

The prevalence estimates provided by NCD-RisC sound the alarm for large-scale, effective action to reduce the health and economic impact of diabetes. Improvements in prevention and management, together with better surveillance, should be prioritised in response to this call.

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I declare no competing interests.

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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 colleagues⁴ present the first strong evidence that Zika virus can cause Guillain-Barré syndrome.

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% of patients left with a significant disability.⁵ Several other flaviviruses have been found to be rare triggers of 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 study⁴ is based on 42 notified cases of Guillain-Barré syndrome in French Polynesia during their 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 these 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; 31 [74%] of the Guillain-Barré syndrome patients vs 11 [11%] of control patients) 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 the control group), 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 previous study⁷ 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, Colombia, and Venezuela have reported increases in cases of Guillain-Barré syndrome coincident with their Zika virus



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epidemics, including three PCR-confirmed infections.^{9,10} However, it is important that these increases are verified to ensure they are not 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 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 and we do not know whether the current Zika virus is identical to 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 of these cases should include tests for Zika when there is a possibility of infection by that virus. Whether Zika will be proven to pose a greater threat in causing Guillain-Barré syndrome than its various flavivirus cousins remains to be determined.

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Are we ready for immune checkpoint inhibitors for advanced non-small-cell lung cancer?

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Are we ready to embrace the routine use of immune checkpoint inhibitors in patients with advanced stage non-small-cell lung cancer? In *The Lancet*, Roy Herbst and colleagues¹ report the results of KEYNOTE-010, a randomised phase 2/3 study in 202 academic medical centres in 24 countries that compared two doses of pembrolizumab (2 mg/kg and 10 mg/kg) with docetaxel (75 mg/m²) every 3 weeks in 1034 patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer. This biomarker-enriched study had two primary endpoints of overall survival and progression-free survival both in the total population and in the subgroup of patients with tumour proportion score of 50% or more, which is defined as the percentage of tumour cells expressing PD-L1 assessed by immunohistochemistry using antibody 22C3. In the total study population, there was significant improvement in overall survival with pembrolizumab compared with docetaxel for both pembrolizumab 2 mg/kg (n=344; hazard ratio [HR] 0.71, 95% CI 0.58–0.88; p=0.0008) and pembrolizumab 10 mg/kg (n=346; 0.61, 0.49–0.75; p<0.0001). Median progression-free survival was similar in all three groups (3.9 months with pembrolizumab 2 mg/kg, 4.0 months with pembrolizumab 10 mg/kg, and 4.0 months with docetaxel) and difference between both doses of pembrolizumab versus docetaxel did not meet the pre-specified threshold for statistical significance

(2 mg/kg 0.88, 0.74–1.05; p=0.070; 10 mg/kg HR 0.79, 95% CI 0.66–0.94; p=0.004). In patients with at least 50% of tumour cells expressing PD-L1, overall survival was significantly longer with pembrolizumab than with docetaxel (for 2 mg/kg median 14.9 months vs 8.2 months, HR 0.54, 95% CI 0.38–0.77, p=0.0002; and for 10 mg/kg 17.3 months vs 8.2 months, 0.50, 0.36–0.70, p<0.0001). Treatment-related adverse events were similar between the two doses of pembrolizumab but less common than with docetaxel.

The results of KEYNOTE-010 support the recent approval of pembrolizumab for the management of advanced non-small-cell lung cancer.² However, these findings need to be interpreted in light of two other randomised phase 3 studies of immune checkpoint inhibitors comparing second-line nivolumab with docetaxel, namely the CHECKMATE-017 and CHECKMATE-057 (table).^{3,4}

Amid the excitement of immuno-oncology, we must remain rational and address key questions related to the practical application of immune checkpoint inhibitors for advanced stage non-small-cell lung cancer. Namely, should immune checkpoint inhibitors be given as second-line or third-line therapy? Is the biomarker of PD-L1 expression according to tumour proportion score reliable and should all patients be tested before starting treatment? What is the optimum dose of pembrolizumab in advanced stage non-small-cell lung