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Research

Zika: the origin and spread of a mosquito-borne virus

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Introduction

Zika, a flavivirus transmitted mainly by mosquitos in the genus *Aedes*, was discovered in 1947 in Uganda. From the 1960s to 1980s, human infections were found across Africa and Asia, typically accompanied by mild illness. The first large outbreak of disease caused by Zika infection was reported from the Island of Yap (Federated States of Micronesia) in 2007, as the virus moved from south-east Asia across the Pacific. During a 2013-14 outbreak in French Polynesia, the neurological disorder Guillain-Barré syndrome was linked to Zika infection. In South America, the first reports of locally transmitted infection came from Brazil in May 2015. In July 2015 Brazil reported an association between Zika virus infection and GBS. In October 2015 Brazil reported an association between Zika virus infection and microcephaly. For neither event was a causal link proven.

In February 2016, as infection moved rapidly through the range occupied by *Aedes* mosquitos in the Americas, WHO declared that Zika infection associated with microcephaly and other neurological disorders constitutes a Public Health Emergency of International Concern (PHEIC). By the start of February 2016, local transmission of Zika infection had been reported from more than 20 countries and territories in the Americas, and an outbreak numbering thousands of cases was under way in Cabo Verde, western Africa. Beyond the range of mosquito vectors, Zika virus infections are expected to be carried worldwide by international travel.

Objective

To describe the temporal and geographical distribution of Zika virus infection, and associated neurological disorders, from 1947 to February

2016.

Methods

To illustrate the spread of Zika virus, and associated neurological complications, we constructed a timeline through a literature search, using “Zika” and “ZIKV” as the search terms in PubMed. In addition, we drew on formal notifications to WHO under the International Health Regulations (IHR 2005),^{4,5} which are archived in the WHO Event Information Site (EIS). EIS contains information about public health events of potential international concern notified to WHO as required by the International Health Regulations. Reports in the timeline below come from EIS unless another reference is given. Notifications of specific events are available from the authors on request.

Findings

The following timeline summarizes the spread of Zika infection, country by country, from the earliest discovery in 1947 to the latest information as of 7 February 2016. Figure 1 provides a chronological map of the presence of Zika only in those countries for which there is evidence of autochthonous or indigenous transmission by mosquitos, excluding the many countries that have notified imported Zika infections.

1947: Scientists conducting routine surveillance for yellow fever in the Zika forest of Uganda isolate the Zika virus in samples taken from a captive, sentinel rhesus monkey.¹

1948: The virus is recovered from the mosquito *Aedes (Stegomyia) africanus*, caught on a tree platform in the Zika forest.^{1,2}

1952: The first human cases are detected in Uganda and the United Republic of Tanzania in a study demonstrating the presence of neutralizing antibodies to Zika virus in sera.³

1954: The virus is isolated from a young girl in Eastern Nigeria.⁴

1958: Two further Zika virus strains are isolated from *Aedes africanus* mosquitos caught in the Zika forest area.⁵

1964: A researcher in Uganda who fell ill while working with Zika strains isolated from mosquitoes provides the first proof, by virus isolation and re-isolation, that Zika virus causes human disease. Though a pink non-itchy rash lasting 5 days eventually covers most of his body, including the palms of his hands and soles of his feet, he reports his illness as “mild”, as he did not experience the “crippling bone pain” associated with dengue and chikungunya infections. Given the mild nature of the illness, the author concludes that “it is not surprising under normal circumstances the virus is not isolated frequently from man.”⁶

1960s-1980s: Zika is now being detected in mosquitos and sentinel rhesus monkeys used for field research studies in a narrow band of countries that stretch across equatorial Africa. Altogether, virus is isolated from more than 20 mosquito species, mainly in the genus *Aedes*. Sporadic human cases are identified, mostly by serological methods, but such cases are rare, and the disease is regarded as benign. No deaths or hospitalizations are reported, and seroprevalence studies consistently indicate widespread human exposure to the

virus.^{7–14} Molecular studies of viruses will later map the disease as it moves from Uganda to western Africa and Asia in the first half of the 20th century.^{15, 16}

