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Chikungunya Fever: An Epidemiological Review of a Re-Emerging Infectious Disease

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Chikungunya fever is an acute febrile illness associated with severe, often debilitating polyarthralgias. The disease is caused by Chikungunya virus (CHIKV), an arthropod-borne virus that is transmitted to humans primarily via the bite of an infected mosquito. Since a re-emergence of CHIKV in 2004, the virus has spread into novel locations, such as Europe, and has led to millions of cases of disease throughout countries in and around the Indian Ocean. The risk of importation of CHIKV into new areas is ever present because of the high attack rates associated with the recurring epidemics, the high levels of viremia in infected humans, and the worldwide distribution of the vectors responsible for transmitting CHIKV. In this review, we will characterize the epidemiology and global expansion of CHIKV, describe the clinical features and laboratory testing for the disease, and discuss priorities for further studies needed for effective disease control and prevention.

Chikungunya fever is an acute febrile illness caused by an arthropod-borne alphavirus, Chikungunya virus (CHIKV). The virus is primarily transmitted to humans via the bite of an infected *Aedes* species mosquito. CHIKV was first recognized as a human pathogen during the 1950s in Africa, and since then, cases have been identified in many countries in Africa and Asia [1, 2].

In 2004, CHIKV re-emerged in Kenya and subsequently spread eastward, causing millions of disease cases throughout countries in and around the Indian Ocean [3–5]. The epidemics resulted in significant morbidity and taxed the health care and public health infrastructure in these regions. By 2007, CHIKV was imported into Europe, causing an outbreak of chikungunya fever in Italy [6]. This outbreak suggested for the first time the significant potential of the virus to move to novel ecological niches, including Europe, Australia, and the Western Hemisphere.

In this review, we will briefly describe the epidemiology and global expansion of CHIKV then focus on the clinical features of chikungunya fever and the laboratory testing for the disease. In particular, we will reflect on what was learned during recent outbreak investigations and discuss priorities for further studies needed for effective disease control and prevention.

EPIDEMIOLOGY AND GLOBAL EXPANSION OF CHIKV

CHIKV likely originated in Central/East Africa [2, 7], where the virus has been found to circulate in a sylvatic cycle between forest-dwelling *Aedes* species mosquitoes and nonhuman primates. In these areas, sporadic human cases occur, but large human outbreaks are infrequent. However, in urban centers of Africa as well as throughout Asia, the virus can circulate between mosquitoes and naive human hosts in a cycle similar to that of dengue viruses. *Aedes aegypti* and *Aedes albopictus* mosquitoes are the main vectors responsible for urban transmission of CHIKV [4].

The first significant urban outbreaks of chikungunya fever were documented in the early 1960s in Bangkok [8] and from 1963 through 1973 in India [9, 10]. Minor outbreaks periodically occurred over the next 30 years, but no major outbreaks were recorded until 2004, when a large epidemic started on the coast of Kenya [4, 5]. This outbreak started a 4-year-period in which CHIKV spread throughout numerous islands of the Indian Ocean, India and parts of Southeast Asia (figure 1) [5, 11, 12]. In addition, at least 18 countries throughout Asia, Europe, and North America documented imported cases of chikungunya fever, with a few of these countries developing local autochthonous transmission of the virus [4].

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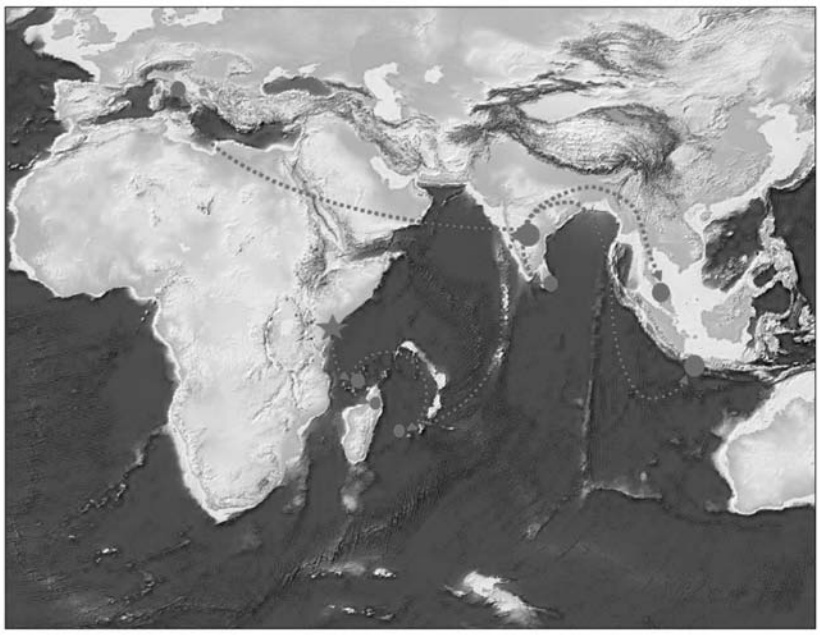

