

Zika virus, emergencies, uncertainty and vulnerable populations

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The World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC) on 1 February 2016. The press immediately latched onto this declaration as confirmation of the threat from the Zika virus. Interestingly, while the Emergency Committee certainly expressed concern regarding the virus, the emergency itself was declared on a health outcome; increasingly observed microcephaly cases as well as other neurologic disorders in areas currently affected by a Zika virus outbreak. Briefly reviewing this virus' story helps us to appreciate these distinctions and what they portend regarding what is known and not yet known about the Zika virus and these outbreaks, what is important and the ways responders and scientists will try to move forward.

The Zika virus was first described in the 1950s in *Transactions of the Royal Society for Tropical Medicine and Hygiene*. An experienced team of UK and US investigators, who worked on identifying and characterising mosquito-vectored viruses in Africa, identified the virus in Zika, Uganda.^{1,2} Working on six tree platforms in the forest separated from Lake Victoria by swamp, placed there to optimize sylvatic yellow fever virus work, the team took a blood sample from a febrile Rhesus monkey in April 1947. Dick et al. describe rapidly cultivating the virus in mice, how it prospered only after intracerebral inoculation and was a filterable agent. In a month the team demonstrated that it could be neutralised by sera from the monkey that had originally been ill, Rhesus 766. Eight months later, again working on yellow fever virus, the team isolated the Zika virus from a collection of *Aedes africanus* (Theobald) mosquitoes captured from the same platforms. Filtrate from the mosquitoes made another Rhesus monkey febrile and gave mice encephalitis. That monkey's sera could neutralise the filterable agents from when it was sick, the mice and Rhesus 766. The team then challenged the Zika virus against dengue and yellow fever virus immune sera, as well as dengue and yellow fever viruses against Zika

virus immune serum. They did not substantially cross-react. A long list of known viruses was brought through the same drill with similar results.

Many mice paid dearly for the team's burgeoning knowledge of the Zika virus, usually with encephalitis and death, sometimes with other neuropathic effects such as motor limb weakness. When the team attempted to assess how monkeys fare with intracerebral inoculation of the virus, as had been done to the mice, they were faced with protective sera in their captive monkeys. This gave them the idea to assess whether people from the area had protective sera against Zika virus. Taking advantage of a sera repository designed for yellow fever virus work, they found highly protective sera in 20% of samples from Bwamba and nearly 10% of those from the West Nile, though none in Zika or Kampala.

Despite a 69-year awareness of the virus, Zika as a search term yields only just over 300 citations indexed in MEDLINE, several of them recently published. Contrast this with chikungunya virus, also discovered and characterised in this early rise of virology and with some similar holistic features, which has 2,627 indexed publications. Perhaps this is because the Zika virus' clinical appearance has been limited and more mild, and observed because of sporadic human cases in Africa and Asia.³ In 2007, a Micronesian outbreak resulted in an estimated 7 of 10 child and adult residents becoming infected.⁴ Despite this astounding attack rate and mild increase in detection with post-outbreak observation in other areas of Asia, subsequent literature remained relatively sparse. Since its emergence in Brazil in May 2015, it has spread across over 20 countries in the Americas.⁵

The virus' success in the New World is no surprise. Like Africa and Asia, the Americas continue to experience extensive dengue and now chikungunya virus transmission from the same cross-over species of mosquitoes that yellow fever virus exploits in its endemic areas when breaking free of its sylvatic cycle

TABLE 1 Reported clinical characteristics of confirmed Zika virus infections in previous outbreaks

