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

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Abstract:	Zika virus (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 mid-20th-century. In the 21st 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 recently associations with Guillain-Barré syndrome and microcephaly have appeared. The final geographical range and ultimate clinical impact of Zika virus are still a matter for speculation.

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

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28 **Abstract**

29 Zika virus (*Flaviviridae*) is an emerging arbovirus. Spread by *Aedes* mosquitoes, it was first
30 discovered in Uganda in 1947, and later in humans elsewhere in sub-Saharan Africa, arriving
31 in south-east Asia at latest by mid-20th-century. In the 21st century, it spread across the
32 Pacific Islands reaching South America around 2014. Since then it has spread rapidly
33 northwards reaching Mexico in November 2015. Its clinical profile is that of a dengue-like
34 febrile illness, but recently associations with Guillain-Barré syndrome and microcephaly
35 have appeared. The final geographical range and ultimate clinical impact of Zika virus are
36 still a matter for speculation.

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38 **Introduction**

39 Zika virus (family *Flaviviridae*; genus *Flavivirus*) is a positive-sense single-stranded RNA
40 arbovirus within a family that includes several other arboviruses of major clinical
41 importance, such as yellow fever virus, West Nile virus, tick-borne encephalitis virus and
42 dengue virus. First isolated in 1947 in the Zika forest region of Uganda from a *Macaca*
43 monkey (Dick et al., 1952), the first human case was detected in Nigeria in 1954
44 (Macnamara, 1954). The arthropod vector is several mosquitos of the genus *Aedes* (Diagne
45 et al., 2015). Both urban (Grard et al., 2014) and sylvatic (Berthet et al., 2014) transmission
46 have been demonstrated. Epizootics occur in monkeys (McCrae and Kirya, 1982) but it is
47 unclear as yet if primates are an obligatory reservoir in the transmission cycle in humans.

48 The classic clinical presentation resembles dengue fever but also chikungunya: a fever
49 accompanied by polyarthralgia, myalgia, maculopapular rash and headache. This

50 complicates differential diagnosis. Serological testing, however, can distinguish Zika virus
51 infection from that of dengue and chikungunya (Aubry et al., 2015). The virus remained one
52 of the many neglected curiosities of tropical medicine and no efforts were made to develop
53 a vaccine or treatment in view of its low case numbers, and low clinical impact relative to
54 other arboviruses. This situation changed in the 21st century, first with the large-scale
55 outbreaks in the Pacific islands, beginning on Yap in Micronesia in 2007 (Lanciotti et al.,
56 2008), and then with the emergence of the first Zika virus disease cases in Brazil in early
57 2015 (Zanluca et al., 2015). Zika virus also began to spread northwards at a rapid rate across
58 South and Central America, reaching Mexico by late November 2015 (ECDC, 2015).

59

60 **The Zika virus genome**

61 The positive strand RNA genome organisation of the virus follows that of related
62 flaviviruses: 5'-C-prM-E-NS1-NS2A-NS2B-NS3-NS4A-NS4B-NS5-3' (Kuno and Chang, 2007),
63 with one single open reading frame encoding the structural proteins C, M and E and the
64 nonstructural proteins which carry out functions in replication and assembly. In all
65 likelihood, antagonism of host responses will be mediated by one or several of these non-
66 structural proteins. 5' and 3' untranslated regions are important in flavivirus genome
67 cyclisation and replication with conserved sequences (CS1-3) found in related flaviviruses.
68 Kuno and Chang (Kuno and Chang, 2007) identified variation in CS1 and CS3 of Zika virus
69 strain MR 766 (order CS3-CS2-CS1) and this should be further investigated when more
70 sequencing data becomes available, as it may influence replication and possibly virus-host
71 interactions and pathogenicity.

72

73 **Phylogenetics, evolution and epidemiology**

74 Analysis of the origins of what is now apparent as a pandemic of Zika virus has been largely
75 retrospective, based on sequencing of isolates collected across Africa and south-east Asia
76 during the course of the 20th century (Faye et al., 2014). Only with the arrival of Zika virus in
77 the Pacific Islands (Lanciotti et al., 2008) did more systematic sequencing efforts commence
78 and the first full-length genome was obtained (Kuno and Chang, 2007). 21 full-length Zika
79 virus genomes are currently available in GenBank and 9 of those have collection date
80 information in their GenBank record. Figure 1A shows a phylogenetic tree constructed using
81 these, illustrating the emergence of the south-east Asian strain from Africa, and the
82 subsequent seeding of the Pacific islands epidemic from south-east Asia as shown elsewhere
83 (Buathong et al., 2015), and Figure 1B shows the wider relationship of Zika virus to other
84 flaviviruses. Active tracking of the spread of Zika virus across the Pacific and into the
85 Americas, and sequencing of older clinical isolates, have produced a total of 215 Zika virus
86 sequences in GenBank, though many are short fragments.

