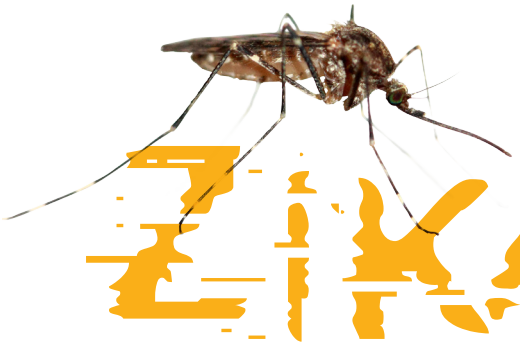

An Update on the ZIKA VIRUS

The Zika virus epidemic in the Americas, and in particular its association with subsequent development of microcephaly in the newborn of infected pregnant women, has resulted in considerable public and medical interest. Will it come into Singapore and what are the implications if it does?

PROFILE

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ABOUT THE ZIKA VIRUS

First, a brief introduction to the virus itself. The Zika virus is a member of the flavivirus family ("flavi" actually translates to "yellow" in Latin and the family is so named because of its most famous member in history: the yellow fever virus), which also includes dengue, Japanese encephalitis and West Nile viruses. Scientists working at the Yellow Fever Research Institute (currently Uganda Virus Research Institute) discovered the virus serendipitously in 1947, in a sentinel monkey set up in the Zika Forest near Entebbe, Uganda. Other than Africa, the Zika virus is also present in Asia, having been described in orangutans in Sabah as well as in travellers from Indonesia, Cambodia and Thailand.

It is maintained in its sylvatic cycle by primates and is transmitted primarily by a variety of *Aedes* mosquitoes, including the two major strains of *Aedes* mosquitoes in Singapore — *Aedes aegypti* and *Aedes albopictus*. The virus can also be transmitted via blood transfusion and in a recent curious discovery, via sexual intercourse (at this point, although we are clear that men can transmit the virus to their partners, as the virus can be found in semen, it remains uncertain whether women can transmit Zika through sex). The incubation period after being bitten by an infected mosquito is "a few days" (variously described as somewhere between two and 12 days). Incubation periods after blood transfusion or sexual transmission are unknown, but likely to be just as brief, if not more so.

As with dengue, up to 80% of infected persons will be asymptomatic. The clinical disease the virus causes is Zika fever, which is often described as a "mild dengue". This is an acute syndrome comprising fever with various combinations of other symptoms such as headache, joint aches, muscle aches, maculopapular rash and non-purulent conjunctivitis. Not many clinicians or researchers were particularly interested in this mild viral illness until the first ever epidemic of Zika occurred on the Micronesian island of Yap in 2007; and even after that, there was little mainstream interest. However, the virus spread inexorably eastward through Micronesia, French Polynesia (2013), Cook Islands (2014) and Easter Island (2014), to finally reach the Americas in 2015. Brazil was the first country in South America to report the Zika epidemic in April 2015 and researchers have postulated that the virus arrived during the 2014 FIFA World Cup held in that country. Since May 2015, the virus has spread throughout most countries of tropical South America, Mexico and parts of

Central America. The virus has also been exported episodically from the Americas as well as Asia since then.

COMPLICATIONS OF THE VIRUS

The huge number of infections in Brazil and other South American countries has unveiled two rare but terrifying complications of the infection. The first is Guillain-Barré syndrome (or, specifically for neurology wonks, the acute motor axonal neuropathy phenotype of Guillain-Barré syndrome) — an immune-mediated neurological condition presenting as progressive paralysis over a period of days to weeks. Researchers have since uncovered strong evidence of its association with prior Zika infections even in the French Polynesian outbreak, although the mechanism by which it happens remains unknown, as the usual auto-antibodies have not been detected. A very small proportion of patients (up to 0.24 per 1,000 Zika-infected persons) may be affected, which explains why the association was not made until fairly recently. It is important to note that asymptomatic infection may also result in Guillain-Barré syndrome, albeit at far lower rates compared to symptomatic Zika disease, according to current evidence.

The second, and much worse, complication is the association of viral infection in pregnant women with grave outcomes for the pregnancy. Microcephaly in the newborn was the first and most obvious manifestation, leading to a sudden surge of public interest in Zika and the enormous public pressure to confirm the association, as well as to "do something about it". The subsequent studies and events have been depressing, demonstrating that the association is likely true and Zika is a cause for fetal complications including microcephaly:

- The Zika virus has been shown to infect and kill neural stem cells in cell culture experiments (ie, biological plausibility).
- The virus was found in the brain of an aborted fetus in Slovenia. The mother had been infected with Zika at Week 13 of pregnancy and had elected to abort the fetus after confirmation of microcephaly and intrauterine growth retardation at Week 32.
- Among nine pregnant travellers to the US, with evidence of Zika infection, there were two fetal deaths and one newborn with microcephaly.
- In a Brazilian cohort of 42 women infected between Weeks 6 and 35 of pregnancy, there were two fetal deaths (4.8%) and 12 with abnormal fetal ultrasound scans (28.6%), including four (9.5%) with microcephaly.

These resulted in travel advisories for countries with ongoing Zika transmission: pregnant women and those actively seeking to get pregnant should not travel to these areas and should either abstain from sex or get their male partners to use condoms if they are in these areas, in addition to minimising the risk of mosquito bites. Several South American governments have urged women to delay pregnancies until the Zika outbreak is over, a recommendation which is unlikely to be helpful. This outbreak has also refuelled the debate on legal abortions and contraception in these highly Catholic nations.

ZIKA IN SINGAPORE?

Will Zika be imported into Singapore? The answer is very likely yes. We have tourists and returning travellers from both South American and Asian countries where Zika is endemic. In addition, it is unlikely that the Zika epidemic in Brazil will be under control by the 2016 Summer Olympics in August, which a fairly large contingent of athletes and other personnel will be attending.

How can we diagnose Zika infections? A travel history is important here, as the disease manifestations are very similar to dengue (with perhaps the exception of conjunctivitis, which is not always present) and can result in false-positive dengue antibody tests (being a related member of the flavivirus family). Of note, the dengue antigen test (usually positive between Days 2 to 9 of dengue infection) will be negative. The only laboratory tests available locally at this point in time are based on the polymerase chain reaction, detecting the presence of absence of the virus directly (and therefore will only be positive from blood samples for the first few days of disease; although it might be positive for a longer duration in urine or semen, the latter might be difficult to collect in a clinic setting), and can be done at either the National Public Health Laboratory or the Environmental Health Institute.

What can we do about it here? It is obviously impossible to quarantine all visitors and returning travellers from countries with ongoing Zika transmission until they are tested negative for the virus. On top of that, the majority of Zika infections are asymptomatic but can potentially spread the disease if bitten by *Aedes* mosquitoes. The key question then is whether a Zika outbreak in Singapore will behave like chikungunya (with less than 200 cases a year and only 42 cases in all of 2015) or dengue. Most local experts currently believe it will be more like the former, partly because our vector control is good (some of us might find this difficult to believe, but it is true) and largely because Zika — unlike dengue — is not rife in the surrounding countries.

There is no Zika vaccine available commercially and the current vaccine candidates will take several years more to be tested, licensed and commercialised. There is also no specific treatment for the infection. Better diagnostic tests, especially more specific serological tests, may be helpful in certain instances, such as the testing of pregnant women who may have potentially been exposed to the virus (either in countries with ongoing Zika transmission or in the scenario where there is an outbreak in Singapore). The only real way forward is continued investment in improving vector control, which has the side benefit of reducing the transmission of a number of other diseases such as dengue and chikungunya. ◆