Imported food risk advice

Zika virus in human milk and human milk products

Context of this risk advice

- Human milk means expressed milk collected from lactating women to be fed to infants that are not the biological infants of the women supplying the milk.
- Human milk products means products derived from human milk that have been specially formulated to meet the specific nutritional needs of infants such as fortifiers and formula.
- The level of risk for this hazard in human milk and human milk products was determined assuming that the most vulnerable category of infants (preterm infants in hospital neonatal intensive care units) would be receiving the products.

Nature of the hazard

Zika virus (ZIKV) is a mosquito-borne arbovirus that belongs to the *Flaviviridae* family of viruses. It is an enveloped virus with a single-stranded positive-sense RNA genome and icosahedral capsid (Wang et al. 2017). All flaviviruses include a vertebrate host and an insect vector in their transmission cycle (Calvet et al. 2018). In Africa, ZIKV is thought to be maintained in a sylvatic cycle[1] involving non-human primates and mosquitoes, but in areas without non-human primates ZIKV is likely maintained in a human-mosquito-human cycle (Musso and Gubler 2016).

When acquired postnatally, ZIKV is a moderate hazard that causes illness of moderate duration and sequelae are infrequent.

ZIKV can be inactivated with alcohol-based disinfectants, hypochlorite, UV light and heat treatment (Müller et al. 2016).

Transmission

The primary mode of ZIKV transmission is through mosquito bites. The virus is almost exclusively transmitted by the female mosquito *Aedes aegypti* (Calvet et al. 2018; DoH WA 2018), although it has been isolated from several other *Aedes* species (Vorou 2016; Wang et al. 2017). There is strong evidence to indicate that ZIKV can be transmitted from human to human through many different routes, including sexual contact, blood transfusion and from mother-to-infant *in utero* (ECDC 2017; Wang et al. 2017).

A number of studies have shown that ZIKV RNA can be detected in colostrum and human milk after delivery (Besnard et al. 2014; Blohm et al. 2017; Dupont-Rouzeyrol et al. 2016; Sotelo et al. 2017). Although earlier studies suggested that ZIKV in human milk was not infectious (Besnard et al. 2014), more recent studies have demonstrated that ZIKV derived from human milk is infective in cell culture (Blohm et al. 2017; Dupont-Rouzeyrol et al. 2016; Sotelo et al. 2017). To date, however, there has been no confirmation that ZIKV is transmitted to infants through human milk, and foodborne transmission of ZIKV has not been described.

Disease severity

ZIKV is a moderate hazard in the general population as it causes an illness of moderate duration and sequelae are infrequent. ZIKV infection is often asymptomatic or has mild symptoms like maculopapular rash, pruritus[2], fever, arthralgia[3], myalgia[4], conjunctivitis, headache or malaise (Brasil et al. 2016; Colt et al. 2017; Haby et al. 2018; Musso and Gubler 2016).

[1] The sylvatic cycle is a portion of the natural transmission cycle of a pathogen spent cycling between wild animals (hosts) and vectors
[2] Severe itching of the skin
[3] Pain in a joint
[4] Pain in a muscle or group of muscles

Epidemiological data from the French Polynesia and other countries of Central and South America suggest that severe neurological complications like Guillain–Barré syndrome (GBS), could be associated with ZIKV infection (Musso et al. 2014; Musso and Gubler 2016). A recent systematic review of literature estimated that ZIKV infection-associated GBS prevalence is approximately 1.23% of all ZIKV infection cases in adults (Barbi et al. 2018). In addition, foetuses and infants infected with ZIKV *in utero* can develop congenital Zika syndrome, which is a unique pattern of severe birth defects including microcephaly[5] and brain damage (CDC 2018a; Wheeler 2018). A study of children born to mothers with confirmed ZIKV infection during pregnancy reported 7% of children aged ≥1 year had a ZIKV associated birth defect and 10% had neurodevelopmental abnormality possibly associated with congenital ZIKV infection (Rice et al. 2018).

