Imported food risk advice

Human herpes viruses (other than herpes simplex virus & cytomegalovirus) 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

Herpes viruses belong to the *Herpesviridae* family of viruses. These are enveloped viruses with a double-stranded DNA genome and icosapentahedral capsids (Whitley 1996). There are more than 100 known herpesviruses but only nine have been identified in humans: herpes simplex virus types 1 and 2 (HSV-1 and HSV-2)[1]; varicella-zoster virus (VZV or HHV-3); Epstein-Barr virus (EBV or HHV-4); cytomegalovirus (CMV or HHV-5)[2]; human herpesvirus 6 (HHV-6: variants A and B)[3]; human herpesvirus 7 (HHV-7); and Kaposi's sarcoma-associated herpesvirus (KSHV or HHV-8). These viruses are transmitted in different ways, from the earliest stages of life. About 80% of the adult population has antibodies to most, if not all, human herpesviruses apart from HHV-8, which is less prevalent, especially in Western countries (Freer and Pistello 2018). All herpesviruses can establish latent infection within specific tissues, which are characteristic for each virus (Whitley 1996).

This report considers risks associated with the potential for VZV, EBV, HHV-6B, HHV-7 and HHV-8 to be present in human milk and human milk products. Aside from VZV, primary infections of these viruses are often asymptomatic. All cause mild or moderate illnesses involving skin rash and fever, with potential for more severe outcomes—including neurological problems—in some cases. Infections in infants are typically of mild severity, with rare complications.

No disease has been causally linked to HHV-6A (Ward 2013). However, as work published before 2011 does not usually distinguish between the two variants of HHV-6, the term HHV-6 is used throughout this statement to refer to HHV-6B or to both variants when no distinction has been made by authors.

Transmission

There is limited or no evidence for transmission of VZV, EBV, HHV-6B, HHV-7 or HHV-8 through breast feeding, although VZV, EBV and HHV-7 DNA have been detected in human milk.

VZV: Varicella (chickenpox) is transmitted by inhalation of droplets or aerosols from the nasopharynx dispersed in air by subjects with acute infection or, rarely, by direct contact with varicella (chickenpox) or zoster (shingles) skin lesions (Freer and Pistello 2018).

(Yoshida et al. 1992) reported on a 2-month-old breastfed infant who developed symptoms 16 days after its mother showed varicella symptoms on her trunk and upper extremities after delivery onset. VZV DNA was detected by PCR

[1] See Herpes simplex virus and human milk risk statement

[2] See Cytomegalovirus and human milk risk statement

[3] In 2011, the International Committee on Taxonomy of Viruses declared that the two human herpesvirus 6 variants—HHV-6A and HHV-6B—met the formal definition of separate herpesvirus species

in the mother's milk, suggesting it as a route of transmission. However, (Lawrence and Lawrence 2004) caution that the authors did not provide adequate proof to exclude more common modes of transmission.

Similarly, (Yoshida et al. 1995) could not rule out transmission via direct contact with herpetic lesions of the skin or nasal aerosols in a case where VZV DNA was detected in milk from a mother showing clinical signs of shingles on one breast. Her 13 month old breastfed infant developed chickenpox 17 days after maternal symptom onset. Human milk was proposed as a possible route of transmission.

EBV: EBV is primarily transmitted through infected saliva (Daud et al. 2015), e.g. by kissing or sharing eating utensils or toothbrushes, but can also be transmitted by blood transfusions, bone marrow transplants and possibly sexual intercourse (Longnecker et al. 2013).

The prevalence of EBV infection in infants varies significantly on the basis of geography, being generally higher in less-developed countries (Longnecker et al. 2013). Depending on the population studied, 25-80% of children may be infected with EBV by the age of two (Junker et al. 1991). After the primary infection, EBV remains as a lifelong, usually asymptomatic latent infection in memory B cells (Coleman et al. 2017; Lennon et al. 2015; Longnecker et al. 2013). Memory B cells are involved in the immune response and can be present in human milk (Tuaillon et al. 2009).

(Kusuhara et al. 1997) showed that EBV seroprevalence in breastfed and bottle-fed infants was similar at 6-11 and 12-23 months of age, indicating that human milk is not a major route of transmission. This is consistent with the finding that there was no significant correlation between breastfeeding and the risk of EBV primary infection up to 14 months of age in a cohort of 121 infants (Huang et al. 1993).

