Risks to the Americas associated with the continued expansion of chikungunya virus

Ann M. Powers

Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, Fort Collins, CO 80521, USA

Abstract

Chikungunya virus is a mosquito-borne virus that has been responsible for over 2 million human infections during the past decade. This virus, which previously had a geographical range primarily restricted to sub-Saharan Africa, the Indian subcontinent and South East Asia, has recently moved to subtropical latitudes as well as the western hemisphere. This expansion into novel habitats brings unique risks associated with further spread of the virus and the disease it causes.

Chikungunya virus (CHIKV) is one of 31 distinct viruses in the family *Togaviridae* and the genus *Alphavirus*. Like most of the alphaviruses, CHIKV is a mosquito-borne, zoonotic virus that is maintained in a cycle between forest dwelling *Aedes* spp. mosquitoes (e.g. *Ae. furcifer, Ae. africanus*) and non-human primates (Jupp & McIntosh, 1988). Genetically, the virus has a ssRNA genome and characterized strains of the virus have been divided into three distinct genotypes that historically were based upon geography (Fig. 1). With the spread of the virus over the past decade, the genotypes have expanded significantly beyond their historical geographical origins with the East, Central and South African (ECSA) genotype spread throughout South East Asia and the Asian genotype in Oceania and the Americas. While there is up to approximately 15 % nucleotide divergence between the genotypes, the viruses cannot be distinguished antigenically from each other (Powers et al., 2000).

Prior to 2006, CHIKV was a little known agent outside its enzootic distribution and the few sites of epidemics. While there have been large documented outbreaks in Thailand in 1962–1964 and in India in 1963–1964 and 1974 (Halstead et al., 1969; Mavalankar et al., 2008), no large scale epidemic activity was reported for over 30 years when in 2004–2005 outbreaks occurred in Kenya and Comoros resulting in over 250 000 infections (Sergon et al., 2007, 2008). After the outbreak in Comoros subsided in the fall of 2005, there was an unexpected resurgence of activity in the French overseas territory of La Réunion. With the onset of the rainy season in December, a tremendous increase in cases occurred in early 2006 when approximately 40 000 cases per week were reported. This increase in cases was associated with a single amino acid change in the E1 gene (alanine to valine at position 226), which was found to increase the ability of the virus to be transmitted by *Ae. albopictus* mosquitoes, the predominant mosquito vector on La Réunion (Vazeille et al., 2007). Because

Correspondence Ann M. Powers, APowers@cdc.gov.

the primary historical epidemic vector, *Ae. aegypti*, was not prevalent on this island, the epidemic may have been halted in 2006 if this mutation had not emerged. From the epidemic in La Réunion, which resulted in an estimated 266 000 cases, numerous viraemic individuals were identified in multiple countries after travellers to La Réunion became infected on the island and then returned to their home countries while still infectious. In particular, several European countries including France, Italy and Spain (where the vector mosquito *Ae. albopictus* was established), documented imported cases (Soumahoro et al., 2010). The virus was also exported from La Réunion to India where an estimated 1.3 million infections occurred during the first year of the outbreak alone and the ECSA genotype was detected for the first time outside Africa (Mavalankar et al., 2008). Given this significant number of infections, not unexpectedly, the virus continued to move to new regions with transmission reported in multiple countries of South East Asia. In 2007, the virus was introduced into Italy via a viraemic traveller from India, this time resulting in autochthonous transmission in the Ravenna region of Italy. The number of cases was small (<300) and the outbreak limited by the onset of cooler weather combined with a rapid local mosquito eradication programme, but the localized transmission of CHIKV in a subtropical region led to significant concerns for other regions not previously exposed to CHIKV but with the presence of the epidemic vectors (Rezza et al., 2007). The epidemic continued to spread further in 2009 and 2010 with a large outbreak of almost 50 000 people in southern Thailand (Rianthavorn et al., 2010) as well as reported local transmission for the first time in China (Wu et al., 2012). Activity continued in 2011, but interestingly not only as an extension of the ongoing outbreak but with at least two independent outbreaks as well. The first was a small cluster of four cases in New Caledonia. While the number of cases found was limited, this detection was significant as the infecting agent was determined to be of the Asian genotype, clearly indicating the independent emergence of the virus from a distinct cycle (Dupont-Rouzeyrol et al., 2012). Another independent emergence was detected that same year in Republic of Congo where the ECSA genotype was found, but the lineage was distinct from that found in the Indian Ocean islands (Kelvin, 2011). Both Asian and ECSA genotypes were detected in 2012 with further outbreaks of CHIKV in the Philippines, Cambodia, Papua New Guinea, Malaysia, Bhutan and in the Middle East (Yemen) for the first time (Zayed et al., 2012). The number of cases continued to increase in 2013 with a record number of local cases in Singapore (992), a record number of imported cases in Australia (127), and new emergence of the virus (Asian genotype) in the Federated States of Micronesia (Yap) affecting over 900 individuals (MOH, 2014; ProMED-mail, 2014). The sequences of isolates from Yap were virtually identical to those from the Philippines and China in 2012, demonstrating the movement of the Asian genotype from East Asia to the western Pacific (Lanciotti & Valadere, 2014). The movement of this lineage further continued in late 2013.

