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Zika virus: A newly emergent vector-borne public health threat in the Americas

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Abstract

Zika virus is a newly emergent mosquito-borne flavivirus. Once almost ignored epidemiologically, recent major outbreaks and links to neurological birth defects have focused attention on this neglected pathogen. We review the discovery, biology and symptomatology of Zika virus, what is known and not known about the mosquitoes that transmit the virus, conspiracy theories currently hampering control efforts, and potential avenues of Zika control. It is likely that Zika virus is here to stay in the Americas, so a thorough understanding of the complete epidemiological transmission cycle and potential effects on the human population will be critical for managing this new disease in the coming years.

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What is Zika virus? Zika virus is a mosquito-borne flavivirus first isolated in the Zika forest of what is now Uganda in 1947 [ATCC product sheet VR-84; http://www.atcc.org/products/all/VR-84.aspx]. The main vertebrate hosts for Zika virus are humans, and to a lesser extent non-human primates [McCrae and Kirya, 1982]. In addition to transmission through the bite of an infected mosquito, Zika virus has other possible modes of transmission including mother to child, sexual and blood transfusion [Foy et al., 2011, Musso et al., 2015]. For many decades, Zika virus was of no major epidemiological concern, causing occasional small outbreaks in Africa and Southeast Asia with only a handful of human cases recorded. This changed in 2007, when the first outbreak outside of Africa or Asia occurred on the island of Yap in Micronesia. The Yap outbreak ended with approximately 100-200 confirmed or suspected cases, and resulted in no hospitalizations or deaths [Duffy et al., 2009]. Zika virus is no longer a mild infection limited to Africa and Asia; autochthonous Zika transmission has been documented in Brazil since May 2015, in other countries in central and south America, and multiple imported cases in the United States [Hennessey et al., 2016] (Figure 1). The World Health Organization (WHO) has declared Zika a global emergency and is estimating approximately 3-4 million cases by the end of 2016 [Gulland, 2016].

Symptoms: Symptoms of classical Zika virus infection are generally mild and self-limiting, and include a characteristic rash, fever, pain and headache, and are similar to those caused by other co-circulating vector-borne pathogens such as dengue and Chikungunya viruses, likely contributing to under-diagnosis in endemic areas. Usually, symptoms resolve in about a week without medical treatment [Hayes, 2009]. However, more recently Zika infection has been associated with the occurrence of severe symptoms such as Guillain-Barré syndrome (an auto-immune disorder triggered by an infection that leads to muscle weakness, paralysis and potentially death if breathing is sufficiently impaired [Oehler et al., 2009]). In the recent Brazilian outbreak, epidemiologists have observed a strong correlation between Zika virus infection in pregnant women and the development of microcephaly, as well as miscarriage and other birth defects in their newborns [Schuler-Faccini et al., 2016]. The US Centers for

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Disease Control (CDC) has recommended that pregnant women avoid travelling to Zika-affected regions, and El Salvador has made the recommendation that women avoid getting pregnant until 2018. The link between Zika virus and microcephaly is not fully resolved at this point, as it had never been observed in other outbreaks prior to Brazil. However, this may be explained by the magnitude of the Brazilian outbreak, coupled with the complete lack of herd immunity in the human population.

Mosquito vectors: Similar to dengue and Chikungunya viruses, the mosquito *Aedes aegypti* is thought to be the primary vector for Zika virus. *Aedes albopictus* (the Asian tiger mosquito) has also been demonstrated to be a highly competent vector in laboratory studies [Wong et al. 2013]. However, there has been a surprising lack of experimental study into the range of mosquitoes that can potentially become infected with and transmit Zika virus. In surveys, Zika virus has been detected in over 25 species of mosquitoes from 5 genera [Diallo et al., 2014, Ledermann et al., 2014, Marcondes et al., 2015] (Table 1). Even more troubling, there are news reports from Brazil that Zika virus has been detected in *Culex quinquefasciatus*, which is widespread and has the potential to act as a major bridging vector into the urban environment. Although merely detecting virus in a mosquito is not proof of transmission, these studies emphasize our lack of knowledge about the transmission biology of this emergent pathogen. Some identified vector species (*Aedes albopictus* and *Aedes aegypti*) are present in the United States, opening the possibility of outbreaks and even local transmission in parts of the USA. If some native mosquito species are competent to transmit Zika, the virus could potentially move into the USA beyond areas currently colonized by *aegypti* and *albopictus*, similar to what was observed with the invasion of West Nile virus in the early 2000's [Venkatesan and Rasgon, 2010].