1969–1983: The known geographical distribution of Zika expands to equatorial Asia, including India, Indonesia, Malaysia and Pakistan, where the virus is detected in mosquitos. As in Africa, sporadic human cases occur but no outbreaks are detected and the disease in humans continues to be regarded as rare, with mild symptoms. Seroprevalence studies in Indonesia, Malaysia and Pakistan indicate widespread population exposure.^{16–19} Researchers later suggest that the clinical similarity of Zika infection with dengue and chikungunya may be one reason why the disease was so rarely reported in Asia.⁷

2007: Zika spreads from Africa and Asia to cause the first large outbreak in humans on the Pacific island of Yap, in the Federated States of Micronesia. Prior to this event, no outbreaks and only 14 cases of human Zika virus disease had been documented worldwide.²⁰ House-to-house surveys among the island's small population of 11 250 people identify 185 cases of suspected Zika virus disease. Of these, 49 are confirmed (RNA identified by PCR or a specific neutralizing antibody response to Zika virus in the serum) and 59 are classified as probable (patients with IgM antibody against Zika virus who had a potentially cross-reactive neutralizing-antibody response). An estimated 73% of Yap residents over three years of age were infected with Zika virus. No deaths, hospitalizations, or neurological complications are reported.^{21, 23}

Although wind-blown mosquitoes can travel distances of several hundred kilometres over the open ocean, introduction of the virus by travel or trade involving an infected person or an infected mosquito is considered the most likely source of this outbreak, especially as no monkeys were present on the island during the outbreak.^{7, 21} The finding on Yap Island that Zika virus can cause an outbreak numbering more than one hundred confirmed and probable cases is striking. In the absence of any evidence that viral mutation can explain changes in epidemic behaviour, several other explanations are suggested including a lack of population immunity; that is, regular exposure to infection in Africa and Asia may have prevented the large outbreaks eventually seen on Pacific Islands and in the Americas. Under-reporting may also be a reason for missing previous outbreaks of infection, due to the clinical similarities of (mild) illness associated with Zika, dengue, and chikungunya infections, and the frequent co-circulation of all three viruses.

2008: A US scientist conducting field work in Senegal falls ill with Zika infection upon his return home to Colorado and infects his wife in what is probably the first documented case of sexual transmission of an infection usually transmitted by insects.²⁴

2012: Researchers publish findings on the characterization of Zika virus strains collected in Cambodia, Malaysia, Nigeria, Senegal, Thailand and Uganda, and construct phylogenetic trees to assess the relationships. Two geographically distinct lineages of the virus, African and Asian, are identified. Analysis of virus from Yap Island strengthens previous epidemiological evidence that the outbreak on Yap Island originated in south-east Asia.^{7, 21, 23, 25}

2013–2014: The virus causes outbreaks in four other groups of Pacific islands: French Polynesia, Easter Island, the Cook Islands, and New

Caledonia.^{26, 27} The outbreak in French Polynesia, generating thousands of suspected infections, is intensively investigated. The results of retrospective investigations are reported to WHO on 24 November 2015 and 27 January 2016. These reports indicate a possible association between Zika virus infection and congenital malformations and severe neurological and autoimmune complications.²⁸ In particular, an increase in the incidence of Zika infection towards the end of 2013 was followed by a rise in the incidence of Guillain-Barré syndrome.^{22, 29} However, because the island was also experiencing an outbreak of dengue, the association between Zika infection and Guillain-Barré syndrome remains suggestive but unproven. The finding does, however, challenge the notion that Zika infection causes only mild illness.^{22, 30, 31}

December 2013: A patient recovering from Zika infection on Tahiti Island in French Polynesia seeks treatment for bloody sperm. Zika virus is isolated from his semen, adding to the evidence that Zika can be sexually transmitted.³²

20 March 2014: During the 2013–14 outbreak of Zika virus in French Polynesia, two mothers and their newborns are found to have Zika virus infection, confirmed by PCR performed on serum collected within four days of birth. The infants' infections appear to have been acquired by transplacental transmission or during delivery.³³

