Reemergence of Chikungunya Virus

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Chikungunya virus (CHIKV) is a mosquito-transmitted alphavirus that causes acute fever and acute and chronic musculoskeletal pain in humans. Since 2004, CHIKV has caused millions of cases of disease in the Indian Ocean region and has emerged in new areas, including Europe, the Middle East, and the Pacific region. The mosquito vectors for this virus are globally distributed in tropical and temperate zones, providing the opportunity for CHIKV to continue to expand into new geographic regions. In October 2013, locally acquired cases of CHIKV infection were identified on the Caribbean island of Saint Martin, signaling the arrival of the virus in the Western Hemisphere. In just 9 months, CHIKV has spread to 22 countries in the Caribbean and Central and South America, resulting in hundreds of thousands of cases. CHIKV disease can be highly debilitating, and large epidemics have severe economic consequences. Thus, there is an urgent need for continued research into the epidemiology, pathogenesis, prevention, and treatment of these infections.

In April 2005, CHIKV was confirmed as the cause of an epidemic of dengue-like illness on the Comoros Islands, which are located off the east coast of northern Mozambique; this was the first known emergence of CHIKV in the southwestern Indian Ocean region. Due to clinical similarities, this outbreak was initially suspected to be caused by dengue virus, highlighting the fact that CHIKV disease is often misdiagnosed and the true number of cases in a particular region may be underestimated. Shortly thereafter, the first cases of CHIKV disease were reported on Mayotte, Mauritius, and the French island of La Reunion. The number of cases in these areas increased rapidly, due in part to attack rates as high as 35% to 75%. By the end of 2005, after an apparent gap of about 32 years during which CHIKV was not detected, India reported CHIKV disease in numerous states, with the official number of suspected cases ultimately reaching more than 1.3 million. The CHIKV outbreak continued to spread, causing large outbreaks in Sri Lanka and many other countries in Southeast Asia. During this epidemic, CHIKV was introduced into countries where it is not endemic by viremic travelers, and autochthonous transmission of CHIKV was observed for the first time in many countries, including Italy, France, New Caledonia, Papua New Guinea, Bhutan, and Yemen. The rapid and explosive spread of CHIKV prompted the Pan American Health Organization (PAHO) and the Centers for Disease Control and Prevention (CDC) to release a preparedness guide that predicted potential future CHIKV epidemics in the Americas. This prediction has now come to fruition, as in December 2013, the World Health Organization (WHO) reported the first local transmission of CHIKV in the Western Hemisphere on the Caribbean island of Saint Martin. By 18 July 2014, CHIKV had caused more than 440,000 cases of disease in more than 20 countries in the Caribbean and Central and South America (Fig. 1). In addition, the CDC has reported more than 230 imported cases of CHIKV infection in the continental United States as well as locally acquired cases in Florida. Thus, in less than 10 years, CHIKV has spread from the coast of Kenya throughout the Indian Ocean, Pacific, and Caribbean regions, causing millions of cases of disease in over 50 countries. In other words, CHIKV has reemerged as a true global pathogen.

CHIKV TRANSMISSION, GENETICS, AND REEMERGENCE

In Africa, CHIKV circulates in an enzootic cycle involving forest-dwelling mosquitoes and nonhuman primates. In Asia, CHIKV primarily circulates in urban areas among Aedes aegypti or Aedes albopictus mosquitoes and humans. However, some studies suggest that a sylvatic CHIKV transmission cycle may also exist in at least some parts of Asia, since CHIKV-specific antibodies have been detected in wild monkeys in Malaysia. During acute CHIKV infection of humans, there is high-titer viremia; thus, the virus can be transmitted in a human-mosquito-human transmission cycle and can be spread by viremic humans. For example, an outbreak in Italy was initiated by a CHIKV-infected traveler from India. Dense human populations and lack of herd immunity likely contribute to the explosive nature of CHIKV epidemics in many regions.

