Commentary

Zika Virus: An Evolving Public Health Threat

Chee Fu Yung, [1]*MBChB, MSt (Camb), FFPH*, Chia Yin Chong, [1]*MBBS, M. Med, FRCPCH*, Kee Thai Yeo, [2]*MD MS FAAP*, Christina Liew, [3]*MSc, PhD*, Lee Ching Ng, [3,4]*PhD*, Natalie WH Tan, [1]*MBBS, MRCPCH, FAMS*, George SH Yeo, [5]*MBBS (Singapore), FRCOG (Lon), FAMS (Singapore)*, Nancy WS Tee,[6] *MBBS, FRCPA*, Raymond TP Lin, [7]*MBBS, FRCPA*, Thiam Chye Tan, [8]*MBBS, MMed*, Victor S Rajadurai, [2]*MRCP, FAMS*, Jerry KY Chan, [9]*MBBCh, ,FRCOG PhD*, Koh Cheng Thoon, [1]*MBBS, M.Med (Paeds), MRCPCH*

Zika virus (ZIKV), a relatively unknown arbovirus, has suddenly come under the spotlight of the media and is causing major concern in public health, infectious disease and perinatal circles. When the Pan American Health Organization (PAHO) issued an alert reporting possible ZIKV transmission in northeast Brazil on 7 May 2015, the geographical spread of the virus from Africa through Asia and the Pacific islands was not surprising.[1] Multiple factors including climate change, urbanisation, air travel and trade had perpetuated previous global spread of arboviruses such as dengue (DENV) and chikungunya (CHIKV) viruses. However, on 1 December 2015, PAHO issued an epidemiological alert warning of a suspected link between ZIKV and neurological syndrome or congenital malformation.[2] Public health authorities in Brazil had detected a 20-fold increase in infants born with microcephaly which correlated with the introduction of ZIKV into the country. On 2 February 2016, the World Health Organization (WHO) declared ZIKV as a public health emergency of international concern (PHEIC).

ZIKV is a flavivirus from the *Flaviviridae* family. DENV, yellow fever and West Nile viruses belong to the same family of viruses.[3] It was first identified in 1947 in Uganda in the rhesus macaque population of Zika forest, from which it derives its name. Since then, it has spread to Southeast Asia with reports of sporadic infections. In 2007, for the first time outside Africa and Asia, a major outbreak occurred on the Yap Islands of Micronesia.[3] This was followed by a bigger outbreak in French Polynesia in 2013 where an estimated 70% of the population on some islands may have been infected.[4] Reports of Guillain-Barre syndrome in adults were reported in association with ZIKV infection but not birth defects. Before these reports, ZIKV was believed to only cause mild disease.

Clinically, ZIKV usually presents with low-grade fever (<38.5˚C), transient arthritis or arthralgia, maculopapular rash and conjunctivitis. It is also associated with general non-specific symptoms such as myalgia, lethargy and headaches. The incubation period is between 3 to 12 days and the symptoms described are short-lived, lasting only 2 to 7 days. Only 20% of people will exhibit symptoms following infection.[3] Therefore, most infections are not recognised or get misdiagnosed as DENV or CHIKV in the absence of laboratory testing. Currently, laboratory confirmation of ZIKV is via polymerase chain reaction (PCR) detection of viral ribonucleic acid (RNA) from clinical specimens, usually blood. However, the viraemic period is short, lasting only for 3 to 5 days after disease onset. ZIKV IgM/IgG antibodies can be detected by serological assays 5 or 6 days postsymptom onset but false positive results due to cross-reactions with related flaviviruses such as DENV or yellow fever do occur.[5-7] Virus neutralisation tests may give more specific results, but this method is not suitable for routine clinical testing.

Microcephaly, the condition currently linked to ZIKV, is a neurodevelopmental anomaly usually defined as head circumference that measures more than 2 or 3 standard deviations (SD) below the mean for age, gender and ethnicity. The SD cutoff, diagnosis and clinical definitions can vary between clinicians and regions.[8] The causes of background microcephaly are not all known but various factors such as host genetics, congenital infections, drugs, alcohol and environmental exposures have been implicated. Laboratory investigations to date have confirmed the presence of ZIKV

[1]Infectious Disease Service, Department of Paediatrics, KK Women's and Children's Hospital, Singapore
[2]Department of Neonatology, KK Women's and Children's Hospital, Singapore
[3]Environmental Health Institute, National Environment Agency, Singapore
[4]School of Biological Sciences, Nanyang Technological University, Singapore
[5]Department of Maternal Fetal Medicine, KK Women's and Children's Hospital, Singapore
[6]Department of Pathology and Laboratory Medicine, KK Women's and Children's Hospital, Singapore
[7]Department of Laboratory Medicine, National University Hospital, Singapore
[8]Department of Obstetrics & Gynaecology, KK Women's and Children's Hospital, Singapore
[9]Department of Reproductive Medicine, KK Women's and Children's Hospital, Singapore
Address for Correspondence: Dr Yung Chee Fu, Infectious Disease Service, Department of Paediatrics, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.
Email: Yung.Chee.Fu@kkh.com.sg

RNA in brain tissue, placenta, and amniotic fluid of a handful of infants with microcephaly and from postmortem samples of foetuses of mothers infected with ZIKV during pregnancy.[9,10] However, it is still not known if ZIKV is the causative agent for microcephaly and/or foetal loss. Children with microcephaly are at risk for long-term developmental problems. Although there is no treatment, early diagnosis and intervention may improve the child's quality of life. Public health authorities in Brazil and globally are extremely worried as a steep increase in such a condition will have important implications in terms of the burden on healthcare systems as well as the economic contributions of a generation or multiple generations if ZIKV becomes endemic. Reports from Brazil have indicated a 20-fold increase but caution is required in interpreting this figure due to changes in case definitions, increased ascertainment following alerts, and the absence of controlled epidemiological studies to quantify excess risk.[2]

