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REVIEW

The Convergence of a Virus, Mosquitoes, and Human Travel in Globalizing the Zika Epidemic

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Abstract The Zika virus was first identified in 1947 in the Zika Forest of Uganda. It was discovered in a rhesus monkey that had been placed in a cage on a sentinel platform in the forest by the Virus Research Institute. When this writer visited the institute and the Zika Forest in 1961, work was underway to identify mosquito species at various levels of the tree canopy. This was done through the placement of traps at various levels of a 120-foot-high steel tower which this writer climbed. At that time, researchers isolated 12 strains of Zika virus from traps on the tower. Over the next six decades, the virus spread slowly to other parts of Africa, and eventually appeared in Southeast Asia, transmitted by *Aedes aegypti* and other *Aedes* mosquito species. By 1981, only 14 cases of illness had been reported as due to the Zika virus. Since most infections with this virus are either mild or asymptomatic, its true geographic spread was not fully appreciated. The current globalization of the Zika epidemic began on the Pacific island of Yap in the Federated States of Polynesia in 2007. This was the first known presence of the Zika virus outside of Africa and Southeast Asia. It was estimated that 73 % of the island's population had been infected. In 2013, the virus spread to French Polynesia where an estimated 28,000 cases occurred in a population of 270,000. During that year and afterwards, microcephaly and other congenital abnormalities were observed in the infants of women who were pregnant when they contracted the virus. It is currently not known if cases of microcephaly have resulted from infection of pregnant women or from infection plus some other co-factor. The epidemic rapidly spread to the Cook Islands and Easter Island. In 2015, Zika virus infection was diagnosed in Brazil where it was associated with microcephaly in the infants of some women who were pregnant when they contracted the disease. Cases of the Guillain-Barré syndrome were also found to be associated with Zika virus infection. How the disease entered Brazil is a matter of conjecture. However, the strain responsible for the epidemic in Brazil and elsewhere in South and Central America is phylogenetically identical to that which caused the epidemic in French Polynesia. The wide distribution of *Aedes aegypti*, a principal vector of the virus, and other *Aedes* species has greatly facilitated the spread of the disease. *Aedes aegypti* is an invasive species of mosquito in the Western Hemisphere that has adapted well to densely-populated urban environments. In addition, male-to-female human sexual transmission has increasingly been demonstrated in the US and elsewhere. In February 2016, the World Health Organization (WHO) declared the current Zika outbreak a Public Health Emergency of international concern. On the recommendation of its Emergency Committee on Zika Virus and Observed Increase in Neurological Disorders and Neonatal Malformations, WHO issued a group of recommendations to contain the epidemic. The globalization of the Zika virus was made possible by the widespread presence in various parts of the world of *Aedes* vectors and increased human travel that facilitated geographic spread. This globalization of Zika follows upon that of West Nile, Ebola, Dengue, and Chikungunya. Its ultimate spread is difficult to predict, but will hopefully be restricted through vigorous preventive measures.

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Introduction

The Zika virus drew worldwide attention in 2016 when it caused a widespread epidemic in Brazil. Many who become infected with the virus remain clinically asymptomatic or else develop a mild illness consisting of fever, headache, malaise, arthralgia, conjunctivitis, and a maculopapular rash. The reason why such an apparently mild viral syndrome is causing concern is the observation that mother-to-child transmission can occur during pregnancy and can lead to microcephaly and other congenital deformities in infants or to miscarriages. Although mother-to-child transmission had long been thought possible, it was the discovery of the virus in the brain tissue, placenta, and other tissues of two newborns who died soon after birth in Rio Grande do Norte in Brazil that established this mode of infection [1]. At about the same time, the incidence of microcephaly in newborns dramatically rose in geographic areas of Brazil where the disease was epidemic [2]. In addition, cases of the Guillain-Barré syndrome were diagnosed as a complication of infection with the virus.

In retrospect, it was the demonstration of the intrauterine mother-to-child transmission of the Zika virus in 2015 as well as the discovery of a carriage state of undetermined length in some who recover from the acute infection that caused global concerns. This, coupled with documented male-to-female sexual transmission of the virus, gave additional urgency to the epidemic [3, 4].

