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Zika virus and Guillain-Barré syndrome: another viral cause to add to the list

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Zika virus was first identified in Africa in 1947, where it continues to cause regular outbreaks in sub-Saharan Africa but with very few clinical cases. In 1966, a distinct Asian lineage was found in Malaysia,[1] but human disease remained uncommon in the Asia–Pacific region, despite serological surveys suggesting widespread occurrence of subclinical infections. The first recognised epidemic happened on the Micronesian island of Yap in 2007. It then spread across the Pacific to Easter Island and in 2015–16, it emerged in South and Central America and the Caribbean.[2] The virus is maintained primarily in a cycle between humans and *Aedes aegypti* mosquitoes.

The symptomatic illness is nearly always a mild, self-limiting illness with fever, rash, joint pain, and conjunctivitis. Normally this would not have attracted the attention of the world in the way that Zika has. Reports linking Zika with microcephaly and fetal deaths in the Americas, and with serious neurological disease, particularly Guillain-Barré syndrome, have led to the WHO declaring the outbreak a global emergency.[3] In *The Lancet*, Van-Mai Cao-Lormeau and colleagues present the first strong evidence that Zika virus can cause Guillain-Barré syndrome.[4]

Guillain-Barré syndrome is a serious immune-mediated illness manifesting as progressive paralysis over 1–3 weeks, with a 5% death rate and up to 20% left with a significant disability.[5] Although it **[A: What are you referring to here? Cases? Reports?]** has been infrequent, several flaviviruses have been found to trigger Guillain-Barré syndrome, including Japanese encephalitis virus, West Nile virus, dengue viruses,[6] and the live-attenuated yellow fever vaccine. So it should not have been a surprise when a tentative Zika-induced case of Guillain-Barré syndrome was reported from French Polynesia in 2013.[7]

This new case-control study[4] is based on 42 notified cases of Guillain-Barré syndrome in French Polynesia during their 2013–14 **[A: Correct change to 2013–14?]** Zika epidemic. Unfortunately, the patients were no longer viraemic at the time of presentation and urine samples, which remain PCR positive for longer,[8] were not available for testing. So the authors faced major challenges in proving recent Zika virus infection in their cases. They relied on serological criteria for diagnosis, a tricky procedure when there is a high background of dengue infection in this population. Flavivirus antibodies are widely cross-reactive across the species, and there are also cross-species immune recall phenomena that can lead to spurious early antibody responses when the person has had another flavivirus infection in the past. In fact, only one of the 42 cases showed the standard criterion of neutralisation titres to Zika virus that are four-fold or higher than the titre to the dengue viruses. Because serum samples were collected weeks after the initial febrile illness, the investigators were unable to test for rising antibody concentrations that might have helped confirm recent Zika infection. The authors instead had to rely on the detection of IgM to Zika in the absence of dengue IgM (to show it was not a cross-reaction; 39 [93%] patients **[A: Data added correct?]**) or the higher rate of Zika neutralising antibodies in patients with Guillain-Barré syndrome compared with the matched non-febrile illness control group (42 [100%] of 42 patients in Guillain-Barré syndrome group *vs* 54 [56%] of 98 in control group] **[A: Data added correct?]**), contrasting with the similar dengue antibody levels across the two groups. However, none of this is perfect, so although it is very likely that these patients had been recently infected with Zika virus, it is possible that the disease, at least in some of them, was due to dengue or might possibly have been unrelated to flavivirus infection.

The cases fitted the acute motor axonal neuropathy (AMAN) phenotype of Guillain-Barré syndrome,[7] which has been postulated to be due to antiglycolipid antibodies.[4] However, the researchers did not find the expected pattern of antibodies, nor did they find evidence for molecular mimicry between Zika virus antigens and the anti-glycolipid antibodies that might induce an autoimmune response. Therefore, they postulate different methods of pathogenesis, including direct viral effects. We clearly need a better understanding of the pathogenesis of this disease.

The study[7] calculated a Guillain-Barré syndrome rate of 0·24 per 1000 Zika virus infections, which could translate into large numbers of cases as the epidemic

continues. Brazil, El Salvador, Columbia, and Venezuela have reported increases in cases of Guillain-Barré syndrome coincident with their Zika virus epidemics, including three PCR-confirmed infections.[9,10] However, it is important that these increases are verified to ensure they are not to the result of enhanced reporting rather than a genuine change.

Because 88% of the cases reported in Cao-Lormeau and colleagues' study reported a preceding clinical illness and because Zika is said to be symptomatic in only 20% of cases based on the Yap outbreak,[11] 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.

Reassuringly, the investigators they did not find any evidence that previous dengue infection enhanced the severity of disease,[7] which could substantially have increased the threat in areas of regular dengue activity. A little caution should be taken because the data are still scarce **[A: Edit to scarce from limited ok?]** and we do not know whether the current **[A: Zika?]** virus is identical to earlier ones **[A: that in previous outbreaks?]**, whether it will behave exactly the same in a different population with a different genetic and immunity background, or whether a cofactor or co-infection is responsible.

Suffice to say Zika virus can be added to our list of viruses that can cause Guillain-Barré syndrome, and investigation **[A: of?]** should include this **[A: Zika?]** if there is a possibility of infection. Whether Zika will be proven to be a bigger Guillain-Barré syndrome threat **[A: Please confirm meaning here]** than its various flavivirus cousins remains to be determined.

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We declare no competing interests.

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