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Review Paper

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

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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.

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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.

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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 forest² 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 2017¹⁴), 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.

This distinction is significant because it meant that the purpose of the PHEIC declaration was to stimulate global action to define the nature of the relationship as well as to identify appropriate public health actions to mitigate the risk, particularly for pregnant women. The PHEIC was not primarily declared to stop the spread of the outbreak although elements of outbreak control were included. By contrast, the Ebola PHEIC declaration was primarily to mobilise resources to stop the epidemic.

Thus the response to the PHEIC for Zika was different to that for Ebola and the criteria for ending the PHEIC were different.

Global response to Zika

Research was always going to be a priority for a decades old disease that seemed to be taking on a new and more threatening role. WHO had been developing a global approach to research and development in outbreaks and emergencies as part of its learning from the Ebola experience.^{15,16} This 'Blueprint' was a foundation for developing an R&D strategy for Zika in response to the PHEIC declaration and produced a first summary of priorities by March.¹⁷ Initial priorities identified included: multiplex tests for flaviviruses, in addition to more traditional tests; protective vaccines based on killed virus (or other non-live) preparations for women of childbearing age and innovative vector-control tools that reduce the mosquito population. As a further extension of learning from Ebola, the UN established a Zika Multi-Partner Trust Fund to help secure funds to support the R&D efforts.¹⁸ In response to the recognised difficulties in diagnostic testing for Zika,¹⁹ WHO issued a Target Product Profile in April to support and direct research efforts to develop better tests.²⁰

The international reaction to the Zika PHEIC declaration was also different to the reaction to the Ebola PHEIC. During the Ebola epidemic, especially after the PHEIC declaration, many countries offered support to WHO and West Africa to help stop the outbreak and eventually to get down to zero cases. However, a number of countries introduced public health measures including restrictions on travel and trade that went beyond WHO recommendations and that were not justified, as noted by the International Health Regulations (IHR) Review Committee on the role of the IHRs in the Ebola outbreak.²¹ In Zika, there was less obvious adverse impact on travel and trade and less evidence of countries instigating measures beyond those recommended by WHO as public health agencies and governments developed advice to their population, in particular the at risk groups, about travel to Zika-affected countries.

Key issues from the Zika response

The Zika outbreak, and the global response to it, has highlighted some significant issues for future outbreak planning:

- > the challenges in maintaining an evidence-based approach to public advice;
- > infections that have a significant impact on pregnancy;

- > sexual transmission of infections;
- > and managing infections that become endemic.

Evidence-based advice

WHO/PAHO, working with health authorities in affected countries and with global response partners, developed a Zika Strategic Response Plan with a focus on evidence-based advice to guide the response, and WHO has published the first quarterly update of the impact of the plan.²²

Despite the focus on evidence, the response to Zika highlighted differences in approaches between countries and public health agencies and the challenges of maintaining a 'pure' public health approach to advice. An example was the scientific debate about vector control measures, especially the value, or otherwise, of disinsection of planes travelling from Zika-affected countries. Although disinsection of planes is routinely practised in many countries as part of a malaria control strategy, the Zika response illustrated that the evidence base for this approach is not robust and there were differences of view among public health agencies about the likely effectiveness of this measure leading to different national government interpretations of appropriate control measures.^{23,24}

There were also challenges in developing advice on travel for pregnant women where, in the face of uncertain evidence on the risk, national governments tended to follow a zero risk approach with very precautionary advice. This was later reflected in advice on sexual transmission of Zika infection as this evidence evolved.

One especially significant area where the evidence-based approach was challenged arose from the hosting of the Olympic and Paralympic Games in Rio de Janeiro during the PHEIC.

Zika, the PHEIC and the 2016 Olympic and Paralympic Games

As the Zika outbreak in Brazil was spreading dramatically in 2016, concerns were raised about the impact of Zika on the Olympic and Paralympic Games to be held in Rio de Janeiro in August and September 2016 and on the impact of the games on global spread of Zika.

