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Chikungunya Virus (CHIKV): Coming to America

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CHIKV Introduction

Chikungunya Virus (CHIKV) is an arbovirus of the alphavirus genus (Togaviridae family) transmitted by the bite of infected Aedes mosquitoes. The word, Chikungunya, translates to "that which bends up", based on the stooped position of patients during the rheumatic symptoms of the disease. The disease was first discovered in Tanzania in 1952-53 [1, 2]. In the past 50 years, there have been outbreaks of CHIKV in Asia and Africa. In 2004, an outbreak in Kenya occurred and spread to the Comoros infecting over 5,000 cases. In 2005-2006, a CHIKV outbreak infected an estimated 300,000 of an island population with about 785,000, with 237 resultant mortalities. The factors favoring this epidemic included viremic travelers from Africa, an immunologically naive population, and a mutation of the CHIKV that expanded the mosquito vector from the *Aedes aegypti* (aka the Yellow Fever Mosquito) to the *Aedes albopictus* (the Asian Tiger Mosquito) which was common on the island [1,3-8].

From the outbreaks in Reunion with the CHIKV mutation (E1-A226V) which improves replication and transmission efficiency in *Ae. albopictus* as well as the original *Ae. aegypti*, outbreaks spread to the India subcontinent [4,9]. A viremic traveler returning from India was the index case that led to autochthonous transmission in Italy [10]. Parola et al describe CHIKV patients from Southern France returning from Reunion Island as well as one autochthonous nosocomial infection from metropolitan France [6].

In December 2013, alerts posted by the Centers for Disease Control (CDC) and Pan American Health Organization (PAHO) reported autochthonous cases of CHIKV in the Caribbean island of Saint Martin [11,12]. Prior reports of imported cases in the Americas were reported in Brazil, Canada, French Guyana, Martinique, and the United States [12-14]. In late December 2013, updates on the CHIKV cases reported confirmed or suspected cases on Saint Martin, Guadeloupe, Martinique, and Saint Barthelemy islands. The European Centre for Disease Prevention and Control (ECDC) urged vigilance to clinicians, travel authorities and blood safety authorities about the spread of CHIKV, due to enhanced travel during the Christmas holidays [15]. Since the CHIKV vectors (*Ae. aegypti* and *Ae. albopictus*) are present in various Caribbean islands and the United States, and complicated with the delayed of symptoms of CHIKV viremic patients, it is only a matter of time before the mainland United States reports autochthonous cases of its own. The following text provides further evidence supporting this theory.

Symptoms of CHIKV

CHIKV onset of symptoms is usually rapid, one to 12 after infection (averaging three days) [1,16]. But, the infected traveler from CHIKV infected countries may not demonstrate symptoms until three days later; ample time for air travel to various virally naive countries. The symptoms include high fever (40C), rash, myalgia, and polyarthralgia (NOTE: the arthralgia is usually symmetrical and affects more than one joint) [1,7,16]. Also, other symptoms reports include headaches, photophobia, skin rash, and some reports of lethal encephalitis [1,7,16]. Although the acute symptoms can subside in 1 to 2 weeks, the arthralgia can persist for months or years [16]. Schilte et al. [17] reported in a long term study of CHIKV patients; that patients with the presence of arthralgia 4 months after infection and being over 35 years of age were at risk for long-term arthralgia. The morbidity for CHIKV is high at least 35% and the mortality is low (below 1%); but "silent" infections are rare and thought to be no more than 15% of infected individuals [1]. Laboratory diagnostic tests for CHIKV infection are serological methods, viral isolation, and reverse-transcription-PCR (RT-PCR) [1,10,13,16].

Upon onset of the acute phase, the viral load of CHIKV can rise to 10^8 viral particles per milliliter of blood [1], which enhances the development of the human-mosquito-human transmission cycle [14]. Furthermore, Reiskind et al [18] reported that *Ae. aegypti* and *Ae. Albopictus*, both common to Florida were able to rapidly become infected with the mutated Reunion CHIKV strain (E1-A226V).

The virus following the mosquito bite replicates in skin fibroblasts and then spreads via the bloodstream to target the liver, muscle, brain, joints, and lymphoid tissue (1,7,16). Sourisseau et al [7] reports that CHIKV has been found to replicate in human epithelial, endothelial, primary fibroblasts, and monocyte-derived macrophages. The CDC has listed CHIKV category C priority pathogen [10,19]: that is could be engineered as for mass production and as a potential biological weapon due to ease of production and dissemination, availability, and potential for high morbidity and mortality rates and major health impact.

Threat to the United States

The primary threat of CHIKV introduction into the US is from viremic travelers. Several incidents have already been reported of travelers entering the US with CHIKV [12-14] as well as documented cases of CHIKV infected travelers returning to European countries, Australia, and Asia [6,13,14]. Although little is known of potential zoological reservoirs in the US, Thiboutot et al [13] describes the sylvantic cycle with non-human primates and forest mosquitoes in Africa, as well as describe the urban cycle which consists only of human-mosquito-human transmission.