The transmission cycle of ZIKV is similar to DENV. ZIKV in east Africa is maintained in a sylvatic cycle. It causes cyclical epizootics amongst non-human primates with transmission via a wide variety of sylvatic and peridomestic *Aedes* mosquitoes.[11-14] The *Aedes aegypti* mosquito which is also the main vector for dengue is considered an important vector for ZIKV. The virus has been detected in wild-caught *Aedes aegypti* mosquitoes in Malaysia in the 1960s.[15,16] Experimental infection work including studies done using mosquitoes caught locally in Singapore have confirmed the ability of both *Aedes aegypti* as well as *Aedes albopictus* to transmit ZIKV.[17] Similar laboratory experiments have also identified the *Aedes hensilli* mosquito as the species behind the Yap island outbreak.[18] From a vector perspective, it is highly plausible for ZIKV to follow a similar path to the spread of DENV following the global expansion of the *Aedes* mosquito. Being an emerging arbovirus, populations will be immunologically naïve with virtually no protection, which will facilitate its transmission. Any country or region with endemic DENV and the presence of *Aedes* mosquitoes including Singapore is vulnerable. Furthermore, current reports of relatively high *Aedes aegypti* population from prolonged warmer weather due to El Nino is worrying.[19] Immediate intensified effort amongst all stakeholders in reducing mosquito population is required.

As of 1 February 2015, there has been no reported cases of ZIKV in Singapore. Testing of residual blood from 690 febrile patients negative for DENV and CHIV in 2009 and 2010 did not identify any ZIKV positive cases.[20] This surveillance has been enhanced, with 150 samples tested each week and ZIKV has not been detected. However, as highlighted above, the duration of ZIKV viremia is short-lived and hence, these small surveys have limited sensitivity to pick up low disease prevalence. Furthermore, febrile patients only represent a small proportion of infected cases due to the high asymptomatic rate. Amongst our neighbouring countries in Southeast Asia, acute ZIKV infection have been detected in Thailand, Cambodia, Philippines and Indonesia while serological evidence of ZIKV has been reported from Malaysia.[21-25] The reported numbers are likely the tip of the iceberg. The absence of any systematic surveillance and testing for ZIKV means that the true epidemiology and burden of ZIKV in our region remains unknown. Interestingly, despite evidence of dispersed circulation in Southeast Asia over 30 years (60 years in Africa), no reported increase in microcephaly or Guillain-Barre syndrome had been reported. Genomic sequencing of the virus did not identify any major change or mutation which could explain an increase in virulence.[26] It is possible that previous outbreaks may have been too small or health systems were just not able to recognise new cases of these neurological disorders.

There is currently no medical treatment or vaccine available for ZIKV. Public health prevention, education, outbreak control and risk communication will be the predominant strategy against ZIKV. Singapore's dengue vector control programme will contribute to containing or mitigating any ZIKV introduction into the country. However, escalating surveillance systems with more systematic notification and testing of suspected human cases, particularly amongst pregnant women may urgently need to be set up. Healthcare professionals will need to be provided with information on the signs and symptoms of ZIKV and criteria for testing. Testing for ZIKV amongst symptomatic pregnant women should be considered in view of the challenges of clinical diagnosis due to similarities with dengue infection. Early identification of at-risk pregnant ZIKV cases will ensure they are managed and counselled appropriately with referral to specialist centres. Furthermore, this would also allow early detection to inform vector control activities as well as provide updates to engage with at risk neighbourhoods for community mobilisation. The detection of foetal microcephaly may also warrant testing of serum and possibly amniotic fluid for ZIKV as an aetiologic pathogen in addition to excluding the common intrauterine infections viz. cytomegalovirus, toxoplasmosis, herpes simplex, syphilis and rubella. Pregnant women are currently being advised by the United States of America (USA) Centers for Disease Control and Prevention (CDC) against travelling to ZIKV affected countries.[7] If a pregnant woman chooses to travel, she should be provided with information to reduce the risk of mosquito bites including wearing long-sleeved shirts, long trousers, staying in screened or air-conditioned rooms and use insect repellents. Insect repellents (DEET, picaridin and IR3535) are safe for pregnant women but must be used as directed in the product label.[7]

It is important to emphasise that the association between ZIKV infection and microcephaly is still being investigated. Evidence of ZIKV infection have been found in placentas of aborted foetuses and in the brains of babies with microcephaly who died soon after birth.[9,27,28] Further epidemiological analysis with controls, molecular analysis and experimental laboratory work are urgently needed. Regardless, investment in public health preparedness is warranted as the consequences of inaction can prove to be very damaging from an individual as well as societal perspective if the link is confirmed. Worryingly, the first controlled analysis of the link between Guillain-Barre syndrome in adults and ZIKV in French Polynesia have shown a strong causative association. A surge in Guillain-Barre syndrome will also need to be considered as part of preparedness plans.[29] Locally, the Ministry of Health Singapore has added ZIKV to the list of notifiable diseases.[30] Doctors suspecting a case of ZIKV must inform the Ministry of Health. Currently, one of the criteria for a suspect case is having travelled to ZIKV-affected areas in the last 2 weeks prior to the onset of symptoms. The emergence of ZIKV following Ebola virus from West Africa and nosocomial outbreak of Middle East respiratory syndrome coronavirus (MERS-CoV) in South Korea, is a timely reminder of the ease with which infectious diseases can spread globally. Hence, improving clinical vigilance, developing strong epidemiological and public health infrastructures, and engaging with the community will provide dividends for us in the long run against future novel pathogens.

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