87 Phylogenetic studies using these sequences (Faye et al., 2014) have nevertheless enabled
88 the date of emergence of Zika virus in east Africa to be estimated at 1920 with a confidence
89 range on this date of 1892-1947. Serological surveys carried out in Uganda in the wake of
90 the initial discovery of the virus in the late 1940s showed seropositivity of 6.1% in humans
91 (Dick et al., 1952). However, by the late 1960s, Kenya demonstrated seropositivity to Zika
92 virus at 52% overall, but with wide variation between areas (Geser et al., 1970). Levels of
93 seropositivity were lower in Nigeria during the late 1960s (Moore et al., 1975) but had risen
94 to 56% by 1980 (Adekolu-John and Fagbami, 1983). Zika virus has subsequently been

95 reported across a wide range in central and west Africa, with some examples referenced
96 here (Berthet et al., 2014, Grard et al., 2014).

97 The same phylogenetic study (Faye et al., 2014) also dated the transmission of east African
98 Zika virus to south-east Asia around 1945 (confidence range 1920-1960), where the virus
99 was first detected in the late 1960s in Malaysia (Marchette et al., 1969) and subsequently
100 across south-east Asia. Various phylogenetic analyses have confirmed that Pacific Island
101 Zika virus is related to the Asian lineages (for instance: Buathong et al., 2015, Alera et al.,
102 2015) (see Fig. 1). Zika virus's first appearance in this new eastward movement was on the
103 Micronesian island of Yap in 2007 (Duffy et al., 2009, Lanciotti et al., 2008). Confounding
104 factors in establishing the exact dates of dispersion of Zika virus are the ease with which Zika
105 virus disease can be confused with dengue fever and chikungunya fever.

106 The next Pacific outbreak occurred in French Polynesia in 2013 (Cao-Lormeau et al., 2014)
107 and were associated with 42 cases of Guillain-Barre syndrome (Roth et al., 2014). The
108 observation that blood samples collected from 2011 to 2013, had only 0.8% seropositivity to
109 Zika virus, suggests that the introduction to Polynesia was not long before the identification
110 of the index case (Aubry et al., 2015). The scale of the Polynesian outbreak was
111 unprecedented with 28,000 infections recorded in the first four months. Further
112 phylogenetic analyses (for instance: Buathong et al., 2015, Alera et al., 2015) showed
113 Polynesian Zika virus to be more closely related to the south-east Asian strains than to the
114 Yap Island outbreak sequences, suggesting an independent introduction to Polynesia from
115 south-east Asia. Subsequent spread in the Pacific occurred in 2014 to New Caledonia
116 (Dupont-Rouzeyrol et al., 2015), the Cook Islands (Pyke et al., 2014) and Easter Island
117 (Tognarelli et al., 2015).

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

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

132

133 **Clinical presentation of American Zika virus**

134 The African form of Zika virus replicated many of the symptoms often associated with
135 arboviruses. The 2007 outbreak in Micronesia presented with rash, fever, arthralgia and
136 conjunctivitis as the most common symptoms and headache, vomiting and oedema in a
137 minority. The disease is acute but self-limiting. Symptoms across six case clusters from
138 1962-2010 are reviewed by Heang et al (2012). The observation of Guillain-Barré syndrome
139 among Zika cases in Polynesia represented an increase in the potential clinical severity of
140 the disease (Roth et al., 2014).

141 On 21st November 2015, the WHO notified the presence of 739 cases of microcephaly in 9
142 states of north-eastern Brazil ([http://www.who.int/csr/don/27-november-2015-](http://www.who.int/csr/don/27-november-2015-microcephaly/en/)
143 [microcephaly/en/](http://www.who.int/csr/don/27-november-2015-microcephaly/en/)), the same region as the Zika virus outbreak in that country. The
144 association is not yet directly demonstrated but has been integrated into risk assessments
145 by the European Centre for Disease Prevention and Control; additionally three deaths from
146 Zika virus disease (one newborn, one 16 year old, one adult) have been reported, the first
147 known occurrences (ECDC, 2015). The strong possibility exists of sexual transmission in two
148 cases (Musso et al., 2015, Foy et al., 2011), perinatal transmission in two cases (Besnard et
149 al., 2014) and a theoretical possibility of transmission by transfusion based on the presence
150 of virus in 3% of asymptomatic Polynesian blood-donors (Musso et al., 2014). Such
151 observations suggest that Zika virus, once introduced from an area of arboviral
152 transmission, could lead in some cases to disease even in absence of vector-based
153 transmission.

