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Consequences of congenital Zika virus infection

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The 2015 Zika virus (ZIKV) epidemic in the Americas led to the discovery that ZIKV causes congenital abnormalities including microcephaly, intrauterine growth restriction, and eye disease that can result in blindness. Studies in animal models and human organoid cultures, together with human epidemiological studies, have shown that ZIKV crosses the placenta and subsequently replicates within fetal tissues including the developing brain. Preferential infection of neural cell precursors causes damage to the developing fetal brain. However, a majority of congenitally infected humans do not develop microcephaly or other overt congenital abnormalities, so longitudinal epidemiological studies are necessary to more completely define the long-term consequences of in utero ZIKV infection.

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Introduction

The *Flaviviridae* family is comprised of a diverse group of RNA viruses, including more than 70 flaviviruses that are transmitted by mosquitos (e.g. Zika (ZIKV), Dengue (DENV), West Nile (WNV), St. Louis encephalitis (SLEV), Yellow Fever (YFV), Japanese encephalitis (JEV) viruses) or ticks (e.g. Powassan (POWV) and Tick-borne encephalitis (TBEV) viruses). Many of these viruses are neurotropic and have the capacity to invade the brain and cause encephalitis (e.g. WNV, ZIKV, SLEV, JEV, YFV, POWV, TBEV). By contrast, DENV is less neuroinvasive, but causes large epidemics of fever in humans, including life-threatening hemorrhagic fever, with nearly 400 million infections per year [1]. Thus, flavivirus infections represent a major global public health concern that is being addressed with even greater urgency since the discovery that ZIKV causes congenital infection resulting in microcephaly, blindness, intrauterine growth restriction (IUGR), and fetal demise [2•,3,4•,5]. New animal models of transplacental ZIKV infection have yielded insights into potential consequences of this emerging infectious disease [6•,7••,8]. Additionally, recent human epidemiological studies are beginning to define the impact of congenital ZIKV infection in humans.

Transplacental flavivirus transmission

Long before the discovery that ZIKV causes congenital abnormalities, there were numerous case reports and animal studies describing transplacental infection by other flaviviruses [9–23]. However, the clinical relevance of congenital flavivirus infection was not well defined, perhaps due to the fact that some flaviviruses cause relatively smaller or geographically confined outbreaks [24]. The enormity of the ZIKV epidemic in the Americas likely made the phenomenon of congenital flavivirus infection more discoverable than it had been in previous outbreaks [25]. For example, an analysis of the French Polynesian ZIKV outbreak also demonstrated an association with microcephaly, which was uncovered only in retrospect [26•,27].

The spread of flaviviruses is largely influenced by host–vector interactions [28]. Humans are incidental dead-end hosts for many of the encephalitic flaviviruses including WNV, JEV, SLEV, POWV and TBEV, which depend on amplification by transmission between non-human hosts and arthropod vectors [29–31]. By contrast, DENV, YFV, and ZIKV can perpetuate transmission between humans and mosquitos [1,31–33]. Many flaviviruses (e.g. SLEV and POWV) cause only small outbreaks in humans, whereas other flaviviruses (e.g. ZIKV, TBEV, YFV, and DENV) have caused larger outbreaks [1,34]. Additionally, ZIKV has the capacity for human-to-human sexual and non-sexual transmission [35–37], which likely has implications for the ability of this virus to spread intercontinentally.

Since the 1970s, the biomedical research community has produced numerous reports of transplacental infection by a variety of flaviviruses, which are summarized in Table 1, although most of these studies received little attention [9–23,38]. For example, there are some reports of congenital JEV and WNV infection in humans [15,21], resulting in a variety of disease phenotypes including fetal demise and stillbirth during a JEV outbreak [15], and retinal damage and blindness in a case of congenital WNV

Table 1

Consequences of congenital flavivirus infection in mammals. Congenital flavivirus infection has been described in a variety of mammals in nature (columns 2–4) and in animal models (columns 5–6). Consequences of congenital infection with ZIKV resemble the consequences of infection with other flaviviruses, including spontaneous abortion, ocular abnormalities, and neurological malformations

