Imported food risk advice

Live vaccines 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 live vaccines

Live vaccines contain an attenuated (weakened) form of the virus or bacteria, and are used to produce an immune response in the recipient without causing the serious effects of the disease. Examples of live vaccines include those for measles virus (MeV), mumps virus (MuV), poliovirus (PV), rotavirus, rubella virus (rubella), typhoid fever (*Salmonella* Typhi), varicella-zoster virus (VZV) and yellow fever virus (YFV) (ATAGI 2018; WHO 2019).

There are three types of typhoid vaccines recommended by the WHO: the oral live attenuated vaccine (*S.* Typhi strain Ty21a), the unconjugated Vi polysaccharide vaccine (ViPS), and a typhoid conjugate vaccine that contains the Vi polysaccharide antigen linked to the tetanus toxoid protein (TCV) (WHO 2018). The scope of this assessment only includes the oral live attenuated *S.* Typhi Ty21a vaccine.

In general there is no evidence of live attenuated vaccines being transmitted to infants through human milk, except for rubella and YFV. Via this route of transmission, the rubella vaccine strain can cause asymptomatic to mild illness, while the YFV vaccine can cause severe disease.

Transmission

RNA of the attenuated MeV vaccine has been isolated from the breast milk of vaccinated mothers (2/169) (Hisano et al. 2016). This study was designed to evaluated the efficacy of MeV vaccination in the postpartum period and collected prevalence data, it was not associated with transmission to and/or illness in infants. There are no reports of human milk as a source of MeV vaccine transmission to infants (Hisano et al. 2016; TGA 2016a).

MuV vaccine causes a subclinical non-communicable infection (CDC 2015). No reports of secondary transmission via breastfeeding of the MuV vaccine have been documented and there are no reports of MuV vaccine being present in human milk (TGA 2016a).

There are two types of polio vaccines – inactivated polio vaccine and the oral polio vaccine (OPV). The attenuated PV strain(s) contained in the OPV are able to replicate effectively in the intestine and confer intestinal immunity, thereby preventing viral replication and shedding of wild poliovirus. Although the OPV has reduced transmissibility, the vaccine virus can be shed in nasopharyngeal secretions and faeces and is able to be transmitted to close contacts (WHO 2016, 2019). However, detection of the OPV in human milk and secondary transmission via breastfeeding has not been documented.

Rotavirus vaccine is a paediatric vaccine and is not indicated for use in adolescents and adults (TGA 2016b, 2017b). Detection of rotavirus vaccine in human milk and secondary transmission via breastfeeding has not been documented.

Rubella vaccine virus has been isolated from the milk of lactating mothers for up to 34 days post-immunisation, resulting in asymptomatic infection in breastfeeding infants (Losonsky et al. 1982). A case report by Landes et al.

(1980) documented a neonate who developed symptomatic rubella infection after the mother received rubella vaccination. However it could not be determined if the neonate's illness was due to transmission of the vaccine strain from the mother, or whether it was a wild-type rubella infection. Breastfeeding is not a contraindication to rubella vaccination (ATAGI 2018; CDC 2015). However caution should be exercised in lactating women, as immunisation of these women may lead to secretion of the vaccine virus in their breast milk and transmission to breast-fed infants. Rubella-containing vaccines are generally given in the immediate postpartum period if required (TGA 2016a).

The *S.* Typhi Ty21a vaccine strain is not contraindicated in breastfeeding women (ATAGI 2018). Detection of the *S.* Typhi Ty21a vaccine strain in human milk and secondary transmission via breastfeeding has not been documented.

VZV vaccine has not been detected in human milk and no reports of secondary transmission via breastfeeding from a vaccinated individual have been documented (TGA 2018). In a study by Bohlke et al. (2003) in which post-vaccination breast milk samples were collected from twelve women, VZV DNA was not detected in any human milk samples (n=217).

