

Zika Virus: The New Rubella Epidemic

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Abstract

The explosive epidemic of Zika virus with resultant central nervous system malformations in children born to infected mothers has now reached epidemic proportions. This disease is reminiscent of our struggle with rubella prior to the development of safe and effective vaccines in the 1960s. Both are benign infections in children and adults, but capable of affecting fetal brain development in pregnant women.

Keywords: Zika virus; Congenital infection; Epidemic; Pandemic; Viral infection

Epidemiology

Zika virus is a flavivirus that was first isolated in 1947 from a rhesus monkey in the Zika forest of Uganda, thereby gaining its name. This virus was actually identified incidentally during an effort to isolate the yellow fever virus in that region [1]. The first reported case of Zika virus infection causing human illness was in Nigeria in 1953. Subsequently, there have been outbreaks of Zika virus infections in West Africa (Nigeria, Sierra Leone, Gabon and Senegal) and Asia (Pakistan, Indonesia and Malaysia) [2]. In 2007, an outbreak of Zika virus infected an estimated 73% of residents of the Yap State of Micronesia [3]. By 2013, Zika virus had spread across the Pacific Ocean to French Polynesia followed by the Cook Islands, Easter Island, Vanuatu and the Solomon Islands [4,5]. Despite the spread of the Zika virus and its epidemic potential, there had been no reported neurologic or fetal complications to trigger public health concerns. However, the most recent outbreak in Brazil in 2014, with its subsequent rapid spread through South America, Central America and Mexico, along with emerging reports of microcephaly in neonates born to mothers who were infected with Zika virus during their pregnancy, had prompted the World Health Organization (WHO) to declare the Zika virus a Public Health Emergency of International Concern on February 1, 2016 [6].

Currently, there are 56 countries and territories with active Zika virus transmission, including Cape Verde, Oceania/Pacific Islands, countries in South America and Central America and Mexico [7]. As of August 2016, the United States Centers for Disease Control (CDC) has also acknowledged 29 autochthonous cases of Zika virus infection in Miami, Florida thereby documenting Zika virus spread to the United States [8,9].

Modes of Transmission

From case reports and data from related flavivirus infections, the incubation period is estimated to be 3 to 14 days after inoculation from the *Aedes aegypti* or *Aedes albopictus* mosquitoes, and duration

of viremia is estimated to be approximately 11 days. There are currently 21 reported cases of male to female and 1 case female to male sexual transmission in the US [9,10]. Other documented modes of Zika virus transmission include vertical, intrapartum and perinatal transmission, laboratory exposures, and possibly blood transfusions [11-14]. This has prompted the US Food and Drug Administration (FDA) to revise its guidance to recommend that all donated blood in the US and its territories to be screened for Zika virus.

Clinical Findings

Clinical studies suggest that up to 80% of children and adults infected with Zika virus are asymptomatic. Clinical symptoms of acute illness are usually mild and self-limiting, lasting just 2 to 7 days, manifesting as fever, headache, arthralgia, and maculopapular rash in only 20% of patients that were infected [15]. Suspicion for infection is warranted if a patient has:

1. Travelled to, or resided in, an affected area, or had sexual intercourse with someone who had travelled to or resided in an affected area within the past 2 weeks and
2. Has ≥ 2 of the following manifestations: low grade fever ($>37.2^{\circ}\text{C}$), pruritic maculopapular rash, non-purulent conjunctivitis, arthralgia, headaches or myalgia [15].

Neurologic and Congenital Complications

Zika virus has been implicated in several cases of Guillain-Barré syndrome (GBS). This includes an outbreak in French Polynesia from 2013-2014, during which an increase in cases of GBS preceded by an increase in Zika virus infections was first noted [16,17]. In the only case control study in that region, published by Cao-Lormeau et al. 41 of 42 patients with GBS during the 2013-2014 Zika outbreak had Zika virus antibodies, compared to 35 of 98 in the control group [17]. There have also been increasing reports of GBS and acute disseminated encephalomyelitis following Zika virus infection in other regions of the world, although a causal link has not been clearly established [18].

Despite the limited evidence available to directly link Zika virus with neurological effects, the WHO is preparing for the potential

severe public health impact by instituting Zika virus prevention measures in pregnancy including mosquito control, mosquito avoidance and guidance for sexual contact and blood transfusions. Similarly, the US Health and Human Services and CDC has responded to the growing number of Zika virus infections in the US and its territories, officially calling the outbreak a public health emergency while offering similar preventive guidelines. As of August 2016, there have been 11,528 laboratory-confirmed cases of Zika in the US and its territories, including 1,396 pregnant women and 33 GBS cases [9,19].