154 **Conclusions and Future Prospects**

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

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275

276 **Figure legends**

277

278 **Figure 1. Molecular phylogenetic analysis of dated Zika virus genomes. A:** Zika virus

279 genomes **B:** selected Flavivirus genomes. For both trees, genomes at, or near, full length

280 were used to construct a maximum likelihood tree in MEGA (Tamura et al., 2013), under the

281 GTR+G substitution model. Bootstrap confidence levels are given on nodes where >70%.

282 Scale: substitutions per site. Sequence KF993678/Canada originated in Thailand.

283

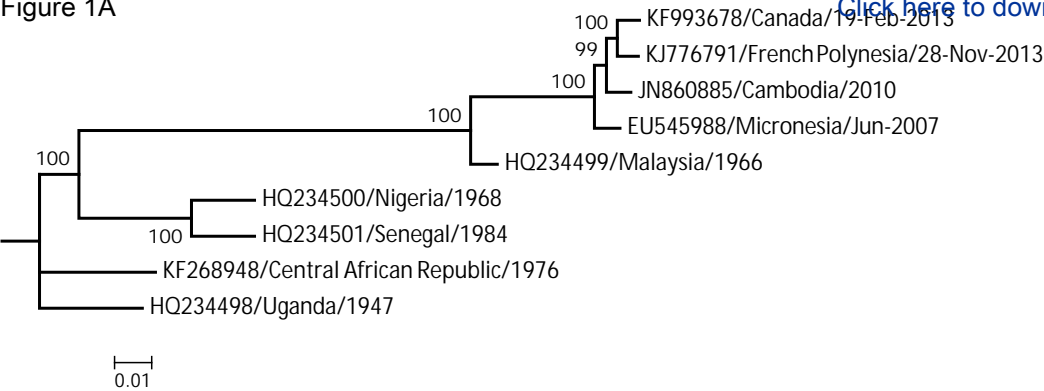
284 **Figure 2. Spread of Zika virus.** This is inferred from phylogenetic analysis where available in

285 the literature, otherwise reconstructed from patterns of case report clusters or

286 seropositivity in populations. Map background: Wikimedia commons public domain.

Figure 1A

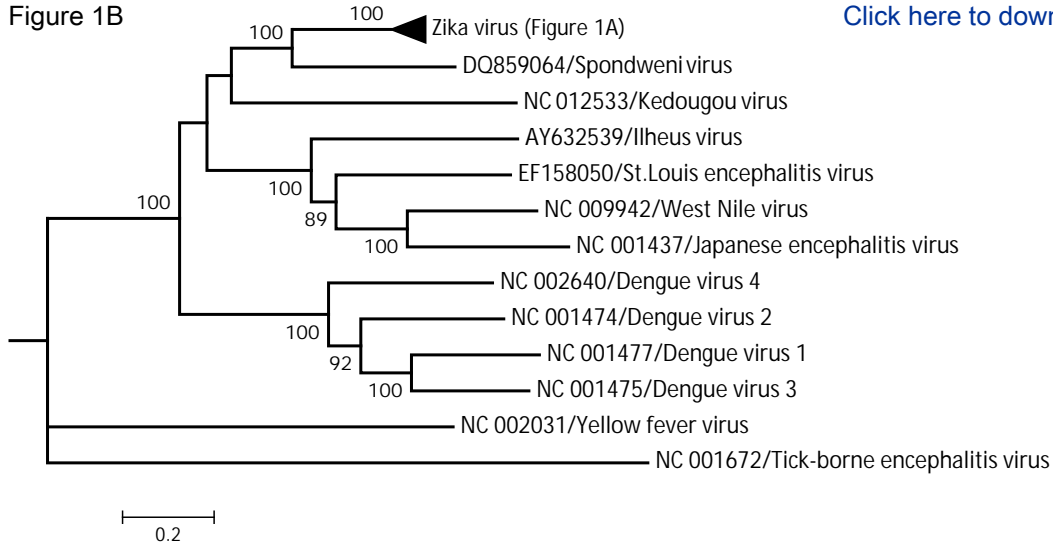
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