Virus	Congenital infection in humans	Congenital infection in other mammals (in nature)	Consequences (in nature)	Congenital infection (in animal models)	Consequences (in animal models)
JEV	Yes [15]	Swine [42]	**Human**: Spontaneous abortion [15]; **Swine:** Stillbirth, neonatal death [42]	Bat [43]; Mouse [16]	**Mouse:** Fetal and neonatal death [16]
SLEV	No	Not described	N/A	Bat [43]; Mouse [11,12]	**Mouse:** Delayed postnatal growth, encephaloceles, hydrocephalus, neonatal death [12]
WNV	Yes [21]	Horse [39], Sheep [40]	**Human:** Chorioretinal changes and brain abnormalities on MRI [21] **Horse:** Spontaneous abortion [39] **Sheep:** Spontaneous abortion, stillbirth, neonatal death [40]	Mouse [22,23]	**Mouse:** Stillbirth, neonatal death [22]
YFV	Yes [9]	Not described	N/A	Not described	N/A
ZIKV	Yes [5,53,54]	Not described	**Human:** Fetal demise, IUGR, microcephaly, brain abnormalities on MRI, ocular abnormalities and blindness [2•,3,5,54,75,76]	Macaque [7••,8]; Mouse [6•,63•,65••,67•]; Hamster [64]	**Macaque:** Fetal brain lesions [7••]; **Mouse:** Fetal demise, IUGR, microcephaly [6•,63•,65••,67•]

infection [21]. Congenital WNV infection also has been reported to cause spontaneous abortion in other mammals [39,40]. Transplacental transmission of YFV in humans also occurred after inoculation with an attenuated YFV vaccine [9]. Similarly, mouse model studies have demonstrated transplacental SLEV and WNV transmission, which resulted in either severe neurological abnormalities (due to SLEV) or diminished litter size (due to WNV) [11,12,22,23]. Several studies have shown congenital JEV infection in mice, swine, and bats [16–18,41–43]. However, case reports of congenital infections with flaviviruses had been sporadic prior to the ZIKV epidemic. Unlike the relatively smaller outbreaks of WNV and JEV in humans, the 2015 ZIKV epidemic resulted in more than 1 million infections [34]. Thus, it is intriguing to consider whether other flaviviruses may cause congenital infection in humans on a more limited basis than ZIKV. Furthermore, prior ZIKV outbreaks in the developing world also might have caused congenital infection without being noticed by the medical community.

The discovery and emergence of ZIKV

ZIKV was first isolated from a febrile rhesus macaque at a yellow fever research station in the Zika Forest in Uganda in 1947 [44]. At the time, many local inhabitants were found to be seropositive for antibodies against ZIKV [45], but no clinical symptoms were directly linked to the virus until much later. There had been some speculation that clinical ZIKV infection may cause jaundice, in part because ZIKV is related to YFV [46]. In an attempt to define clinical manifestations of ZIKV infection, Dr. William Bearcroft injected the virus into his own arm in 1956 [47]. He reported having only mild clinical symptoms (e.g. fever and headache), which resolved within a few days [47]. Thus, the clinical consequences of ZIKV infection were thought to be very mild until the virus began to emerge over the last decade.

From the time of its discovery in 1947 until the 2015 ZIKV epidemic in the Americas, only three animal model studies of ZIKV pathogenesis had been described [48–50], the most recent of which was published in 1976 [48]. In 2007, ZIKV began to spread to the Islands of the Pacific, including a large outbreak on the Island of Yap, Micronesia [51]. A 2013 outbreak in French Polynesia revealed an association between ZIKV infection and Guillain–Barre syndrome [52], a neurological autoimmune disease characterized by peripheral demyelination resulting in ascending paralysis and respiratory failure requiring mechanical ventilation. When ZIKV spread to the Americas in 2015, millions of individuals were infected and an epidemiological association was made for the first time between ZIKV infection and microcephaly [53].

Clinical manifestations of congenital ZIKV infection

There are numerous unanswered questions about congenital ZIKV infection, including: Firstly, how common is transplacental ZIKV infection? Secondly, what is the range of clinical outcomes resulting from congenital infection? and Thirdly, what are the long-term clinical consequences of congenital infection? To begin to address these questions, clinical researchers began conducting epidemiological studies in 2016 to define the consequences of ZIKV infection in human neonates. In parallel, scientists rapidly developed mouse and