What we need to know about Zika virus

Zika is an emerging disease. Because congenital Zika infections are almost certainly the cause of the epidemic of microcephaly detected in Brazil, the World Health Organization has declared a public health emergency of international concern.

Background

The Zika virus was isolated in 1947 from monkeys in the Zika forest in Uganda; since then sporadic case reports and some surveys have shown evidence of active virus circulation in specific areas (Dick et al, 1952). The epidemiological pattern seems to have changed in the last decade, with outbreaks in Oceania and in the Americas, and Zika virus circulation seen on all continents (Hayes, 2009).

Zika virus is a RNA flavivirus genetically close to dengue, West Nile, yellow fever and Japanese encephalitis virus. It is transmitted by *Aedes* species (*A. africanus*, *A. luteocephalus*, *A. albopictus*, *A. furcifer*, *A. vittatus* and *A. aegypti*), a vector which has been difficult to control (Duffy et al, 2009). Since Zika and dengue are transmitted by the same mosquito, there is a high probability of Zika spreading to those countries (over 100) where dengue transmission is established.

The classical clinical presentation is fever, maculopapular rash, arthralgia, arthritis, myalgia, headache, conjunctivitis, pruritus and oedema (similar to dengue and chikungunya). Symptoms usually begin 2–7 days after being bitten by an infected mosquito and can last for 1 week (Duffy et al, 2009). Serological cross-reactions mean that patients with Zika infection may show a positive result on a dengue blood test. Virus RNA can be detected from blood, urine, saliva or semen samples (Paixão et al, 2016) collected less than 5 days after the onset of symptoms but the detection rate is low.

Ms Enny S Paixão is PhD Candidate in the Department of Infectious Disease, London School of Hygiene and Tropical Medicine, London WC1E 7HT

Professor Laura C Rodrigues is Professor in the Department of Infectious Disease, London School of Hygiene and Tropical Medicine, London

Correspondence to: Ms ES Paixão (enny.cruz@lshtm.ac.uk)

The first large and well-documented Zika outbreak occurred in Yap, an island within the Federated States of Micronesia, in 2007. The rate of transmission was high – it was estimated that 73% of the population was infected during the outbreak and 20% developed clinical symptoms. No hospitalization or deaths caused by Zika were reported in the small population of the island (Duffy et al, 2009). In 2013, a Zika epidemic occurred in French Polynesia, with an estimated asymptomatic attack rate of 11.5% (estimation based on patients that used health-care facilities) (Malet et al, 2015).

The current epidemic

There are no estimates of the rate of clinical or subclinical Zika infection in Brazil: until 18 February 2016 Zika was not a notifiable disease in Brazil, and there are no prevalence surveys. Cases of an atypical exanthematous disease were reported in Brazil in late 2014; outbreaks were reported in 2015 and Zika virus was identified as the aetiological agent in April 2015. In October 2015, health authorities were notified by doctors of an increase in the number of live newborns with microcephaly; calcifications on brain imaging suggested congenital infection.

In November, the Ministry of Health in Brazil declared a public health emergency, and on 1 December the Pan American Health Organization issued an epidemiological alert. In February 2016, with 4783 cases of suspected microcephaly notified in Brazil (not all will be confirmed by imaging), and Zika detected in 27 American countries, the World Health Organization declared the ongoing Zika crisis a public health emergency of international concern.

Until late 2015, Zika virus had never been considered a cause of neurological complication or congenital infections. The number of neurological disorders such as Guillain–Barré syndrome increased during the Zika outbreaks in French Polynesia, Brazil, Venezuela and El Salvador (Paixão et al, 2016). At the time of writing, at the end of February 2016, the causal relationship between Zika and microcephaly has not been unanimously accepted, but the World Health Organization declared a link between the illness and cases of microcephaly as 'strongly suspected'.

As Teixeira et al (2016) have shown, the evidence that Zika has been causing microcephaly is growing:

1. The spatial distribution of cases of microcephaly and Zika outbreaks are similar
2. The peak levels of Zika virus infections are suspected to be 6–7 months before cases of microcephaly started to show up
3. Zika virus is neurotropic
4. Brain imaging suggests congenital infection
5. Cases were negative for TORCH (toxoplasmosis, others (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus and herpes) infections (some of the most common infections associated with congenital anomalies)
6. Perinatal transmission of Zika was confirmed in two reported cases
7. Zika virus RNA was found in amniotic fluid samples from two pregnant women with fetal microcephaly (the two women had Zika-like symptoms at weeks 18 and 19 of gestation)
8. Among 35 infants with microcephaly born from women suspected to have had Zika infection during pregnancy in northeast Brazil, 26 (74%) of the mothers reported having a rash during the first or second trimester (Schuler-Faccini et al, 2016)
9. Microcephaly cases were identified in the fetuses of women who were pregnant during the outbreak in French Polynesia after the suspicion was raised in Brazil

© 2016 MA Healthcare Ltd

10. More recently a case report of fetal autopsy, after a mother who had lived in Brazil during the Zika epidemic requested termination of pregnancy, showed severe fetal brain injury with multifocal dystrophic calcifications, and Zika virus was found in the brain tissue. There were indications of viral replication in the brain and the complete genome sequence of the Zika virus was recovered, indicating the presence of two major amino acid substitutions in the Asian lineage (Mlakar et al, 2016).

