disorders and other complication but are not an indispensable requisite. Age has been reported as a significant risk factor for severe manifestations in the elderly (>65 years)[90,93] and in infants.[94]

A recent systematic review[77] described the frequency of reported neurologic syndromes and diseases. The most frequent are encephalopathy and encephalitis, myelopathy and myelitis, Guillain-Barre´ syndrome, acute disseminated encephalomyelitis, neonatal hypotonia, and neuro-ocular disease. Other manifestations are described less frequently, such as behavioral changes, seizure with and without fever, stroke, cerebellitis, meningism, third nerve palsy, encephalopathy, and bilateral total ophthalmoplegia.

Mortality

Although morbidity is debilitating, CHIKV mortality rates are low. As with most viral illnesses, people at a higher risk for more severe disease include the newborn, the elderly, and those with comorbid illnesses such as diabetes, heart disease, chronic liver and kidney disease, and human immunodeficiency virus. An increase in mortality has been observed in the last epidemics, probably as a result of neurologic disorders mainly in neonates, immunocompromised patients, and the elderly.[55,63,95] In Europe, the case fatality rate was 2.5 per 1000 clinical cases,[30] lower than that reported in the 2007 outbreak in Italy (0.5%) but consistent with that reported from Reunion Island (1 death per 1000 clinical cases).[27,96]

LABORATORY DIAGNOSIS

Several laboratory tests are available for diagnosing CHIK using serum or plasma to detect the virus, viral nucleic acid, or virus-specific immunoglobulin (Ig) IgM, and neutralizing antibodies. Given the high viral load during viremia, CHIKV viral RNA can be detected during the first 5 to 8 days of illness using commercial tests with high sensitivity and specificity. The choice between the types of tests is dictated by the timing of the sampling with respect to the beginning of the symptoms and the vol- ume of the samples available.

Serologic Tests

CHIKV IgM antibodies normally develop toward the end of the first week of illness, and to definitively rule out the diagnosis, convalescent-phase samples should be obtained from patients whose acute-phase samples test negative. Serologic diagnosis of CHIK is made by detecting CHIKV-specific IgM in serum samples for 5 to 7 days after symptom onset, or by demonstrating a 4-fold increase (or seroconversion) of CHIK-specific IgG antibody titers in a pair of serum samples at least 15 days apart (acute and convalescent phase of the disease). IgM antibodies specific for CHIKV may persist for up to 1 year, particularly in patients with long-term arthralgia, but typically persist for 3 to 4 months. The specific CHIKV IgG can be detected for many years after initial infec- tion. Serologic cross-reactions and false-positive tests have been reported due to infection with closely related alphaviruses belonging to the Semliki forest virus. An enzyme-linked immunosorbent assay may confirm the presence of IgM and IgG anti-CHIKV antibodies. IgM antibody levels are highest 3 to 5 weeks after the onset of illness and persist for about 2 months. Samples collected during the first week after the onset of symptoms should be tested by both serologic and virologic methods (reverse transcriptase-polymerase chain reaction [RT-PCR]).

Molecular Diagnostic Tests

PCR detection of specific CHIKV RNA can be detected by RT-PCR in serum or plasma/EDTA samples obtained from patients during the acute phase of infection (typically s7 days after the onset of symptoms). CHIKV infection causes high levels

of viremia, which usually last for 4 to 6 days after the onset of symptoms. This is a favorable situation for diagnosis. Real-time RT-PCR is the ideal test for the diagnosis of CHIKV infections in the acute phase of infection. RT-PCR can typically be performed within the first 7 days of symptom onset to confirm CHIKV infection. The virus may be isolated from the blood during the first few days of infection. Various RT-PCR methods are available but are of variable sensitivity. Some are suited to clinical diagnosis. RT-PCR products from clinical samples may also be used for genotyping of the virus, allowing comparisons with virus samples from various geographic sources.

Viral culture may detect the virus in the first 3 days of illness; however, CHIKV should be handled under biosafety level 3 conditions.

TREATMENT

Supportive Treatment

There is no effective antiviral treatment, and thus treatment of CHIK is supportive and symptomatic. It should be adapted to the clinical context and risk groups aimed at controlling fever and pain, treating dehydration, organ support, and preventing iatrogenic complications and functional impairment. Infection control procedures should be instituted to reduce the risk of iatrogenic infection to health care and laboratory workers.