The Zika Epidemic

The current epidemic of Zika virus infection emerged from an earlier slow worldwide spread because of increased travel and the globalization of mosquitoes of the genus *Aedes*, which are the chief arthropod vectors for the virus. *A. aegypti*, which is the principal vector for Zika virus, is a robust invasive mosquito species that is an effective transmitter for a number of viral infections including Yellow Fever, Dengue, Chikungunya, and West Nile. *A. albopictus* is also an efficient vector for Zika virus infection.

A. aegypti most probably entered the Americas on sailing ships from Africa, and quickly adapted to the tropical climates of Central and South America. It was less successful over the decades in establishing itself in Europe and North America because of intolerance to winter temperatures. Other *Aedes* species, however, are more adaptable to these colder temperatures and could potentially serve as vectors for the Zika virus. The recent invasion of *A. albopictus* in the Americas and Europe is of particular concern because it could serve as a vector for several arboviral diseases in urban temperate areas [5].

The slow but inexorable invasion of *Aedes aegypti* over many decades in effect laid the groundwork for the eventual spread of arboviral diseases such as Zika virus infection. At present, there has not been any autochthonous transmission of Zika in either Europe or the United States by *Aedes* species. However, that may possibly change as warmer weather approaches, and *A. albopictus*, which is widely distributed, becomes active.

Discovery of the Zika Virus

The Zika virus was first identified in the Zika Forest of Uganda in 1947. It was discovered at the Virus Research Institute in a rhesus monkey that had been placed in a cage on a sentinel platform in the forest. The Zika Forest consisted then as now of a small dense belt of lake shore (Lake Victoria) high canopy growth containing large clumps of trees that runs parallel to the road between Entebbe and Kampala [6]. At the time of the isolation of the Zika virus, the Virus Research Institute was supported by the Rockefeller Foundation. The Institute was later re-named the East African Virus Research Institute and then the Uganda Virus Research Institute in 1977.

In 1960, a 120-foot-high steel tower was moved from the Mpanga Forest to the Zika Forest to study the vertical distribution of mosquito species in the forest. This writer climbed up to the various levels of this tower in 1961 while on a visit to the Zika Forest and the East African Virus Research Institute. Mosquito traps were strategically placed at different levels of the tower. This facilitated both the identification of mosquito species and isolation of arboviruses from them. The mosquito tower was located close to the Kampala-Entebbe road (Fig. 1).

On the other side of the road was the Kisubi Catholic Mission, then the largest of its kind in East Africa. The mission school was staffed by a teaching order of brothers, the Brothers of Christian Instruction, most of whom were French Canadians. The mission also had an excellent collection of African butterflies, many of which were caught across the road in the Zika Forest. While visiting the Zika Forest, I was a guest at the Kisubi Mission.

First Cases of Zika Virus Infection

At the time of my visit to the Zika Forest, Dr. A. J. Haddow and his colleagues had begun their studies of arboreal mosquitoes as vectors of arboviral viruses. In 1964, he and

Fig. 1 The 120-foot-high steel mosquito tower in the Zika Forest in 1961 (photograph by Pascal James Imperato)

his associates reported on the isolation of 12 strains of Zika virus [7]. Following these early scientific studies, few cases of Zika infection were reported in humans. Only some 14 cases were reported in the medical literature between 1964 and 1981 [8–11]. However, this may have been because some 80 % of cases of Zika virus infection are asymptomatic. Also, while so few cases were reported, serologic studies sometimes indicated that significant proportions of those tested demonstrated antibodies to the virus, indicating previous exposure to the virus [10]. Less than adequate reporting of cases and outbreaks, as well as complications such as mother-to-infant transmission during pregnancy and male-to-female sexual transmission, may have obscured the true incidence of the disease in Africa and Southeast Asia for many years.

Beginning of the Zika Virus Epidemic

The global epidemiological situation for the Zika virus abruptly changed in 2007 when 49 confirmed and 59 probable cases were documented on the Pacific island of Yap in the Federated States of Micronesia. This represented the first occurrence of the disease outside of Africa and Southeast Asia. Duffy et al. [12] verified that all cases were mild, consisting of rash, fever, arthralgia, and conjunctivitis, and that no one required hospitalization. They also undertook a household survey to determine the extent of the outbreak and risk factors for infection. They sampled 200 (16 %) of the 1276 households on Yap, and concluded that 73 % of residents 3 years of age and older had been recently infected. The predominant insect vector was *Aedes hensilli* [12].