Figure 1. Map of chikungunya fever epidemics occurring during the period 2004–2008. On the basis of molecular analysis of outbreak strains and the epidemiology of the outbreaks of Chikungunya virus, Chikungunya virus was believed to re-emerge from Kenya starting in 2004 (*star*). From there, the disease spread eastward throughout the islands in the Indian Ocean before becoming established in India. From India, the disease spread further, leading to autocthonous transmission both regionally and as far away as Italy. The base map was obtained from ArcGIS software (ESRI).

Molecular epidemiology of the strain responsible for this outbreak indicated it originated from Kenya [13, 14]. Starting in 2004, Kenya experienced 2 outbreaks of chikungunya fever. The first outbreak in Lamu resulted in an estimated 13,500 cases, which represents >70% of the population of the island [5]. The outbreak was initially thought to be due to malaria, but eventually, testing determined that CHIKV was the cause. A few months following the outbreak in Lamu, a second outbreak occurred in the city of Mombasa.

Previous outbreaks in Africa had rarely led to spread of the disease outside of continental Africa. However, by January 2005, an outbreak of dengue-like illness was detected in the Union of the Comoros. Over the next several months, the outbreak on the main island led to 63% of the population being infected with CHIKV [11], suggesting that over 225,000 infections had occurred. Entomological investigations detected CHIKV in *Ae. aegypti* mosquitoes [15].

Movement of goods and people among the islands of the Indian Ocean led to introduction of CHIKV into La Reunion island [12]. The virus was first detected there in the spring of 2005 with only a limited number of cases until January 2006, when there was a substantial increase in the number of cases. At the peak of the epidemic on La Reunion, over 40,000 cases were reported per week [16]. Overall, 266,000 cases were believed to have occurred. This outbreak was the first time that a number of neurological manifestations, fetal infections, and mortality were reported to be associated with CHIKV [17, 18]. Additionally, unlike in Comoros or Kenya, it was speculated that in La Reunion the virus was transmitted primarily by the secondary vector, *Ae. albopictus,* because *Ae. aegypti* mosquitoes were present in limited numbers on the island [19, 20]. Follow-up studies revealed that 1 point mutation in the E1 glycoprotein increased infectivity in *Ae. albopictus* [20, 21]. This genetic change likely contributed to the magnitude and distribution of outbreaks, because areas without *Ae. aegypti*, such as La Reunion, could still have autochthonous transmission if *Ae. albopictus* were present.

In addition to the spread of the Central/East African genotype of CHIKV among the Indian Ocean Islands, this genotype was imported to India where it had never been reported [13, 14, 22]. The outbreak that ensued in India has continued for >3 years, resulting in millions of cases [3]. The persistence of cases of infection in India is presumably attributable to vast numbers of immunologically naive people, who help sustain viral transmission. This is in contrast to other affected areas, primarily islands with limited populations, which did not report cases after the epidemic swept through, most likely because of the development of herd immunity.

CHIKV in India served as the source of viral introduction to Italy. A viremic traveler returning to his home after a visit to India was the index case that led to subsequent autocthonous transmission with local *Ae. albopictus* mosquitoes [23]. A study of the epidemic curve of cases identified in Italy combined with detection of the virus in local *Ae. albopictus* mosquitoes estab-

lished that CHIKV was maintained locally in a mosquito-human-mosquito cycle [6].