31 March 2014: During the same outbreak of Zika virus in French Polynesia, 1505 asymptomatic blood donors are reported to be positive for Zika by PCR. These findings alert authorities to the risk of post-transfusion Zika fever.³⁴

2 March 2015: Brazil notifies WHO of reports of an illness characterized by skin rash in northeastern states. From February 2015 to 29 April 2015, nearly 7000 cases of illness with skin rash are reported in these states. All cases are mild, with no reported deaths. Of 425 blood samples taken for differential diagnosis, 13% are positive for dengue. Tests for chikungunya, measles, rubella, parvovirus B19, and enterovirus are negative. Zika was not suspected at this stage, and no tests for Zika were carried out.

29 March 2015: Brazil provides further details on reports of an illness, in four northeastern states, characterized by skin rash, with and without fever. The case definition used is “person having rash with or without fever, of unknown etiology, and whose clinical profile does not fit in suspected case definitions of dengue, measles or rubella.” Cases were first identified in Pernambuco in December 2014. In Maranhao, Rio Grande do Norte, and Bahia, cases were identified in February and March 2015.

29 April 2015: Bahia State Laboratory in Brazil informs WHO that samples have tested positive for Zika virus, but full laboratory confirmation is pending.

7 May 2015: Brazil's National Reference Laboratory confirms, by PCR, Zika virus circulation in the country. This is the first report of locally acquired Zika disease in the Americas.

7 May 2015: The Pan American Health Organization and WHO issue an epidemiological alert to Zika virus infection.³⁵

15 July 2015: Brazil reports laboratory-confirmed Zika cases in twelve states.

17 July 2015: Brazil reports detection of neurological disorders associated with a history of infection, primarily from the north-eastern state of Bahia. Among these reports, 49 cases were confirmed as Guillain-Barré syndrome. Of these cases, all but 2 had a prior history of infection with Zika, chikungunya or dengue.

5 October 2015: Health centres in the Republic of Cabo Verde begin reporting cases of illness with skin rash, with and without fever, in the capital city of Praia, on the island of Santiago. By 14 October, 165 suspected cases are reported.

8 October 2015: Brazil reports the results of a review of 138 clinical records of patients with a neurological syndrome, detected between March and August. Of the 138, 58 (42%) present neurological syndrome with a previous history of viral infection. Of the 58, 32 (55%) have symptoms that are said to be consistent with Zika or dengue infection.

8 October 2015: Colombia reports the results of a retrospective review of clinical records which reveals the occurrence, since July, of sporadic clinical cases with symptoms consistent with Zika infection. A sudden spike is reported between 11 and 26 September. Altogether, 90 cases are identified with clinical symptoms consistent with, but not proven to be, Zika infection.

16 October 2015: Colombia reports PCR confirmed cases of locally acquired Zika infection.

21 October 2015: Cabo Verde confirms, by PCR, the country's first outbreak of Zika infection.

22 October 2015: Colombia confirms, by PCR, 156 cases of Zika in thirteen municipalities, with most confirmed cases concentrated in the densely populated Bolivar department.

30 October 2015: Brazil reports an unusual increase in the number of cases of microcephaly among newborns since August, numbering 54 by 30 October.

2 November 2015: Suriname reports two PCR confirmed cases of locally acquired Zika infection.

5 November 2015: Colombia confirms, by PCR, 239 cases of locally acquired Zika infection.

11 November 2015: Brazil reports 141 suspected cases of microcephaly in Pernambuco state. Further suspected cases are being investigated in two additional states, Paraiba and Rio Grande do Norte.

11 November 2015: Brazil declares a national public health emergency as cases of suspected microcephaly continue to increase.

12 November 2015: Suriname reports 5 PCR confirmed cases of locally acquired Zika infection.

12 November 2015: Panama reports cases with symptoms compatible with Zika.

17 November 2015: The Pan American Health Organization and WHO issue an epidemiological alert asking PAHO Member States to report observed increases of congenital microcephaly and other central nervous system malformations under the International Health Regulations.³⁶

17 November 2015: Brazil reports the detection of Zika virus in amniotic fluid samples from two pregnant women from Paraíba whose fetuses were confirmed by ultrasound examinations to have microcephaly. Altogether, 399 cases of suspected microcephaly are being investigated in seven northeastern states.