Continued Spread of the Zika Virus

In 2013, several years after the disease appeared on Yap, an outbreak occurred in French Polynesia in which an estimated 28,000 cases occurred, representing 11 % of the population of 270,000 scattered over 67 islands. There were no severe clinical cases reported during this epidemic which lasted just over a year. There was also no history of Zika virus infection having previously occurred on these islands. The vector in this outbreak was identified as *Aedes polynesiensis*. Eventually, the disease spread to the Cook Islands in the west, and Easter Island in the east. Phylogenetic analyses demonstrated that the French Polynesia strain was closely related to that isolated in Cambodia in 2010, and on Yap in 2007. Thus, the French Polynesia strain was of Asian lineage [13, 14].

Spread to the Western Hemisphere

Spread to South America possibly occurred in either 2014 or 2015. Speculation has centered on importation from French Polynesia to Brazil during the 2014 World Cup Soccer Tournament or in 2015 from either the Cook Islands, French Polynesia, New Caledonia, or Easter Island, whose canoeing teams attended the Va'a World Sprint Championships in Rio de Janeiro.

The first speculation has been challenged by Musso, who makes a number of cogent observations about the geographic spread of the disease in the Pacific. He notes that phylogenetic studies show that the closest strain to the one that has emerged in Brazil was isolated in samples from case-patients in French Polynesia that subsequently spread to other Pacific islands. He makes an important point in saying that the assumption that the virus was introduced to Brazil during the World Cup Soccer Tournament may not be correct since no Zika-endemic Pacific countries participated in the event. Rather, he suspects that introduction of the virus to Brazil took place at the Va'a World Sprint Championship canoeing race in Rio de Janeiro. Zika-infected islands such as French Polynesia, New Caledonia, the Cook Islands, and Easter Island participated in this sporting event in several categories. This information, combined with the phylogenetic studies of Zanluca et al. and Campos et al., suggest that this event may have been a catalyst for the introduction of Zika into Brazil [15–17]. As convincing as this evidence is, it is also possible that a traveler or travelers from infected Pacific islands visited Brazil outside of the context of these sporting events.

The spread of Zika in the highly populated countries of Central and South America was rapid. In large measure, this spread was facilitated by the presence of an efficient arthropod vector, female *Aedes* mosquitoes, densely populated large urban centers with many areas with poor environmental sanitation, and population mobility.

Other Modes of Transmission

In early 2016, a number of male-to-female sexually transmitted cases of Zika virus infection were documented in the US [18]. The women who sexually contracted the disease had no history of travel to affected areas. However, their male partners had traveled to countries where the virus is present. The onset of symptoms in these women was within 2 weeks of those experienced by their male partners. These cases highlight not only a mode of transmission other than through a mosquito vector, but also a possible post-infection carriage state in human semen. Prior to documentation of the transmission of Zika through sexual intercourse in the US, scientists in Tahiti confirmed the presence of the virus in the semen of a man 2 weeks or more after he recovered from a second bout of the disease [19].

The risk of the Zika virus being transmitted through transfusion of blood or blood products has also been a serious concern [20]. In an attempt to address this issue, the World Health Organization (WHO) issued guidance on blood transfusions in Zika areas on 19 February 2016. However, it is widely recognized that it is impossible in many Zika areas to halt blood transfusions, as recommended, and import blood from non-infected areas. WHO also recommended that red blood cells in affected areas be quarantined for seven to 14 days. If, after this period, the donor does not show any of the symptoms and signs of Zika infection, the red blood cells could be released. Unfortunately, there is currently no blood test for Zika infection other than the Zika RNA analysis, which is not routine [21].

Temporary Recommendations of the World Health Organization (WHO)

Following the advice of the Emergency Committee on Zika Virus and Observed Increase in Neurological Disorders and Neonatal Malformations, the Director General of the World Health Organization (WHO) issued Temporary Recommendations on 1 February 2016. These recommendations, while primarily focused on the clusters of microcephaly and other neurological disorders and their possible association with Zika virus, also address measures to prevent and control the epidemic [22]. These latter initiatives will hopefully help in containing the spread of the virus (Table 1).

Following the issuance of the Temporary Recommendations, WHO strongly recommended the use of contraception for women in Zika-affected areas. WHO also called for access to emergency contraception for women who had unprotected sex and were concerned about contracting the Zika virus. Pope Francis later stated that contraception would be permissible to prevent the spread of the Zika epidemic. This was a significant pronouncement given that the Roman Catholic Church has in general opposed birth control [23].