Country	Year	Cases	Description and comment
Nigeria	1952	3	All patients experienced mild to moderate illness with fever – a 30-year-old man with arthralgia and cough though no other pulmonary findings, a 10-year-old girl with headache and a 24-year-old man with arthralgia, headache, retro-orbital pain and loose stools. The clinical course for each spanned weeks. ⁹
Indonesia	1977–78	7	In this study of in-patients with acute fever, 7 patients were shown to have acute and convalescent sera responses to Zika virus near the end of a wet season. In addition to fever, these patients experienced abdominal discomfort, anorexia and 'dizziness' ¹⁰
Yap Island, Federated States of Micronesia	2007	49	There were an additional 59 probable cases reported. 31 of the 49 confirmed cases were clinically characterised: rash (28), fever (20), arthralgia (20), conjunctivitis (17, non-purulent), myalgia (15), headache (14), retro-orbital pain (12), oedema (6), vomiting (3). A linked retrospective household and entomologic survey estimated that nearly 3 in 4 residents were infected, 900+ of those (approximately 1 in 4–5) had a consistent clinical illness. ⁴
French Polynesia	2013–14	8,723	Among more than 8,000 reported confirmed and suspected patients meeting a case definition of rash or fever with two additional symptoms (conjunctivitis, arthralgia or myalgia, oedema), with an estimated case burden exceeding 30,000 patients, authorities reported a total of 73 patients with neurologic and auto-immune complications. This included Guillain-Barré Syndrome (43), meningo-encephalitis (15), other neurologic complications such as paraesthesia, facial paralysis, and myelitis (23), immune-associated thrombocytopenia (8), ophthalmologic disorders (2) and at least one cardiac complication. ^{12,13}
Thailand	2012–14	7	Clinical information was available for 5 of the patients captured in this national, serology-based case finding activity; 4 women and 1 man ranging from 12–39 years old, their signs and symptoms included fever (5), rash (5), arthralgia (2), conjunctivitis (2), sore throat (2), headache (1), myalgia (1), rhinorrhoea (1). All of the patients had mild clinical courses. ⁷
Brazil (Bahia)	2015	7	Researchers validated the diagnosis of a small cluster of cases from a single hospital. Among 6 women and 1 man, they experienced fever (3), rash (6), myalgia (4), headache (3). While they did not list arthralgia or conjunctivitis among these confirmed cases, the authors said that the outbreak triggering this work was one of 'an illness characterised by maculopapular rash, fever, myalgia/arthralgia, and conjunctivitis'. ⁸
Brazil (Natal)	2015	8	Among 8 confirmed patients in the northeast of Brazil, 7 were women. Ranging in age from 18–65, these patients demonstrated fever (6), rash (8), small and medium joint arthralgia (7, 6 with arthritis), myalgia (6), retro-orbital pain (4), lymphadenopathy (3), leukopaenia (2). Fever lasted up to 8 days and joint pain generally less than 2 weeks. 5 of the 6 patients assessed on a pain scale of 10 scored 7 or higher. ¹¹

into encroaching human populations. The Zika virus is a member of the Flavivirus genus, and yet within that genus has a very interesting phylogeny. In a recent, ambitiously broad genomic characterisation of Flaviviruses in the context of their mosquito vectors, assessed Zika virus strains clustered closest to the predominantly *Culex* carried members of the genus.⁶ These include some of the family most notoriously known for neurotropism such as Japanese encephalitis, St Louis encephalitis and West Nile viruses; insofar as any Flavivirus is much like another in this very diverse viral genus. After the *Culex* favouring group, the Zika virus was next closest to the dengue viruses, also carried by *Aedes* mosquitoes. The diversity of vector, carrier and amplifying species that contribute to a Zika virus outbreak is not yet known. Several Flaviviruses in both *Culex* and *Aedes* mosquitoes are passed to progeny through transovarial transmission, infecting

new generations of mosquitoes in between the amplifying events of human outbreaks. Consequently, the Zika virus, even in the setting of improved control, is unlikely to leave us soon. It is worth exploring the virus' impact in humans further.

Zika virus infection seems to have a high asymptomatic or sub-clinical rate. When ill patients present, they seem to do so with an influenza-like illness, frequently with rash, which could be easily confused in care settings for dengue or chikungunya viruses, early leptospirosis, scrub typhus or others. Patients often have fever, as well as variable combinations of other symptoms such as rash, arthralgia, myalgia, conjunctivitis, headache, retro-orbital pain and abdominal complaints.^{4,7,8–11} Table 1 describes the clinical manifestations reported from previous outbreaks. Neurologic sequelae, including Guillain-Barré syndrome, were observed in the large French Polynesia

outbreak in 2013 and early 2014, at a rate among presented cases of approximately 1%.¹²⁻¹⁵

The burgeoning story of microcephaly associated with the Zika virus outbreaks is even less clear than that of the primary clinical syndromes. According to a Pan American Health Organization report, by October 2015 Brazil had reported 141 cases of microcephaly against a usually observed case count of 10 in the context of its Zika virus epidemic.¹⁶ By November, the total microcephaly count climbed under proactive identification to over 1,200 cases.¹⁷ Also in November, French Polynesia authorities reported that 17 fetal malformations may have occurred in connection with its 2014 Zika virus infection epidemic, 12 cerebral malformations and five with brainstem dysfunction.¹⁸ Four of these 17 mothers were assessed for non-specific Flavivirus exposure and were positive, though none reported a consistent clinical illness.