The epidemics of CHIKV infections occurring from 2004 through 2008 demonstrated the ease with which this virus can spread and infect humans. Several factors likely contributed to the spread, including very high attack rates associated with the recurring epidemics [5, 11], high levels (often >5 $\log_{10}$ plaque-forming units per mL of blood) of viremia associated with infection in humans [24], and the worldwide distribution of the vectors responsible for transmitting CHIKV [25–29].

CLINICAL FEATURES OF CHIKUNGUNYA FEVER

The first case series of patients infected with CHIKV, published in 1955, described 115 hospitalized patients in Tanzania with acute onset of high fever, severe joint pain, and rash [1]. The illness was initially diagnosed as a "dengue-like" disease until laboratory evaluation confirmed CHIKV as the source of illness. Since then, many CHIKV outbreaks have occurred that have helped to further characterize chikungunya fever [17, 30–32].

The incubation period for chikungunya fever is typically between 3–7 days (range, 2–12 days). Not all individuals infected with the virus develop symptoms. Serosurveys indicate that 3%–25% of persons with antibodies to CHIKV have asymptomatic infections [33–35].

Symptoms of CHIKV infection start abruptly with fever (temperature, usually >38.9°C). The fevers typically last from several days up to 2 weeks and can be biphasic in nature [36, 37]. Shortly after the onset of fever, the majority of infected persons develop severe, often debilitating polyarthralgias. The joint pains are usually symmetric and occur most commonly in wrists, elbows, fingers, knees, and ankles but can also affect more-proximal joints [38]. Arthritis with joint swelling can also occur. The lower extremity arthralgias can be severely disabling, resulting in a slow, broad-based, halting gait, which can persist for months.

Published reports suggest that rash is another common symptom [30, 33, 39]. However, the portion of individuals with rash is highly variable between studies, making it a less reliable sign of the disease. When it occurs, the rash appears after fever onset and is typically maculopapular involving the trunk and extremities but can also involve palms, soles, and the face. Other skin lesions recognized during recent outbreaks include vesiculobullous lesions with desquamation, aphthous-like ulcers, and vasculitic lesions [17, 40].

Additional symptoms that can occur during the acute illness include headache, fatigue, nausea, vomiting, and conjunctivitis; myalgias, although not specific for febrile illnesses, occur very commonly. Cervical lymphadenopathy can also occur in the acute illness; however, it is not seen as frequently as with o'nyong nyong fever, another alphavirus infection also associated with fever and arthralgias [41]. Blood test abnormalities, such as leukopenia, thrombocytopenia, hypocalcemia, and a mild to moderate increase in liver function test results [17, 38], are seen with acute infection but are not specific and do not occur frequently enough to be diagnostic.

During early epidemics, rare but serious complications of the disease were noted, including myocarditis, meningoencephalitis, and mild hemorrhage [8, 39, 42, 43]. From recent epidemics, further neuroinvasive complications have been recognized, including Guillan-Barré Syndrome, acute flaccid paralysis, and palsies [44–48]. Additionally, new complications, such as uveitis and retinitis, have been described [49–51]. Death caused by chikungunya infections appears to be rare. However, increases in crude death rates have been reported during the 2004–2008 epidemics [52–54]. With CHIKV infections, older individuals with underlying medical conditions and individuals with coinfections appear to be more likely to suffer complications and to have a higher risk of death [55–57].

Following the acute phase of the illness, some patients develop prolonged symptoms, lasting several weeks to months, including fatigue, incapacitating joint pain, and tenosynovitis or edematous polyarthritis of their digits [38]. Recent studies have also noted carpal or cubital tunnel syndrome and Raynaud phenomenon after the acute illness [58]. In long-term follow-up studies, up to 64% of patients with chikungunya fever reported joint stiffness and/or pain >1 year after the initial infection, and 12% still reported symptoms 3–5 years later [59–61]. One study found 4 out of 5 patients with long-term joint symptoms were of tissue haplotype HLA-B27, suggesting a possible genetic association with prolonged joint symptoms [62].

