

The 2016 Outbreak of Zika in Singapore

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The eponymous Zika virus (ZIKV) originated from Africa, and was discovered incidentally in rhesus macaques in the Zika forest in Uganda in 1947 as a result of Rockefeller Foundation-sponsored programmes on yellow fever.¹ ZIKV was not thought to be an important human pathogen, with a paucity of published clinical reports, until the explosive outbreak in the Americas. The Brazil 2015-2016 outbreak received international concern due to the association with alarming rates of microcephaly and the Guillain Barre Syndrome.^{1,2} This led the World Health Organization (WHO) to declare Zika a “public health emergency of international concern” in February 2016, calling for a “coordinated international response” to address the pressing questions surrounding the lack of available knowledge about the virus and neuropathogenesis.³

Phylogenetic studies of ZIKV suggest that the virus was probably exported to Asia in the 1940s and then circulated throughout the region, forming a distinct Asian lineage (as opposed to the African lineage).^{1,4} Human serosurveys of ZIKV in Southeast Asia from the 1950s—which must be interpreted with caution because of the different testing methodology and the cross-reactivity of ZIKV serological tests with other flaviviruses such as dengue—have found that 4% to 75% of the sample population tested had antibodies to ZIKV.¹ The epidemic in the Americas was caused by the Asian lineage ZIKV that crossed into Brazil via French Polynesia.¹

Singapore had ZIKV on its radar as a re-emerging pathogen with local epidemic potential due to factors such as high volume of global travel, available *Aedes spp.* vector populations and a presumed Zika-naïve dense population in a dengue endemic area. The first case occurred in a permanent resident who had returned from Brazil in May 2016, and extended vector control coupled with active screening around the patient’s home in Watten Estate found no further cases.⁵ However, despite having initiated preparedness plans at the national level, the subsequent outbreak appeared to have caught everyone off guard, probably because Zika was

anticipated to be associated with travel to the Americas. In brief, a group of general practitioners alerted the Ministry of Health (MOH) on 22 August 2016 that they had seen a spike of non-dengue febrile illnesses associated with rash at Sims Drive since the second week of August.⁶ Although the initial cases were all from the construction site of the Sims Urban Oasis condominium, there are now almost 400 cases of laboratory-confirmed Zika infections at the time of writing, with multiple other clusters of cases beyond the original Aljunied/Sims Drive cluster.⁷

Confirmed Zika-infected patients have generally presented with a mild, brief illness consisting of fever, rash, myalgia and conjunctivitis as is widely reported, with a significant proportion of patients not having all the symptoms in the clinical case definition.¹ At the first notice of the outbreak, MOH and the National Environment Agency (NEA) attempted a trial of ‘containment strategy’ coupled with aggressive vector control measures akin to how chikungunya was contained in 2008.⁸ From the outset however, it was clear that this was a far more challenging proposition. The ZIKV outbreak in August had already been ongoing for at least a couple of weeks before containment was attempted. Unlike chikungunya, approximately 80% of Zika-infected persons are asymptomatic but are still able to transmit the virus either via an *Aedes spp.* vector or rarely via sexual intercourse. ZIKV is also able to spread vertically (transovarial transmission) in the mosquito population, and thus technically does not require a susceptible primate population for maintenance.⁹ When community transmission continued and new clusters arose after the initial week of containment, MOH stopped mandatory hospital quarantine of Zika viraemic patients. It is likely that Zika will become endemic in Singapore, but case numbers and associated complications will evolve with changing population immunity.

ZIKV is associated with Guillain-Barre syndrome, but this is reportedly rare, affecting 2.4 per 10,000 infected persons based on data from the French Polynesian outbreak.¹

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The greatest concern regarding Zika infections has been the congenital Zika syndrome, in particular microcephaly. *In vitro* studies have shown that ZIKV can infect foetal neuroprogenitor cells by using the AXL receptor tyrosine kinase—which is found abundantly in neuroprogenitor cells but not in mature neurons—for entry.¹⁰ The impact on pregnancy is highest during early trimesters of pregnancy, although later trimester infection may also cause foetal adverse events (growth restriction, bone dysgenesis) supposedly via placental infection and insufficiency.¹ The real risk of an infected pregnant woman (symptomatic or asymptomatic) giving birth to a baby with congenital Zika syndrome and microcephaly is not known at present. If the data from Bahia, Brazil is discounted, however, then the rates of congenital Zika syndrome would be closer to 1% than 13.2%, acknowledging inherent limitations in the variability of definitions and reporting among diverse countries.²

Whether Singapore will see cases of microcephaly and other adverse neonatal outcomes is unknown, although we should be prepared for them. Of importance, there can be manifestations of the congenital Zika syndrome such as hearing loss, impaired neurodevelopment, and loss of sight that may not be apparent in the neonatal stage, hence infants will need careful longitudinal follow-up.

There are several urgent areas of research with regard to Zika. At this time, there is a lack of a sensitive serological test that can reliably discriminate between Zika and dengue. There is also a need for a systematic approach to surveillance, case detection, monitoring and management of high-risk outcomes in both the pregnant and non-pregnant populations. The potential keys to the control of Zika and other flaviviruses lie in effective vaccine(s) and mosquito control, for which novel strategies are needed. Candidate Zika vaccines will need to be studied and evaluated with respect to performance in a dengue endemic area such as Singapore in terms of efficacy and safety, especially for pregnant women.

In conclusion, each emerging and re-emerging disease pathogen will have its unique implications in terms of public

health and clinical care, as well as new research questions that will arise. Singapore has long had an established public health infrastructure and vector control expertise to deal with dengue, but the re-appearance of Zika on our landscape has its own challenges which will need a multidisciplinary and concerted approach to address the concerns at hand, both for Singapore and the international community.

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