It remains unclear if EBV can be transmitted from mother-to-infant via human milk (Lawrence 2011). Several studies have reported the presence of EBV DNA in the milk of EBV seropositive mothers (Coleman et al. 2017; Daud et al. 2015; Glenn et al. 2012; Junker et al. 1991), but only (Daud et al. 2015) have demonstrated the presence of encapsidated, infective virions. No studies have confirmed transmission to infants through human milk.

HHV-6: Primary infection with HHV-6 occurs during early childhood, typically between 5 and 24 months of age (Hall et al. 2006). Oral transmission—from the saliva of siblings or parents—is regarded as the main route of transmission of HHV-6 to infants, though this has not yet been fully clarified (Mukai et al. 1994; Ward 2005).

Seroepidemiological studies suggest that breastfeeding is not a major source of HHV-6 infection in infants. No difference was observed between the seroprevalences of HHV-6 in breast-fed and bottle-fed children at 12-23 months of age (Kusuhara et al. 1997), and there was no correlation between breastfeeding and risk of HHV-6 infection in infants up to 14 months of age (Huang et al. 1993).

(Dunne Jr and Jevon 1993) did not detect HHV-6 DNA in 120 individual, randomly selected human milk samples tested by PCR. (Fujisaki et al. 1998) reported similar results from testing of twenty-nine breast milk mononuclear cell samples. Given the high seroprevalence of HHV-6 in a normal population (Levy et al. 1990), these findings suggest that human milk is not a common route of transmission for this virus.

HHV-7: Primary infection with HHV-7 occurs during early childhood. Oral transmission—from the saliva of siblings or parents—is regarded as the main route of HHV-7 infection (Fujisaki et al. 1998). It is not clear why HHV-7 tends to infect children later than the closely related HHV-6 (Ward 2005), being gradually acquired over the first 5 or 6 years of life (Huang et al. 1997).

(Fujisaki et al. 1998) found HHV-7 DNA in mononuclear cells in human milk by PCR, but saw no statistically significant difference in the seropositivity rate for HHV-7 of breastfed and bottle-fed children at 12, 18, and 24 months old, implying that breastfeeding was not a major route of transmission.

HHV-8: Transmission of HHV-8 through breastfeeding is unlikely, based on evidence for the absence of the virus in human milk and the epidemiology of its spread. In an area of endemic HHV-8 infection, (Brayfield et al. 2004) did not detect HHV-8 DNA in 75 human milk samples collected at 2, 4, and 6 months after delivery from HHV-8–seropositive mothers who had recently given birth, or in two colostrum samples obtained close to the time of birth. They concluded that HHV-8–infected cells are rarely, if ever, present in breast tissue and milk, and that human milk is not a likely route of transmission to infants. In general, HHV-8 infection is extremely rare in infants, even in areas of endemicity, which further supports that conclusion (Gessain et al. 1999; Goedert et al. 1997; Lyall et al. 1999; Mantina et al. 2001; Mayama et al. 1998; Renwick et al. 1999).

Disease severity

VZV: VZV causes two different diseases during primary infection and reactivation, varicella (chickenpox) and zoster (shingles), respectively.

Varicella typically occurs during childhood due to primary infection by VZV. Varicella typically develops as an itchy rash in the trunk that spreads to the neck and limbs. This rash is preceded by generalized symptoms—usually mild in children—including malaise, nausea, loss of appetite, high fever and headache. Complications are rare in healthy children, but can include bacterial infection of the disease pustules, laryngitis, pneumonia, thrombocytopenia[4] and neurological problems (Freer and Pistello 2018).

Infants (of seronegative mothers) exposed postnatally to VZV in the first 28 days postpartum have increased risk of severe illness (including pneumonia and encephalitis) and death compared to older children (Heuchan and Isaacs 2001; Preblud et al. 1985).

Zoster (shingles) occurs due to reactivation of latent VZV (Freer and Pistello 2018), and is uncommon before the age of 12 years (Queensland Government 2018).

EBV: The majority of primary EBV infections in infants and young children are asymptomatic or result in mild symptoms not necessarily recognised as related to EBV, including sore throat, rash, fever, conjunctivitis, runny nose and/or enlargement of the liver and/or spleen (Biggar et al. 1978; Krabbe et al. 1981; Lawrence 2011; Slyker et al. 2013).

