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Insight Review

Zika virus: a previously slow pandemic spreads rapidly through the Americas

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Zika virus (family *Flaviviridae*) is an emerging arbovirus. Spread by *Aedes* mosquitoes, it was first discovered in Uganda in 1947, and later in humans elsewhere in sub-Saharan Africa, arriving in south-east Asia at latest by the mid-twentieth century. In the twenty-first century, it spread across the Pacific islands reaching South America around 2014. Since then it has spread rapidly northwards reaching Mexico in November 2015. Its clinical profile is that of a dengue-like febrile illness, but associations with Guillain–Barré syndrome and microcephaly have appeared recently. The final geographical range and ultimate clinical impact of Zika virus are still a matter for speculation.

Introduction

Zika virus (family *Flaviviridae*; genus *Flavivirus*) is a positive-sense ssRNA arbovirus within a family that includes several other arboviruses of major clinical importance, such as *Yellow fever virus*, *West Nile virus*, *Tick-borne encephalitis virus* and *Dengue virus*. First isolated in 1947 in the Zika forest region of Uganda from a *Macaca* monkey (Dick *et al.*, 1952), the first human case was detected in Nigeria in 1954 (MacNamara, 1954). The arthropod vectors are several mosquitoes of the genus *Aedes* (Diagne *et al.*, 2015). Both urban (Grard *et al.*, 2014) and sylvatic (Berthet *et al.*, 2014) transmission have been demonstrated. Epizootics occur in monkeys (McCrae & Kirya, 1982), but it is unclear as yet whether primates are an obligatory reservoir in the transmission cycle in humans.

The classic clinical presentation resembles dengue fever, but also chikungunya: a fever accompanied by polyarthralgia, myalgia, maculopapular rash and headache. This complicates differential diagnosis. Serological testing can, however, distinguish Zika virus infection from that of dengue and chikungunya (Aubry *et al.*, 2015). The virus remained one of the many neglected curiosities of tropical medicine, and no efforts were made to develop a vaccine or treatment in view of its low case numbers and low clinical impact relative to other arboviruses. This situation changed in the twenty-first century, first with the large-scale outbreaks in the Pacific islands, beginning on Yap in Micronesia in 2007 (Lanciotti *et al.*, 2008) and then with the emergence of the first Zika virus disease cases in Brazil in early 2015 (Zanluca *et al.*, 2015). Zika virus also began to spread northwards at a rapid rate across South and Central America, reaching Mexico by late November 2015 (ECDC, 2015).

Zika virus genome

The positive-strand RNA genome organization of the virus follows that of related flaviviruses: 5′-C–prM–E–NS1–NS2A–NS2B–NS3–NS4A–NS4B–NS5-3′ (Kuno & Chang, 2007), with one single ORF encoding the structural proteins C, M and E, and the non-structural proteins which carry out functions in replication and assembly. In all likelihood, antagonism of host responses will be mediated by one or several of these non-structural proteins. The 5′ and 3′ untranslated regions are important in flavivirus genome cyclization and replication with conserved sequences (CS1–3) found in related flaviviruses. Kuno & Chang (2007) identified variation in CS1 and CS3 of Zika virus strain MR 766 (order CS3–CS2–CS1) and this should be further investigated when more sequencing data become available, as it may influence replication, and possibly virus–host interactions and pathogenicity.

Phylogenetics, evolution and epidemiology

Analysis of the origins of what is now apparent as a pandemic of Zika virus has been largely retrospective, based on sequencing of isolates collected across Africa and south-east Asia during the course of the twentieth century (Faye *et al.*, 2014). Only with the arrival of Zika virus in the Pacific islands (Lanciotti *et al.*, 2008) did more systematic sequencing efforts commence and the first full-length genome was obtained (Kuno & Chang, 2007). Twenty-one full-length Zika virus genomes are currently available in GenBank and nine of those have collection date information in their GenBank record. A phylogenetic tree reconstructed using these is shown in Fig. 1(a), illustrating the emergence of the south-east Asian strain from Africa