Even with the exceptional number of cases as early as 2005 (~250 000 cases in Kenya and Comoros), broader awareness of CHIKV did not occur until the epidemic moved to the island of La Réunion. As the La Réunion outbreak progressed, great awareness of the virus resulted from the intense media attention generated by reports of infected travellers moving the virus from outbreak regions to new habitats. This was of particular note and concern when the virus was not only identified in areas of coastal Italy but also found being

transmitted autochthonously. Up to this point, the predominant epidemic vector *Ae. aegypti* was not present in Italy. Due to this unexpected event, public health officers throughout South East Asia, India and Pacific Ocean islands, and now Europe were increasing their surveillance efforts. Additionally, as infected travellers were identified in the French West Indies, French Guiana, USA, Canada and Brazil, surveillance and preparedness efforts were increasing in the western hemisphere as well. The increased reporting and visibility of the ongoing CHIKV epidemic at least partially contributed to the identification of the virus in additional countries where the virus had never previously been, and CHIKV laboratory testing was therefore likely not a priority. One such example was the detection in New Caledonia when four cases of CHIKV infection were confirmed in 2011. Similarly, the identification of CHIKV in Yemen in 2012, which occurred during a dengue virus outbreak, may not have resulted had the local officials not been aware of the increased risk of CHIKV transmission. Increased awareness of the possibility of CHIKV transmission in subtropical areas and new ecological niches may have also contributed to the finding of local transmission in south-western France in 2011.

As early as 2007, concerns of transmission of CHIKV in Europe and the Americas were additionally heightened by the recognition of the unique risks associated with the presence of the virus in these ecologies where the virus had never before been transmitted. First, the lack of any previous exposure meant that entire populations were susceptible as no pre-existing immunity was present. While other alphaviruses such as Sindbis virus, Mayaro virus and the equine encephalitis viruses existed in Europe and the Americas, they would have been unlikely to provide any cross-protection against CHIKV even if a substantial proportion of the population had antibodies to them. Second, both of the known epidemic vectors, *Ae. aegypti* and *Ae. albopictus,* were present in substantial geographical areas not previously affected. *Ae. albopictus* was known to be present in southern portions of Europe and the USA, while both mosquito vectors were broadly distributed throughout Central and South America and the Caribbean. Given the range of the mosquito vectors and the population of the naive areas, over 500 million people would be estimated to be at risk of infection in the Americas alone. Third, because CHIKV would not have been a pathogen considered in the differential diagnosis of febrile illness in previously unaffected regions, clinician awareness of the virus, the clinical presentation and diagnostic options would have been widely unknown. Additionally, clinical diagnosis would be challenging because the signs and symptoms of CHIKV infection are similar to those of malaria, dengue fever, leptospirosis and numerous other agents that are commonly found in many of the tropical areas of the Americas. In particular, CHIKV infection appears clinically to be extremely similar to dengue fever, with illness onset characterized by rapid onset of a high fever (>102°F) and severe joint pain that may be accompanied by other signs and symptoms such as generalized maculopapular rash. Like dengue fever, CHIKV infection may result in lymphopenia or thrombocytopenia, but these laboratory parameters are not sufficient for diagnosis (Staples et al., 2009) leaving clinicians unfamiliar with CHIKV unable to easily distinguish these similar illnesses. Fourth, before significant cases were identified in the new areas, diagnosis would be further confounded by the limited regional availability of CHIKV reagents or diagnostic kits as well as laboratory personnel trained in the implementation of specific CHIKV testing protocols. With the increased awareness of CHIKV emergence and

