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EDITORIAL

Chikungunya: here today, where tomorrow?

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Until 2005, chikungunya virus (CHIKV) was a relatively little-studied pathogen restricted to parts of Africa and Asia. Epidemics were sporadic and separated by years of quiescence. In late 2004, the East Central South African genotype of CHIKV moved from Kenya onto the Indian Ocean island of Comoros. The global onslaught of CHIKV had begun. In November of 2005, viral isolates were identified with, what might normally be regarded as an insignificant, single alanine to valine mutation at position 226 of the envelope E1 gene.[1] This simple mutation had a remarkable effect; making the virus approximately 100 times more infectious to the Asian tiger mosquito, *Aedes albopictus*, and it was this species that was transmitting the virus rather than the usual vector, *Aedes aegypti*.[2] Subsequent 'second-step' mutations further enhanced the ability of the virus to infect and/or disseminate from the midgut to the salivary glands in *Ae. albopictus*.[3] However, these viruses can still be transmitted by *Ae. aegypti*. Within a year of the Indian Ocean lineage emerging, over 250 000 people had been infected. An epidemic in Asia began within months and has infected several million people in India and other Asian countries. Chikungunya infections occurred in many countries as a result of people travelling from areas with active transmission. The presence of tiger mosquito vector has been critical to enable localized CHIKV outbreaks in Italy and France. This species continues to invade new territory,[4] being identified in the United Kingdom for the first time in 2014.

In October 2013, the global onslaught of CHIKV took a new direction and reached the shores of Caribbean islands. CHIKV continues to spread through South and Central America with human-*Aedes* mosquito transmission cycles (i.e., autochthonous cases) reportedly in many countries, including Brazil, Columbia, Costa Rica, El Salvador, Honduras, Mexico, French Guiana, Guatemala, Guyana, Nicaragua, Panama, Paraguay, Suriname and Venezuela. By the end of 2014, it seems likely that over one million people will have been infected.

One aspect of CHIKV has been only briefly mentioned in most scientific reports. Unlike in Asia, where the transmission cycle seems to be strictly maintained in a human-mosquito cycle, the virus is maintained in Africa in a zoonotic sylvatic cycle involving wild primates. An important question that nature may answer before laboratory experiments can be performed, is whether or not a sylvatic transmission cycle of CHIKV can occur in any or all of these new ecosystems/niches? With over 130 species of new world primates, many of which are listed as endangered and all of which are naïve to CHIKV, the consequences are uncertain. It has been over 100 years since yellow fever virus was introduced into the Americas, and still new world primates can suffer fatal infections, in contrast to the old world primates that can survive.[5]

Carey, in 1971, suggested that CHIKV occurred in the Caribbean in the 1800s, but failed to establish.[6] With widespread transmission in South and Central America, it seems likely that this time CHIKV is here to stay for the foreseeable future.[7] In North America, over 1800 travel-related cases have been reported since May via the ArboNET system (http://www.cdc.gov/chikungunya/geo/united-states.html) (Figure 1). Since CHIKV is not a reportable disease, this is inevitably an underestimate. Currently, only 11 cases of transmission have been reported in the USA, all in Florida. Due to the lack of wild primates in the USA, the risk of permanent establishment is likely to be low. In support of this suggestion, one can compare CHIKV with dengue viruses, which are also transmitted by *Ae. aegypti*. Although travel-related dengue cases are reported every year in the USA, autochthonous cases are relatively rare and quickly contained by aggressive vector control programs and education efforts to raise public awareness of the importance of mosquito avoidance, using insect repellants and eliminating mosquito breeding sites. During the winter, mosquitoes effectively disappear from many states precluding local transmission. However, in many southern states, mosquitoes including *Ae. aegypti* and *Ae. albopictus* are active year round. The risk of more autochthonous cases remains if travel-associated cases continue. This is also true for Europe where local transmission of CHIKV has already occurred, and where the threat of introduction by travelers from the epidemic in the Americas is of concern.[8] Infections originating in