Discussion

The WHO recommended measures will hopefully help to control spread of the disease and the incidence of congenital abnormalities among women infected during pregnancy. What is not yet known is the length of time that the Zika virus lingers in a carriage state among recovered patients. This presents potential parents with the serious challenge of how long to wait after infection with Zika before attempting to have a child. It also poses challenges regarding the length of quarantine periods for blood collected from people in Zika areas, and the risk of male-to-female sexual transmission.

The recent increase in cases of microcephaly in infants born in Zika affected areas is thought to be due to maternal

Table 1 Temporary recommendations of the World Health Organization's Emergency Committee on Zika Virus and observed increase in neurological disorders and neonatal malformations

Microcephaly and other neurological disorders
Surveillance for microcephaly and GBS [Guillain-Barré syndrome] should be standardized and enhanced, particularly in areas of known Zika virus transmission and areas at risk of such transmission
Research into the etiology of new clusters of microcephaly and other neurological disorders should be intensified to determine whether there is a causative link to Zika virus and/or factors or co-factors
Zika virus transmission
Surveillance for Zika virus infection should be enhanced, with the dissemination of standard case definitions and diagnostics to at-risk areas
The development of new diagnostics for Zika virus infection should be prioritized to facilitate surveillance and control measures
Risk communications should be enhanced in countries with Zika virus transmission to address population concerns, enhance community engagement, improve reporting, and ensure application of vector control and personal protective measures
Vector control measures and appropriate personal protective measures should be aggressively promoted and implemented to reduce the risk of exposure to Zika virus
Attention should be given to ensuring women of childbearing age and particularly pregnant women have the necessary information and materials to reduce risk of exposure
Pregnant women who have been exposed to Zika virus should be counseled and followed for birth outcomes based on the best available information and national practice and policies
Longer-term measures
Appropriate research and development efforts should be intensified for Zika virus vaccines, therapeutics, and diagnostics
In areas of known Zika virus transmission, health services should be prepared for potential increases in neurological syndromes and/or congenital malformations
Travel measures
There should be no restrictions on travel or trade with countries, areas and/or territories with Zika virus transmission
Travelers to areas with Zika virus transmission should be provided with up-to-date advice on potential risks and appropriate measures to reduce the possibility of exposure to mosquito bites
Standard WHO recommendations regarding disinsection of aircraft and airports should be implemented
Data sharing
National authorities should ensure the rapid and timely reporting and sharing of information of public health importance relevant to this PHEIC [Public Health Emergency of International Concern]
Clinical, virologic, and epidemiologic data related to the increased rates of microcephaly and/or GBS, and Zika virus transmission should be rapidly shared with WHO to facilitate international understanding of these events, to guide international support for control efforts, and to prioritize further research and product development

Source: World Health Organization

infection during pregnancy. However, some have raised the possibility that a co-factor may also be involved. Research underway at present among pregnant women in Zika affected areas of Colombia and elsewhere may clarify this issue in several months [24]. Of increasing concern is the growing evidence for male-to-female sexual transmission of the virus through infected seminal fluid. This represents a second known mode of transmission in which the carriage state in semen is of unknown duration.

As with many communicable diseases, herd immunity in local populations will eventually bring the Zika epidemic under control. Yet, if it turns out that the post-recovery carriage state for the virus is lengthy, then flare-ups could occur among young non-immunes given the absence of an effective vaccine.

The Zika virus epidemic is the latest in a recent series of globalized emerging infections. During the past decade, epidemics of Dengue, West Nile, Chikungunya, and Ebola have spread out of what was once assumed to be their restricted geographic spaces. Given the continued influences of globalization, it is probable that other infections will emerge and require prompt interventions so as to negate their consequences in terms of both personal and population health.

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Compliance with Ethical Standards

Conflict of interest The author declares no conflict of interest.