movement, more options are now becoming available but the distribution of these products is sometimes limited. Broader development and commercialization of reagents and kits, while relieving some of the burden on the public health system, brings an additional challenge as these products are often lacking in external validation leading to the possibility of inaccurate results. If diagnostic assays were to miss true positive samples, public health officials could be unaware of transmission foci until the extensive activity would preclude a timely response. All of these concerns associated with the potential introduction of the virus into new areas such as the western hemisphere were amplified by the ability of infected individuals to move rapidly anywhere within the world. The long duration of viraemia (up to 1 week) exacerbates the likelihood that a viraemic traveller will still be infectious to local mosquitoes upon their return to previously unaffected areas. Of these significant risks recognized to be issues of concern before the virus reached new ecological habitats, two of these (the training of public health personnel and development of reagents) could both be overcome with training, communication and the dissemination of epidemiological information.

Given the ever increasing risk of CHIKV expansion, substantial preparedness activities were undertaken by public health agencies in the USA, Latin America and Europe. The Centers for Disease Control and Prevention (CDC) in collaboration with the Pan American Health Organization (PAHO) developed and published preparedness guidelines for the eventual arrival of CHIKV in the Americas and the Caribbean subregion (PAHO, 2011, 2012). These documents encompass a variety of topics of interest to public health officials including information on epidemiology, clinical presentation, case management, laboratory testing, mosquito surveillance and control, and risk and outbreak communications. Similar reference materials were developed by the European CDC (ECDC) for European Countries (ECDC, 2014). While the first of these guidelines were published in 2011 for the Americas, surveillance and preparedness activities continued with the hope that the virus would not invade the Americas despite the lack of any barriers to introduction and the known risks specific to the area. However, in late 2013, local transmission of CHIKV did indeed occur with the reports in December of the first activity identified in the Caribbean island of St. Martin (Omarjee et al., 2014). Rapid identification and characterization of the virus indicated that the virus was of the Asian genotype and most closely related to strains from East Asia and Yap. By the end of 2013, the virus had been discovered in four Caribbean countries with approximately 300 suspected cases. Following the characteristic pattern of rapid spread of the virus, local transmission has been reported in 26 Caribbean countries, four countries in South America, three countries in Central America and one country in North America with an estimated 651 000 cases in just the first 9 months after the reported introduction to the Americas (Fig. 2) (Fischer et al., 2014; PAHO, 2014). In July of 2014, local transmission of CHIKV was detected for the first time in Florida, USA. To date, no localized transmission has been reported elsewhere in the USA but 44 states documented travel-associated cases as of 16 September 2014. Many of these states are not likely to be at risk of local transmission because the relevant vectors are not present. However, many southern and east coast states could be at risk of autochthonous transmission. Information regarding the vectors involved in the western hemisphere transmission has not yet been verified but both *Ae. aegypti* and *Ae. albopictus* in the Americas have been shown to be

permissive for CHIKV. With the high attack rates of CHIKV and the highly suitable conditions for spread in the Americas (and other new habitats), continued spread of CHIKV is certainly expected. However, the efforts undertaken to prepare for the introduction of this pathogen have increased awareness of the need for continued monitoring for novel pathogens and emergence events of this nature in our global community.

ACKNOWLEDGEMENTS

REFERENCES

Dupont-Rouzeyrol M, Caro V, Guillaumot L, Vazeille M, D'Ortenzio E, Thiberge JM, Baroux N, Gourinat AC, Grandadam M & Failloux AB (2012). Chikungunya virus and the mosquito vector *Aedes aegypti* in New Caledonia (South Pacific Region). Vector Borne Zoonotic Dis 12, 1036–1041. [PubMed: 23167500]

ECDC (2014). European Centre for Disease Prevention and Control: Chikungunya. http://www.ecdc.europa.eu/en/healthtopics/chikungunya_fever/pages/index.aspx.

Fischer M, Staples JE & Arboviral Diseases Branch, National Center for Emerging and Zoonotic Infectious Diseases, CDC (2014). Notes from the field: chikungunya virus spreads in the Americas - Caribbean and South America, 2013-2014. MMWR Morb Mortal Wkly Rep 63, 500–501. [PubMed: 24898168]

Halstead SB, Scanlon JE, Umpaivit P & Udomsakdi S (1969). Dengue and chikungunya virus infection in man in Thailand, 1962-1964. IV. Epidemiologic studies in the Bangkok metropolitan area. Am J Trop Med Hyg 18, 997–1021. [PubMed: 4390977]

Jupp PG & McIntosh BM (1988). Chikungunya virus disease In The Arbovirus: Epidemiology and Ecology, vol. II, pp. 137–157. Edited by Monath TP. Boca Raton, FL: CRC Press.

