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EDITORIAL

Zika: where it has been, where it is going, and how to stop it

The unique challenges of the Zika virus outbreak that is unfolding promise valuable teachings that cross interdisciplinary boundaries

Particularly over the past few decades, emerging and re-emerging infectious diseases have provided insights into the dynamic complexity of the host–pathogen interface. By late 2012, at least 219 human viral species were recognised, and three to four new human viruses are discovered annually (1). Most known and emerging human viruses are zoonoses (2,3). The natural reservoirs of zoonotic pathogens often remain elusive, despite extensive research efforts that sometimes span decades. For example, even though the first human Ebola virus outbreaks were reported in 1976 (4,5), direct evidence that bats might be the natural reservoir came only in 2005 (6), and the virus itself has still not been isolated from bats (7–9).

In recent months, the attention of the professional community and that of the general public was captivated by Zika virus, which has been rapidly emerging in the Western Hemisphere (10). Twenty countries and territories on the American continent reported Zika virus circulation as of 22 January 2016 (10).

A mosquito-borne flavivirus transmitted through the bite of *Aedes* mosquitoes (11), Zika virus was discovered in April 1947 in Uganda, when it was isolated from the serum of a pyrexial rhesus monkey in the Zika forest (12,13). The second isolation occurred in January 1948, in the same forest, from

Aedes africanus mosquitoes (12). Afterwards, the virus was confined to Africa and Asia and remained relatively obscure, with few human cases (14). The first human outbreak was reported in 2007 on Yap Island from the Federated States of Micronesia (15). The infection was characterised by a rash, conjunctivitis and arthralgia, and 73% of the residents 3 years or older on the island were estimated to have become infected (15). Zika virus subsequently spread to French Polynesia, where it caused an outbreak in 2013–2014 (16), and to other Pacific Islands, including New Caledonia, Cook Islands, Easter Island, Vanuatu and Solomon Islands (16). Its introduction to Easter Island is suspected to have occurred from French Polynesia during an annual festival (16).

The first report of local Zika virus transmission in the Americas came in March 2015, in the state of Rio Grande do Norte from northeastern Brazil, where several patients developed mild fever, rash, conjunctivitis and arthralgia (17,18). Subsequently, the epidemic spread to other states in Brazil, where it is estimated to involve as many as 1,300,000 suspected cases (18,19). No specific antiviral therapy is available and supportive care is recommended (20). In the over 60 years prior to its arrival to the Americas, Zika virus has not been linked to hemorrhagic fever or death (21). However, as of November 2015, three deaths had been attributed to the virus in Bra-

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zil, and these include a newborn with microcephaly (14).

Phylogenetic analyses described two major Zika virus lineages, Asian and African, and the virus first isolated from patients in Brazil, who presented with a 'dengue-like syndrome', belonged to the Asian lineage (17,22). It was suggested that a sporting event held in August 2014 in Rio de Janeiro, and to which teams from French Polynesia, New Caledonia, Cook Islands and Easter Island also participated, facilitated the introduction of the virus into Brazil (16).

The reservoir and the factors that facilitated Zika virus spillover to humans and the subsequent outbreak will most likely be active topics for years to come. The virus was isolated from monkeys (23) and antibodies were detected in rodents (24). The dynamics of the virus interaction with the vector is yet another insufficiently explored topic. The virus is predominantly transmitted by mosquitoes of the genus *Aedes* (17,25). Several species were proposed to be competent vectors, including *Ae. africanus* in Uganda (12), *Ae. hensilli* on the island of Yap (26), *Ae. polynesiensis* in French Polynesia (27), *Ae. luteocephalus* in Nigeria and Burkina Faso (28,29) and *Ae. aegypti* and *Ae. albopictus* in Brazil (30). However, concerns about transmission during blood transfusion were raised when, during the outbreak from French Polynesia, 2.8% (42/1505) of the asymptomatic blood donors were found to be positive by PCR (31). Perinatal transmission was also reported (32). Additionally, in what most likely represents the first example of intrauterine transmission, the virus was detected by amniocentesis and quantitative real-time PCR in two pregnant women from the state of Paraíba, Brazil, who had been diagnosed with fetal microcephaly, despite negative blood tests for the virus (33). Sexual transmission, a route that has been previously suspected to be plausible (34,35), was reported in Texas on 2 February 2016, in what also represents the first instance of Zika virus transmission within the USA during the current outbreak (36,37).

