Little risk of severe complications associated with Zika infection in New Zealand

Gareth J Parry, Matthew Peacey, Eric J Buenz

ABSTRACT

Zika virus infection has raised considerable concern in New Zealand, but the risks faced by most New Zealanders, while real, are quite small as New Zealand does not harbor the primary mosquito vector. Furthermore, in individuals with a competent immune system, the acute illness caused by Zika virus infection is generally mild. Serious complication associated with Zika virus infections include microcephaly and Guillain-Barré Syndrome. Pacific Island countries have reported cases of Zika virus infection and these climates support the mosquito vector. Thus, travelers to these areas are at risk of infection. New Zealand travelers returning from endemic areas have developed the illness associated with the virus, but the probability of autochthonous transmission in New Zealand is very small.

Zika virus infection typically results in a mild, unremarkable, viral infection

Zika virus infection causes a generally mild febrile illness similar to many acute viral infections. The incubation period is unknown, but is likely a few days to two weeks. A pruritic maculopapular rash is common, as are arthralgias, myalgias, headache and conjunctivitis. Symptoms persist for a few days and resolve without treatment. Only about 20% of infected individuals are symptomatic and those with symptoms rarely seek medical attention. Death during the acute illness is rare and is restricted to the elderly or those with concomitant illnesses. None of the manifestations of the acute infection are sufficiently characteristic to enable a confident clinical diagnosis in patient seen in non-endemic area such as New Zealand, but a history of travel to an endemic area is a critical clue.

During times of epidemic infection in endemic areas, the diagnosis is straightforward, but at other times or in non-endemic regions, such as New Zealand, a high index of suspicion is needed so that appropriate testing can be employed. In the earliest stages of infection, the presence of virus can be identified by reverse-transcriptase polymerase chain reaction (RT-PCR) with specific assays able to identify genetic sequences unique to the Zika virus and so distinguish from other endemic flaviviruses such as Dengue. By the end of the first week of illness, IgM and neutralising antibodies can be measured, but they cross-react with the other flaviviruses, which do not seem to be associated with the same complications as Zika, making a specific serological diagnosis challenging.

Zika virus similar to other viruses in mosquito-transmitted Flavivirus family

Zika virus is a positive-sense, single-stranded RNA virus approximately 11,000 nucleotides in length. The genome is encapsulated by the virus’s structural proteins and enveloped in a host-derived membrane, 40 nm in diameter, modified with viral glycoproteins. The Zika virus is most closely related to the Spondweni virus, belonging to the Flavivirus genus and so is related to West Nile, yellow fever, Japanese encephalitis and dengue viruses. Like other arboviruses, Zika virus is maintained through a transmission cycle between host and vector.
Vector-mediated transmission occurs when Zika virus present in the saliva of mosquitoes is injected by blood-feeding females into the skin of the host. In humans, infection initially occurs via the interaction of the viral envelope protein with specific receptors of skin immune cells, including dermal fibroblasts, epidermal keratinocytes and immature dendritic cells. The outcome of infection is determined by the interplay of viral proliferation and the resulting immune response. As seen with other Flavivirus epidemics, Zika virus has adapted to infect humans, reaching viral titres high enough to infect the mosquito vector, negating the need for a non-human host reservoir to maintain the transmission life-cycle.

Recent phylogenetic analysis of the Zika virus shows three distinct lineages, two from Africa and one from Asia, sharing a common ancestor estimated to have emerged around 1920 (1892–1947). The emergence of the Asian lineage from Africa has subsequently led to the seeding of this Asian genotype across the Pacific and into the Americas.

Mutations in the other members of the Flavivirus genus have resulted in their increased rate of spread and clinical severity, but the role viral mutation and population susceptibility have played in the spread of Zika virus is still unknown. Changes in the glycosylation patterns of the structural E protein of Zika virus have been implicated in enhanced viral infectivity in certain mosquito vectors. Recently it has been hypothesised that selective pressure has resulted in viral mutations adapting the codon usage for more efficient transcription of viral proteins in the human host. This, in turn, could result in an increased viral titre allowing the spread of Zika virus from human host to mosquito vector to human host and the outbreak of Zika in human populations. As yet, with comparatively little sequence data, these reports do not conclusively demonstrate the spread of Zika virus is the result of virus mutation alone.