Kelvin AA (2011). Outbreak of Chikungunya in the Republic of Congo and the global picture. J Infect Dev Ctries 5, 441–444. [PubMed: 21727642]

Lanciotti RS & Valadere AM (2014). Transcontinental movement of Asian genotype chikungunya virus. Emerg Infect Dis 20, 1400–1402. [PubMed: 25076384]

Mavalankar D, Shastri P, Bandyopadhyay T, Parmar J & Ramani KV (2008). Increased mortality rate associated with chikungunya epidemic, Ahmedabad, India. Emerg Infect Dis 14, 412–415. [PubMed: 18325255]

MOH (2014). Singapore Ministry of Health, Weekly Infectious Disease Bulletin. https://www.moh.gov.sg/content/dam/moh_web/Statistics/Infectious_Diseases_Bulletin/2013/December/2013_week_52.pdf.

Omarjee R, Prat C, Flusin O, Boucau S, Tenebray B, Merle O, Huc-Anais P, Cassadou S & Leparc-Goffart I (2014). Importance of case definition to monitor ongoing outbreak of chikungunya virus on a background of actively circulating dengue virus, St Martin, December 2013 to January 2014. Euro Surveill 19, 1–3.

PAHO (2011). Preparedness and Response for Chikungunya Virus: Introduction in the Americas. Washington, DC: Pan American Health Organization (PAHO) http://www.paho.org/hq/index.php?option=com_content&view=article&id=6464%3Apaho,-cdc-publish-guide-on-preparing-for-chikungunya-virus-introduction-in-the-americas&catid=740%3Anews-press-releases&Itemid=1926&lang=en

PAHO (2012). Preparedness and Response Plan for Chikungunya Virus: Introduction in the Caribbean sub-region Caribbean Sub-regional Training Workshop. Introducing the new guidelines: Preparedness and Response for Chikungunya Virus Introduction in the Americas in the context of Dengue. Kingston, Jamaica 2012. http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&gid=23768&Itemid=

PAHO (2014). Chikungunya. Number of Reported Cases of Chikungunya Fever in the Americas. http://www.paho.org/hq/index.php?option=com_content&view=article&id=9053&Itemid=40695&lang=en.

Powers AM, Brault AC, Tesh RB & Weaver SC (2000). Re-emergence of Chikungunya and O'nyong-nyong viruses: evidence for distinct geographical lineages and distant evolutionary relationships. J Gen Virol 81, 471–479. [PubMed: 10644846]

ProMED-mail (2014). Chikungunya (12): Australia, Imported. ProMED-mail 2014, Feb 2: 20140202:2250560. http://www.promedmail.org

Rezza G, Nicoletti L, Angelini R, Romi R, Finarelli AC, Panning M, Cordioli P, Fortuna C, Boros S & other authors (2007).Infection with chikungunya virus in Italy: an outbreak in a temperate region. Lancet 370, 1840–1846. [PubMed: 18061059]

Rianthavorn P, Prianantathavorn K, Wuttirattanakowit N, Theamboonlers A & Poovorawan Y (2010). An outbreak of chikungunya in southern Thailand from 2008 to 2009 caused by African strains with A226V mutation. Int J Infect Dis 14 (Suppl 3), e161–e165.

Sergon K, Yahaya AA, Brown J, Bedja SA, Mlindasse M, Agata N, Allaranger Y, Ball MD, Powers AM & other authors (2007). Seroprevalence of Chikungunya virus infection on Grande Comore Island, union of the Comoros, 2005. Am J Trop Med Hyg 76, 1189–1193. [PubMed: 17556634]

Sergon K, Njuguna C, Kalani R, Ofula V, Onyango C, Konongoi LS, Bedno S, Burke H, Dumilla AM & other authors (2008). Seroprevalence of Chikungunya virus (CHIKV) infection on Lamu Island, Kenya, October 2004. Am J Trop Med Hyg 78, 333–337. [PubMed: 18256441]

Soumahoro MK, Fontenille D, Turbelin C, Pelat C, Boyd A, Flahault A & Hanslik T (2010). Imported chikungunya virus infection. Emerg Infect Dis 16, 162–163. [PubMed: 20031074]

Staples JE, Breiman RF & Powers AM (2009). Chikungunya fever: an epidemiological review of a re-emerging infectious disease. Clin Infect Dis 49, 942–948. [PubMed: 19663604]

