NZPSU Study of Possible Congenital Zika Syndrome (CRZ)
- Background

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Principal Investigators

A/Prof Nigel Dickson, Co-Director NZPSU, University of Otago
Dr Lesley Voss, Infectious Disease Paediatrician, Auckland DHB
Dr Simon Rowley, Neonatal Paediatrician, Auckland DHB
Dr Paul Shillito, Paediatric Neurologist, Canterbury DHB

Background

Zika virus infection was declared a public health emergency of international concern by the World Health Organization (WHO) in early 2016, following reports from Brazil of an association between Zika in pregnancy and microcephaly. The causal relationship has subsequently been confirmed, with fetal Zika infection, particularly in the first trimester, being shown to be associated with microcephaly and other neurological abnormalities.[1] [2] This is now refered to as Congenital Zika Syndrome (CZS).

Zika is a flavivirus discovered in 1947 in Eastern Africa, which is most commonly spread by *Aedes* mosquitoes. Sexual transmission, predominantly from male to partner, has also been reported. Although the transmission of Zika through blood transfusion has yet to be reported, it is considered likely given the transmission of other flaviviruses in this way.

The first outbreak of Zika outside Africa and Asia occurred on the island of Yap in the Federated States of Micronesia in 2007. Subsequently there were outbreaks in French Polynesia and other Pacific islands in 2013/2015. Since then, Zika has spread to much of South and Central America.

By mid-July 2016, 1752 cases of microcephaly and other CNS malformations potentially linked to Zika had been reported by 13 countries; in three of these countries infants were born to mothers with a recent history of travel to Zika-affected countries.

An increased rate of microcephaly was found in a retrospective review of pregnancies in French Polynesia occurring during the Zika outbreak.[3]

As of 20 July 2016, the European Centre for Disease Prevention and Control (ECDC) reported “widespread transmission” of Zika in most countries in South, Central America and the Pacific (including Samoa, Tonga, Fiji, and the Federated States of Micronesia), and also Thailand in Asia.[4]

The commonest mosquito vector for Zika - *Aedes aegypti* – exists in these countries. While it does not exist in New Zealand, others potential vectors might be able to survive in some areas in the future.

Further information about Zika and advice of New Zealanders can be found on the Ministry of Health website:
http://www.health.govt.nz/our-work/diseases-and-conditions/zika-virus

Surveillance of CZS

In response to the WHO advice that governments implement surveillance of Zika, the New Zealand Paediatric Surveillance Unit (NZPSU) is establishing surveillance among specialist paediatricians of infants and young children presenting with a possibility of CZS. Paediatric Surveillance Units in Britain and Ireland, Australia and Canada are also establishing similar – but not identical – surveillance.

The Pan American Health Organization/WHO has recently produced interim case definitions for suspected, probable and confirmed cases of CZS as shown in Table 1.[5] These might change as knowledge increases.

Table 1 WHO Definitions of suspect, probably and confirmed cases of congenital syndrome associated with Zika infection

Suspected case of congenital syndrome associated with Zika virus
Live newborn who presents with:

- Microcephaly: head circumference below -2 standard deviations for gestational age and sex, measured at 24 hours post-partum according to the standardized reference; **OR**
- Other congenital malformation of the central nervous system;

AND whose mother:

- traveled to, or resided in, an area where Zika virus vectors were present during her pregnancy; **OR**
- had unprotected sex during pregnancy with a partner who resided in, or traveled to, an area with the presence of Zika virus vectors.

Probable case of congenital syndrome associated with Zika virus
Live newborn who meets the criteria for a suspected case of congenital syndrome associated with Zika virus **AND**

- who has intracranial morphological alterations detected by any imaging method, and not explained by other known causes; **OR**
- whose mother had rash during pregnancy

Confirmed case of congenital syndrome associated with Zika virus
Live newborn who meets the criteria for a suspected case of congenital syndrome associated with Zika virus **AND** Zika virus infection was detected in specimens of the newborn, regardless of detection of other pathogens.