During recent outbreaks, pregnant women were found to be infected with CHIKV and to have symptoms and outcomes similar to those in other individuals. Most CHIKV infections occurring during pregnancy do not appear to result in transmission of the virus to the fetus [63]. However, if the pregnant woman is viremic at the time of delivery, there is a risk for mother-to-child transmission with a vertical-transmission rate of 49% [18]. Intrapartum transmission resulted in neonatal complications including neurologic disease, hemorrhage, and myocardial disease. First trimester abortions following maternal CHIKV infection have been rarely reported [64]. There is no evidence that the virus is transmitted through breast milk [57]. Transmission has also been documented through exposure with infected blood [65], which suggests that CHIKV infections could occur through transfusion of blood products.

Treatment for chikungunya fever is limited to supportive care: rest, fluids, antipyretics, and analgesics. Although there have been in vitro studies and limited clinical data suggesting a role for certain drugs, such as chloroquine, acyclovir, ribavirin, interferon-α, and corticosteroids, in treating infections with CHIKV [38, 50, 66–69], there are insufficient data to

conclude that these and other interventions are beneficial and cost-effective.

CHIKV infections are often confused with dengue viral infection, because both diseases can present with high temperatures and myalgias in people living in or returning from tropical areas. In addition, both viruses are transmitted by the same species of mosquitoes and may cocirculate, leading to dual infections and concurrent epidemics [8, 70–73]. Although these diseases share similar clinical features, prominent and prolonged arthalgias affecting multiple joints are more consistent with CHIKV, and hemorrhage is more common in cases of dengue virus infection [8, 72, 74]. The prevalence of specific symptoms or signs may help in differentiating between the 2 diseases, especially where diagnostic testing is not readily available (table 1). Other alphaviruses, such as Ross River, Mayaro, Barmah Forest, Sindbis, and O'nyong nyong viruses, can also present with fever and arthalgias [31]. However, the travelers' itinerary may help in differentiating between alphaviruses, because most, except for O'nyong nyong, occur in areas where CHIKV has not yet been recognized [75, 76]. With o'nyong nyong fever, as mentioned above, cervical lymphadenopathy is more prominent [77]. Finally, malaria is often confused with CHIKV in travelers returning from tropical areas, but again, CHIKV tends to cause more prominent arthralgias.

Table 1. Comparison of the Clinical Features of Chikungunya Fever and Dengue Fever

Clinical features	Chikungunya virus infection	Dengue virus infection
Fever (temperature, >38.9°C)	+++	++
Myalgias	+	++
Arthalgias	+++	+/−
Headache	++	++[a]
Rash	++	+
Bleeding dyscrasias	+/−	++
Shock	−	+/−
Leukopenia	++	+++
Neutropenia	+	+++
Lymphopenia	+++	++
Thrombocytopenia	+	+++

NOTE. The mean frequencies of symptoms were determined from studies where the 2 diseases were directly compared among patients seeking care. Symbols indicate the percentage of patients exhibiting each feature: +++, 70%–100% of patients; ++, 40%–69%; +, 10%–39%; +/−, <10%; −, 0% [8, 65].

[a] Headache was often retro-orbital.

LABORATORY DIAGNOSTIC TESTS FOR CHIKUNGUNYA FEVER

Infections with CHIKV are confirmed by the detection of the virus, viral RNA, or CHIKV-specific antibodies in patient samples. The type of testing performed is typically dictated by the timing and volume of samples available. Historically, infections were diagnosed on the basis of serology, but with the advent of numerous molecular techniques, viral RNA can be easily detected by reverse transcriptase-polymerase chain reaction (RT-PCR) in serum specimens obtained during the acute phase of infection.

CHIKV infections cause high levels of viremia (up to $1 \times 10^{6.8}$ plaque-forming units per mL), which typically last for 4–6 days but can persist for up to 12 days after the onset of illness [24, 78]. Because of this, RT-PCR or viral culture performed on an acute-phase specimen can frequently be used to confirm CHIKV infection. Virus isolation is possible from serum specimens collected during the first 7 days of the illness, whereas viral nucleic acid is detected for a few additional days with use of real-time RT-PCR [24, 32]. In 2008, real-time assays, including those based on an assay developed at the Centers for Disease Control and Prevention (CDC), became commercially available (Focus Diagnostics) in limited markets; however, the validity and sensitivity of these new commercial assays have not yet been independently confirmed. RT loop-mediated isothermal amplification has also been used to detect CHIKV [79]. This technique has the advantage of not needing specialized equipment such as thermocyclers. Molecular assays can usually be completed within 1 day, whereas viral isolation often occurs within 48 h.