Analgesics

Analgesia based on acetaminophen therapy is preferred. Using nonsteroidal anti-inflammatory drugs (NSAIDs) and salicylates is not recommended in the 14 days after onset of the disease because of the risk of bleeding complications related to dengue fever unless this diagnosis is ruled out, and Reye syndrome induced by aspirin. Using analgesics (weak opioids) is required if acetaminophen is not effective: tramadol alone or in combination with acetaminophen.

The treatment of the post-acute stage should be based primarily on analgesics (stages 1 and 2), neuropathic drugs, and NSAIDs.

Nonsteroidal Anti-Inflammatory Drugs

No NSAID class has demonstrated superiority of effectiveness on post-CHIK symptoms. A local anti-inflammatory therapy (topical or infiltration) should be prescribed in case of tenosynovitis, bursitis, tunnel syndrome, capsulitis, or synovitis inade- quately controlled by oral treatment, to limit the therapeutic excess. The risk of drug toxicity by overdose (self-medication) or drug interaction is high for acetaminophen as well as for other analgesics, anti-inflammatory drugs, long-term treatments, and traditional medicines used for self-medication.[86]

Use of Steroids

The use of corticosteroids is not recommended. Steroids may also cause severe rebound of arthritis and tenosynovitis. Systemic corticosteroids should be used only for inflammatory polyarticular presentations, especially when associated with tenosynovitis, active synovitis, or in case of resistance or contraindication to NSAIDs.

Newer Therapies

Off-label use of other US Food and Drug Administration-approved drugs in a therapeutic manner has been proposed and is under consideration. In animal models of CHIKV infection, prophylaxis with CHIKV IgG or CHIKV-specific monoclonal antibodies was found to be protective,[97] suggesting that antibody-based therapies may be a promising disease prevention strategy for individuals who are at risk for severe

CHIKV infection. In cell-based screens of compounds against CHIKV infection, several drugs with antiviral activity have been identified, some of which target distinct steps in the CHIKV replication cycle. These include chloroquine[98] and chlorpromazine,[99] which affect virus entry. Harringtonine and homoharringtonine[100] have been found to affect viral protein translation. Others, including trigocherriolide A,[101] ribavirin,[102] interferon-alpha,[103] apigenin, and silybin[99] affect virus replication. More extensive pre- clinical evaluation of these and other identified drugs in animal models of CHIKV dis- ease are necessary before they are proposed for use in humans.

PREVENTION

At present, there is no effective vaccine against CHIKV infection. The proximity of mosquito vector breeding sites to human habitation is a significant risk factor for CHIKV. Prevention and control rely on reducing the number of natural and artificial water-filled container habitats that support breeding of the mosquitoes. This requires mobilization of affected communities.

Vector Control and Breeding Reservoirs

Vector control depends on reducing the number of natural and artificial water-filled container habitats that support breeding of mosquitoes. Accumulation of stagnant water should be prevented. Water in vases should be changed once a week. Using saucers underneath flower pots should be avoided. Water containers should be tightly covered. Air-conditioner drip trays should be free of stagnant water. All used cans and bottles should be placed in covered dustbins. During outbreaks, insecticides may be sprayed to kill flying mosquitoes, applied to surfaces in and around containers where the mosquitoes land, and used to treat water in containers to kill the immature larvae.

Clothing and Insect Repellants

For protection during CHIK outbreaks, clothing that minimizes skin exposure to the day-biting vectors is advised. Repellents can be applied to exposed skin or to clothing in strict accordance with product label instructions. Repellents should contain DEET (*N*,*N*-diethyl-3-methylbenzamide), IR3535 (3-[*N*-acetyl-*N*-butyl]-aminopropionic acid ethyl ester), or icaridin (1-piperidinecarboxylic acid, 2-(2-hydroxyethyl)-1-methylpropylester). For those who sleep during the daytime, particularly young children, or sick or older people, insecticide-treated mosquito nets afford good protection. Mos- quito coils or other insecticide vaporizers may also reduce indoor biting.

Miscellaneous Advice to Travelers

Basic precautions should be taken by people traveling to risk areas, and these include use of repellents, wearing long sleeves and pants, and ensuring rooms are fitted with screens to prevent mosquitoes from entering bedrooms. General measures on preventing mosquito-borne diseases include wearing loose, light-colored, long-sleeved tops and trousers, and use of insect repellent on exposed parts of the body and clothing. Use of fragrant cosmetics or skin care products should be avoided. Clothing, tents, and bed nets should be treated with permethrin (an insecticide). Travelers who return from affected areas and feel unwell, for example, have a fever, should be advised to seek medical advice promptly and provide travel details to the doctor.