New Zealand Ministry of Health guidance for clinicians addressing potential Zika virus infection

The New Zealand Ministry of Health has provided a centralised resource on Zika virus infection for health professionals. This resource provides an overview of Zika virus, guidance on dealing with Zika virus in pregnancy, sexual transmission of Zika virus, symptoms of Zika virus infection, and links to other resources global Zika virus resources.

Low probability of autochthonous (individual to individual) Zika virus transmission in New Zealand

Zika virus was first identified in Africa in 1947, but few cases of human disease were identified over the next six decades. Surveillance programs tracked its passage across to Asia and the Pacific but it was not until the last five years that it has invaded high-population areas such as Central and South America, and may have increased infectivity. This increase in viral fitness may be related to a mutation in the virus. Despite this apparent increase in infectivity, the acute illness generally remains mild.

The Aedes genus of mosquitoes is the vector for Zika virus, with A. aegypti almost exclusively responsible for human transmission cycles. It is of concern that the virus has adapted to A. albopictus, a much more widely distributed mosquito which is found throughout tropical regions but also in the US and parts of Europe. It has been suggested that the Aedes genus is adapting to colder climates as yellow fever, another flavivirus infection transmitted by Aedes, was endemic across the US, at the time of the Revolutionary War. The presence of this flavivirus suggests that the requisite mosquito vector is capable of adapting to the North American climate.

The Aedes mosquito is not endemic in New Zealand, but our major trading partners Australia, the Pacific Islands and Southeast Asia harbor the mosquito. The New Zealand climate is capable of supporting a population of the Aedes mosquito and the mosquito is occasionally identified at the borders, so continuing vigilance is essential.

New Zealand had 57 confirmed human cases of Zika infection in 2014, 6 in 2015 and 11 through the end of January this year, coinciding with the spread across the Pacific, the Americas and elsewhere. There has been one case of Guillain-Barré syndrome associated with Zika infection in New Zealand. All cases were thought to have been contracted overseas.
The virus has been identified in human saliva and semen as well as blood, and direct human-to-human transmission is strongly suspected by sexual transmission,\textsuperscript{12,13} by blood transfusion\textsuperscript{14} and from infected mothers to their infants at parturition.\textsuperscript{15} No transmission has been documented through saliva, but the World Health Organization has urged caution regarding kissing any potentially infected patient. The NZ Blood Service has instituted measures to minimize the risk of contracting Zika virus infection from transfusions. This includes routinely questioning donors about their recent travel history and not allowing people to donate blood for 28 days after leaving an endemic area.

**Microcephaly a possible complication of Zika virus infection for infants in utero**

While there are case reports of intrauterine infection with Zika virus and microcephaly,\textsuperscript{16,17} a causal relationship between the infection and microcephaly has not been established.\textsuperscript{18} Nonetheless, two epidemiologically-associated outbreaks of Zika virus and microcephaly have formed the basis for establishing this relationship,\textsuperscript{5,19} and recent molecular data\textsuperscript{20} further strengthen this correlation. A recent report\textsuperscript{20} documented direct persistent viral infection of the brain of a fetus whose mother had become infected in the 13th week of pregnancy. Ultrasound showed the head circumference to be increasing normally at 14 and 21 weeks of pregnancy but thereafter, fetal growth and particularly head circumference dramatically slowed and the pregnancy was terminated at 32 weeks. Virus was identified in amniotic fluid and in brain tissue but not in other organs, suggesting strong neurotropism of the virus. Based on the strength of this association, the World Health Organization has issued a Public Health Emergency of International Concern\textsuperscript{21} and guidelines have been developed for pregnant women to mitigate the risk of Zika virus infection during pregnancy.\textsuperscript{22}

In the event that a link between Zika virus and microcephaly is established, questions such as the proportion of pregnancies with infection that lead to microcephaly, a potential mechanism of action, and the risk of microcephaly at specific stages of pregnancy will be important to address.

In the meantime, New Zealand women should avoid pregnancy while travelling in endemic areas and, if pregnant, should avoid sexual contact with potentially infected partners since the virus can probably be transmitted sexually.