Vazeille M, Moutailler S, Coudrier D, Rousseaux C, Khun H, Huerre M, Thiria J, Dehecq JS, Fontenille D & other authors (2007). Two Chikungunya isolates from the outbreak of La Reunion (Indian Ocean) exhibit different patterns of infection in the mosquito, *Aedes albopictus*. PLoS ONE 2, e1168. [PubMed: 18000540]

Wu D, Wu J, Zhang Q, Zhong H, Ke C, Deng X, Guan D, Li H, Zhang Y & other authors (2012). Chikungunya outbreak in Guangdong Province, China, 2010. Emerg Infect Dis 18, 493–495. [PubMed: 22377135]

Zayed A, Awash AA, Esmail MA, Al-Mohamadi HA, Al-Salwai M, Al-Jasari A, Medhat I, Morales-Betoulle ME & Mnzava A (2012). Detection of Chikungunya virus in Aedes aegypti during 2011 outbreak in Al Hodayda, Yemen. Acta Trop 123, 62–66. [PubMed: 22469818]
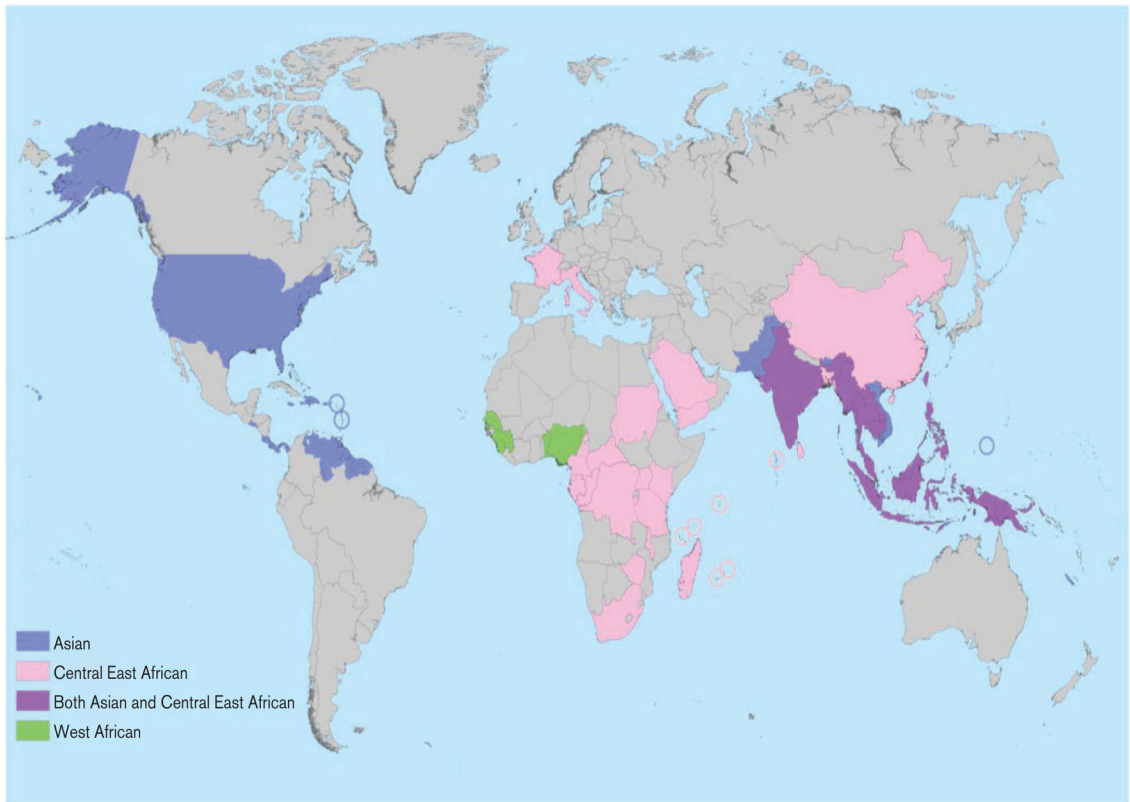
Fig. 1.
Countries and territories where local transmission of chikungunya virus has been reported.
Reported genotype distribution is noted by colour. (Figure courtesy of Nicole Lindsey,
CDC.)

Fig. 2.
Countries and territories in the Americas where locally acquired cases of chikungunya virus have been reported from PAHO (as of 9 September 2014), figure from http://www.cdc.gov/chikungunya/geo/americas.html.