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How Great is the Threat of Chikungunya Virus?

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Summary

In the last decade, chikungunya virus (CHIKV) has emerged from an obscure arbovirus that caused limited outbreaks of disease in Africa and Asia to the cause of a pandemic affecting millions of people and spanning five continents. Two separate CHIKV genotypes have been responsible for outbreaks during this period, including strains adapted to transmission in *Aedes albopictus* mosquitos. Further spread of this virus into new regions of the Western Hemisphere is predicted during the present rainy season in the tropics, and recurrent viral introductions and disease outbreaks, as occurred in Réunion in 2010, should be expected. CHIKV no longer simply threatens; it has arrived as a significant, global pathogen.

Keywords

chikungunya virus; alphavirus; emerging infectious diseases; arbovirus; *Aedes albopictus*

As recently as 2004, chikungunya virus (CHIKV) was a relatively obscure arbovirus that only caused sporadic outbreaks of human disease [1]. Human infection with this alphavirus (Family: *Togaviridae*) results in an acute, systemic febrile illness that is typically associated with debilitating arthralgia and a rash [2]. While descriptions of an illness compatible with chikungunya fever can be found as early as 1779, CHIKV was not identified until the 1950s following an outbreak on the Makonde Plateau of what is now southern Tanzania [2]. Interest in the virus eventually waned as CHIKV did not appear to spread outside of Africa and Asia. In 2004, however, an outbreak in Kenya touched off a CHIKV pandemic that has resulted in millions of human cases and documented virus transmission throughout the Indian Ocean, South Pacific, South and Southeast Asia [1,3]. For the first time, CHIKV transmission has been confirmed in the Western Hemisphere, with estimates approaching one million cases in the Americas as of October 17, 2014 [4]. Autochthonous transmission has been reported in both France and the United States in 2014. These events, combined

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with past autochthonous cases in Italy (2007) and France (2010), demonstrate that it may only be a matter of time before large CHIKV outbreaks occur outside of the tropics.

One explanation for the dramatic emergence of CHIKV has come from sequencing the viral RNA genome of strains isolated over the past decade. Phylogenetic studies of CHIKV performed prior to 2004 identified three distinct genotypes: West African, East-Central-South African (ECSA), and Asian [1]. The spread of CHIKV from East Africa was associated with the emergence of an Indian Ocean lineage of the ECSA genotype, including CHIKV strains adapted to the mosquito vector, *Aedes albopictus* [5]. Previously, this mosquito had served only as a secondary vector for CHIKV, which was predominantly spread to humans by *A. aegypti*. A single amino acid change in the E1 protein (E1-A226V), in association with specific mutations in the E2 protein, accounts for increased transmission by *A. albopictus*, and the E1-A226V mutation has developed through convergent evolution on multiple separate occasions since 2005 [5–7]. The significance of this can be seen in the example of Malaysia, which had experienced limited CHIKV outbreaks (~300 cases in each of 3 outbreaks from 2006–2007) associated with Asian and ECSA genotype viruses. Between 2008 and 2010, following the introduction of an ECSA strain bearing the E1-A226V mutation, a nationwide epidemic occurred that resulted in over 10,000 cases with additional cases observed across the Thai border [8]. While the rise of the Indian Ocean lineage has been associated with massive outbreaks in the Indian Ocean and Asia, the ongoing epidemic in the Americas has actually resulted from CHIKV strains of the Asian genotype, which are most similar to isolates from China and the Philippines [9]. While detailed genetic studies of these viruses are forthcoming, previous studies using Asian genotype strains have documented amino acid substitutions in the E1 glycoprotein that limit the ability of these viruses to adapt to the *A. albopictus* vector [10]. This finding lends support to theories that CHIKV emergence in the past decade may have been linked to initial adaptive mutations that improve transmission by *A. aegypti* [11]. It remains possible, then, that outbreaks in the Western Hemisphere may actually worsen, if an *A. albopictus*-adapted strain is introduced into the region.