Ae. aegypti (commonly called the Yellow Fever Mosquito) has been present in the US since early colonization and is believed to have been introduced from Africa from ships used by European explorers and early colonization efforts [20]. It can thrive and reproduce in urban settings and even un-used flower pots, drainage ditches, and spare tires. The female feeds to produce eggs and is active during the daytime

[20], but can feed at night under artificial lighting [21]. Although survival is poor in hot, dry climates, the mosquito can spread in the Eastern US from the Gulf states to the Mid-Atlantic and beyond to New York. This would include summer time proliferation to high population urban areas such as Washington, DC, New York, Philadelphia, Baltimore, and Atlanta to name just a few cities. The eggs can withstand desiccation for a long period of time which would increase the spread of the mosquito depending on the mode of transportation [20]. The species is active in the Northern parts of the US during the summer and active year round in the Southern US [21].

Ae. Albopictus (Commonly called the Asian Tiger Mosquito) has been established in the southeast of the US and in the Caribbean [16]. The mosquito is common in urban areas and flourishing in 36 states in the US [13,14]. The mosquito can survive both urban and rural environments, has a flight radius of 400 to 600 meters and is an aggressive daytime biter [1,22]. *Ae. Albopictus* eggs are long-lived and cold hardy enhancing the invasive spread of this vector [22].

Benedict et al [22] using ecological niche model, GARP (Genetic Algorithm for Rule Set Production), provided an ecological risk map of the spread of the mosquito globally, but this study included of the Gulf Coast, Mid-West, Mid-Atlantic states of the US as well as some infestations into southern New England states. The Benedict et al study also describes how *Ae. Albopictus* demonstrates the ability to inhabit either relatively cold and dry or warm and wet climates; both found in Eastern and Gulf states, especially urban zones.

Rochlin et al used the environmental modeling model, Maxent, on the spread of *Ae. Albopictus* in the northeastern US [23]. The Rochlin et al study uses predictions based on the invasive spread of the mosquito through 2099 taking into account future climatic projections due to global warming. The study finds that the mosquito will reach the coastline of New England states including Maine as well as metropolitan Boston areas by 2080 [23]. Although the Rochlin et al study differs slightly in the spread of *Ae. Albopictus* from the GARP study, both predictive models indicate the invasive spread of a vector with the potential to spread CHIKV to high population areas of the Northeastern part of the US.

It must be noted that several cases of laboratory infection of CHIKV from blood samples have been reported [24-26]. Hence, the risk to public blood supplies and enhanced CHIKV transmission from infected blood transfusions is great, IF the CHIKV enters the urban population areas [10].

Finally, the use of the invasive species of mosquitoes to transmit CHIKV could be an act of bioterrorism to a naive population [27,28]. Lockwood [29] describes a bioterrorism scenario of using *Ae. aegypti* to spread Yellow Fever to Mardi Gras partiers in New Orleans with the help of viremic Yellow fever martyr to ensure the infected mosquitoes spread their bioweapon to the unsuspecting populace in the city. CHIKV has the potential for similar weaponization and bioterrorism applications.

Counterstrategies

The counterstrategies are difficult and limited as are the treatments for CHIKV. The only treatments at present are anti-inflammatory drugs and a few studies suggest anti-viral may help reduce viral activity, but no large scale study on antiviral drugs as a cure exists at present [1,16]. At present, viral vaccines have been slow and difficult in development due in part to the limited funding and the risks associated with live attenuated, inactivated viral vaccines, or genetically recombinant genetically engineered vaccines [1,2,13]. Several studies from the US Army and other research centers in France have reported progress [2]. The studies have been spurred on especially due to concerns that CHIKV could be used as a biological weapon by terrorists. Furthermore, passive immunotherapy using purified immunoglobulin extracted from recovering CHIKV patients has demonstrated effectiveness in neutralizing CHIKV in vitro and in vivo studies [30].

Controlling the spread will require rapid diagnostics and education of clinicians and laboratory workers to avoid infection during testing as previous mentioned in the Cordel study [24]. Furthermore, the risks of contamination from a Category C pathogen [19] may require delays in getting diagnostic samples to diagnostic labs properly suited for handling and testing of CHIKV. These delays may hamper detection of viremic patients and may require testing of antibodies during the convalescent period [1,16]. Furthermore, training such as the PAHO provided to Caribbean clinical workers [31] may be required for public health officials as well as clinicians especially in large urban communities BEFORE CHIKV arrives into the US.

Further, in pursuit of controlling the spread of CHIKV, vector control will be essential. Although the familiar response to mosquito control has been insecticide spraying and control of breeding sites (such as trash and tire removal), other strategies will require further investigation. Some promising studies using a specific strain of the endosymbiotic bacterium *Wolbachia* have been found to induce resistance to CHIKV in both *Ae. aegypti* and *Ae. albopictus* [32,33]. Previous studies using *Wolbachia* strains have demonstrated that the bacterium induces disease-resistance genes in the mosquitoes as well as inhibits viral reproduction in Dengue (another alphavirus similar to CHIKV) virus in *Ae. Aegypti* [34]. This research warrants further research, development, and commercialization.

Final plans

CDC and state and local public health agencies have to prepare now for the eventual invasion of CHIKV into the US. Planning, education, and expansion of clinical testing facilities as well as precise training of laboratory personnel will be key. The responses during the outbreak of CHIKV by an informed and prepared public health service will mean the difference between a controlled, effective, and intelligent response or a public panic, unrestrained vector born outbreak, and needless suffering of CHIKV infected patients.

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