# Imported food risk advice

## Viral haemorrhagic fevers 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**

Viral haemorrhagic fevers (VHFs) refers to a group of illnesses that are caused by over 20 different enveloped RNA viruses that belong to five distinct families: *Arenaviridae* (e.g. Lassa virus, Junin virus and Machupo virus), *Bunyaviridae* (e.g. Crimean-Congo haemorrhagic fever virus and Rift Valley fever virus), *Filoviridae* (e.g. Ebola virus and Marburg virus), *Flaviviridae* (e.g. dengue virus and tick-borne encephalitis) and *Paramyxoviridae* (e.g. Nipah virus) (CDC 2014; MacDermott et al. 2016; Paessler and Walker 2013). The majority of these viruses have a zoonotic cycle; rodents and arthropods (e.g. ticks and mosquitoes) are the main reservoirs (Cobo 2016). Viruses that cause VHFs are transferred to humans through direct or indirect contact with the reservoir host, or the bite of an arthropod vector (Smith et al. 2014).

VHFs have the potential to cause haemorrhagic symptoms as part of the disease process. In the paediatric population, some of these haemorrhagic fever viruses cause relatively mild illness, but many of these viruses can also cause severe, life-threatening disease (MacDermott et al. 2016).

Haemorrhagic fever viruses are susceptible to a broad range of hospital disinfectants (Cobo 2016). Also, heat treatment can be effective at inactivating some of these viruses, such as dengue virus, Ebola and Marburg virus (Hamilton Spence et al. 2017; Idris et al. 2018).

**Transmission**

Most viruses associated with VHFs are zoonotic and can be transmitted to humans through contact with infected fluids from the host such as urine, faecal matter, saliva or other excretions, and some may be transmitted through bites when the vector is a mosquito or a tick (CDC 2013; Cobo 2016; NJDHSS 2008). Some of these viruses can infect livestock and can then be transmitted to humans when they contact the infected animal. Secondary transmission from person-to-person through close contact with infected people or their body fluids can occur for Ebola virus, Marburg virus and Lassa virus (CDC 2013).

Epidemiologic studies in humans do not indicate that VHFs are readily transmitted from person-to-person by the airborne route. However, airborne transmission of VHFs is a hypothetical possibility, particularly during procedures that may generate aerosols (Health Protection NSW 2014; Pshenichnaya and Nenadskaya 2015).

It has been suggested that viruses like Nipah virus can also be transmitted through contaminated food. In outbreaks in Southern Asia, fruits or fruit products contaminated with urine or saliva from infected fruit bats were considered the most likely source of infection (IOM 2012; WHO 2018). Other viruses, such as Rift Valley fever virus and tick-borne encephalitis, can be transmitted to humans by ingestion of unpasteurised milk from infected animals (CDC 2014; Cobo 2016).

For the majority of viruses that cause VHFs there is a lack of evidence about their presence in human milk, or human milk as a route of transmission. Documented cases of potential mother-to-infant transmission via human milk are mainly anecdotal based on case reports for dengue virus and Ebola.

Cases of neonates with dengue fever have been reported in which dengue virus RNA was detected in the milk from the infected mothers (Arragain et al. 2017; Barthel et al. 2013). However, although it has been postulated that mother-to-infant transmission could have occurred via human milk, *in utero* transmission could not be ruled out.

During the Ebola outbreak in Uganda in 2000, a study documented the presence of Ebola virus in numerous body fluids including breast milk. Breast milk samples from two different women taken during the acute and convalescent phase tested positive for Ebola virus by RT-PCR and cell culture. Although the breastfed children of both mothers died of laboratory-confirmed Ebola virus, it was not possible to determine if the virus was transmitted through human milk (Bausch et al. 2007).

In 2015, during the Ebola virus outbreak in Guinea, the virus was detected in human milk derived from an Ebola-positive mother. Her infant, who was exclusively breasted until maternal symptom onset, remained healthy and tested negative for Ebola virus (Nordenstedt et al. 2016). During the same outbreak, another study reported a 9 month old infant who died from Ebola with an unknown epidemiological link. While the parents did not report any previous illness, laboratory analyses revealed persisting Ebola virus RNA in the mother's breast milk and father's seminal fluid. Further analyses revealed a closer phylogenetic relation between the infant and mother's viral sequence, suggesting transmission of the virus through human milk (Sissoko et al. 2017).

Although Ebola virus transmission through human milk is suspected, it has not been definitely confirmed.

**Disease severity**

VHFs are a severe hazard as they may cause potentially life threatening illnesses with chronic sequelae. The severity of disease caused by the viruses ranges from those with extremely high fatality rates (e.g. Ebola) to those that generally cause relatively mild illness but can progress into severe, life-threatening disease (e.g. dengue virus).