Evolution of the Zika virus genome is of particular concern. An analysis of viral strains collected in several African countries revealed that Senegal and Côte d'Ivoire experienced at least two independent introductions of the virus during the 20th century (25). The virus appears to have undergone several adaptive changes during its evolution, including recombination events and modifications in protein glycosylation patterns (25). The ability of Zika virus to adapt to *Ae. albopictus*, a vector that has spread to 36 states in the USA, where its range continues to expand (10,38,39), and to many countries in Europe, Central and South America (40,41) has the potential to

develop into a public health challenge (21,42). In this context, it is relevant to remember that a mutation in the Chikungunya virus E1 envelope glycoprotein gene enhanced its fitness for *Ae. albopictus*, and a recent 2005–2006 outbreak on the Reunion Island and several other islands in the Indian Ocean basin were primarily attributed to enhanced vector competency and transmission efficiency (43–46).

In this age of global inter-connectedness, predicting where local transmission will occur next is particularly challenging, yet critical and actionable. A recent study identified airports located within 50 km from areas conducive for year-round Zika virus transmission in Brazil and, using data from the International Air Transport Association between September 2014 and August 2015, mapped the final destinations of travellers departing from these airports (19). Of the 9.9 million departing travellers, 65% travelled to the Americas, 27% to Europe and 5% to Asia. The greatest traveller volumes were to the USA, Argentina, Chile, Italy, Portugal and France, a finding that could become disquieting if we consider that > 60% of the population in Argentina, Italy, and the USA reside in areas that are conducive to seasonal Zika virus transmission (19).

There is one aspect that sets this virus apart from many other known human viruses. In a cohort of 35 infants with microcephaly born between August and October 2015 in eight of Brazil's 26 states, the mothers of all 35 infants had lived in or visited Zika virus-affected areas during pregnancy, and 71% of the infants (25/35) had severe microcephaly, defined as a head circumference > 3 standard deviations below the mean for sex and gestational age (11). The response of the Brazilian health authorities, which promptly declared a national health emergency, is commendable. Subsequently, several countries, including Brazil, Colombia, Ecuador, El Salvador and Jamaica recommended women to avoid or delay becoming pregnant (13,47), with the recommendation lasting until 2018 in El Salvador (13).

A consideration of tremendous importance is the intimate juncture between an infectious disease outbreak and reproductive health education. This interface, neither novel nor unexpected, is assuming new and unexplored dimensions in the case of a vector-borne infectious disease linked to congenital malformations. The world population was projected to rise from 6.5 billion in 2005 to 9.2 billion in 2050, and nearly all this future growth is predicted to occur in Africa, Asia (excluding Japan, Australia and New Zealand) and Latin America (48). While some progress has been made, adolescents in Latin America continue to face major reproductive health

challenges as a result of inadequate counselling and substantial barriers to sexual and reproductive health education and services (49, 50). Latin America is experiencing some of the largest inequalities in the use of modern contraceptives among the poor (51). Additionally, Latin America has some of the most restrictive abortion laws and, along with Africa and Southeast Asia, is one of the regions with the highest incidences of unsafe abortions (52). Integrating dialogues and initiatives on sexual and reproductive health into the epidemic and pandemic preparedness framework is instrumental towards managing the Zika virus outbreak. This task is intimately intertwined with the need to close the gender gap and empower women globally. While historically we have often visualised these initiatives on a country-to-country basis, a global framework is more critical than ever before.

Due to the fact that serologic testing for the virus was not yet available in Brazil at the time of the Zika outbreak, its causal association with the present 20-fold increase in the incidence of microcephaly in parts of Brazil is still considered presumptive (53). It is, however, relevant that after an expectant mother in Brazil developed a febrile illness and rash at the end of her second trimester, and ultrasonography showed microcephaly and fetal brain and placental calcifications, she underwent termination of her 29-week pregnancy, and a fetal autopsy revealed micrencephaly, almost complete agyria, hydrocephalus, and multiple cortical and subcortical white matter calcifications (54). Reverse transcriptase PCR confirmed

the presence of Zika virus in the fetal brain, and the complete viral genome was recovered (54). Neither the virus nor pathological changes were described in other fetal tissues, pointing towards a strong neurotropism of Zika virus. As part of the current outbreak, it is imperative to focus efforts towards determining whether the link between Zika virus and microcephaly is causal, while in parallel exploring other potential causes, such as environmental chemicals, many of which have historically been found to be teratogens.

Virus surveillance, mosquito control, enhanced diagnostic vigilance and prompt information sharing as part of a multidisciplinary platform are some of the key considerations that will be decisive during the current outbreak. We most definitely will learn novel things about the Zika virus, and hopefully capitalise on teachings that previous outbreaks have provided. And, if global reproductive health will become an integral part of the framework of this outbreak, our *Global Village* will most definitely be on its way towards becoming better equipped for future public health challenges, not necessarily limited to infectious diseases.

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Disclosure

None.

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