Zika virus seems adept at getting into a multitude of human tissues. It has been identified in blood banked specimens from asymptomatic patients, saliva of ill patients and semen in the setting of haematospermia.¹⁹⁻²¹

The idea, then, that it may cross the placenta is plausible. A recently published report from an imported case in Slovenia demonstrated the virus in the brain of a deceased foetus with microcephaly.²² Additionally, perinatal assessment of the amniotic fluid of two fetuses diagnosed with microcephaly by ultrasound in Brazil also has demonstrated the Zika virus.²³ Reports of human trans-placental infection by Flaviviruses are sparse but show the potential. Isolated examples of fetal impact have been demonstrated for West Nile virus and, more recently, dengue virus infections.²⁴⁻²⁷ Neurotropism by Flaviviruses is also a known phenomenon. Table 2 provides examples of various Flavivirus associations with neurologic disease. Even among the known encephalitic viruses, host factors may play a role in whether neuropathic illness develops from a Flavivirus as well as its severity. These have included polymorphisms in CCR5, interferon pathways and toll-like receptor 3 pathways.²⁸ Whether the virus might be associated with non-neurologic developmental abnormalities has not yet been fully explored.

The Zika virus infection as both a perinatal infection risk and potential neurologic hazard is plausible. However, acknowledging plausibility and declaring causality across a population are very different acts. From the publically reported data, assessing the overall severity of the microcephaly is a challenge let alone ascribing the presence of the Zika virus in more than the occasional case. There are myriad infectious and non-infectious causes of microcephaly. Even if each of the cases had the presence of the Zika virus, the possibilities that the virus may be a bystander, enabler for other causations either from stress, co-infection, toxicities, or even whether the

TABLE 2 Examples of Flaviviruses that have been associated with neurologic syndromes

Encephalitis	Meningitis	Guillain-Barré Syndrome, other neuropathy or non-central myelitis
Dengue [‡] Ilhéus Japanese encephalitis Murray Valley encephalitis Negishi Rocio encephalitis SPH 16111-related St. Louis encephalitis Tick-borne encephalitis Usutu Wesselsbron [‡] West Nile Yellow Fever [‡] Zika [‡]	Dengue [‡] Modoc Rio Bravo Tick-borne encephalitis Zika [‡]	Dengue [‡] Tick-borne encephalitis [‡] West Nile Zika [‡]

*a relatively infrequent clinical manifestation

‡ principal vector for human disease is an Aedes mosquito

mother's immune response to Zika virus plays a role in pathogenesis all exist.

Another confounder to understanding is the ever present threat of observation bias. How well reported is microcephaly in other circumstances in these locations? Those data are not evident, though Brazilian researchers are taking measures to improve these observations as well as their understanding of what they might mean.^{29,30}

Nonetheless, this PHEIC declaration is very appropriate. This rests with the purpose that determining a PHEIC serves WHO and the global health community. A PHEIC focuses minds and attention on the threat, in this instance not Zika virus per se, but the health, wellness and prospects of vulnerable populations; in this case women and children in poverty. Reported microcephaly and other neurologic manifestations should be investigated and characterised. Those affected and their communities should be assessed broadly for their health and social risks. Contributing factors, infectious and non-infectious, nutritional and environmental, should be addressed to mitigate consequences and enhance development. The explosion and pervasiveness of the Zika virus in these newly affected areas should draw attention and efforts to known and novel approaches to targeted mosquito control. These steps are important not only for the Zika virus but the continued broad challenges that

dengue, chikungunya and, in some areas, interceding epidemics of yellow fever virus pose from these same collections of vulnerabilities and risks.

We should take note of the Zika virus and learn and act, but focus on the basic lessons to be learned, applicable to the slate of related risks, and intervene holistically in those communities that remain vulnerable and affected by all of them.

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