Control: While the Brazilian Zika outbreak has stimulated research into the development of a vaccine, it will likely be several years before a vaccine becomes available (if at all). At the moment, the only way to control Zika virus is to control the

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mosquitoes that transmit it. There are already significant *Aedes aegypti* control efforts ongoing (based primarily on insecticides) in Zika-affected areas to suppress dengue virus transmission, and due to similar epidemiology these efforts will likely have an affect on Zika virus. However, novel vector control strategies based on mosquito genetic modification and heritable bacterial symbionts are taking center-stage in Brazil. The British/American Company Oxitec has been releasing genetically modified sterile *Aedes aegypti* mosquitoes in Brazil for several years [Carvalho et al. 2015]. These releases suppress the mosquito populations, reducing their ability to sustain dengue virus transmission. Oxitec is now preparing releases for Zika control, and all indications are that properly conducted releases will reduce Zika virus transmission in a similar manner to what has been observed for dengue virus. An alternative strategy relies on the bacterial endosymbiont *Wolbachia*. When mosquitoes are artificially infected with *Wolbachia*, they often become resistant to infection and transmission of pathogens [Moreira et al. 2009, Hughes et al., 2011]. The EliminateDengue program has initiated field releases of *Wolbachia*-infected *Aedes aegypti* for dengue virus control in 5 countries, including Brazil (Eliminatedengue.org). While the effects of *Wolbachia* on mosquito pathogen transmission can be variable [Dodson et al., 2014, Hughes et al., 2014], the strain being released in Brazil to block dengue virus transmission seems to block Zika virus to a similar extent (S. O'Neill, personal communication).

Conspiracy theories: With the public panicking about the speed and magnitude of the current multi-country Zika outbreak, conspiracy theories about the "real" cause of Zika emergence and microcephaly have become widely disseminated. There are two major conspiracy theories. The first is that release of genetically modified mosquitoes has resulted in the emergence of a highly virulent Zika virus strain or was the cause of microcephaly. This theory originated on an Internet message board specializing in conspiracy theories, and was further developed by an article in the online publication "The Ecologist", which proposed that the piggyBac transposon used to genetically modify the mosquitoes was transferred into the Zika virus genome, which was then transferred to the developing fetal brain during gestation. This theory ignores the fact

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that piggyBac is a DNA transposon (which can only transpose into DNA) while Zika has an RNA genome, as well as the fact that the size of the transposon construct was a significant fraction of the size of the Zika genome. In addition, the genetically modified mosquitoes were not released in the same area of the initial Zika outbreak, but rather in a different city of the same name.

The second conspiracy theory is that treatment of drinking water with the insect juvenile hormone analogue pyriproxyfen is the true cause of microcephaly. This theory was put forth by an Argentinian group calling themselves “Physicians in Crop Sprayed Towns”, which seems to be an environmentalist group opposed to pesticide usage. There is no plausible rational for this theory. Pyriproxyfen is an analogue of insect juvenile hormone and has been widely used across the globe for over 20 years. It is poorly absorbed by vertebrates, and what is quickly degraded. At exposure levels from treated drinking water, a person would have to consume hundreds of gallons per day to even approach toxic levels (which are > 1g/kg body weight in lab studies) [WHO, 2006]. Despite this, some states in Brazil have suspended water treatment with this insecticide, which will undoubtedly result in the outbreak getting worse.

Conclusion: The speed and extent of the Zika outbreak has taken scientists, public health officials and medical practitioners by surprise. The upcoming summer Olympics and the carnival in Brazil could greatly exacerbate the epidemic by allowing Zika to move broadly across the globe. Controlling this emergent pathogen will rely on a rapid public health response in affected countries, as well as proactive preparation in countries likely to see virus introductions. With a vaccine several years off (at best), vector control remains the only way to control the virus. Research risk assessment priorities should focus on defining the mosquito vector range both in areas currently experiencing outbreak and in areas where the virus is likely to be introduced, and the refinement of strategies (both traditional and novel) to suppress or control the mosquito vectors. Epidemiological research needs to confirm or refute the link between Zika virus infection and birth defects, and if confirmed, family planning recommendations for those in affected areas need to be addressed. Conspiracy theories that ultimately hamper

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control efforts need to be addressed through education campaigns. Ultimately, it is likely that Zika virus is here to stay in the Americas, so a thorough understanding of the complete epidemiological transmission cycle and potential effects on the human population will be critical for managing this new disease in the coming years.