The future

There is much that we still do not have: no vaccine, no treatment to prevent infected pregnant women transmitting the infection to the fetus, no effective vector control, no good reliable diagnostic tests.

There is also much that we do not know: what is the absolute risk of microcephaly by gestational week of infection, does Zika confer immunity, what is the spectrum of the congenital Zika syndrome, why did Zika become epidemic, was it causing microcephaly when it was restricted to Africa? Are the genetic differences between the African Zika virus and the Asia Zika virus relevant? Chikungunya infections seem to arise at the same time as Zika infections arise in specific areas – is this true and, if so, why? Can Zika be transmitted by other vectors? Can it be transmitted sexually (virus has been isolated in sperm) and if so is this relevant to the course of the epidemics? Will it spread to South Asia?

Conclusions

It does not appear that the Zika epidemic will be like the Ebola epidemic, where a concerted international effort stopped the outbreak in 18 months. The scientific community has reacted swiftly and much research and development has already started, but this time, until a vaccine or better mosquito control methods are developed, or maybe until the outbreaks run their course leaving the adult population with a high level of immunity, we must prepare to live with congenital Zika for a few years. Time will probably define the emergence of Zika as one of the biggest personal tragedies and scientific challenges for international public health this decade. **BJHM**

KEY POINTS

- Since Zika and dengue are transmitted by the same mosquito, there is a high probability of Zika spreading to countries where dengue transmission is established.
- Despite the classical Zika clinical presentation being self-limited, it is almost certain that congenital Zika infections can cause microcephaly.
- There is much we still do not have to control the spread of Zika, and there is much we still do not know about Zika.
- Despite the efforts of health authorities and the scientific community we must prepare to live with congenital Zika for a few years.

Dick GWA, Kitchen SF, Haddow AJ (1952) Zika virus (I). Isolations and serological specificity. *Trans R Soc Trop Med Hyg* **46**: 509–20

Duffy MR, Chen TH, Hancock WT et al (2009) Zika virus outbreak on Yap Island, Federated States of Micronesia. *N Engl J Med* **360**: 2536–43 (doi: 10.1056/NEJMoa0805715)

Hayes EB (2009) Zika virus outside Africa. *Emerg Infect Dis* **15**: 1347–50 (doi: 10.3201/eid1509.090442)

Malet H, Vial A, Musso D (2015) Epidemiological and statistiques health information bulletin [in French]. www.hygiene-publique.gov.pf/IMG/pdf/no13_-_mai_2015_-_zika.pdf (accessed 25 January 2016)

Mlakar J, Korva M, Tul N et al (2016) Zika virus associated with microcephaly. *N Engl J Med* (doi: 10.1056/NEJMoa1600651)

Paixão ES, Barreto F, Costa MCN, Teixeira MG, Rodrigues L (2016) History, epidemiology and clinical manifestations of Zika: a systematic review. *Am J Public Health* (doi: 10.2105/AJPH.2016.303112)

Schuler-Faccini L, Ribeiro EM, Feitosa IM et al (2016) Possible Association between Zika Virus Infection and Microcephaly—Brazil, 2015. *MMWR Morb Mortal Wkly Rep* **65**(3): 59–62 (doi: 10.15585/mmwr.mm6503e2)

Teixeira MG, Costa MCN, Oliveira WK, Nunes ML, Rodrigues L (2016) The epidemic of microcephaly in Brazil related to Zika virus: a public health emergency of international interest. *Am J Public Health* (doi: 10.2105/AJPH.2016.303113)

BRITISH JOURNAL OF HOSPITAL MEDICINE

Correspondence

If you would like to comment on any of the articles in *British Journal of Hospital Medicine*, please write in no more than 250 words to:

Professor Rob Miller, Editor-in-Chief, BJHM
c/o Rebecca Linssen, MA Healthcare
St Jude's Church, Dulwich Road, London SE24 0PB

Email: rebecca.linssen@markallengroup.com | Fax: 020 7978 8316

© 2016 MA Healthcare Ltd