The spectrum of clinical features that might be observed in new-borns who acquire ZIKV during the postnatal period is currently unknown. Besnard et al. (2014) documented two cases of perinatal transmission of ZIKV. Even though both new-borns had similar ZIKV RNA loads in serum, one of the infants remained asymptomatic and the second one developed maculopapular rash and thrombocytopenia[6] with favourable clinical evolution (Besnard et al. 2014). While there is no evidence that postnatal ZIKV infection is any more severe than the benign adult illness (Goodman et al. 2016; Li et al. 2017), there is no published data on the long-term outcomes of early postnatal infection (CDC 2018b).

Infectivity

The infective dose of ZIKV in human milk is not known. ZIKV transmission through human milk has not been confirmed and foodborne transmission of the virus has not been described.

Besnard et al. (2014), analysed human milk samples from two infected mothers a few days after delivery. The ZIKV RNA load in these samples were 2.9×10^4 and 2.05×10^6 copies/ml, but were not infective in cell culture. Both infants were infected; one infant was asymptomatic while the other had mild symptoms. However, the study concluded that transmission most probably occurred either *in utero* or during delivery rather than via human milk. In 2016, Dupont-Rouzeyrol et al. showed that human milk collected from a ZIKV-infected mother before the first breastfeed contained a viral load of 8.5×10^5 copies/ml, which was infective in cell culture. However, the outcome of possible transmission to the infant was not known. More recently, Sotelo et al. (2017) detected a viral load of 2.44×10^6 copies/ml and 2.16×10^5 copies/ml in colostrum and milk (nine days after delivery) samples respectively, from a ZIKV-infected mother. Breastfeeding was not recommended due to the presence of ZIKV in the breast milk. The author also demonstrated the infectivity of the virus derived from these samples in cell culture. These studies suggest that large quantities of potentially infective ZIKV viral units are shed from ZIKV-infected mothers into their milk, however, transmission through this route is uncertain and possibly inefficient.

Risk mitigation

Controls are needed to minimise contamination of human milk with ZIKV. In human milk, when samples were artificially inoculated with different strains of ZIKV at levels of 1.11×10^6 Tissue Culture Infectious Dose 50 ($TCID_{50}$)/mL and pasteurised at 63^{o}C for 30 min, ZIKV infectivity was reduced below the limit of detection (Pfaender et al. 2017). This study indicates that Holder pasteurisation (62.5^{o}C, 30 min) should inactivate ZIKV. International human milk banks, including those in Australia, routinely perform Holder pasteurisation on human milk to ensure the microbiological safety of donor human milk (Hartmann et al. 2007; HMBANA 2015; UKAMB 2003)

Evaluation of uncertainty

There is uncertainty around the transmissibility of ZIKV through human milk and the viral load required for this potential mode of transmission. The prevalence of ZIKV infection amongst potential human milk donors is unknown. Although postnatal ZIKV infection seems to cause mild illness, long-term outcomes among infants and children with early postnatal ZIKV infection remain unknown.

Pooling of human milk from multiple donors is common practice amongst many human milk banks and would dilute the viral load from a single donor, however some milk banks only pool milk from individual donors (Haiden and Ziegler 2016). The Australian Red Cross milk bank pasteurises human milk in single donor batches (Australian Red Cross 2018).

[5] Abnormal smallness of the head associated with incomplete brain development

[6] Low blood platelet count

Risk characterisation

There is evidence of ZIKV shedding in human milk from infected mothers, however there has been no confirmation of virus transmission through this route. There is a low likelihood of exposure to ZIKV as although ZIKV has been found in human milk, foodborne transmission of this virus has not been demonstrated, there is limited evidence that ZIKV has caused infection in infants through this route, and prevalence amongst donors is unknown. ZIKV is a moderate hazard if infection occurs postnatally given that documented cases of such infection suggests it has a mild presentation and sequelae are infrequent.

ZIKV in imported human milk and human milk products does not present a potential medium or high risk to public health and safety.

This risk advice was compiled in: November 2018, updated October 2019

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