Vaccines

After the reemergence of CHIKV in 2004 and its rapid expansion throughout the Indian Ocean and Southeast Asia, and unexpected autochthonous transmission in Europe in

2007 and later in 2017, there has been renewed interest in developing a vaccine against CHIKV. Several approaches have been used for the development of CHIKV vaccines, including noninfectious[104] and infectious DNA vaccines,[105] viruslike particles (VLP), and inactivated virus. Live attenuated vaccines under development include rationally attenuated alphavirus chimeras[106] and deletion mutants[107]; a vesicular stomatitis-vectored vaccine[108]; and an internal ribosome entry site-modified CHIKV strain.[109] To date, 3 CHIKV vaccines have progressed to clinical trials. The strain 181/clone25, developed by the US Army in the 1980s,[110] proved highly immunogenic but mildly reactogenic in phase 2 trials.[111] A VLP vaccine produced by expression of the CHIKV structural proteins in vertebrate cells demonstrated efficacy in preclinical studies in mice or Rhesus macaques.[112] Phase 1 clinical studies showed strong immunogenicity after 2 to 3 doses. Currently, this vaccine is not licensed to a commercial partner. A CHIKF vaccine in advanced stages of clinical development uses an attenuated measles virus strain as a vector to express the CHIKV structural proteins.[113] In a phase 1 trial, this vaccine was well tolerated and induced neutralizing antibodies in 44% of volunteers receiving a single low dose, 92% receiving a medium dose, and 90% receiving a high dose. A booster raised seroconversion to 100%, and immunogenicity was not affected by pre-existing anti-measles immunity. This vaccine is now in a phase 2 trial.[114]

Table 5
CHIKV: addressing gaps in knowledge and strengthening public health preparedness

Knowledge Gaps/Needs	Actions Required
Understanding the epidemiology and pathogenesis of CHIKV across geographic settings	Appropriately funded, well-designed longitudinal and cross-sectional clinical, pathogenesis, and epidemiologic studies of sylvatic, rural, and urban cycles (animal and human studies)
The spectrum of the vertebrate intermediate hosts	Evaluate the possibility of endemic circulation of CHIKV by means of virus identification at the human-animal interface
Prevalent mosquito vectors and their behavior	Integrating entomologic and human surveillance
Improved diagnostic, treatment, prognostic, prevention, and surveillance tools	More investments into development and evaluation of: a. Newer, affordable, field-friendly rapid diagnostic tests and sequencing platforms b. New biomarkers of disease progression c. Newer treatments (antivirals, immunotherapies, and host-directed therapies) d. New vaccines
Defining the animal and environmental host reservoirs	Cross-sectional and longitudinal studies at the human-animal interface
Customization of vector control measures adapted to local culture and norms in the context of the population behavior	Close collaboration between medical and social science/anthropologists/animal-human-environmental sectors and local communities
Establish the cocirculation of other arboviruses	Appropriate use of serology and metagenomics analysis during outbreaks
Lack of understanding of factors underlying the pathogenesis of organ involvement and complications; eg, acute and persisting synovial pathology and arthritis; and of maternal-infant transmission and infection rate of newborns	Longitudinal cohort studies during outbreaks
New surveillance tools, early warning systems, and real-time data management	The integration of different surveillance tools and the combination with entomologic surveillance in a One Health dedicated surveillance system should facilitate the detection, response, and control of arboviruses spreading, including CHIKV

SUMMARY

Several challenges are involved in the development of tools and strategies for prevention of zoonotic and re-emerging infections with epidemic potential, including CHIK (Table 5): early identification of human cases, developing rapid point of care diagnostics, and effective treatments and vaccines. The establishment of more effective collaborative research networks involving different disciplines, such as medical entomologists, virologists, veterinarians, infectious diseases clinicians, social science experts, anthropologists, community leaders, and policymakers, is required to enable more effective definition of host reservoirs, improving outbreak response and control activities. Given the unpredictability and paucity of CHIK and other zoonotic outbreaks, public health response and preparedness should be ready to perform research immediately during an outbreak, allowing for evaluation of existing and newer diagnostics, treatments, and vaccines. These are being addressed through increasing research capacity during interepidemic periods with an integrated One Health (human-environmental-animal health) approach[115,116] to assist in rapid investigations of zoonotic outbreaks and development of local capacity to improve national public health institutions.

DISCLOSURE

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