Zika virus infection – short facts assembled by the Society for Virology in Germany

Contributed by the working group "pregnancy-associated virus infections" of the Gesellschaft für Virologie (GfV).

The virus

Zika virus is a mosquito-transmitted flavivirus belonging to the Spondweni virus group. It has a single-stranded plus-strand RNA-genome of 10.617 base pairs surrounded by a capsid and envelope (Baronti *et al*., 2014). An African and an Asian genetic lineage are known. The virus presently circulating in the Americas belongs to the Asian lineage.

Epidemiology

Zika virus was first isolated in 1947 from a rhesus macaque that was kept for studies on yellow fever in Zika forest near Entebbe, Uganda. Primates including humans are considered natural hosts. In addition, there is evidence for sporadic mosquito-borne transmission to other vertebrates. Human cases have long been known in Africa and Asia. Significant outbreaks occurred in 2007 and 2008 in Micronesia (Yap islands) as well as in 2013 in French Polynesia, from where the virus subsequently spread to New Caledonia. Imported cases from these epidemics were reported in several European countries, Japan, as well as the Easter islands (Marano *et al*., 2015).

A change in the general perception of Zika virus distribution occurred in early 2015, when Brazil reported first patients who had acquired their infection in the country (autochthonous cases). The autochthonous circulation in Brazil extended to 18 federal states through December 2015. On February 18th autochthonous transmissions were reported from 32 countries or regions (www.cdc.gov). In large parts of South- and Middle America the virus meanwhile present. WHO declared the Zika outbreak a public health emergency of international concern (PHEIC) on February 1st, 2016.

Transmission

Zika virus is transmitted by mosquitos of the species *Aedes aegypti*, which also transmit dengue and yellow fever virus (Marconedes and Ximenes, 2015). Zika virus has occasionally been found in other species of the same genus of mosquitos (*Ae. polynesiensis, Ae. dalzieli, Ae. africanus, Ae. luteocephalus, Ae. vittatus, Ae. apicoargenteus, Ae. furcifer*). In a study conducted in 2007 in Gabon, Zika virus RNA was found in pools of *Ae. albopictus*, a species that is also endemic in large parts of southern Europe (Grard *et al.*, 2014). However, these results do not prove vector competence of *Ae. albopictus* as mosquitos were sampled in a natural context in an endemic area where they could have taken up the virus via blood meal but might not be able to transmit the virus further.

Another study showed replication and salivary secretion of Zika virus in *Ae. albopictus* under defined laboratory conditions (Wong *et al.* 2013). However, the appropriate experimental conditions to represent virus uptake from infected humans are unknown, and the virus dose used in mosquito infection studies has very strong influence on the result. Further studies using appropriate control settings with dose titration, as well as transmission trials in primates will be necessary to define vector competence for *Ae. albopictus* and other mosquito species endemic in temperate climate zones.

There are rare descriptions of direct human-to-human transmission including reports of 2 newborns with perinatal infection during the outbreak in French Polynesia (Besnard *et al*., 2014). The mothers in both cases had an acute infection at the time of birth. There is evidence for the presence of virus in semen and sexual transmission via semen (Foy et al. 2011; Musso *et al.*, 2015). In all cases reported so far, males had symptomatic disease and females showed symptoms 10 to 14 days after sexual intercourse.

In spite of a short time of viremia, transmission via blood donations cannot be excluded. During the outbreak in French Polynesia, viral RNA was detected in 2.8 % of 1,505 blood donors by RT-PCR (Musso *et al.*, 2014). Blood donations from donors infected with the related dengue- and West Nile virus are known to transmit the disease to recipients (Petersen and Busch, 2010).

Clinical features

(I) Clinical presentation in children and adults

Symptoms appear after a short incubation period of 3 to 12 days and are usually mild and self-limiting. Up to 80 percent of infections are clinically silent. Symptoms can include fever, arthralgia, headaches, retro-orbital pain, conjunctival injection, digestive disorder and pruritic maculopapular rash usually spreading from face to limbs, including soles and palms. Other complications of Zika virus infection are rare. In Brazil, one patient who was on corticosteroid treatment and another patient without known underlying disease died after Zika virus infection.

During the outbreak in French Polynesia 2013-2014 health authorities reported an increase of Guillain-Barré-Symdrome (GBS) cases. The association of acute Zika virus infection with GBS was recently demonstrated by a case-control study conducted in French Polynesia (*Cao-Lormeau*, 2016). An increase of GBS cases has also been reported during the ongoing outbreak in Brazil, Colombia, Venezuela and El Salvador. The pathogenesis of GBS after Zika virus infection is not yet clear.

(II) Congenital disease

In October 2015 the Brazilian Ministry of Health reported an increase of the number of cases of microcephaly over the past months, coinciding with the expanding outbreak of Zika virus infection. Until the end of February 2016 almost 6,000 cases of suspected microcephaly were notified, mainly in the northeastern regions of Brazil. During the past weeks, Brazilian health authorities started re-examinations to confirm microcephaly in these children. These examinations are still ongoing. At present, in about one third of 1.687 case that had been re-examined microcephaly was confirmed. In 12.8% of confirmed microcephalic children diagnostic markers for Zika virus infection were observed (Ministry of Health, Brazil). Several case reports implicating Zika virus infection to cause microcephaly were published. A recent publication presents data of Zika virus genomes to be detectable by RT-PCR in brain tissue of an aborted fetus suffering from microcephaly. In addition, flavivirus-like particles were detected by electron microscopy. During springtime and summer 2015, the pregnant woman had lived in Natal (Brasilia) and reported an episode of high fever, myalgia and arthralgia in combination with an itchy exanthema during week 13 of gestation. After returning to Europe (Slovenia), ultrasound examination performed at week 29 of gestation showed microcephaly in combination with several further abnormalities indicative of severe impairment of brain function. As a consequence of these findings, pregnancy was terminated (Mlakar et al., 2016). In a fetus with induced abortion in week 32 due to microcephaly, intracranial calcifications and *hydrops fetalis*, Zika virus was found in amniotic fluid and brain tissue, but not in any other tissue (Sarno et al., 2016).

