

The Asia-Pacific origins of the current outbreaks of Zika virus



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Zika virus (ZIKV) is a mosquito-borne arbovirus from the *Flaviviridae* family, first isolated in 1947 from a monkey in Uganda. In the ensuing decades up to the 2000s, there have been sporadic reports of infections and seropositivity in humans in Africa and Asia^{1,2}. The first isolation of ZIKV outside Africa was from *Aedes aegypti* mosquitoes in Malaysia in 1966³. Seropositivity has also been reported in wild monkeys in Malaysia³, although the relevance of this in sylvatic transmission of ZIKV is unknown. These studies suggest that there was endemic and mostly undetected transmission in Asia during this period. Re-emergence from Asia has now brought this relatively neglected virus into the focus of global attention.

Following the first ever reported outbreak in Yap Island, in the Western Pacific in 2007⁴, epidemics occurred in several countries in the Pacific between 2013 and 2016, starting with French Polynesia⁵, and spreading to 20 other Pacific countries, including New Caledonia, the Cook Islands, Easter Island (Chile), the Solomon Islands, Tonga and American Samoa^{1,6}. ZIKV was probably introduced in Brazil in early 2014⁷, although cases were only first diagnosed there in 2015, before rapidly spreading to 48 other countries in the Americas and Caribbean⁶. The extent of the epidemics, and their occurrence in continents where ZIKV had never previously been reported was unprecedented. ZIKV usually causes either no symptoms or a mild febrile illness accompanied by rash, myalgia, arthralgia and conjunctivitis. However, the sheer number of affected patients also revealed startling new evidence of the neurotropism of the virus, as increased incidence of neurological diseases such as Guillain-Barré syndrome and congenital Zika syndrome (including microcephaly, and abnormalities of the brain, eye and musculo-skeletal system) was seen⁶.

There are two genotypes of ZIKV, African and Asian, with the 1966 Malaysian isolate representative of the Asian ancestral strain⁸. Phylogenetic analysis shows that ZIKV sequences of the Asian genotype obtained from Southeast Asian countries between 2010 and 2014 are situated basally to viruses from the recent 2013-2016 outbreaks in the Pacific and Americas^{8,9}. This suggests that the outbreaks in the Pacific and subsequently the Americas likely originated from Southeast Asia, where the virus continues to circulate endemically. Interestingly, when chikungunya virus (another mosquito-borne virus) re-emerged between 2004 and 2016, it reached the Americas by a similar route, originating in Southeast Asia before spreading to the Pacific and then to the Americas⁵.

The main mosquito vector of ZIKV in the recent outbreaks is *Ae. aegypti*¹⁰, which also transmits dengue and chikungunya viruses. *Ae. albopictus*, which played the key role in the worldwide epidemics of chikungunya virus, was implicated in a ZIKV outbreak in Gabon¹¹ and has shown high competence for ZIKV in several laboratories¹². *Ae. albopictus* may therefore potentially be an important vector in future outbreaks. These two *Aedes* species are distributed throughout tropical Asia. However, the full extent of vectors competent for ZIKV is not known, in particular the roles of more locally-relevant species in areas with little or no *Ae. aegypti*. For example, *Ae. bensilli* is by far the most predominant mosquito species on Yap Island and has been shown to be susceptible to ZIKV¹³.

Despite the extensive epidemics in the Pacific and the Americas in recent years, there has only been one outbreak reported in Asia, which occurred in Singapore in August 2016 and affected 455 people¹⁴. Sporadic, autochthonous (locally-acquired) cases - some identified retrospectively - have been reported in Southeast Asian countries including Cambodia, Indonesia, Malaysia, Philippines, Vietnam and Thailand (reviewed by Lim *et al.*³). It is unclear why there have not been large outbreaks reported in Asia, apart from Singapore. In the past, this may have been due to lack of ZIKV-specific diagnostics and surveillance, and difficulties in distinguishing ZIKV disease from other tropical illnesses with similar symptoms, such as dengue. However, even Southeast Asian countries with recent focused surveillance have found very low levels (0.02–1.3%) of ZIKV RNA in patients with dengue-like symptoms^{2,15}, supporting the clinical reports. A possible explanation

for this is pre-existing population immunity against ZIKV in these ZIKV-endemic countries, based on limited historic studies showing 4–44% seropositive rates², whereas populations in the Pacific and the Americas were ZIKV-naïve. To assess this possibility, contemporary population serosurveys are required in Asia using specific assays to minimise confounding by other flavivirus infections.

What is the risk of ZIKV in Australia? Vector competence studies of local mosquito species show that *Ae. aegypti* is the most likely vector, although it is currently confined to northern Queensland^{16,17}. *Ae. albopictus*, which is present in the Torres Strait islands but not in mainland Australia, is a potential invasive threat¹⁶. No or low rates of dissemination and transmission of ZIKV was reported for other common *Aedes* species, including *Ae. notoscriptus*, *Ae. vigilax* and *Ae. camptorhynchus*^{16,17}. Between 2013 and 2017, there were 133 imported cases of ZIKV in Australia (although mostly in areas where *Ae. aegypti* does not occur), comprising 63 from Pacific countries, 56 from the Americas or the Caribbean, and 13 from Southeast Asia¹⁸. This shows that while the main risk is from travellers coming from countries experiencing outbreaks, there is a background risk from travellers from Southeast Asia. Thus, as Australia has competent mosquito vectors and imported cases, and continuing extensive traffic with other countries in the Asia-Pacific region, there remains an ongoing threat of a ZIKV outbreak in Australia¹⁹. This can be mitigated by continued surveillance for human cases, infected mosquitoes and potential mosquito vectors, and effective vector control programs²⁰.

Numerous important questions about ZIKV in Asia remain. What is the true burden of ZIKV in Asia? Why has there not been more clinically-apparent disease, such as outbreaks of illness and microcephaly? With the apparent low level of circulation in humans, how is the virus maintained in nature, and what is the role of non-human primates? What were the underlying reasons for its recent global emergence from Asia, and can these be predicted for prevention of future outbreaks? Even as the WHO declared an end to ZIKV as a Public Health Emergency of International Concern in November 2016, there is still much urgent work to be done.

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Biography

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