21 November 2015: Brazil reports that 739 cases of microcephaly are being investigated in nine states.

24 November 2015: El Salvador reports its first 3 PCR confirmed cases of locally acquired Zika infection.

24 November 2015: French Polynesia reports the results of a retrospective investigation documenting an unusual increase in the number of central nervous system malformations in fetuses and infants from March 2014 to May 2015. At the date of reporting, at least 17 cases are identified with different severe cerebral malformations, including microcephaly, and neonatal brainstem dysfunction.

25 November 2015: Mexico reports three PCR confirmed cases of Zika infection, of which two were locally acquired. The third case had a travel history to Colombia.

26 November 2015: Guatemala reports its first PCR confirmed case of locally acquired Zika infection.

27 November 2015: Paraguay reports six PCR confirmed cases of locally acquired Zika infection.

27 November 2015: The Bolivarian Republic of Venezuela reports seven suspected cases of locally acquired Zika infection. Four samples test positive by PCR.

28 November 2015: Brazil detects Zika virus genome in the blood and tissue samples of a baby with microcephaly and other congenital anomalies who died within 5 minutes of birth.

28 November 2015: Brazil reports three deaths among two adults and a newborn associated with Zika infection. As deaths from Zika infection are extremely rare, these cases are reported in detail.

1 December 2015: The Pan American Health Organization and WHO issue an alert to the association of Zika virus infection with neurological syndrome and congenital malformations in the Americas. The alert includes guidelines for laboratory detection of the virus.³⁷

2 December 2015: Panama reports its first 3 PCR confirmed cases of locally acquired Zika infection.

6 December 2015: Cabo Verde reports 4744 suspected cases of Zika. No neurological complications are reported.

14 December 2015: Panama reports four PCR confirmed cases of locally acquired Zika infection, and 95 cases with compatible symptoms.

15 December 2015: Samples taken from patients in Cabo Verde test positive, by PCR, for Zika.

16 December 2015: Honduras reports two PCR confirmed cases of locally acquired Zika infection.

21 December 2015: French Guiana and Martinique report their first two PCR confirmed cases of locally acquired Zika infection.

22 December 2015: Brazilian researchers publish evidence, drawn from case reports in several countries, that depictions of Zika as “a mild cousin of dengue” may not be accurate due to the possibility of more serious disease symptoms, especially in immunocompromised patients.³⁸

30 December 2015: Brazil reports 2975 suspected cases of microcephaly, with the highest number occurring in the north-east region.

31 December 2015: The United States reports the first PCR confirmed case of locally acquired Zika infection in the Commonwealth of Puerto Rico, an unincorporated territory of the United States.

5 January 2016: Researchers report the first diagnoses of intrauterine transmission of the Zika virus in two pregnant women in Brazil whose fetuses were diagnosed with microcephaly, including severe brain abnormalities, by ultrasound. Although tests of blood samples from both women are negative, Zika virus is detected in amniotic fluid.³⁹

7 January 2016: The Maldives reports that a Finnish national who worked in the country became ill upon his return to Finland, where he tested positive, by PCR, for Zika infection.

7 January 2016: Scientists in Guyana publish the results of Zika genome sequencing of viruses from four patients in Suriname whose sera were negative for dengue and chikungunya viruses but positive for Zika virus. Suriname strains belong to the Asian genotype and are almost identical to the strain that circulated in French Polynesia in 2013.⁴⁰

7 January 2016: Ophthalmologists in Brazil report severe ocular malformations in three infants born with microcephaly.⁴¹

12 January 2016: In collaboration with health officials in Brazil, the United States Centers for Disease Control and Prevention release laboratory findings (notified to WHO under IHR protocol) of four microcephaly cases in Brazil (two newborns who died in the first 24 hours of life and two miscarriages) which indicate the presence of Zika virus RNA by PCR and by immunohistochemistry of brain tissue samples of the two newborns. In addition, placenta of the two fetuses miscarried during the first 12 weeks of pregnancy test positive by PCR. Clinical and epidemiological investigations in Brazil confirm that all four women

presented fever and rash during their pregnancy. The findings are considered the strongest evidence to date of an association between Zika infection and microcephaly.⁴²

