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Review Paper

The rise of Zika infection and microcephaly: what can we learn from a public health emergency?

B. McCloskey [a,*], T. Endericks [b]

[a] Global Public Health, Public Health England, UK
[b] WHO Collaborating Centre on Mass Gatherings and Global Health Security, Global Public Health, Public Health England, UK

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ABSTRACT

Objectives: To consider why Zika was declared a Public Health Emergency of International Concern (PHEIC), why it stopped being one and what we can learn from this for the future.
Study design: This paper reviews the sequence of events and evidence base for the decision to declare Zika a PHEIC, the global response to this, the challenges in maintaining an evidence-based approach to outbreak response and identifies learning outcomes.
Methods: Evidence review, all published articles in reputable UK and international journals were identified.
Results: The association between Zika virus infection and congenital malformations including microcephaly became a PHEIC on 1st February 2016 and was declared to be no longer an emergency in November 2016. This shaped the global response led by WHO in the first global emergency since Ebola in West Africa.
Conclusion: The response to Zika highlights important issues and lessons for future outbreaks that might pose an international risk. Particular challenges arose in trying to maintain an evidence-based approach to public risk communication when the evidence is unclear or still evolving. The Zika incident also demonstrates the importance of public health practitioners and agencies understanding the political context in which outbreaks must be managed and understanding the competing factors that shape the political response.

Introduction

On 18 November 2016, the 5th Emergency Committee on Zika infection and microcephaly recommended that Zika no longer met the criteria of a Public Health Emergency of International Concern (PHEIC).[1] This recommendation was accepted by Margaret Chan, Director General of WHO and the PHEIC was formally ended. The association of Zika infection with clusters of microcephaly and other neurological disorders was originally declared a PHEIC on 1 February 2016, so was in place for just over 9 months.

* *Corresponding author.*
E-mail address: Brian.McCloskey@phe.gov.uk (B. McCloskey).
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It is instructive to look at why Zika became a PHEIC, why it stopped being one and what we need to learn for the future.

Epidemiology and history of Zika virus infection

Zika was first identified, in a rhesus monkey, in the Zika forest of Uganda in 1947.[2] The following year, the virus was recovered from an *Aedes africanus* mosquito caught in the Zika forest[2] and in 1952 the first human cases of Zika were detected in Uganda and Tanzania.[3] A researcher in Uganda was infected with Zika while working on the virus in 1964 confirming that Zika virus causes human disease.[4] From the 1960s through to the 1980s Zika human infection was confirmed through blood tests; cases were generally mild and no deaths or hospitalisations were reported, but studies consistently showed widespread human exposure to the virus. The virus was also then seen across West Africa and into Asia.[5,6] However, because Zika causes a mild illness with clinical similarities to dengue and many other tropical infectious diseases seen in the region, it was almost certainly mis-diagnosed and under-reported. The first large human outbreak was in the Pacific island of Yap in Micronesia in 2007.[7]

Following this, between 2012 and 2014, the pattern of mosquito borne diseases in the Pacific islands changed with first an increase in dengue infections (and increased diversity of serotypes) and then increases in chikungunya and Zika.[8] Zika outbreaks were documented in French Polynesia, New Caledonia, Cook Island and Easter Island. Between November 2013 and February 2014, increased incidence of neurological complications, including 42 cases of Guillain-Barré syndrome, was a unique and worrying feature of the French Polynesia outbreak.[8] In March 2014 French Polynesia also showed evidence of transplacental transmission of Zika infection for the first time.[9]

It seems likely that Zika had arrived in Brazil by early 2015 with an outbreak of an unusual, but mild, illness in February to April. Zika was not suspected (as it had not previously been known in South America) and was not initially tested for. Phylogenetic analysis of virus from seven early Zika patients has subsequently indicated that Zika may have been imported to Brazil between March and December 2013.[10] However, in May 2015, Brazil confirmed the presence of circulating Zika virus and the Pan American Health Organization (PAHO—WHO's regional office for the Americas) recommended that countries in the Americas where the natural vector—*Aedes aegypti*—was present should develop and maintain surveillance systems for Zika and the capacity to diagnose it.[11] Shortly after this, Brazil reported neurological disorders including Guillain-Barré syndrome apparently linked to Zika infection. Increasing numbers of cases led WHO to state: 'Given the worldwide spread of chikungunya and dengue, associated with urbanisation and globalisation, there is a potential risk of outbreaks of urban Zika virus infection in urban settings in any part of the world where the mosquito vector is present or may become established in future'.[12] Through 2016, numbers of suspected and confirmed cases of Zika infection rose steadily to a peak of ~18,000 cases per week before declining to the current (December 2016) weekly average of ~270 cases per week.

In October 2015, Brazil reported an increase in notifications of microcephaly in newborn babies and this escalated so rapidly that on 11 November 2015 microcephaly was declared a national public health emergency in Brazil. The rise in microcephaly was temporally and spatially linked to the rise in Zika infection, and in late November Brazilian authorities confirmed the presence of Zika virus first in amniotic fluid from 2 pregnant women whose foetuses had microcephaly and then in tissue samples from a child who had died from microcephaly. This led to WHO/PAHO issuing an alert on the association of Zika virus infection with neurological syndrome and congenital malformations in the Americas on 1 December 2015.

Over the following months, the evidence of an association between Zika infection and microcephaly grew. In January 2016, evidence of transplacental transmission was discovered in Brazil,[13] and on 1 February 2016, WHO declared that: 'the recent association of Zika infection with clusters of microcephaly and other neurological disorders constitutes a Public Health Emergency of International Concern'. Following an extensive programme of research and a review of the literature, on 1st September, WHO confirmed its view that Zika virus infection during pregnancy was the cause of microcephaly (and other congenital abnormalities) rather than just associated.

According to the most recent situation report from WHO (10 March 2017[14]), 84 countries, territories or subnational areas have evidence of vector-borne Zika virus (ZIKV) transmission, with sixty-one areas globally having ongoing transmission following new introduction reported from 2015 onwards or with reintroduction in an area where transmission has previously been interrupted. In addition, 13 countries have reported evidence of person-to-person transmission of Zika virus and 31 countries or territories have reported microcephaly and other central nervous system malformations potentially associated with Zika virus infection, or suggestive of congenital infection.

PHEIC declaration—February 2016

In February 2016, in response to rising international concerns about Zika infections in South America, especially in Brazil, and to the postulated link to rising numbers of babies born with the congenital abnormality known as microcephaly, WHO declared the situation to be a PHEIC.

It is important to recognise that the original PHEIC declaration was based on the increase in microcephaly notifications in Brazil, documented in late 2015 and early 2016, and the possibility of this being linked to Zika infection in pregnancy, not on the escalating Zika outbreak per se. Zika as a clinical infection would be unlikely to qualify as a PHEIC given that the infection is usually asymptomatic or mild.

Although Zika virus had been known since 1947, and known to cause human illness since 1952, there had been relatively few human cases and no real documented outbreaks until 2007. Between 2007 and 2015, although Zika outbreaks in Micronesia had been investigated, no link to congenital malformations had been identified.