The NZPSU is asking paediatricians, through their monthly mail-out, to report any infant and young child <6 months of age with possible CZS. The case definition to be

used by the NZPSU is based on that developed by the British Paediatric Surveillance Unit (BPSU). The BPSU study was designed prior to the WHO definitions being published.

Table 2 NZPSU case definition of Possible Congenital Zika Syndrome

An infant or child <6 months of age with

- Head circumference >2 standard deviations below the mean for gestational age and sex (equivalent to <3rd percentile), whose mother (or her partner) has spent time in a country with active Zika transmission during (or 3 months prior to) pregnancy
  OR
- Any neurological abnormality requiring investigation whose mother (or her partner) has spent time in a country with active Zika transmission during (or 3 months prior to) pregnancy
  OR
- Head circumference below >3 standard deviations below the mean for gestational age and sex (equivalent to <0.1th percentile)

The NZPSU study differs from BPSU one insomuch as we are asking for reports of all children with severe microcephaly (>3SD below the mean) as well as those with microcephaly (>2SD below the mean) or another neurological abnormality whose mother's (or partner) have been in a Zika area. The definition being used differs from that developed by the PAHO/WHO for a suspected case by, including (a) children after the newborn period but below 6 months of age, and (b) children with a neurological abnormality requiring investigation; and excluding children whose mother (or partner) had been in an area where Zika vectors were present but Zika was not circulating.

On the NZPSU website are links to up-to-dated information on countries with transmission of Zika in the past nine months, and to the Intergrowth 21st study website that can be used to determine whether an infant or young child had a head circumference >3 (and >2) SDs below the mean.

Paediatricians reporting a case will be asked to complete a web-based questionnaire asking for details of the infant/child's head circumference (and other measurements), neurological abnormalities, the mother's pregnancy and her (and her partner's) travel history, and investigations undertaken on the infant/child and mother.

<u>Outcome</u>

It is hoped that the NZPSU surveillance study will provide a definitive indication of the presence or absence of CZS among infants and young children born in New Zealand. Success of the project would be indicated by a number of notifications being made, and with the children (and their mothers) being appropriately investigated. The ideal outcome would be that none of the children are affected!

There is a possibility that pregnancies affected by Zika might have been aborted or terminated, so data on these need to be collected as well as on infants born alive.

Ethical Approval

Ethical approval for this study has been given as an extension to that given for the NZPSU work by the National Ethics Committee.

Further Reading

There was a very comprehensive review of Zika published in the New England Journal of Medicine in April that covers most of the important issues known at the time. (Petersen, L. R., Jamieson, D. J., Powers, A. M., & Honein, M. A. (2016). Zika virus. *New England Journal of Medicine*, *374*(16), 1552-1563.

References

1 Brasil, P., Pereira, Jr, J. P., Raja Gabaglia, C., Damasceno, L., Wakimoto, M., Ribeiro Nogueira, R. M., ... & Calvet, G. A. (2016). Zika virus infection in pregnant women in Rio de Janeiro—preliminary report. *New England Journal of Medicine*.

2 Broutet, N., Krauer, F., Riesen, M., Khalakdina, A., Almiron, M., Aldighieri, S., ... & Dye, C. (2016). Zika virus as a cause of neurologic disorders. *New England Journal of Medicine*, *374*(16), 1506-1509.

3 Cauchemez, S., Besnard, M., Bompard, P., Dub, T., Guillemette-Artur, P., Eyrolle-Guignot, D., ... & Fontanet, A. (2016). Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study. *The Lancet*, *387*(10033), 2125-2132.

4 http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/zika-outbreak/Pages/Zika-countries-with-transmission.aspx. Accessed 20 July 2016

5 http://www.paho.org/hq/index.php?option=com_content&view=article&id=11117&Itemid=41532&lang=en. Accessed 20 July 2016