The games in Rio were the first Olympiad to be held in the context of a PHEIC specifically affecting the host country. Although spread of infectious diseases is a key planning consideration for any mass gathering, in reality there is little evidence of significant global spread related to Olympic and Paralympic Games.²⁵

However, the prospect of large-scale international travel to and from Brazil in the context of the games raised questions about the risk of augmenting global spread of Zika. Ultimately a flawed analysis of this risk led to calls for cancellation of the Rio Games.^{26,27}

The real risk of spread of Zika caused by the games needs to be considered in the context of three factors. First, the

games were scheduled for August and September which is the low season for mosquito activity in Rio when historical data shows that the incidence of dengue fever, an illness caused by a similar virus carried by the same mosquito vector as Zika, falls considerably and the same reduction could reasonably be anticipated for Zika. Second, enhanced active vector control plans were in place in Rio and were to be continued throughout the games period. Third, the additional volume of travellers associated with the games, although important, was not significant against the background level of trade and tourist travel to Rio. Indeed, Rio had already hosted the annual Rio Carnival, with larger numbers of visitors than were anticipated for the Olympics and Paralympics and at a high point in the Zika epidemic and peak mosquito season, without any evidence of generating global spread of Zika.

Analysis by WHO²⁸ and the US Centers for Disease Control (CDC)²⁹ suggested that the additional impact of the games on Zika spread would not be significant.

In the event, the robust evidence-based response by WHO proved to be the right advice and the games went ahead with no known discernible impact on Zika spread in Brazil or globally. This reaffirms the need for infectious disease planning as a key part of planning for mass gatherings.³⁰

Pregnancy and emerging infections

In the years since Severe Acute Respiratory Syndrome (SARS), a number of attempts have been made to predict or anticipate what will cause significant global outbreaks in the future and to preplan for the response and research challenges associated with them. None of these included infections that might have an impact on pregnancies and fetuses. The link between Zika infection and microcephaly therefore came as a surprise and the appropriate planning had not been considered, either in respect of the response or the research that became necessary. In the absence of a vaccine, public health agencies, national governments and clinicians had little to offer women of child bearing age apart from advice on avoiding mosquito bites, delaying pregnancy or avoiding travel to areas with active Zika transmission. In regions with limited access to contraception and family planning services, this advice was not always practical. In areas without access to, or acceptance of, termination of pregnancy services, there was even less for clinicians to offer pregnant women who were identified as at risk.

Although prior consideration of the possibility of an emerging infection might not have increased the options available to clinicians and governments, it could have facilitated the development of better risk communication strategies.

Sexual transmission

A significant concern that emerged in the Zika response was the evolution of evidence of sexual transmission of Zika infection. The fact that Zika could be sexually transmitted was recognised in 2011³¹ but it was following the outbreak in Brazil that this started to gain greater significance; persistence of

Zika virus RNA in semen was documented in a patient from the outbreak in French Polynesia³² and evidence of sexual transmission began to accumulate.^{33–35} WHO, public health agencies and national governments began to develop advice on sexual transmission alongside their travel advice. This proved a substantial challenge to the agencies and governments involved as the evidence evolved quickly and it was not always easy to interpret the real significance of new findings.

A similar situation arose with Ebola as evidence accumulated about persistence of Ebola virus in semen. It would seem reasonable to consider that sexual transmission could be possible in any new emerging disease and plan for this from the early stages, including developing advice for the public if sexual transmission becomes a possibility.

Current testing strategies for outbreaks may reduce the likelihood of demonstrating the possibility of sexual transmission early as they tend to focus on Polymerase Chain Reaction (PCR) testing of blood samples and often do not include testing of other bodily fluids such as urine and semen.

The future

The current position with Zika is that it is, or is becoming, endemic and seasonal in a range of countries around the world where the appropriate vector exists. It seems likely that, as predicted by WHO in 2015, there will be outbreaks in any country where the vector exists. Genetic sequencing of Zika virus identified in Southeast Asia outbreaks suggests it has been endemic in those countries for many years, but undetected.³⁶ Indeed it is probable that Zika already exists in other countries where it has not yet been detected due to a combination of the mild illness and an absence of Zika testing.

It is this evolution in our understanding that has changed the nature of the perceived risk and prompted the ending of the PHEIC declaration.