In general, the term 'viral haemorrhagic fever' is used to describe severe febrile illnesses with abnormal vascular regulation and vascular damage. The vascular dysregulation frequently manifests early in the course of illness as mild hypotension, flushing of the skin, postural hypotension[1], and vasodilation of the conjunctiva[2]. Haemorrhages (bleeding) are more prominent in some diseases, such as Crimean-Congo haemorrhagic fever, and occur infrequently in other infections, such as Lassa fever (even in fatal cases). Haemorrhages usually occur, especially when the patient has thrombocytopenia[3] or severe platelet dysfunction. These haemorrhages are rarely life threatening. In severe cases, vascular dysregulation and vascular damage with capillary leakage lead to shock, which is characteristic of the terminal phase of VHFs (CDC 2013; Paessler and Walker 2013). In children fever, weakness, headache, myalgia[4], vomiting, diarrhoea and haemorrhage, are amongst the most common symptoms associated with VHFs, however, each virus presents a particular cluster of symptoms (MacDermott et al. 2016). The fatality varies significantly amongst viruses that cause VHFs, with up to 10% for dengue virus (in cases of severe infection which consist of dengue haemorrhagic fever and dengue shock syndrome) and up to 90% (in infants under 1 year of age) for Ebola virus (MacDermott et al. 2016).

Long term sequelae have been reported amongst survivors of Ebola virus. Headache, myalgia and fever are the most commonly reported sequelae over extended periods of time (Mohammed et al. 2017). Eye problems including eye irritation, eye pain, eye discharge, itchy eye, poor vision, blurred vision, uveitis[5] (Mohammed et al. 2017; Shantha et al. 2017) and neurological sequelae like memory impairment, peripheral neuropathy[6], tremor and stroke have also been reported (Howlett et al. 2018; WHO 2016).

[1] Form of low blood pressure that happens when standing up from sitting or lying down. It can make the person feel dizzy or lightheaded, and maybe even faint

[2] Dilation of the blood vessels in the conjunctiva, the membrane that covers the front of the eye

[3] Low blood platelet count

[4] Pain in a muscle or group of muscles

[5] Inflammation of the eye

[6] Damage to peripheral nerves, often causing weakness and numbness/pain in hands and feet

**Infectivity**

In human milk, the infective dose of viruses that cause VHFs is not known. It has been suggested that viruses that cause VHFs require only 1-10 infective units in the aerosol form to cause disease (Franz et al. 1997). However, there is very limited published literature on the infective dose of viruses that cause VHFs via any transmission route.

Viral load of dengue virus has been reported in human milk collected during the postpartum period at levels of <100 to >$10^4$ RNA copies/ml (Arragain et al. 2017; Barthel et al. 2013). However, these levels were not correlated with the infectivity of the virus through ingestion of human milk.

**Risk mitigation**

Controls are needed to minimise contamination of human milk with viruses that cause VHFs. Pasteurisation at 62.5$^o$C for 30 minutes (Holder pasteurisation) of human milk samples artificially inoculated with Ebola virus or Marburg virus at levels of up to $10^5$ PFU/mL, reduced viral infectivity to below the limit of detection (Hamilton Spence et al. 2017). Dengue virus (2.3 x $10^3$ PFU/mL) has been reported to be inactivated by heating at 56$^o$C for 30 min (Idris et al. 2018). Therefore, Holder pasteurisation should be an effective method to minimise the risk of these viruses in human milk. International milk banks, including those in Australia, routinely perform Holder pasteurisation on human milk to ensure the microbiological safety of donor human milk (Bharadva et al. 2014; Hartmann et al. 2007; HMBANA 2015; UKAMB 2003).

There is limited information on the prevalence of latent VHFs amongst potential human milk donors. However, donor screening questionnaires that include questions about recent illnesses and general health at the time of donation could be used to exclude mothers with VHFs and therefore reduce the risk of exposure to these viruses through human milk.

**Evaluation of uncertainty**

Apart from Ebola and dengue virus, there is insufficient evidence about the presence of viruses that cause VHFs in human milk. There is uncertainty around the transmissibility of Ebola and dengue virus through human milk, and the viral load required for this potential mode of transmission is unknown. The prevalence of VHF infection amongst potential human milk donors is uncertain, but is assumed to be very low due to the severity of the disease, as sick mothers are highly unlikely to donate milk.

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).

**Risk characterisation**

From all the viruses that cause VHFs, only Ebola and dengue virus have been detected in human milk, and transmissibility through human milk has not been confirmed. Viral infectivity through this potential route is unknown. Due to the severity of illness associated with VHFs, the likelihood of human milk donors being viremic and shedding virus in breast milk is considered to be extremely low. Ebola virus and in some instances dengue virus can cause severe fatal disease, however there is a very low likelihood of exposure with no reported outbreaks associated with human milk.

Therefore, Ebola and dengue virus in imported human milk and human milk products do not present a potential medium or high risk to public health and safety.

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