Enzyme-linked immunosorbent assays (ELISAs) detect both anti-CHIKV immunoglobulin (Ig) M and IgG antibodies from either acute- or convalescent-phase samples. Testing of samples from imported cases found that CHIKV-specific IgM antibodies develop rapidly (typically present by 5–7 days after illness onset but noted as early as the day of illness onset) and persist for several months [24, 32]. The ELISA is also quite specific, with very little crossreactivity with related alphaviruses. IgG detection can be useful to identify a 4-fold increase in antibody titer in the unlikely event that all testing from the acute-phase specimen is negative. Rapid dipstick variations of the CHIKV ELISA were recently developed to help diagnose chikungunya fever in the field [79], but the sensitivity has not been well characterized, and these tools are not widely available.

Other tests described for the detection of CHIKV antibodies include immunofluorescence assays [80] and a plaque reduction neutralization test (PRNT). Immunofluorescence assays are sensitive and specific but lack the ability to quantify antibodies, are subjective, and require special equipment and training. However, these tests are commercially available and are an option for laboratories that routinely use this method for detection of other infectious agents. PRNTs are extremely useful because they are quite specific for alphaviruses and are the gold standard for confirmation of serologic test results. The major drawback to PRNT is that it requires the use of live virus. Because CHIKV is a biosafety level 3 agent that requires special

laboratory containment because of its history of laboratory-acquired infections [81], this test is available only in a limited number of reference laboratories.

Given the available diagnostic tests for CHIKV, testing of both acute- and convalescent-phase samples, collected at least 3 weeks apart, from a patient presenting with a high fever combined with severe joint pain and recent travel to a CHIKV outbreak area should be sufficient to confirm the infection. However, cryoglobulinemia has recently been reported in several CHIKV-infected patients [82]. Therefore, if a patient presents with appropriate clinical syndrome and travel to an affected area, this should be considered if serologic test results are negative. Efforts should be made to identify a qualified laboratory that can perform viral culture and/or molecular assays for CHIKV on acute-phase specimens, particularly those in which IgM may not yet be present. Health care providers should contact their state or local health department or the CDC for assistance with diagnostic testing.

PRIORITIES FOR FUTURE STUDIES OF CHIKV

Although a fair amount of knowledge has been gained from the recent outbreaks and subsequent investigations, further studies are needed. For instance, additional studies evaluating vector competence and potential transmission factors could further our understanding as to why this particular Central/East African strain was so effective in spreading. Sensitive and specific models incorporating ecologic, entomologic, and virologic factors could be explored as a way to help predict factors contributing to the spread of the disease and ultimately help predict future outbreaks of CHIKV. Such models have already been developed for other arboviral diseases, such as Rift Valley Fever [83].

Physicians will likely have a role in detecting cases and need to consider CHIKV infections in patients presenting with a high fever combined with severe joint pain and recent travel or exposure to someone with recent travel to a CHIKV outbreak area. Local health departments should be promptly notified of any suspected cases, to detect and potentially prevent subsequent local transmission. Further improvements in the availability and validity of diagnostic tests for CHIKV will be essential for the early detection and risk reduction through implementation of aggressive vector control measures and health communications.

Research should continue into the pathogenesis of persistent arthralgias and into possible therapeutics, such as antivirals, which can treat the disease and potentially curb the high viremia and significant morbidity associated with CHIKV infection. A live, attenuated vaccine was originally advanced through Phase II human trials, but its development was halted because of its reactogenicity and a lack of demand [84, 85]. The study of this and other potential vaccine formulations, such as chimeric alphavirus vaccines [86], should be renewed. In the meantime, physicians need to take an active role in educating their patients who are traveling to affected areas about the risk of chikungunya infections and measures to prevent the disease, including strategies to minimize mosquito bites.

Through the recent epidemics, CHIKV has demonstrated its ability to spread and infect large proportions of the population. There is a very good chance that CHIKV will continue to spread unless measures are taken to improve the recognition of the disease, to control the vectors responsible for the transmission, and to rapidly communicate epidemiological information to vector control experts and other public health officials. Hopefully, timely sharing of accurate information will help control the spread and magnitude of future outbreaks.

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