References

1. Schuler-Faccini, L., Ribeiro, E. M., Feitosa, I. M., et al. (2016). Possible association between Zika virus infection and

microcephaly—Brazil, 2015. *Morbidity and Mortality Weekly Report, 65*(3), 59–62.
2. Olivera Melo, A. S., Malinger, G., Ximenes, R., et al. (2016). Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: Tip of the iceberg? *Ultrasound in Obstetrics and Gynecology, 47*(1), 6–7.
3. Triunfol, M. (2016). A new mosquito-borne threat to pregnant women in Brazil. *Lancet Infectious Diseases, 16*(2), 156–159.
4. Oster, A. M., Brooks, J. T., Stryker, J. E., et al. (2016). Interim guidelines for prevention of sexual transmission of Zika Virus—United States, 2016. *Morbidity and Mortality Weekly Report, 65*(5), 120–121.
5. Weaver, S. C., & Reisen, W. K. (2010). Present and future arboviral threats. *Antiviral Research, 85*(2), 328–345.
6. Dick, G. W. A., Kitchen, S. F., & Haddow, A. J. (1952). Zika virus. Isolations and serological specificity. *Transactions of the Royal Society of Tropical Medicine and Hygiene, 46*(5), 509–520.
7. Haddow, A. J., Williams, M. C., Woodall, J. P., Simpson, D. I. H., & Goma, L. K. H. (1964). Twelve isolations of Zika virus from *Aedes* (Stegomyia) *africanus* (Theobald) taken in and above a Uganda forest. *Bulletin of the World Health Organization, 31*(1), 57–69.
8. Simpson, D. I. (1964). Zika virus infection in man. *Transactions of the Royal Society of Tropical Medicine and Hygiene, 58*(7), 335–338.
9. Moore, D. L., Causey, O. R., Carey, D. E., et al. (1975). Arthropod-borne viral infections of man in Nigeria, 1964–1970. *Annals of Tropical Medicine and Parasitology, 69*(1), 49–64.
10. Fagbami, A. H. (1979). Zika virus infections in Nigeria: Virological and seroepidemiological investigations in Oyo State. *Journal of Hygiene, 83*(2), 213–219.
11. Olson, J. G., Ksiazek, T. G., & Suhandiman, T. (1981). Zika virus, a cause of fever in Central Java, Indonesia. *Transactions of the Royal Society of Tropical Medicine and Hygiene, 75*(3), 389–393.
12. Duffy, M. R., Chen, T. H., Hancock, W. T., et al. (2009). Zika virus outbreak on Yap Island, Federated States of Micronesia. *New England Journal of Medicine, 360*(24), 2536–2543.
13. Musso, D., Nelles, E. J., & Cao-Lormeau, V.-M. (2014). Rapid spread of emerging Zika virus in the Pacific area. *Clinical Microbiology and Infectious Diseases, 20*(10), 595–596.
14. Cao-Lormeau, V.-M., Roche, C., Teissier, A., et al. (2014). Zika virus, French Polynesia, South Pacific, 2013. *Emerging Infectious Diseases, 20*(6), 1085–1086.
15. Musso, D. (2015). Zika virus transmission from French Polynesia to Brazil. *Emerging Infectious Diseases, 21*(10), 1887.
16. Zanluca, C., de Melo, V. C. A., Mosimann, A. L. P., et al. (2015). First report of autochthonous transmission of Zika virus in Brazil. *Memorias do Instituto Oswaldo Cruz, 110*(4), 569–572.
17. Campos, G. S., Bandeira, A. C., & Sardi, S. I. (2015). Zika virus outbreak, Bahia, Brazil. *Emerging Infectious Diseases, 21*(10), 1885–1886.
18. Tavernise, S. (2016). Fourteen new reports of sexual transmission of Zika in US. *The New York Times, CLXV*(57142), A3.
19. Musso, D., Roche, C., Robin, E., et al. (2015). Potential sexual transmission of Zika virus. *Emerging Infectious Diseases, 21*(2), 359–361.
20. Musso, D., Nhan, T., Robin, E., et al. (2014). Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014. *Eurosurveillance, 19*, 2077.
21. Saint Louis, C. (2016). WHO issues guidelines on blood in Zika areas. *The New York Times, CLXV*(57148), A5.
22. WHO statement on the first meeting of the International Health Regulations. (2005). *(IHR 2005) Emergency committee on Zika virus and observed increase in neurological disorders and neonatal malformations (1 February 2016)*. Geneva: World Health Organization.
23. Tavernise, S. (2016). WHO recommends contraception in countries with Zika virus. *The New York Times, CLXV*(57147), A14.
24. McNeil, D. G, Jr. (2016). Proof on virus and defects is expected to take months. *The New York Times, CLXV*(57148), A5.