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In Focus

Zika Virus: More Questions Than Answers

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The recent Zika virus (ZIKV) outbreak has been declared a Public Health Emergency of International Concern (PHEIC) by the World Health Organization in February 2016. It started in Brazil in 2015, rapidly spread through South and Central America, and is expected to reach the continental US in the summer of 2016. The appearance of ZIKV has been connected with an increase in cases of microcephaly in newborns of the affected areas and Guillain–Barré Syndrome (GBS) (WHO, 2016). Since the virus' first isolation in Uganda in 1947, the two major outbreaks happened in Micronesia (2007) and in French Polynesia (2013). The 2013 outbreak is the only precedent where ZIKV was associated with serious complications (GBS) and a causal link between ZIKV infection and GBS was suggested based on a large study (Cao-Lormeau et al., 2016). The mechanism of ZIKV-induced GBS is not clear, but one possibility is cross-reactivity between a viral antigen and the self-peptide myelin.

The evidence for ZIKV causing fetal microcephaly has been under debate due to the small number of studies reported, but as new reports appear every week the evidence seems clearer, although it has not been scientifically proven yet. A recent cohort study of 88 pregnant women in Brazil showed that 29% of infected mothers delivered babies with fetal abnormalities (Brasil et al., 2016). Furthermore, from nine current reported cases of ZIKV-positive pregnant women in the US that traveled to ZIKV endemic areas, five pregnancies resulted in fetal abnormalities or death, two in healthy babies while two women are still pregnant (Meaney-Delman et al., 2016). ZIKV has also been found both in the amniotic fluid and in fetal brain after pregnant mothers were infected, supporting the causal link between ZIKV-infected mothers and fetal microcephaly (Marrs et al., 2016). There are precedents of closely related neutrotropic flaviviruses that cause neurological diseases. West Nile Virus (WNV) can cause encephalitis and meningitis, and chikungunya virus (CHIKV) can cause neonatal encephalopathy and microcephaly (Gerardin et al., 2014). Additionally, other viruses causing congenitally acquired infections (TORCH) like rubella virus, cytomegalovirus, herpes simplex virus, varicella zoster virus or HIV have been associated with microcephaly in neonates. ZIKV can bind different cell receptors (Hamel et al., 2015), some of them present in neurons, and can infect and replicate in murine neurons and astroglia (Bell et al., 1971). Although pregnant women infected with ZIKV do not show neurological disease, hormonal-induced changes in immune responses, infections in ZIKV-naïve women or specific genetic factors might facilitate increased replication of the virus in the mother, cross-placental barrier accessibility and ultimately ZIKV presence in the fetus during early stages of brain development. Nevertheless, the neuropathogenic effect of ZIKV is unknown. Similarly to GBS, the induction of mimicry, where antibodies produced against a viral protein by the mother will recognize a self-protein in the fetus (i.e. during brain development), is possible, or the presence of ZIKV in the brain could also cause tissue damage.

ZIKV is a mosquito-borne virus of the family *Flaviviridae*, genus *Flavivirus*. The natural vector for ZIKV transmission is *Aedes sp*. mosquitoes, mainly *A. aegypti* and *A. albopictus* species, which also transmit other flaviviruses as dengue virus (DENV) and CHIKV. This mosquito is endemic in tropical areas, and may have facilitated ZIKV dispersion during outbreaks. ZIKV has been also reported to be transmitted by blood transfusion and sporadically by sexual contact, from a sexual partner infected while traveling to ZIKV areas. Detection of infective ZIKV in semen has been confirmed, and an increasing number of potential sexual transmission cases are currently being investigated by the CDC (Hills et al., 2016). This poses new challenges to control the epidemic.

ZIKV infection is asymptomatic in 80% of the cases and the remainder 20% suffer mild symptoms similar to those induced by DENV: fever, headache, red eyes, rash, fatigue, muscle and joint pain. In the current outbreak, cross-reactivity with antibodies from DENV and CHIKV in the affected areas has stalled the use of ELISA to detect ZIKV antibodies. The only reliable diagnostic technique available is RT-PCR testing of serum, but is only positive during the viremia, usually 3–7 days, and of urine, where virus can be detected from 4 up to 30 days after the onset of infection. Tests for semen and saliva are still under development. Amniotic fluid sampling for PCR has been recommended for pregnant women, especially when the blood test results are negative. Ultrasound testing can confirm fetal microcephaly, and additional testing may be performed on fetal tissue, like RT-PCR on tissue and electron microscopy to detect virus particles, and direct immunofluorescence suggestive of viral infection within neurons.

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1. Open questions and concluding remarks

Many questions need to be addressed, such as: How does ZIKV induce microcephaly and GBS? What is the real frequency of developing those complications after ZIKV infection? What would be the risk phase of pregnancy for ZIKV transfer to the fetus? Can asymptomatic mothers transmit the virus to the fetus? Are all the fluids positive for ZIKV contagious? What is the risk of sexual transmission of ZIKV? Is there a reservoir organ that can shed ZIKV for long periods?

To answer those questions and to effectively track the ZIKV epidemic, the main effort should be to develop optimal diagnostic techniques. This will allow tracking all the real ZIKV infection cases for epidemiological studies and correlation analyses with microcephaly/GBS. It will facilitate surveillance and cohort studies, to determine the real percentages of vertically transmitted ZIKV and of fetal death, miscarriage, microcephaly or other fetal malformations. A registry has been created in the US to track and follow up children of mothers infected during pregnancy, which will provide important information regarding the long-term effects of ZIKV infection during pregnancy (Oduyebo et al., 2016).

There is no treatment or vaccine for ZIKV infection, only preventive and supportive care. More research on therapeutic approaches to suppress ZIKV spread is needed. Some strategies used for closely related flaviviruses could be applied to ZIKV, like drugs targeting host factors or viral proteins required for viral infection. The development of successful vaccines, similarly to the one for Yellow Fever virus (YFV) and other flaviviruses, is also a priority and is currently under way in several laboratories, although this may be a long process.

Animal models like guinea pigs, successfully used for the study of other congenital and perinatal infections as cytomegalovirus (CMV), or mice previously tested for ZIKV infection, will be crucial to study ZIKV infection, neurotropism, and host responses. They will also facilitate the study of potential vertical transmission of ZIKV and the confirmation of ZIKV as the causative agent of the neurological disorders in the fetus as well as confirmation of sexual transmission by Koch's postulates.

In conclusion, the current ZIKV outbreak has been followed in real time and highlights the need for coordinated responses to understand how viruses interact with the host and what factors determine severity of symptoms. The rapid declaration of PHEIC by the WHO has initiated a global response from the scientific community to hamper the spread of the virus and to gain knowledge on its pathogenic potential.

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