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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.

Chikungunya virus (CHIKV), a mosquito-transmitted alphavirus with a single-stranded, positive-sense RNA genome of ~12 kb, was first isolated from the blood of a febrile individual in Tanzania in 1953 during a large outbreak of disease characterized by crippling joint pains and severe fever, locally referred to as chikungunya (1). In 1958, CHIKV was isolated from patients in Bangkok, Thailand (2), where it had spread apparently from Africa. Since these first documented epidemics, sporadic CHIKV outbreaks have been reported in numerous African and Asian countries.

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-

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FIG 1 CHIKV in the Western Hemisphere. 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 (50,455), 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.)

quencing of virus isolates also revealed genetic changes in viruses isolated during the second phase of the epidemic on La Reunion island, including an alanine (A)-to-valine (V) switch at amino acid 226 of the E1 envelope glycoprotein, that were not present in strains isolated during the outbreaks in coastal Kenya or on Comoros. In contrast to coastal Kenya and Comoros, where *A. aegypti* was the primary vector, *A. albopictus* was the primary CHIKV vector species in La Reunion, and the E1 A226V mutation was later shown to greatly enhance CHIKV infectivity of *A. albopictus* mosquitoes (6). Consistent with this, large CHIKV outbreaks transmitted by *A. aegypti* occurred in several Indian states in the absence of the A226V mutation (7), while in 2007 in the Indian state of Kerala, CHIKV isolates contained the E1 A226V mutation and *A. albopictus* was the predominant vector. In addition to being detected in La Reunion and India, the E1 A226V mutation was detected in CHIKV strains from outbreaks in Cameroon in 2006 and Gabon in 2007, and *A. albopictus* played an important role in these and numerous other CHIKV outbreaks in the Indian Ocean region and Europe. Thus, the adaptation of CHIKV to *A. albopictus* mosquitoes likely contributed to the dramatic spread of CHIKV.

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 arthritogenic alphavirus, 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 serum levels of specific cytokines and chemokines, with high levels of interleukin-6 (IL-6), IL-1β, RANTES, monocyte 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). Cytokines 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 patients 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 becomes 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 treatments or vaccines against CHIKV infection are not yet available. A variety of CHIKV vaccine candidates are in development, including 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 antiviral 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 outbreaks have highlighted many critical research needs. These include increased surveillance for CHIKV infection or antibodies in humans and animals, increased mosquito control programs, implementation 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 biology, pathogenesis, treatment, and prevention.

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