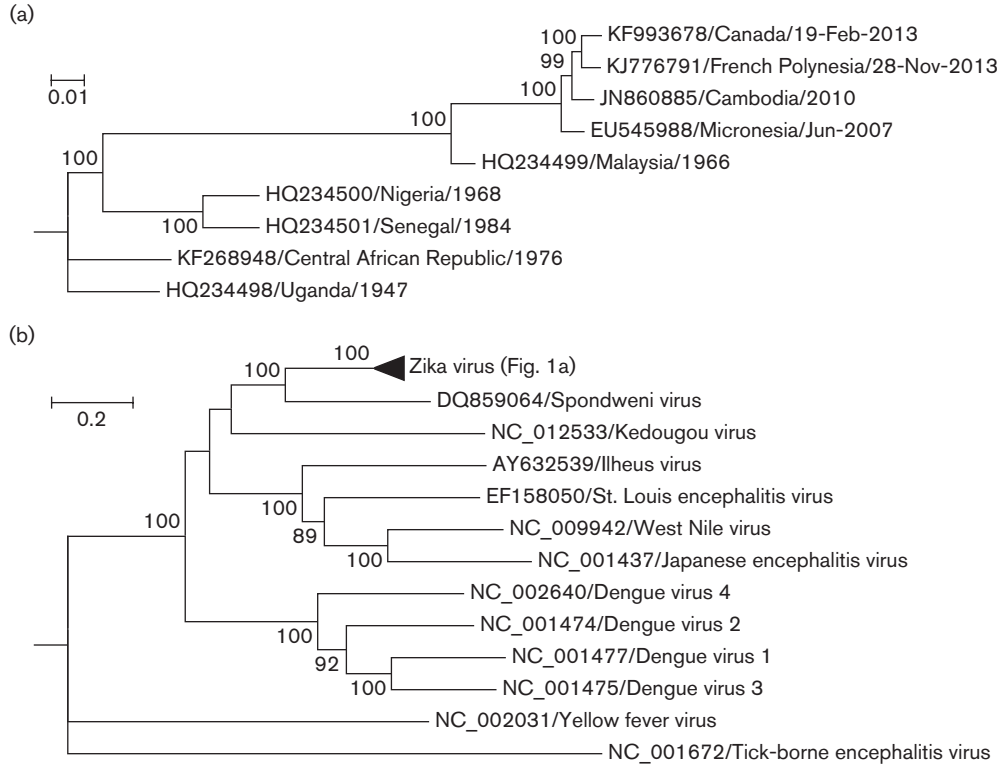

Fig. 1. Molecular phylogenetic analysis of dated Zika virus genomes. (a) Zika virus genomes. (b) Selected flavivirus genomes. For both trees, genomes at, or near, full length were used to reconstruct a maximum-likelihood tree in MEGA (Tamura *et al.*, 2013) under the GTR+G substitution model. Bootstrap confidence levels are given on nodes where >70%. Scale bar indicates substitutions per site. GenBank accession numbers are indicated. Sequence KF993678/Canada originated in Thailand. The alignment from which the figure was calculated is available at http://dx.doi.org/10.17635/lancaster/researchdata/55.

and the subsequent seeding of the Pacific islands epidemic from south-east Asia, as shown elsewhere (Buathong *et al.*, 2015); the wider relationship of Zika virus to other flaviviruses is shown in Fig. 1(b). Active tracking of the spread of Zika virus across the Pacific and into the Americas, and sequencing of older clinical isolates, have produced a total of 215 Zika virus sequences in GenBank, although many are short fragments.

Phylogenetic studies using these sequences (Faye *et al.*, 2014) have nevertheless enabled the date of emergence of Zika virus in East Africa to be estimated at 1920, with a confidence range on this date of 1892–1947. Serological surveys carried out in Uganda in the wake of the initial discovery of the virus in the late 1940s showed seropositivity of 6.1% in humans (Dick *et al.*, 1952). However, by the late 1960s, Kenya demonstrated seropositivity to Zika virus at 52% overall but with wide variation between areas (Geser *et al.*, 1970). Levels of seropositivity were lower in Nigeria during the late 1960s (Moore *et al.*, 1975), but had risen to 56% by 1980 (Adekolu-John & Fagbami, 1983). Zika virus has subsequently been reported across a wide range in Central and West Africa, with some examples referenced here (Berthet *et al.*, 2014; Grard *et al.*, 2014).

