

Chikungunya in Singapore—the Battle Continues

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In the past decade, Singapore has been confronted by outbreaks caused by novel viruses, namely Nipah virus in 1999, severe acute respiratory syndrome (SARS) coronavirus in 2003, and chikungunya virus in 2008. While Nipah virus and SARS coronavirus disappeared after causing a season of crisis, we continue to see importation of the chikungunya virus after the initial elimination in 2009. In early 2013, chikungunya fever re-emerged in Singapore, culminating in 1059 cases by the end of the year.¹ At the point of writing this commentary, the transmission has subsided.

The chikungunya virus, transmitted by mosquitoes, belongs to the family *Togaviridae* and genus *Alphavirus*. The virus is believed to have originated from Africa, where it is maintained in a sylvatic cycle involving wild primates and forest-dwelling mosquitoes. In urban or rural areas in Asia, chikungunya fever is largely transmitted from human to human via *Aedes aegypti* and *Aedes albopictus*. The disease is characterised by an abrupt onset of high fever, severe arthralgia or arthritis, myalgia, headache and rash. While largely self-limiting, some patients experience joint pain that continues for years.²

Chikungunya virus may have been introduced into Singapore as early as the 1960s but until 2008, there were only sporadic imported cases.^{3,4} Singapore's population remained immunologically naive to the virus as evidenced by the low seroprevalence of 0.4% among 531 young healthy adults tested in 2002 to 2003.⁵ The first reported local transmissions of chikungunya in Singapore occurred in January 2008 in a small outbreak of 13 cases in Little India, a densely populated urban area.³ Despite a successful containment of the virus in Little India in February 2008, the virus emerged again in rural and suburban parts of Singapore in the middle of the year. By 2009 when the outbreak subsided, a total of 1033 chikungunya cases were reported.⁶ Over 75% of the cases were indigenous and 83% of the clusters involved rural or suburban areas.⁴ Between 2010 and 2012, chikungunya fever reverted to

the pre-2008 scenario of mainly being an imported disease, with only 12 indigenous cases and a total of 60 cases, and it appeared that the battle against this virus was won.⁷⁻⁹ However, in 2013, Singapore experienced a resurgence of chikungunya, of which 95% were indigenous cases, mainly in suburban areas in Singapore.¹ Interestingly, the chikungunya epidemic has come on the back of the largest dengue epidemic in Singapore since 2005, suggesting that similar factors may be at play in the resurgence of these two mosquito-borne diseases.

The control of chikungunya is multi-pronged, involving an understanding of the interplay of the mosquito vector, virus, and host factors. The mosquito vector in Singapore's first outbreak in Little India was *Ae. aegypti*, the same urban mosquito vector which drives dengue epidemiology in Singapore.³ In contrast, *Ae. albopictus*, which is mostly associated with greenery, was the predominant vector in the second outbreak in 2008 to 2009 and the current 2013 to 2014 outbreak.³ This explains the higher intensity of transmission in suburban and rural areas of Singapore during these outbreaks. The virus involved in the first outbreak was a wild type virus with alanine at codon 226 of the envelope 1 gene. Virus strains isolated from the latter outbreaks showed the alanine to valine (A226V) mutation, which is known to significantly enhance the transmissibility of the virus by *Ae. albopictus*. The mechanism of the enhancement include the lowering of the oral infectious dose and the increase of viral dissemination in the mosquito.¹⁰

Genetic fingerprints of the viruses detected since 2006 revealed that there have been multiple importations; at least 4 different strains, closely related to strains from India, Malaysia and Sri Lanka, have been associated with outbreaks.³ Insights gained from molecular epidemiology suggested that the 2008 outbreaks were most likely due to importations of the virus from these countries, which were also battling with the disease during the same periods, and subsequent spread to the local naive population.³ Investigation of the 2013 to 2014 outbreak is still unfolding.

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Singapore is not alone in its battle against chikungunya. Since the recent outbreak in Kenya in 2004, the virus has spread globally in a series of epidemics across the Indian Ocean to the Indian subcontinent. It subsequently spread to Southeast Asia and even to southern Europe.¹¹ In December 2013, it arrived at the Caribbean, showing evidence of gaining a foothold in a new territory.¹² Millions of people have been infected in at least 40 countries.¹³ The resurgence in Singapore is facilitated by several factors, and the situation reflects the larger global picture. Firstly, there are vast immunologically naïve local and international populations to a disease that has been rather dormant globally in the last few decades. Secondly, an increase in international travel has allowed the cross-border spread of the disease, and local travel and migration have facilitated further spread within countries, including to rural isolated areas. Thirdly, the genetic adaptation of the virus to *Ae. albopictus* has contributed to the waves of epidemics across the globe.¹⁰ *Ae. albopictus*, originally native to Asia, has greatly expanded its geographic range in the last two decades to include Africa, the Americas, Europe and the Middle East, spanning tropical and temperature latitudes.¹⁴ Fourthly, rising population density in countries such as Singapore provides abundant opportunities for interactions between humans and the mosquito vector. Lastly, environmental factors such as temperature and rainfall probably play an important role in chikungunya transmission.¹¹ It is interesting that chikungunya outbreaks are driven by different environmental factors in different settings. In Singapore, peak chikungunya outbreaks are associated with rainy seasons, while reports have described that the outbreak in Kenya in 2004 was associated with drought conditions.¹⁵

Vector control is the sole method for reducing transmission of chikungunya as no vaccine is available. Having *Ae. albopictus* as the main mosquito vector for the chikungunya virus presents additional challenges to vector control services already over-taxed by the dengue epidemic. In contrast to *Ae. aegypti* which mainly inhabits urban areas, *Ae. albopictus* is largely outdoors, so measures such as outdoor fogging, residual spraying of external walls and clearing of unkempt vegetation will have to go hand-in-hand with current vector control strategies aimed at reducing dengue transmission.¹⁶ *Ae. albopictus* is relatively long-lived (4 to 8 weeks), has a flight radius of 400 m to 600 m and its eggs are highly resistant to drying. Its association with nature and greenery may render its population even more difficult to reduce and eliminate as compared to *Ae. aegypti*, which is already a challenge both locally and worldwide. In the Hawaiian islands, an extensive mosquito control campaign virtually eliminated *Ae. aegypti*, thus controlling their dengue epidemic in 1943 to 1944, but *Ae. albopictus* remained widespread.¹⁷

The chikungunya epidemiology clearly demonstrates the vulnerability of the globalised and immunologically naïve human population to diseases vectored by mosquitoes that share the same ecological niche as the human population. In Singapore, these characteristics of chikungunya epidemiology mirror that of dengue.¹⁸ Though the extensive national vector control programme may have moderated the impact of these diseases, the increasing challenges call for novel approaches to augment the effectiveness of the programme in tackling these diseases. This includes the use of new technology such as population replacement or suppression by the *Wolbachia*-infected *Aedes* or genetically modified sterile male *Aedes*.

The battle against chikungunya involves an understanding of the complexity of vector-virus-host-environment interactions and how they can affect disease epidemiology. In particular, the study of virus evolution is key to understanding virus adaptation to the vector and subsequent transmission. There is a continued need for intense surveillance, improved diagnostics, and rigorous research of this virus in order to succeed in the battle.

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