**Guillain-Barré Syndrome (GBS) a complication of Zika virus infection**

GBS is an acute paralytic illness that, in about 70% of cases, can be linked to an antecedent infection\textsuperscript{23} or, in a single incident, vaccination, specifically the 1976 strain of influenza.\textsuperscript{24} Although most cases follow an upper respiratory infection, the exact microbe is seldom identified. The most commonly identified antecedent infection is *Campylobacter jejuni*, a particularly common cause of acute gastroenteritis in New Zealand.\textsuperscript{25} The worldwide incidence of GBS is 1.5–2.0 cases/100,000 annually although the incidence in New Zealand is higher, up to 2.9 cases/100,000/year, with the excess being entirely attributable to *C. jejuni* infection.\textsuperscript{26} About 70% of GBS cases make a full motor recovery and about 5% die, with the remainder showing varying degrees of residual weakness.\textsuperscript{23}

Several countries have noted a striking increase in the number of cases of GBS coincident with the spread of Zika virus infection throughout the Pacific and the Americas. French Polynesia in 2014 saw 73 cases of GBS in a population of 270,000, a 10–20-fold increase in GBS over that expected.\textsuperscript{6} Brazil saw a 19% increase of GBS cases in 2015 compared to 2014. Similar increases have been seen in Mexico and several Central America countries including Ecuador, Guatemala and El Salvador. One report in the popular press noted a mortality rate of over 50% but this has not been confirmed by others and may represent the poor standard of care in impoverished areas that typically see most cases of Zika. The association between Zika virus infection and GBS does not prove that the association is causative; it is possible that some other infection has increased simultaneously. However, it seems highly likely that the Zika virus itself is causing these cases of GBS. At the moment little is known of the exact clinical and electrophysiological manifestations of GBS associated with Zika virus infection and more research is needed.
The exact mechanism whereby Zika might trigger GBS is unknown. The only established mechanism for any infection to trigger GBS is molecular mimicry of the glycolipids in the peripheral nerve with the surface lipo-oligosaccarides in *C. jejuni* but this has not been established for other antecedent infections, including Zika virus. Research into the molecular sequence of Zika virus searching for homology with components of peripheral nerve axons or myelin will be important to determine this mechanism.

Treatment of GBS with plasma exchange or intravenous immunoglobulin improves speed of recovery but not degree of recovery or mortality which remains around 5%. Treatment is most effective if initiated early, within a week of onset of weakness. Any individual returning to NZ from a Zika-endemic area with a febrile illness should be promptly evaluated for possible Zika infection and, if positive, carefully followed for signs of GBS so that early treatment can initiated if necessary.

**Travelers returning to New Zealand most at risk of Zika virus complications**

As the risk of autochthonous transmission of Zika virus in New Zealand is low, returning travelers to regions with active epidemics (Figure 1) are most at risk of infection. These patients will present with typical symptoms of a viral infection and the infection is generally self-limiting. Medical practitioners in New Zealand most need to be aware of the potential increased risk of post-infectious GBS which can be managed using established protocols and the potential risk of microcephaly resulting from intrauterine infection; however currently these two risks of infection need to be considered associations and a causative relationship has not been established.

**Figure 1:** World map indicating countries (grey) that have documented transmission of the Zika virus during the current epidemic as of 22 February 2016. It is important to consider that travelers in juxta-position locations to countries with documented epidemics may also warrant suspicion—there is little reason to assume that Zika virus is not in Peru or Uruguay, for example.

---

**Competing interests:**
Dr. Buenz reports personal fees from Terumo BCT, from null, outside the submitted work.

**Author information:**
Gareth Parry, Nelson Marlborough Institute of Technology, New Zealand; Matthew Peacey, Nelson Marlborough Institute of Technology, New Zealand; Eric J Buenz, Nelson Marlborough Institute of Technology, New Zealand.

**Corresponding author:**
Gareth Parry, Nelson Marlborough Institute of Technology, 322 Hardy Street, Nelson.
gareth.parry@nmit.ac.nz

**URL:**
REFERENCES:
9. de Melo Freire CC, Jamarino A, de Lima Neto DF, de Andrade Zanotto PM. Spread of the pandemic Zika virus lineage is associated with NS1 codon usage adaptation in humans. bioRxiv. 2015:032839.