The ending of the PHEIC does not mean that Zika has gone away or that it is no longer a significant public health challenge. The fifth meeting of the Emergency Committee on Microcephaly and Zika infection recognised that ‘Zika virus and associated consequences remain a significant enduring public health challenge requiring intense action’ but also concluded that it ‘no longer represents a PHEIC as defined under the IHR’. Zika is now a long-term public health issue rather than an emergency and the Emergency Committee recommended that: ‘this should be escalated into a sustained programme of work with dedicated resources to address the long-term nature of the disease and its associated consequences’. In many ways, the Zika story is analogous to a previous generation recognising the transition from an AIDS outbreak to an HIV global public health challenge.

The most significant outstanding needs are in relation to understanding the pregnancy risk and developing an effective strategy to manage those risks and the associated ongoing risk communication to the public.

In countries where Zika is, or is becoming, endemic, vaccine availability is a priority, but vaccination in pregnancy, or in the population most likely to become pregnant, against a disease that apart from the impact on fetuses is clinically mild, is not without its own risks and challenges. Therefore,

the population must also learn to recognise the risks and learn how to reduce those risks by understanding the disease and its seasonality and to avoid high-risk contacts (in a way similar to reducing the risks from Rubella in pregnancy before vaccination became widely available). This will need an effective, coordinated, approach to risk communication from WHO and national public health agencies.

The world also needs effective, workable and travel advice. Much effort went into developing travel advice for those who might need, or want, to visit affected countries during the first year of the outbreak in South America. While that advice is still mostly valid and appropriate in public health terms, applying that advice to a much wider range of countries across the globe, and over a prolonged time period (probably indefinitely), is much more problematic. Travellers have, for the most part, learnt to live with the risks of malaria in different forms in different countries and to adopt appropriate preventative measures based on an assessment of the risk. It seems likely that a similar approach will be needed for Zika in the future—recognise that the risk exists in many countries and to make choices based on understanding the risk and the options to mitigate them.

The Zika story also highlights the recurring fragility of global public health systems that often depend on a continuing threat to sustain funding and capacity. Cuba, Panama and Brazil had very effective mosquito control programmes in the first half of the 20th century that all but eliminated yellow fever,³⁷ but when yellow fever stopped being an immediate problem the funding for the vector control started to disappear. Eventually the mosquitoes returned, followed first by yellow fever, then by dengue, then chikungunya and finally (for now) Zika. Global recognition of the importance of sustainable vector global control programmes must remain a priority beyond Zika and we need to maintain a focus on prevention of outbreaks alongside a reliance on improved surveillance systems and preparing for the response.

Summary

Zika represented another international challenge for WHO and the global community; but one that was different in nature to Ebola and required a different response. Whereas the intention with Ebola was to stop the outbreak (and get to 'zero'), with Zika there has always been a recognition that the disease was likely to become endemic in many countries and the challenge was to understand the risks, particularly for pregnancy and fetuses, and to find ways to mitigate that risk.

This required WHO to mobilise support in a different way to that learnt from the Ebola outbreak, with more emphasis on research and development and less on outbreak response, although that was also necessary. The WHO R&D Blueprint showed it has the potential to deliver effective R&D response to outbreaks but it also highlighted the need for more, and more effective, coordination and for more global support—including rapid access to financial support from major agencies and donors.

The Zika outbreak has also demonstrated again the challenges in maintaining a clear evidence-based approach to

outbreak response, especially when it comes to advice to the public from national governments. By its nature, the evidence is not always clear in the early stages of an outbreak and often cannot answer the questions that national leaders and politicians want answered. It would also be naive to think that public health advice is the only factor considered by national governments in formulating advice to their populations—there will always be a range of factors to be considered and these will lead to different governments taking different views of the same evidence. The default approach from politicians is, understandably, always likely to be precautionary with a low tolerance for risk. Public health organisations need to learn to work with governments and politicians, to understand the factors that they need to consider, and to work within that to develop advice that best meets the needs of the situation. The challenge is to ensure that advice is not contrary to the evidence, and should be led by WHO, and that nothing is done that might harm the public's health.

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