14 January 2016: Guyana reports its first PCR confirmed case of locally acquired Zika infection.

15 January 2016: The United States issues interim travel guidance for pregnant women which, “out of an abundance of caution,” advises pregnant women in any trimester to consider postponing travel to areas with ongoing local transmission of the virus, or to take precautions against mosquito bites if they must travel.⁴³

15 January 2016: Ecuador reports its first two PCR confirmed cases of locally acquired Zika infection. The next day, the country confirms an additional 6 cases, of which 2 are locally acquired, three imported from Columbia, and one from the Bolivarian Republic of Venezuela.

15 January 2016: Barbados reports its first three PCR confirmed cases of locally acquired Zika infection.

15 January 2016: The Hawaii Department of Health (USA) reports a case of microcephaly in Hawaii, born to a woman who had resided in Brazil early in her pregnancy.

16 January 2016: The Plurinational State of Bolivia reports its first PCR confirmed case of locally acquired Zika infection.

18 January 2016: Haiti reports its first five PCR confirmed cases of locally acquired Zika.

18 January 2016: France reports the first PCR confirmed case of locally acquired Zika in Saint Martin.

19 January 2016: El Salvador reports an unusual increase of Guillain-Barré syndrome. From 1 December 2015 to 6 January 2016, 46 cases of the syndrome were reported, including two deaths.⁴⁴ Of the 22 patients with a medical history, 12 (54%) presented with fever and skin rash in the 7 to 15 days before the onset of symptoms consistent with Guillain-Barré syndrome.

21 January 2016: Brazil reports 3893 suspected cases of microcephaly, including 49 deaths. Of these, 3381 are under investigation. In six cases, Zika virus was detected in samples from newborns or stillbirths.

22 January 2016: Brazil reports that 1708 cases of Guillain-Barré syndrome have been registered by hospitals between January and November 2015. Most states reporting cases are experiencing simultaneous outbreaks of Zika, chikungunya, and dengue. The potential cause of the upsurge in this syndrome cannot be established.

23 January 2016: The Dominican Republic reports its first 10 PCR confirmed cases of Zika infection, of which 8 were locally acquired and 2 were imported from El Salvador.

25 January 2016: France reports two confirmed cases of Guillain-Barré syndrome in Martinique. Both cases require admission to an intensive

care unit. One patient tests positive for Zika virus infection.

25 January 2016: The United States reports the first PCR confirmed case of locally acquired Zika infection in St Croix, one of the three main islands in the United States Virgin Islands.

27 January 2016: Nicaragua reports its first two PCR confirmed cases of locally acquired Zika infection.

27 January 2016: French Polynesia reports retrospective data on its Zika outbreak, which coincided with a dengue outbreak. From 7 October 2013 to 6 April 2015, 8750 suspected cases of Zika were reported, with 383 PCR confirmed cases and an estimated 32 000 clinical consultations (11.5% of the total population). The outbreak ended in April 2014. During the outbreak, 42 cases of Guillain-Barré syndrome were diagnosed, representing a 20-fold increase in incidence over previous years. Though 10 of these patients required admission to an intensive care unit, none died. All 42 cases tested positive for Zika and dengue. Tests excluded other known causes of Guillain-Barré syndrome, including *Campylobacter jejuni*, cytomegalovirus, HIV, Epstein-Barr and herpes simplex viruses. The investigation concluded that successive dengue and Zika virus infections might be a predisposing factor for developing Guillain-Barré syndrome.

28 January 2016: Curacao reports its first PCR confirmed case of locally acquired Zika.

29 January 2016: Suriname reports 1,107 suspected cases of Zika, of which 308 are confirmed, by PCR, for Zika virus.

30 January 2016: Jamaica reports its first PCR confirmed case of locally acquired Zika.

1 February 2016: WHO declares that the recent association of Zika infection with clusters of microcephaly and other neurological disorders constitutes a Public Health Emergency of International Concern.

