Zika virus threat
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The widening Zika virus epidemic in Central and South America, and the continuing spread of the virus in the Pacific, are having an escalating impact on public health services globally, including those in New Zealand. Concern about the reported increase in clusters of neonatal microcephaly in Brazil and mounting evidence of neurological disorders suspected of being associated with Zika virus infection—particularly Guillain-Barré syndrome—has culminated in the World Health Organization (WHO) declaring a Public Health Emergency of International Concern (PHEIC) 1 February 2016.1

Prior to the current Central and South American outbreak, Zika virus has been reported in Africa, Asia and the Pacific. Most infections with Zika virus are generally asymptomatic, however when disease does occur, it is usually mild and complications rare. Indeed, before 2007 only a handful of cases of clinical disease due to Zika virus were reported in Asia and Africa over the previous 50 years, despite a number of countries having serological evidence of virus circulation.2 The virus is spread to humans by Aedes sp. mosquitoes, mainly Aedes aegypti, which has a distribution throughout most of the tropical and sub-tropical regions of the world. Various primate species are believed to constitute the natural reservoirs of this virus. The limited capacity for laboratory diagnosis, along with the general lack of concern about this virus, has contributed to the many gaps in our knowledge base on Zika virus and the disease it causes.

Over the past decade, the virus has been reported in the Pacific (Federated States of Micronesia in 2007; French Polynesia in 2013) and most recently in the Americas (Brazil and Colombia) in 2015. As of the 1 March 2016, Zika virus transmission has been reported in 8 Pacific Island countries3 and 31 countries in Central and South America, suggesting the rapid geographic expansion of this virus.4

The current circulation of Zika virus in Tonga, the Marshall Islands, New Caledonia, Samoa and American Samoa presents a real threat to New Zealanders visiting these virus-affected areas.5

The virus
Zika virus is an emerging mosquito-borne virus member of the Flavivirus genus within the family Flaviviridae, first isolated from a sentinel Rhesus monkey in the Zika Forest in Uganda in 1947 and shortly after from the mosquitoes Aedes africanus,6 and from a human infection in Nigeria in 1954.7 The virus was first isolated in Asia in Malaysia from Aedes aegypti mosquitoes.8 Other closely related flaviviruses include yellow fever, Japanese encephalitis, West Nile and the dengue viruses. Genetic analysis has shown that Zika virus occurs as two lineages, an African lineage and an Asian lineage.9 Molecular analysis indicates that the virus spreading widely in the Americas is most closely related to an Asian lineage virus isolated from French Polynesia in 2013–2014.10

Virus transmission
The competent mosquito vectors for Zika virus spread to humans are Aedes aegypti and Aedes albopictus—the same mosquitoes that spread dengue, chikungunya and yellow fever viruses. These mosquitoes usually bite during the morning, and late afternoon/evening hours. The virus replicates within the mosquito and is then transmitted to a
human host via its saliva during the process of taking a blood meal. Humans are usually dead-end hosts for most arboviruses (with the exception of dengue and yellow fever), however it is not known whether Zika virus will grow to sufficiently high titres in humans for it to be able to infect a mosquito in order to maintain a transmission cycle, although epidemiological data would suggest it does. This is an important question as it has major implications in understanding transmission and in possible control strategies. While Zika virus has been isolated from a wide variety of mosquito species, the presence of the virus does not necessarily indicate a competence for the mosquito to be able to transmit the virus to a new host.\textsuperscript{11,12} Much more work on vector competence is urgently needed, but it is probable that a number of other species of mosquito may be able to transmit under local conditions.

In New Zealand, competent vectors for Zika virus transmission are not known to exist, thus Zika virus infection is primarily a travel-related infection, occurring in travellers returning after living in or visiting Zika virus-affected countries.

There are major concerns that Zika virus may also be transmitted by infected pregnant women to their unborn babies,\textsuperscript{9,13} and there is mounting evidence that sexual transmission can also occur.\textsuperscript{14-16} Indeed, unlike other arboviruses, patients presenting with haematospermia have been shown to have infectious viral particles and ribonucleic acid (RNA) in their semen. Other routes of transmission may also occur, such as through blood transfusions, perinatal transmission during delivery,\textsuperscript{13} via breast milk, close contact after delivery via exchange of saliva or other bodily fluids,\textsuperscript{17} or via transplantation. Blood transfusions are an important potential mode of transmission, as demonstrated by the finding of Zika viral RNA in 2.8% of blood donors in French Polynesia,\textsuperscript{18} and must be of particular concern.\textsuperscript{19} In New Zealand, a suspected sexual transmission to a female who had not travelled to a Zika-affected country has been documented.\textsuperscript{20}