Three genotypes of CHIKV, called West African, East/Central/South African (ECSA), and Asian, have been defined (3). Phylogenetic analysis showed that an ECSA genotype virus was responsible for the epidemics on islands in the Indian Ocean, and this ECSA virus had originated in coastal Kenya, where outbreaks of CHIKV had occurred on Lamu Island and in Mombasa between May and December 2004 (4). The outbreak in Lamu Island likely spread to islands in the Indian Ocean, whereas the outbreak in Mombasa spread to the Indian subcontinent (5). Nucleotide se-
The World Health Organization (WHO) reported the first local transmission of CHIKV in the Western Hemisphere on the island of Saint Martin in December 2013. By 18 July 2014, the Pan American Health Organization (PAHO) reported more than 440,000 suspected and confirmed cases of chikungunya fever in more than 20 countries, with the majority of suspected and confirmed cases occurring in the Dominican Republic (251,951), Guadeloupe (64,328), Haiti (62,436), Martinique (30,455), Saint Martin (4,453), and Dominica (3,243). CHIKV has also spread to countries on mainland South America (French Guiana [881], Guyana [16], Suriname [17], Venezuela [2]), Central America (El Salvador [1,783], Costa Rica [1]), and the continental United States (Florida [2]). The number of cases in most of these countries continues to increase, and the virus continues to spread to new regions. The map (Maps for Design) shows the incidence rate of CHIKV infection in countries, territories, or states with autochthonous transmission as of 18 July 2014. (Case number and incidence rate data were obtained from PAHO, http://www.paho.org/hq/index.php?option=com_topics&view=article&id=343&Itemid=40931.)

Since 2004, ECSA genotype viruses spread from the coast of Kenya throughout much of the Indian Ocean region, principally by viremic travelers, causing a series of outbreaks of CHIKV infection of unprecedented scale. Thus, it was quite unexpected when the ongoing outbreaks in the Caribbean region were found to be due to an Asian genotype virus. Sequence analysis revealed that the virus circulating in the Caribbean is phylogenetically related to Asian genotype strains recently circulating in Indonesia, China, and the Philippines (8). To date, the outbreaks in the Caribbean region have been primarily transmitted by A. aegypti, and studies have demonstrated that Asian genotype CHIKV strains are constrained in their ability to adapt to A. albopictus mosquitoes (9), suggesting that this may limit the spread of Asian genotype CHIKV strains into temperate regions, including much of the southern United States, where A. albopictus mosquitoes are more commonly found than are A. aegypti mosquitoes. However, at least in the laboratory, Asian genotype CHIKVs are efficiently transmitted by both A. aegypti and A. albopictus mosquitoes collected from North, Central, and South America (10).

CHIKUNGUNYA DISEASE: CLINICAL MANIFESTATIONS AND PATHOGENESIS

Clinical manifestations. Chikungunya, which translates as “disease that bends up the joints,” is characterized by an abrupt onset of fever with severe joint pain, and the pain may persist for weeks to years (11). In contrast to infections with many other arboviruses, only 5 to 25% of CHIKV infections are asymptomatic. The arthralgia is typically symmetrical and primarily affects peripheral joints, including wrists, knees, ankles, and the small joints of the hand. Additional disease signs and symptoms include arthritis, with joints often exhibiting tenderness and swelling, tenosynovitis, skin rash, and myalgia, particularly in the lower back and leg muscles. In addition to these clinical features, severe neurologic and cardiac manifestations and, in some instances, deaths have been associated with CHIKV infection. These more severe outcomes often occur in neonates, in patients more than 65 years of age, and in those with underlying medical conditions. In addition, reports indicate that mother-to-infant transmission of CHIKV during delivery results in high rates of morbidity (12). Chronic CHIKV disease can be highly debilitating, and large epidemics have severe economic impacts, highlighting the significant public health threat posed by CHIKV.

