SHORT COMMUNICATION

Zika virus and its potential re-emergence in Malaysia

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SUMMARY

Zika virus (ZIKV) has re-emerged to cause explosive epidemics in the Pacific and Latin America, and appears to be associated with severe neurological complications including microcephaly in babies. ZIKV is transmitted to humans by *Aedes* mosquitoes, principally *Ae. aegypti*, and there is historical evidence of ZIKV circulation in Southeast Asia. It is therefore clear that Malaysia is at risk of similar outbreaks. Local and international guidelines are available for surveillance, diagnostics, and management of exposed and infected individuals. ZIKV is the latest arbovirus to have spread globally beyond its initial restricted niche, and is unlikely to be the last. Innovative new methods for surveillance and control of vectors are needed to target mosquito-borne diseases as a whole.

KEY WORDS:
Zika virus, arbovirus, flavivirus, emerging infectious disease, epidemiology, Malaysia

INTRODUCTION

The emergence of Zika virus (ZIKV) has transformed it from an obscure and neglected virus to the cause of explosive outbreaks attracting global attention. The ZIKV outbreaks in Latin America led to a declaration of a Public Health Emergency of International Concern on 1 February 2016 by the WHO, due to possible but unconfirmed links to neurological disorders (including Guillain–Barré syndrome) and microcephaly.[1]

Microcephaly has been the particular focus of media reports, as it is a prominent feature of an apparent congenital ZIKV syndrome. Microcephaly is associated with severe neurological problems such as cerebral atrophy, intracranial calcification, cerebellar hypoplasia, and ocular and hearing manifestations.[2] The surge of microcephaly reports in Brazil coincided temporally and geographically with reported ZIKV outbreaks,[3] although the true extent and causality is obscured by non-standardised definitions of microcephaly, lack of laboratory confirmation of ZIKV infections in mothers, and use of historical rates which are almost certainly underestimates as comparators. A recent study in northeastern Brazil suggests that seasonal spikes in microcephaly births actually predated the introduction of ZIKV.[4] Nevertheless, ZIKV RNA has been detected in several cases in amniotic fluid, placenta, and brain tissues of stillbirths and newborns,[2,3,5] strongly indicating that ZIKV does appear to vertically transmit to foetal brains. Improved surveillance and research efforts are being urgently implemented to determine whether there is a causal link between ZIKV and these disorders.[1] The ZIKV epidemic has also raised sociopolitical interest, as the disease disproportionately affects those in poorer areas, which are more prone to mosquito infestation. Concerns about microcephaly have also led to heated debates about the poor access to contraception and pregnancy termination services in this predominantly Catholic region.

ZIKV is an arthropod-borne virus from the *Flaviviridae* family, which includes dengue virus, Japanese encephalitis virus and yellow fever virus. It is named after the Zika Forest in Uganda, where it was first isolated from a sentinel monkey in 1947, and then an *Aedes africanus* mosquito in 1948.[6] In Africa, ZIKV is believed to be maintained in a sylvatic cycle by non-human primates and zoophilic mosquitoes.[7] Human-to-human cycles are maintained principally by *Ae. aegypti,* although *Ae. albopictus* was shown for the first time to be involved in human disease in Gabon in 2007.[8] Notably for Malaysia, *Ae. albopictus* from nearby Singapore are competent vectors for ZIKV.[9] This is a worrying development as *Ae. albopictus* has greatly expanded its global distribution in recent years. A shift of principal vector from *Ae. aegypti* to *Ae. albopictus* was critical to the recent worldwide spread of chikungunya virus.

ZIKV infection is often asymptomatic, or results in a mild dengue-like illness, with fever, myalgia, maculopapular rash, arthralgia, headache, and conjunctivitis.[10] Human-to-human transmission is unusual, but may occur through vertical or sexual routes, or via blood transfusion. From the 1950s-1980s, mosquito infection, sporadic human cases and serological evidence of human infection were detected in several countries in Africa and Southeast Asia.[7] Most ZIKV infections are asymptomatic, mild, or difficult to distinguish from dengue, and as laboratories do not routinely test for it, ZIKV is almost certainly underdiagnosed.