1 February 2016: Cabo Verde reports 7081 suspected cases of Zika between end September 2015 and 17 January 2016. The number of cases peaked at the end of November and began to decline. Though the reporting of cases of microcephaly is mandatory, no neurological complications are detected.

2 February 2016: Chile reports its first three PCR confirmed cases of Zika virus on the mainland in travellers returning from Colombia, the Bolivarian Republic of Venezuela, and Brazil.

2 February 2016: The United States reports a case of sexual transmission of Zika infection in Texas. One patient developed symptoms of illness after returning from the Bolivarian Republic of Venezuela. The second patient had not recently travelled outside of the United States, but subsequently developed symptoms after sexual contact with the traveller. This is the third indication that the virus can be sexually transmitted, which appears to be a rare event.⁴⁴

4 February 2016: Brazilian health officials confirm a case of Zika virus infection transmitted by transfused blood from an infected donor.

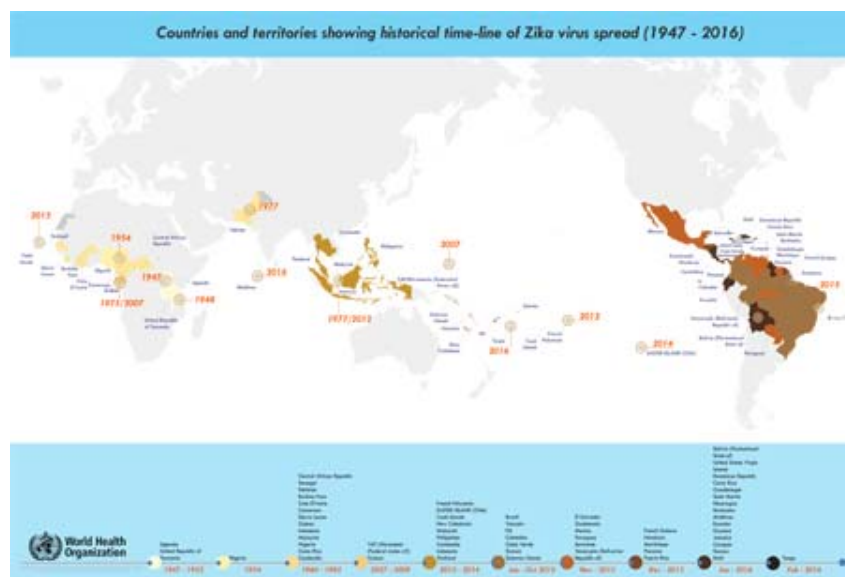
7 February 2016: Suriname reports an increase in Guillain-Barré syndrome, beginning in 2015, with 10 cases of Guillain-Barré syndrome positive for Zika (PCR test on urine sample). Four Zika-related deaths are reported over the preceding 2 weeks (including one Dutch visitor), with symptoms of diarrhoea or vomiting, dehydration and joint pain, rapidly followed by death. All deaths occurred in older males with underlying illnesses or risk factors that may have contributed to the fatal outcomes.

Conclusion

Human Zika virus infection appears to have changed in character while expanding its geographical range. The change is from an endemic, mosquito-borne infection causing mild illness across equatorial Africa and Asia, to an infection causing, from 2007 onwards, large outbreaks, and from 2013 onwards, outbreaks linked with neurological disorders including Guillain-Barré syndrome and microcephaly across the Pacific region and the Americas. The future transmission of Zika infection is likely to coincide mainly with the distribution of *Aedes* mosquito vectors, although there may be rare instances of person-to-person transmission (other than mother to child, e.g. through semen). Beyond the range of mosquitos, infection has been, and will continue to be, carried widely by international travel.

Figure 1. The temporal and geographical distribution of Zika virus from 1947 to February 2016. Dates refer to events reported in the published literature (cited in the text), or drawn from WHO's Event Information Site (EIS).

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Microcephaly/Zika virus »

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Epidemiological Update:

Region of the Americas

Neurological syndrome, congenital anomalies, and Zika virus infection