**The disease**

Zika virus infections are generally asymptomatic, however when illness occurs (in about 20% of infections) it is generally mild. After an incubation period of 3–12 days, the symptoms include a slight fever, muscle and joint pains, conjunctivitis, a maculopapular rash and general malaise.\textsuperscript{21} Zika illness is generally self-limiting with most symptoms resolving within 3–7 days.\textsuperscript{12}

Complications are rare, but recent reports of both neurological and congenital complications have led to the heightened awareness of this disease. The severe neurological complications, particularly cases of Guillain-Barré syndrome, were first observed in French Polynesia in 2013–14,\textsuperscript{22} and increased numbers of cases of Guillain-Barré syndrome have subsequently been observed in Brazil, Colombia, El Salvador and Venezuela.\textsuperscript{23} Because 88% of the cases described in French Polynesia reported a preceding clinical illness,\textsuperscript{22} and because Zika is said to be symptomatic in only 20% of cases based on the Yap outbreak,\textsuperscript{24} asymptomatic infection might pose a much lower risk of Guillain-Barré syndrome than does symptomatic disease. However, that is assuming that the case-to-infection ratio in the current outbreak is the same as that in the Yap outbreak, which is also yet to be confirmed.\textsuperscript{25}

Microcephaly is the most prominent and commonly reported clinical feature of suspected congenital Zika syndrome.\textsuperscript{26-28} The various manifestations of the syndrome have been reviewed by Chan et al (2016).\textsuperscript{12} While there has been some laboratory support for the possible causal link between Zika virus infection and microcephaly, including the detection of viral RNA in amniotic fluid of two pregnant women with ultrasonic evidence of microcephaly, in blood and brain tissues from deceased neonates, and in babies born with microcephaly,\textsuperscript{12,23,26,27} a causal link between these events is yet to be confirmed. Furthermore, the geographic variation in the incidence of congenital malformations might suggest that other factors or co-factors could be involved.\textsuperscript{23,29}

Thus, further studies are urgently needed to clarify this.

**Diagnosis**

The clinical diagnosis of Zika virus infection is based on symptoms and a recent history of travel to an area where Zika virus is known to be present. However, dengue,
chikungunya and other viruses (including measles and rubella), which cause similar illnesses, may also be present in Zika virus-affected countries. Laboratory testing is the most reliable way to confirm a Zika virus diagnosis. Molecular testing by reverse transcriptase polymerase chain reaction (RT-PCR) is the test of choice with Zika virus RNA able to be detected in blood during the first week and urine during the first 2 weeks of an illness. The major limitation of this test is the relatively short time after acute onset of Zika virus illness, that viral RNA can be detected. Serological tests are also available and include IgM detection using immunofluorescence (IIFT), IgM-capture ELISA (MAC-ELISA) and plaque reduction neutralisation tests (PRNT). Zika IgM antibody is typically detectable from 4 days after symptom onset for approximately 12 weeks. In some instances, the detection of Zika virus IgG can be diagnostically useful, specifically if seroconversion can be demonstrated and infection with other circulating flaviviruses has been excluded.

The limitations of serological assays are that they are slow to perform and cross-reactions with other flaviviruses either as a result of infection or vaccination (yellow fever and Japanese encephalitis) can occur.30

In New Zealand, RT-PCR testing for Zika virus is available from LabPlus (Auckland), ESR (Wellington) and CHL (Christchurch). Also available are RT-PCR assays for the presence of dengue and chikungunya viral RNA, dengue NS1 antigen detection, dengue and chikungunya virus IgM and IgG antibody detection.

New Zealand’s response

Although the risk to New Zealanders is considered to be very low for Zika virus infection, the Ministry of Health has issued general advice including specific advice to health care professionals and interim guidance to health care professions dealing with Zika virus in pregnancy.31,32 This latter advice addresses the concerns of the population at increased risk of poor outcomes following infection.

Travellers are returning from Zika virus-affected countries who have been exposed to Zika virus and possibly other mosquito-borne viruses (dengue and chikungunya) present in these areas. Some are presenting to the healthcare system either because of illness or concern over their possible exposure. Clinical astuteness in obtaining a full clinical and travel history, the dates of travel and onset of symptoms and the timely collection of samples for laboratory testing are required. Laboratory testing has become more important for the confirmation of infection, however consultation with a microbiologist or infectious diseases specialist may be required to advise on laboratory test result interpretation as the diagnostic accuracy of RT-PCR assays, especially when applied to Zika virus exposed but asymptomatic individuals, is largely unknown.

A possible future risk to New Zealanders is the establishment of competent mosquito vectors in New Zealand. It is believed that the current conditions in New Zealand are unfavourable for the establishment Aedes aegypti and Aedes albopictus mosquitoes, reducing the likelihood of human infection from a locally transmitted source.33 However, ongoing surveillance—especially at our borders—for these vectors is essential to mitigate this risk.
EDITORIAL

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