The adaptation of CHIKV to *A. albopictus* is also significant as this mosquito is present over a larger geographic range than *A. aegypti*. Indeed, this mosquito was responsible for CHIKV transmission in Italy (2007) and France (2010) as well as outbreaks of CHIKV in new regions of Africa, such as Gabon in 2007 and 2012 [12,13]. Vector competence studies using CHIKV strains with the E1-A226V mutation have routinely demonstrated highly efficient infection of and transmission by *A. albopictus*, and other *Aedes spp.* have also proven competent as potential CHIKV vectors [12]. Disease modeling studies predict the continued spread of CHIKV into new areas, including regions of the United States, Central and South America, and a study employing climate change projections identified regions of Europe that may support CHIKV transmission over the coming century [14,15]. While it appears likely that CHIKV will spread into regions that currently experience dengue virus (DENV) transmission, other factors must also be taken into consideration. The presence of competent mosquito vectors and measures of vector indices have not proven reliable for the prediction of DENV outbreaks, and despite the introduction of 1471 CHIKV cases into the United States in 2014 (as of October 21), only 11 autochthonous cases have been recorded

[16,17]. One explanation for this discrepancy is the presence of social factors that affect the likelihood of CHIKV dissemination but are difficult to model in disease projections. For example, in a study of the 2005–2006 outbreak on Mayotte in the Southwest Indian Ocean, CHIKV incidence was higher among individuals with less education, traditional housing and outdoor plumbing [18]. Though we expect that outbreaks of CHIKV will occur in the United States, particularly in the Southeast and along the Gulf of Mexico, these should not be viewed simply as the expected result of global warming or high vector indices. Rather, these cases may serve to document the deterioration of social services and the growing gap between rich and poor in America.

Concerns surrounding CHIKV emergence include not only its potential to spread into new populations, but also the clinical disease and patient outcomes that result from infection. Seroprevalence studies performed in the wake of recent CHIKV outbreaks demonstrate high rates of infection in naïve populations. This has ranged from 10% in northeastern Italy to 75% on Lamu Island, Kenya [1,3]. In contrast to DENV, where high rates of asymptomatic infection have been reported, approximately 80% of CHIKV infected individuals develop symptomatic disease [19]. Furthermore, cases of prolonged arthritis have been reported in a number of settings. Chronic symptoms occur more commonly among older individuals and can significantly impact a patient's quality of life [20]. The overall mortality from CHIKV has been estimated at 1 in 1000 cases or less, but severe disease, atypical clinical manifestations, and mortality have all been associated with patient age and the presence of medical comorbidities [1,21]. In a study of 610 atypical cases on Réunion, mortality was 10.6%, and 36.4% of patients required support of at least one vital function. Comorbid illnesses were associated with severe disease, and mortality was associated with age and alcohol use [21]. These findings are concerning in the face of potential outbreaks among populations with large numbers of elderly individuals and patients with multiple medical comorbidities. In terms of other vulnerable populations, the clinical manifestations and outcomes of CHIKV infection in the immunocompromised host are largely unknown. CHIKV infection in pregnant women does not appear to affect the course of the pregnancy itself. However, perinatal mother to child CHIKV transmission can occur, and neonates are at high risk for the development of severe disease and significant neurocognitive impairment [22].

Currently, there is no specific antiviral treatment for CHIKV, and patient care is largely supportive. Laboratory confirmation of chikungunya may be useful in limiting unnecessary medical interventions and alerting public health authorities to a possible outbreak. Accurate diagnosis requires the use of reverse-transcriptase PCR (RT-PCR) in the acute setting or the specific detection of anti-CHIKV IgM. RT-PCR is not widely available in many affected countries, however, and serological testing is insensitive in the first four days of illness [2,23]. This results in missed diagnoses particularly if patients present early in the disease course. Although many vaccines are in development, none are close to approval at this time, and the appropriate use of a CHIKV vaccine, once available, remains to be determined.

In conclusion, CHIKV has emerged over the last decade from its niche in the forests of Africa and Asia to infect millions of people and spread across five continents. As the rainy season approaches, further CHIKV outbreaks in the tropical Western Hemisphere loom on

the horizon. Transmission continues in many regions of the world, and recurrent viral introductions and disease outbreaks, as occurred in Réunion in 2010, should be expected. CHIKV no longer simply threatens; it has arrived as a significant, global pathogen. The recent history of CHIKV as a rapidly emerging arboviral disease should only heighten our concern for the evolution of new arboviral threats from the ranks of old enemies.

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