Pathogenesis. The pathogenesis of CHIKV infections is not well understood and is an area of intense investigation, with small animal and nonhuman primate models of acute and chronic disease recently being developed (13). Studies of humans and animal models have shown that disease signs and symptoms following infection with CHIKV are associated with CHIKV infection of...
cells in musculoskeletal tissues, such as fibroblasts and osteoblasts, and infiltration of inflammatory cells—consisting predominantly of monocytes, macrophages, natural killer cells, and T cells—in musculoskeletal tissues. Recent work has demonstrated that both Rag1−/− mice, which lack mature T and B cells, and CD4−/− mice, which lack CD4+ T cells, had reduced joint swelling and less severe musculoskeletal tissue injury during the acute stage of CHIKV disease (14, 15), suggesting a pathogenic role for CD4+ T cells in CHIKV disease. In addition, studies in a well-established mouse model of Ross River virus infection, a related arthropitog alpha-virus, suggested that recruitment of monocytes into joints by factors secreted from virus-infected osteoblasts promotes the development of arthritis (16). CHIKV disease in humans is associated with elevated levels of specific cytokines and chemokines, with high levels of interleukin-6 (IL-6), IL-1β, RANTES, mono-
cyte chemoattractant protein 1 (MCP-1), monokine induced by gamma interferon (MIG), and IP-10 linked to CHIKV disease severity (13). Importantly, the cause of persistent CHIKV joint disease is unclear, and there is little evidence for the development of autoimmunity in individuals with chronic disease (11). Cyto-
kines may also contribute to chronic CHIKV disease, as persistent arthralgia has been associated with elevated levels of IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) (17). In addition, mildly elevated C-reactive protein (CRP) in pa-
tients with chronic symptoms suggests ongoing chronic inflammation. Chronic CHIKV joint disease may result from persistent CHIKV infection in musculoskeletal tissues. CHIKV antigen and RNA were detected in synovial tissue biopsy specimens collected from a patient suffering from chronic joint pain (18). CHIKV antigen was also detected in muscle satellite cells in a muscle tissue biopsy specimen collected from a patient during a relapse of chronic musculoskeletal pain (19). Persistence of CHIKV RNA and antigen in tissues has also been detected in animal models (15, 20), further suggesting that CHIKV establishes chronic infections that may promote immune-mediated chronic disease.

CONCLUSIONS
In summary, in the last decade, CHIKV has reemerged as a major threat to global public health. The extent to which CHIKV be-
comes established in new regions remains to be seen; nevertheless, it seems likely that the current epidemic will continue to spread throughout much of the Americas. Unfortunately, specific treat-
ments or vaccines against CHIKV infection are not yet available. A variety of CHIKV vaccine candidates are in development, includ-
ing live-attenuated, inactivated, virus-like particles, subunit, DNA, and measles virus- and poxvirus-based vaccines. Many of
these vaccine candidates have shown promising results in animal models and in phase I clinical trials in humans. Numerous antivi-
rnal compounds, monoclonal antibodies, and immunomodulatory
drugs that could be used to prevent or treat CHIKV infection are also in the early stages of investigation. Thus, the reemergence of
CHIKV and the enormous scale of the CHIKV-associated out-
breaks have highlighted many critical research needs. These in-
clude increased surveillance for CHIKV infection or antibodies in humans and animals, increased mosquito control programs, im-
plementation of protocols for detecting CHIKV in donated blood, organs, and tissues for transplantation, and increased basic and translational research to enhance our knowledge of CHIKV biol-
ogy, pathogenesis, treatment, and prevention.

ACKNOWLEDGMENTS
I thank Kathryn V. Holmes and Mark T. Heise for critical readings of this article. I apologize to all whose work could not be directly referenced due to formatting and length restrictions.

Work in my laboratory was or is supported by NIH-NIAID grants U54 AI065357, U19 AI109680, and R01 AI108725.

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