The growing concern with Zika virus is its potential as a new TORCH agent with its association with fetal neurological manifestations. A recent case study showed evidence of neurotropism of the virus in a 32 week fetal autopsy whose mother had presented at 13 weeks pregnant in Brazil with fever, retroocular pain, pruritus, maculopapular rash, concerning for Zika virus infection [20]. Fetal ultrasound was first abnormal at 29 weeks showing microcephaly and calcifications. Autopsy was done at 32 weeks after medical termination of pregnancy and found Zika virus only in neural tissues, which showed extensive inflammation and injury from astrocyte and microglial activation, suggesting major neurotropism [20].

The evidence from Brazil and Polynesia regarding microcephaly and Zika virus during pregnancy indicate that the first trimester poses the most risk to the fetus developing microcephaly [21]. In addition to microcephaly, other effects to the fetus include early fetal death and a variety of ocular abnormalities including hypoplasia and cupping of the optic disc, abnormalities in pigment and chorioretinal atrophy [21].

Furthermore, in a recent study by Hughes et al, it was shown that Zika virus has a greater affinity for immature neurons than for mature neurons *in vitro*, possibly causing cell death and decreased neuronal cell-layer proliferation leading to microcephaly [22]. In addition to recovery of Zika virus in neural tissues and the increasing rate of reported microcephaly in regions of the Brazilian Zika virus outbreak, Zika RNA has also been found in the amniotic fluids, placenta, and blood of infants with microcephaly providing further evidence supporting a direct link between Zika virus infection and congenital Zika syndrome [23].

Diagnosis

Real-time reverse-transcription polymerase chain reaction (rRT-PCR) molecular assay, which is now commercially available, is the preferred test to diagnose Zika virus infection because it is rapid and highly specific. However, commercial laboratories do not have Zika IgM enzyme-linked immunosorbent assay (ELISA) or confirmatory serologic testing (plaque reduction neutralization test, PRNT) so additional samples may be necessary if the rRT-PCR assay is negative [24]. Due to the decline in viremia levels with time and inaccurate dating of symptoms onset, a negative rRT-PCR cannot rule out Zika infection. It is recommended that providers retain and store an aliquot of the patient's serum (at 2-8°C) or collect a second serum sample within 12 weeks of symptom onset. The most optimal samples are serum collected within 7 days and urine collected within 14 days after symptom onset. Other body fluids such as CSF, amniotic fluid and semen may also be used [25,26].

Patients presenting 2-12 weeks after symptom onset should be tested for Zika virus IgM antibody. Positive Zika virus IgM with confirmatory serum neutralizing antibody titers greater than fourfold

of dengue or chikungunya virus neutralizing antibody titers is diagnostic of Zika infection [26].

Ultrasound examination within 3-4 weeks of symptom onset or travel is recommended for pregnant women living in or who have travelled to areas with Zika virus. Findings suggestive of congenital infection include intracranial calcifications, microcephaly, ventriculomegaly, arthrogryposis and other brain and eye abnormalities. Reassuring initial ultrasound does not preclude congenital infection, and must be followed by serial or subsequent ultrasounds dependent on maternal infection status. It is currently not known how long after infection a woman can transmit the virus to the fetus or how long the amniotic fluid will be PCR positive [27].

Recommendation

Women diagnosed with Zika virus should wait at least 8 weeks after symptom onset to try to conceive. Men diagnosed with Zika virus should wait at least 6 months after symptom onset to attempt to conceive. Asymptomatic women and men with possible exposure to Zika virus should wait at least 8 weeks after exposure before attempting to conceive [28].

Zika virus RNA has been detected in many body fluids including blood, urine, saliva and amniotic fluid, but no health-care associated transmission has been documented. There is currently no evidence to warrant contact precaution or respiratory isolation of Zika virus infected patients [11,13,14].

Although there are reports of low levels of Zika virus in breast milk, the benefits of breastfeeding outweigh a likely mild infection in neonates, and infected women are recommended to continue breastfeeding [29,30].

Due to overlap of symptoms with dengue fever, NSAIDs should be avoided in acutely ill patients until dengue virus is ruled out due to potential hemorrhagic complications.

Prevention and Future Directions

As there is no current treatment or vaccine for Zika virus infection, the current recommendation is to avoid exposure to mosquitos and symptomatic treatment if infection is suspected or confirmed. It is evident that the only way to control this epidemic is with the development of a safe and effective vaccine to prevent disease in women as was the approach for the rubella epidemics. Efforts are currently underway in the United States to achieve this goal, with the latest vaccine entering its phase 1 trials as of August 2016. Hopefully our government will provide the resources and support to accomplish this task and to further our research for a better understanding of the congenital Zika syndrome.

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