Primary EBV infection acquired at an early age is potentially a risk factor for the subsequent development of a number of diseases, including Burkitt's lymphoma (BL), Hodgkin's and non-Hodgkin lymphomas and nasopharyngeal carcinoma (Dunmire et al. 2018; Rochford 2016; Slyker et al. 2013). However, development of these malignancies is typically associated with concurrent immunosuppression, co-infection with another pathogen, or genetic predisposition or anomaly (Dozzo et al. 2017; Johannsen and Kaye 2010). EBV infection is not sufficient, in itself, to cause these diseases.

HHV-6: Primary HHV-6 infection occurs in early childhood. It is usually asymptomatic, but can cause exanthema subitum (roseola infantum) or occasionally a fever without rash, which can be accompanied by convulsions and, rarely, status epilepticus[5] or encephalitis (Hall et al. 1994; Ward 2005; Ward 2013).

HHV-7: Primary HHV-7 is similar to primary HHV-6 infection. It occurs in early childhood, is usually asymptomatic, but can cause exanthema subitum (Huang et al. 1997) or occasionally a fever without rash, which can be accompanied by convulsions and, rarely, status epilepticus or encephalitis (Hall et al. 1994; Ward 2005; Ward 2013).

HHV-8: HHV-8 is the causative agent of Kaposi's sarcoma, primary effusion lymphoma (PEL), and multicentric Castleman's disease (MCD). Most primary infections are asymptomatic (Kaye 2010), but primary infection in children can cause rash, respiratory symptoms and fever, and possibly vomiting and convulsions (Andreoni et al. 2002; Minhas et al. 2010). Development of HHV-8 associated malignancies requires immune suppression or the interaction of the virus with other, as yet poorly understood, factors (Kaye 2010).

Infectivity

The infective doses of these HHVs in human milk or any other transmission route are not known. The high prevalence of antibodies to these viruses (except for HHV-8) in the adult population implies that they are moderately infectious.

Risk mitigation

Human herpesviruses multiply in living host cells but cannot replicate in food (Codex 2012).

There is limited data on inactivation of most of the human herpesviruses. (Gustafsson et al. 2012) demonstrated 2-log inactivation of HHV-6 by treatment at 56°C for 1 hour. Heating EBV at 56°C for 1 hour completely abolishes the ability of the virus to transform (immortalise) cord blood mononuclear cells or primary human B cells (Adhikary et al. 2006; Salek-Ardakani et al. 2004). (Gaudreault et al. 2007) demonstrated that heating at 60°C for 1 hour disrupts intracellular signalling processes that require an intact EBV viral particle. (Hilfenhaus et al. 1986) reported at least

[4] Deficiency of blood platelets, causing bleeding into the tissues, bruising, and slow blood clotting after injury.

[5] Seizures lasting >5 minutes or occurring close together without recovery of consciousness between episodes

3.3 log inactivation of EBV heated in sucrose and glycine enriched culture medium at 60°C for 30 minutes. EBV is also sensitive to non-ionic detergents, standard disinfectants, acid pH and gamma-irradiation (Stramer et al. 2009); and UV light (Gaudreault et al. 2007).

International human milk banks, including those in Australia, routinely perform Holder pasteurisation to ensure the microbiological safety of donor human milk (Bharadva et al. 2014; Hartmann et al. 2007; HMBANA 2015; UKAMB 2003). It is unclear if this is sufficient to inactivate these human herpesviruses.

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).

Suitable hygiene controls in human milk banks would also reduce the potential for post-pasteurisation contamination of human milk with HHVs. International human milk banks follow guidelines for the storage, processing, and handling of human milk and train staff in health, hygiene, and quality and safety controls to ensure the safety of donor milk (Haiden and Ziegler 2016; PATH 2013).

Evaluation of uncertainty

There is uncertainty around the possibility of infection through ingestion of these human herpesviruses in human milk. Only two cases of transmission of VZV have been described, and neither study definitively rules out transmission by other routes.

There are no rigorous studies of thermal inactivation of these viruses, and it is uncertain whether Holder pasteurisation is sufficient to inactivate them.

The aetiology of development of malignant diseases due to either EBV or HHV-8 infection is unclear, but appears to require immunosuppression; co-infection with another pathogen; genetic predisposition or anomaly; or the contribution of other factors.

Risk characterisation

Human herpes viruses (other than HSV and cytomegalovirus) are likely to be of low infectivity, and primary infections in infants typically cause illness of mild severity. There is, at best, limited evidence for their presence in, and subsequent transmission through, ingestion of human milk. These human herpesviruses—VZV, EBV, HHV6, HHV7 and HHV8—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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