**Zika virus and neurological disease – approaches to the unknown**

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The early part of the twenty-first century has seen an unparalleled number of emerging infectious disease events - West Nile virus across the Americas, SARS in China and beyond, chikungunya, avian influenza, MERS coronavirus, Ebola; so many in fact that perhaps we should no longer consider them as extraordinary.

The latest in this series is Zika virus (family *Flaviviridae*, genus *Flavivirus*) a mosquito-borne pathogen that was first isolated from a rhesus monkey in the Zika Forest of Uganda, in 1947, and identified in humans in1952. Since then there have been occasional humans cases of Zika reported in Africa and later in SE Asia, characterized by the fever, arthralgia and rash typical of many arthropod-borne viruses (arboviruses) Phylogenetic studies suggest the virus emerged in East Africa in the early part of the 20th century, later spreading to SE Asia (Faye et al 2014). In 2007 there was a small outbreak in Yap, Micronesia, and in 2013 a larger outbreak in French Polynesia, with 28,000 cases recorded in the first four months. Since the first reports of Zika in Brazil in early 2015, its rapid and explosive spread has resulted in an estimated 1.5 million cases with four million predicted across the continent by the end of the year, and the declaration by the World Health Organization of a Public Health Emergency of International Concern.

Many mosquito-borne flaviviruses are zoonotic, for example Japanese encephalitis virus and West Nile virus, being transmitted naturally among animals, with humans coincidentally infected as dead end hosts. In contrast Zika, like the four dengue viruses, is transmitted between humans by mosquitoes. *Aedes aegypti* is the principle vector, though *Aedes albopictus* (the Asian tiger mosquito) which is also found in southern Europe and parts of the United States may play a role too. In Brazil the abundant numbers of *Aedes* mosquitoes and densely crowded populations of immunologically naïve individuals have likely contributed to this unprecedented situation. Why it had not happened earlier, in the 60 years since Zika was first isolated, is unclear. It is probably simply because the virus had not arrived on the continent. Phylogenetic studies suggest the Brazilian strain originated in the Pacific islands,1 and a viremic traveler to an international canoe racing event in 2014**,** which included Pacific nations as participants, is postulated to be the source 2. For chikungunya virus, another arbovirus which has spread globally in recent years, the rapid spread was associated with a critical change on the virus E2 envelope glycoprotein which increased its transmissibility by *Aedes albopictus* mosquitoes enabling it to extend its range.3 Preliminary data for Zika virus suggest South American isolates are virtually identical to strains previously circulating in the Pacific region.

In the Polynesia Zika outbreak of 2013, an apparent increase in the incidence of Gullain-Barré syndrome (GBS) was noted,4 and this also seems to be the case in Brazil, though details are scant. It is important to distinguish this post- or para-infectious syndrome from direct viral invasion of the anterior horn cells in the spinal cord, which causes a poliomyelitis-like flaccid paralysis, that is usually irreversible.5 The number of children reported born with microcephaly has also risen in Brazil, and Zika virus has been detected in amniotic fluid, placental or fetal tissue in babies with nervous system malformations, including those still-born, or with microcephaly.6 Abnormalities seen on computer tomography scans include calcification in the periventricular parenchyma and thalamic areas, and ventriculomegaly, lissencephaly and pachygyria – the smooth brains with reduced gyral ridges suggestive of cell migration abnormalities and first trimester problems. Although strongly suspected, the causal relation between in-utero exposure to Zika and microcephaly is yet to be established.7 Infection in pregnancy may also result in infants born without microcephaly, but with more subtle neurological and developmental abnormalities. The potential for Zika virus transmission in semen, and through blood transfusions is causing additional concern.

Several theories have been put forward to explain these new observations of neurological complications: could they relate to a high background prevalence of antibodies against related flaviviruses, for example, following dengue infection, or yellow fever vaccination – an antibody-dependent enhancement phenomenon similar to that seen in secondary dengue infection? Does the microcephaly relate to toxins or nutritional deficiencies? Are these simply rarer manifestations of the disease, which have now been recognized because there are hundreds of thousands of infections? Zika virus is similar to dengue in that most patients develop a fever rash syndrome, and there are many unrecognized infections. For dengue controversy over apparent neurological manifestations existed for more than eighty years, until a well-designed case-control study carefully excluded other possible explanations of neurological disease, and proved a definitive link;8 a whole range of neurological complications are now recognized.9 Similar rigorous approaches are needed for Zika virus disease, as well as improved diagnostics.

Currently the only intervention available for Zika is mosquito control, which, for Aedes mosquitoes, is notoriously difficult to sustain. The full range of mosquito vectors for Zika is not yet clear. Growing levels of resistance to insecticides is an important issue, and breeding site destruction, and the prevention of bites, may be better ways forward. Unlike Ebola, for which there were vaccines on the shelf awaiting clinical evaluation, for Zika the cupboard is bare – though investigators are working hard to fill it. Understanding the spectrum of neurological disease in Zika is important not just for the individuals affected, but also to support policy decisions. Experience with Japanese encephalitis in Asia has shown that developing a vaccine is not enough: policymakers need to understand the burden of disease to help guide vaccine implementation.10 This will be some years off. For now there is an urgent priority to understand the scale and full spectrum of neurological disease associated with Zika virus infection.

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