The same phylogenetic study (Faye *et al.*, 2014) also dated the transmission of East African Zika virus to south-east Asia around 1945 (confidence range 1920–1960), where the virus was first detected in the late 1960s in Malaysia (Marchette *et al.*, 1969) and subsequently across south-east Asia. Various phylogenetic analyses have confirmed that Pacific island Zika virus is related to the Asian lineages (e.g. Alera *et al.*, 2015; Buathong *et al.*, 2015) (see Fig. 1). The first appearance of Zika virus in this new eastward movement was on the Micronesian island of Yap in 2007 (Duffy *et al.*, 2009; Lanciotti *et al.*, 2008). Confounding factors in establishing the exact dates of dispersion of Zika virus are the ease with which Zika virus disease can be confused with dengue fever and chikungunya fever.

The next Pacific outbreak occurred in French Polynesia in 2013 (Cao-Lormeau *et al.*, 2014) and was associated with 42 cases of Guillain–Barré syndrome (Roth *et al.*, 2014). The observation that blood samples collected from 2011 to 2013 had only 0.8% seropositivity to Zika virus suggests that the introduction to Polynesia was not long before the identification of the index case (Aubry *et al.*, 2015). The scale of the Polynesian outbreak was unprecedented, with 28000 infections recorded in the first 4 months. Further

phylogenetic analyses (e.g. Alera *et al.*, 2015; Buathong *et al.*, 2015) showed Polynesian Zika virus to be more closely related to the south-east Asian strains than to the Yap Island outbreak sequences, suggesting an independent introduction to Polynesia from south-east Asia. Subsequent spread in the Pacific occurred in 2014 to New Caledonia (Dupont-Rouzeyrol *et al.*, 2015), the Cook Islands (Pyke *et al.*, 2014) and Easter Island (Tognarelli *et al.*, 2015).

Transmission to the Americas appears to have originated in the Pacific Islands, a conclusion again based on phylogenetic analysis (Zanluca *et al.*, 2015). The Brazilian state of Bahia was the first to identify cases (Campos *et al.*, 2015). An official announcement by the Brazilian Ministry of Health was made on 14 May 2015, but patients with Zika symptoms had been reported in the city of Salvador from 15 February 2015 onwards. By 10 December 2015, Zika virus had spread to 18 other Brazilian states (ECDC, 2015). Two events that may have led to Zika virus's introduction to Brazil are the 2014 FIFA World Cup tournament and an international canoe-racing event (Musso, 2015). As Pacific nations were only represented among the canoe racers, the latter may be the likeliest introduction point.

The World Health Organization (WHO) subsequently issued alerts to the presence of Zika virus in several Latin American countries: Colombia, Surinam, Guatemala, El Salvador, Mexico, Paraguay, Venezuela and Panama. The pandemic of Zika virus, drawing on empirical reports of seropositivity, genome sequences with collection information, phylogenetic analyses and WHO reports for the American stages, is shown in Fig. 2.

Clinical presentation of American Zika virus

The African form of Zika virus replicated many of the symptoms often associated with arboviruses. The 2007 outbreak in Micronesia presented with rash, fever, arthralgia and conjunctivitis as the most common symptoms, and headache, vomiting and oedema in a minority. The disease is acute but self-limiting. Symptoms across six case clusters from 1962–2010 are reviewed by Heang *et al.* (2012). The observation of Guillain–Barré syndrome among Zika cases in Polynesia represented an increase in the potential clinical severity of the disease (Roth *et al.*, 2014).