Fewer than 10 human cases had been described before the first recorded outbreak in Yap Island, Micronesia in 2007,[10] which was followed by epidemic spread to other countries in the Pacific, including French Polynesia in 2013, and New

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Caledonia, the Cook Islands and Easter Island in 2014.[11] ZIKV reached Brazil in May 2015, and is now causing explosive outbreaks in 19 Latin American countries as of 20 Jan 2016, with up to a million estimated cases in Brazil alone.[12]

Phylogenetic analysis of ZIKV genetic sequences indicates three main genotypes: East African, West African, and Asian. Asian strains, of which a Malaysian isolate from 1966 is the earliest known ancestor, are the cause of spread from Asia to the Pacific to Latin America.[13] It is interesting that the Asian genotype of chikungunya virus also spread to the Americas following a similar route in 2013.[13]

It is not yet known why ZIKV has abruptly emerged from the forests to cause human outbreaks in the last few years. Re-emergence of the alphaviruses chikungunya and Venezuelan equine encephalitis viruses to cause human epidemics were driven by viral mutations which increased adaptation to mosquito vectors.[14] Vector-adaptive mutations have not yet been demonstrated in ZIKV. However, when compared to other ZIKV lineages, the recent Asian epidemic strains have non-structural protein 1 (NS1) gene sequences with codons which are more adapted to human host cells; it is hypothesised that this leads to more efficient protein translation, a gain in fitness that could contribute to greater spread in humans.[15]

ZIKV has received considerable media coverage; will there be cases in Malaysia? The answer is most likely yes; the key questions are when this will occur, and where the virus will come from. Both *Ae. aegypti* and *Ae. albopictus* are abundant here. While the effects of multiple arboviruses within a specific mosquito vector population are not fully understood, it is clear that ZIKV, chikungunya and dengue viruses can circulate concurrently, as has occurred in the Pacific[16] and Latin America,[17] and could occur in Malaysia, which has similar climatic and environmental risk factors favouring *Aedes* vectors. Historically, the first isolation of ZIKV in Southeast Asia was from *Ae. aegypti* from shophouses in Bentong, Pahang in 1966,[18] meaning that human cases must certainly have occurred in Malaysia, even if never reported. This is supported by findings of ZIKV seropositivity of up to 30% in human samples collected in the 1950s and 1990s in East and Peninsular Malaysia.[19-21] Furthermore, although the sylvatic cycle in Asia is not defined, serological evidence of ZIKV has been documented in monkeys and orangutans in Malaysia.[6,19] Sylvatic vectors are unknown, but of the over 20 species of potential mosquito vectors identified in Africa and the Pacific,[7,10] most of which are *Aedes* species, only *Mansonia uniformis* is present in Malaysia. As recently as 2014, a German traveller to Sabah was diagnosed with ZIKV, although this was based on serology rather than PCR or culture.[22] All these findings indicate that ZIKV is likely to have been present in Malaysia for decades, but why has it not already caused apparent outbreaks here?

If ZIKV does not re-emerge from within Malaysia, it may easily be imported from elsewhere in Southeast Asia. Between 2010-2014, confirmed locally-acquired ZIKV cases were described in Cambodia,[23] Indonesia,[24] the Philippines[25] and Thailand,[26] countries with extensive traffic to and from Malaysia. It is also possible than ZIKV will be imported to Malaysia from the current epidemic areas in Latin America, even though, for example, only 5% of international air travellers from Brazil head for Asia.[27] Impending mass gatherings such as the Olympics (this August) and Paralympics (September) in Brazil, and the Hajj (September) will create further opportunities for Malaysians to be exposed to ZIKV.[28]

The moderate ZIKV seropositivity rates reported in Malaysia in the past may be due to assay cross-reactivity with other endemic flaviviruses, like dengue. However, if these rates are true and do reflect endemic disease, then our population may already have a degree of immunity (absent in Latin America, where ZIKV had never previously been reported) which may help limit future epidemics. Nevertheless, recognising that ZIKV could cause an outbreak here, the Health Ministry has recently issued a Zika alert and guidelines to all hospitals with commendable speed. These include detailed plans for enhanced surveillance for ZIKV including neurological outcomes, new diagnostics, management of cases, and community education particularly of women who are pregnant or of childbearing age.[29] Detailed and specific guidelines for healthcare providers, including the management of pregnant women and infants with suspected ZIKV, are also available from the Centers for Disease Control and Prevention (http://www.cdc.gov/zika/hc-providers/index.html).

ZIKV is the latest arbovirus to have escaped a restricted niche and cause widespread human disease. There is a long list of other arboviruses (with *Aedes* vectors) which have the same potential. ZIKV must give fresh impetus to efforts to prevent mosquito-borne diseases as a whole, rather than have the world in firefighting mode every time a new virus emerges. In Malaysia, this means stripping away our complacency and taking responsibility for the control of *Aedes* vectors. We should look at new paradigms for proactive control of vectors based on epidemiologic and entomologic surveillance, to replace ineffective traditional methods which merely react to notified cases.[30-32]

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