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Table 1. Mosquito taxa from which Zika virus has been isolated.

Genus	species
Aedes	*aegypti*
	africanus
	albopictus
	apicoargenteus
	dalzielii
	fowleri
	furcifer
	grahami
	hensilli
	hirsutus
	jamoti
	luteocephalus
	metallicus
	minutus
	neoafricanus
	opok
	taylori
	unilineatus
	vittatus
Anopheles	*coustani*
	gambiae
Culex	*perfuscus*
	*quinquefasciatus**
Eretmapodites	*inornatus*
	quinquevittatus
Mansonia	*uniformis*

* suspected

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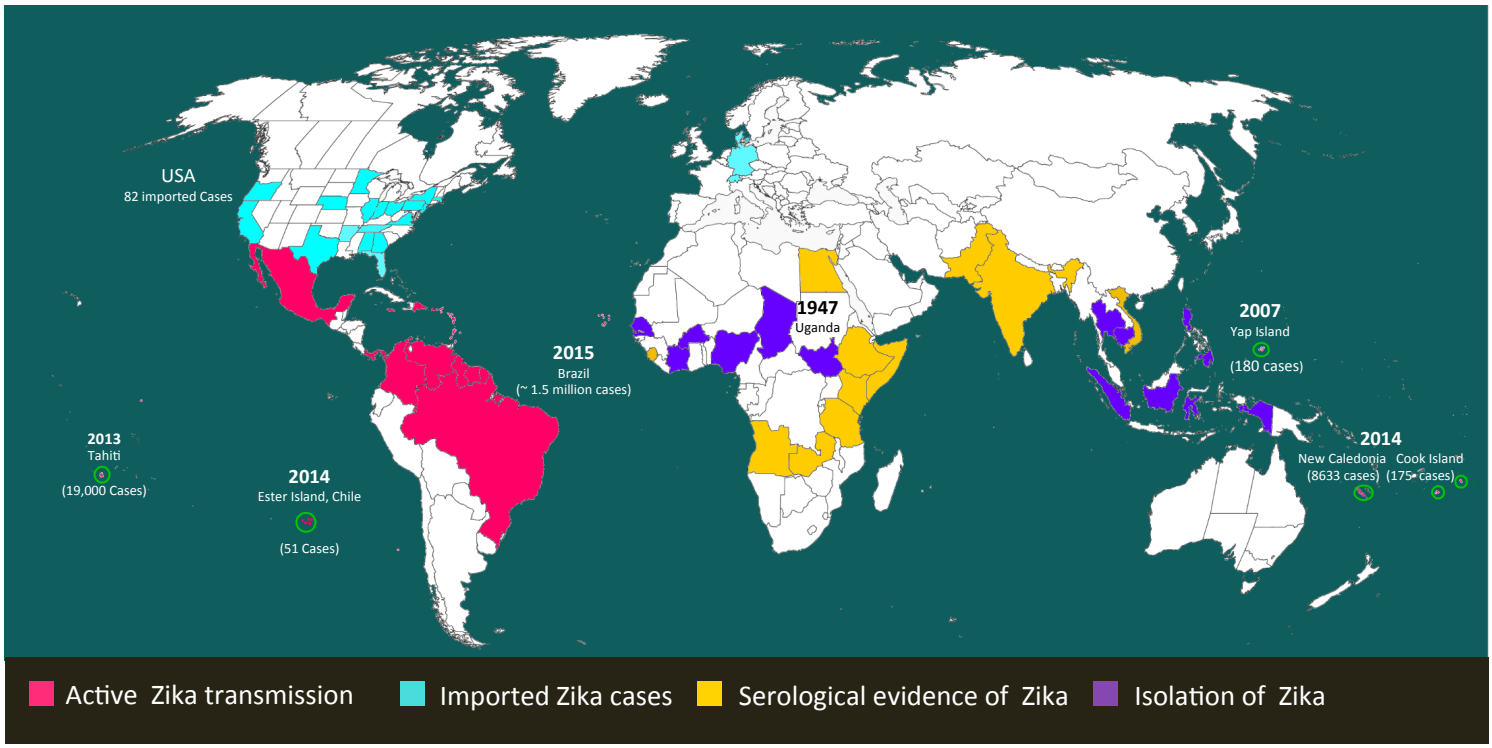
Figure legends

Figure 1. Worldwide distribution of Zika virus detection, isolation, and outbreaks. Information is current as of February 22, 2016.



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