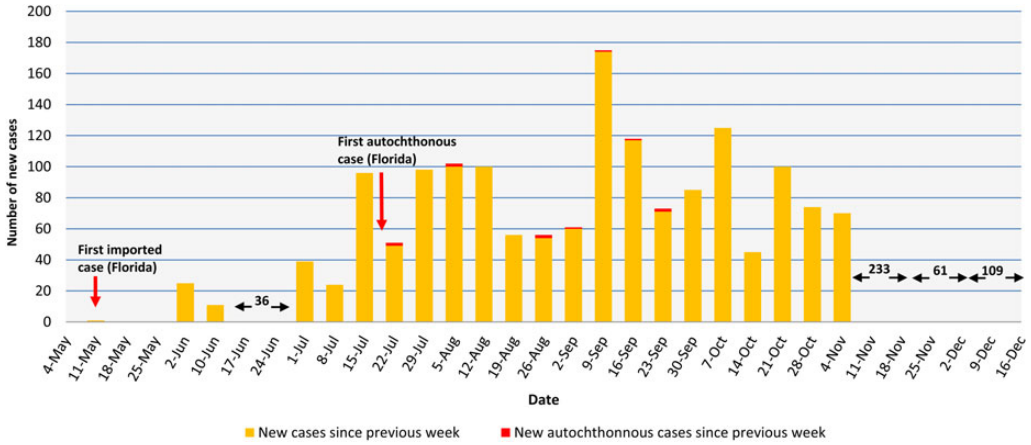

Figure 1. The number of new and autochthonous cases of chikungunya based on data from ArboNET. Note: data not available for 17 June, 18 November and 25 November. New cases not shown were: 36 (10–24 June), 233 (4–18 November) and 61 (18 November to 2 December). This figure is available in black and white in print and in color at International Health online.

the Caribbean, Central or South America have led to over 400 cases reported in France and almost 200 cases in the UK (https://www.gov.uk/government/news/chikungunya-cases-increase-in-the-caribbean). There are also threat from other areas with ongoing current CHIKV transmission including French Polynesia, Samoa, American Samoa and Tokelau in the Pacific Ocean. As the number of cases increases, so too may the risk of transmission via, for example, medical procedures that require blood transfusions.

Interestingly, CHIKV introduced in the Americas is an Asian genotype that does not have the A226 V mutation. Between 2005 and 2007, the adaptive mutation occurred independently via convergent evolution several times in Reunion, Gabon and India presumably as a response to a requirement for greater transmission by *Ae. albopictus*, which in many areas has become more abundant than *Ae. aegypti*.[9] Given the presence of *Ae. albopictus* in the Americas, one cannot exclude the possibility that the key E1 A226 V and perhaps associated mutations may arise. As a consequence, the enhanced infectivity for mosquitoes could accelerate the spread and establishment. The potential for new species of mosquitoes to act as vectors for CHIKV, as happened with for example *Haemagogus janthinomys* for yellow fever, has yet to be determined.

At the 2014 American Society for Tropical Medicine and Hygiene annual meeting, research priorities related to CHIKV were discussed. A better small animal model is certainly needed to determine why some infections cause symptoms that are quickly resolved while others last for years. Although several vaccine candidates have been developed; one based on virus like particles successfully tested to a phase 1 clinical trial,[10] major pharmaceuticals companies are yet to invest. They may believe that there is a limited market, but several million recent victims might disagree. It seems that wherever *Ae. aegypti* and *Ae. albopictus* occur, chikungunya may follow. At a time when the first effective vaccine for dengue is about to go to market, and as mosquitoes infected with *Wolbachia* are being released to suppress populations, or perhaps replace populations with virus-resistant mosquitoes, we are facing a new threat. Chikungunya virus is emerging at an unprecedented rate in new tropical and temperate ecosystems with new naïve species of vertebrates and mosquitoes whose susceptibility is largely unknown. One certainty is that we will need to prepare for many more human cases within an increasing geographical area.

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