Another report describes the presence of Zika virus genomes in amniotic fluid obtained from two pregnant women during weeks of gestation 29 and 30, respectively, when cerebral abnormalities and microcephaly had been recognized (Oliviera Melo *et al*. 2016). An additional report that is not yet formally published described viral RNA detection in a newborn child with microcephaly that died shortly after birth. Prospective analyses are planned to further clarify these observations. As of February 17th, the US CDC has been notified of 9 pregnant women with confirmed Zika virus infection after exposure in endemic regions. 7 of 9 reported high fever during early pregnancy. 2 of 9 had spontaneous early abortion, and in another 2 cases, pregnancies were terminated. Of 3 children born so far, 1 had microcephaly. 2 pregnancies proceed without complications. Zika virus in child or fetus was detectable only in 1 case of early spontaneous abortion.

The etiological link between Zika virus infection and microcephaly has not been established. In general, microcephaly is a fetopathy that manifests in late pregnancy or at the time of birth based on small head circumference. Data from the US and Germany show that 12 or 16 of 10,000 births, respectively, show symptoms of microcephaly (National Birth Defects Prevention Network/USA 2013; Baltzer *et al*., 2016). In early pregnancy, infections (cytomegalovirus, rubella virus, toxoplasma), malnutrition, drug abuse, environmental factors, as well as genetic aberrations can cause microcephaly.

As recommended by the Centers of Disease Control (CDC, Atlanta, USA), laboratory diagnosis should be performed when pregnant women returning from countries with Zika virus circulation report at least two symptoms indicative for Zika disease (sudden onset of fever, itchy exanthema, conjunctivitis and/or arthralgia). If markers for recent and/or acute infection are observed, follow-up by ultrasound examination is recommended in four weekly intervals. In addition, laboratory diagnosis should be performed if ultrasound testing reveals cerebral calcifications and/or microcephaly symptoms in pregnant women with plausible travel history. For pregnant women without travel history, laboratory testing is not recommended (Staples *et al*., 2016).
Since sexual transmission may occur, testing for Zika virus infection may be recommended for partners of pregnant women after returning from epidemic regions. Until the Zika virus infection status is cleared, transmission may be omitted by the use of condoms. This recommendation is based on plausible hypotheses. Until now, is is not known how long infectious virus is secreted in present in seminal fluid following acute infection.

Risk for pregnant women in endemic areas

At present, there is a relatively high risk to be bitten by a Zika virus-infected mosquito in Brazil and several other Latin American countries. Since neural development occurs between the 8th and 15th week of pregnancy, Zika virus infection should be particularly likely to lead to neurologic damage during this period of fetal development. As long as a causal link between these infections and severe fetal damage cannot be excluded, traveling of pregnant women to affected countries is not recommended, particularly during the first trimester. In the case of travelling to affected areas nonetheless, usage of repellents, adequate clothing, mosquito nets etc. is highly recommended to minimize exposure to the mosquito vectors which are active during daytime and dawn.

Risk for pregnant women in Germany

There is no risk of an infection with the Zika virus in Germany at the present time. The probability of importing an infected mosquito that could transmit the virus to a pregnant woman in Germany, is negligible. Continuous presence and spread of *Ae. aegypti* in Germany and Central Europe is highly unlikely under the current climatic conditions. Whether other *Aedes* species that already occur in Southern Germany, such as *Ae. albopictus* and *Ae. japonicus,* can be efficient vectors for the Zika virus requires investigation. Small-scale epidemics and local transmission events following importation of the Zika virus by infected travelers could be more likely in Southern European countries harboring larger *Ae. albopictus* populations during summer. It would be important to know whether animals may be involved in Zika virus transmission cycles to make more precise risk assessments.

Laboratory diagnostics

During the first days of Zika virus disease viral RNA can be detected in blood samples, and up to 4 weeks in urine. Specialized laboratories have already established the appropriate molecular detection methods (qRT-PCRs). The detection of virus-specific antibodies should be performed in reference laboratories. There is a validated, commercial ELISA available for the detection of IgG and IgM against Zika virus. Due to the antigenic relationship to other flaviviruses (dengue, yellow fever,

West Nile virus, TBE) there is a serological cross-reactivity. This is relevant if the patient had already undergone infections with other flaviviruses or has been vaccinated against yellow fever (Lanciotti et al., 2008). If there is a positive result for the detection of antiviral antibodies in indirect immunofluorescence assays or ELISA, it needs to be confirmed by a virus neutralization test (VNT); while the VNT results for ZIKV should be at least four titers above those obtained for a comparative dengue virus VNT (Petersen et al., 2016).
A detailed procedure for laboratory diagnostic evaluation of possible ZIKV infections is available from the Bernhard Nocht Institute in Hamburg, Germany
(https://www.bnitm.de/aktuelles/mitteilungen/954-empfehlungen-zur-diagnostik-der-zika-virus-infektion/).

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