On 21 November 2015, the WHO notified the presence of 739 cases of microcephaly in nine states of north-eastern Brazil (http://www.who.int/csr/don/27-november-2015-microcephaly/en/), the same region as the Zika virus outbreak in that country. The association has not yet been demonstrated directly, but has been integrated into risk assessments by the European Centre for Disease Prevention and Control; additionally three deaths from Zika virus disease (one newborn, one 16-year-old and one adult) have been reported, the first known occurrences (ECDC, 2015). The strong possibility exists of sexual transmission in two cases (Foy *et al.*, 2011; Musso *et al.*, 2015),

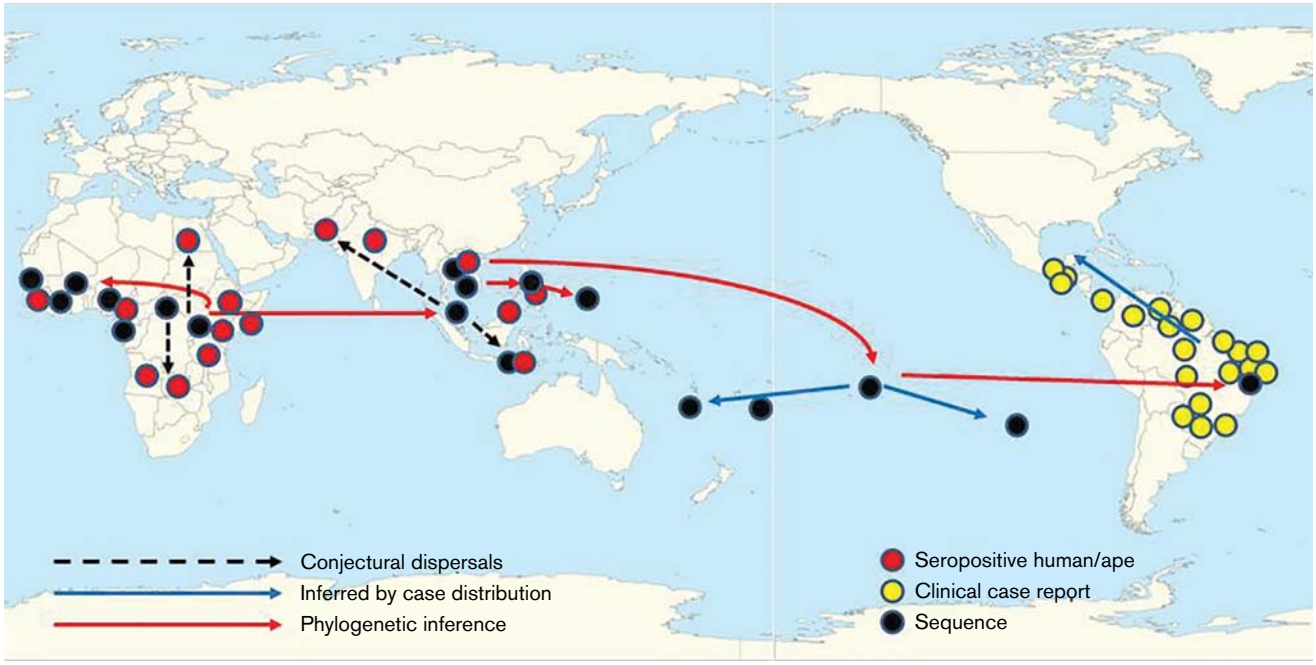

Fig. 2. Spread of Zika virus. This is inferred from phylogenetic analysis where available in the literature, otherwise reconstructed from patterns of case report clusters or seropositivity in populations. Map background: Wikimedia commons public domain.

perinatal transmission in two cases (Besnard *et al.*, 2014) and a theoretical possibility of transmission by transfusion based on the presence of virus in 3% of asymptomatic Polynesian blood donors (Musso *et al.*, 2014). Such observations suggest that Zika virus, once introduced from an area of arboviral transmission, could lead in some cases to disease even in the absence of vector-based transmission.

Conclusions and future prospects

Any country in which mosquitoes of the genus *Aedes* are present could be a potential site for future Zika virus disease outbreaks. This might include southern Europe and the USA, where *Aedes albopictus* has been spreading invasively but other competent species may also be present. Introductions by tourists have already occurred on several occasions, e.g. into Europe (Tappe *et al.*, 2014). Competence studies are required in vulnerable regions in order to inform local risk assessments, and efforts towards a vaccine and therapeutics need to be accelerated. Moreover, precautions need to be taken to avoid the pathogen entering public blood banks.

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