There is evidence that YFV vaccine may be transmitted thorough human milk. The CDC (2010a) documented a case of a mother who received the 17DD YFV vaccine during the postpartum period and transmitted the vaccine virus to her exclusively breastfed infant. The infant subsequently developed yellow fever vaccine-associated neurologic disease. The 17DD YFV vaccine was detected in the infant's cerebrospinal fluid, however no breast milk samples were tested for the presence of YFV. As the possibility that the infant had received the vaccine inadvertently was ruled out, and transmission of the vaccine virus did not occur *in utero*, it was concluded that transmission occurred via breast milk. There are other case studies in which transmission of the YFV vaccine to infants potentially occurred through human milk following maternal YFV vaccination, however vector-borne transmission could not be excluded (Kuhn et al. 2011; Mann et al. 2018; Traiber et al. 2011). There is no evidence of either the wild or vaccine type of YFV being isolated from human milk (Lawrence 2011). The American Advisory Committee on Immunization Practices recommend that yellow fever vaccination should be avoided in breastfeeding women until further information is available on the risk of potential vaccine exposure through breastfeeding (CDC 2010b). In endemic areas, or during outbreaks, the WHO believes the benefits of vaccinating breast feeding mothers outweighs the risk of potential transmission of the vaccine virus to infants (WHO 2010). In Australia YFV vaccination is not recommended for breast feeding women unless when clearly needed and following an assessment of the risks and benefits (TGA 2017a).

Adverse events

Adverse events (AEs) in infants potentially associated with vaccine transmission through breast feeding have only been documented for YFV and rubella vaccines (TGA 2016a, 2017a). As described above, transmission of the YFV and rubella vaccine through human milk may lead to infants developing yellow fever vaccine associated neurotropic disease and mild clinical rubella illness, respectively. For the other live attenuated vaccines considered in this risk assessment, transmission of vaccine-associated infection through human milk has not been demonstrated.

AEs are rare but can occur when vaccines are given through the recommended routine route of delivery.

Risk mitigation

Controls are needed to minimise contamination of human milk with viruses and bacteria, including live vaccine strains. As there is no specific evidence for the thermal inactivation of the vaccine strains, it is assumed that inactivation of the vaccine strains would be similar to the wild-type strains.

MeV, rubella and YFV are inactivated by heat treatment at 56^{o}C for 30 min (PHAC 2010, 2011b, 2017; Song et al. 2010). VZV is easily inactivated by heating to 60^{o}C (Arvin and Gilden 2013; PHAC 2011a) and MuV has been reported as being rapidly inactivated by heat (no temperature reported) (ATAGI 2018; CDC 2015). Therefore it is assumed that Holder pasteurisation (62.5^{o}C, 30 min) would be effective at inactivating these viruses and their respective attenuated live vaccines.

Fatty acids and salts can stabilise PV at 45^{o}C (Dorval et al. 1989). However the CDC (2015) state that PV is rapidly inactivated by heat, so it is assumed that Holder pasteurisation would be effective at inactivating PV. Holder pasteurisation kills most bacterial contaminants found in human milk (Baumer 2004; Picaud and Buffin 2017) and would be expected to inactivate *S.* Typhi.

A study by Araud et al. (2016) showed that heat treatment of rotavirus at 62^{o}C for 30 min in culture medium leads to 3-4 log reduction in rotavirus plaque forming units. As rotavirus and rotavirus vaccine have not been detected in

human milk, Holder pasteurisation would be expected to inactivate rotavirus vaccine should it be present in pooled human milk at very low levels.

International human 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).

As some live vaccines, such as those for rubella and YFV, can potentially be transmitted through human milk for some time after vaccination, a donor should not donate human milk for the allocated exclusion period if she receives a live vaccine. The Human Milk Banking Association of North America and the United Kingdom Association for Milk Banking temporarily exclude donors who have received a live vaccine for 1-2 months after vaccination (HMBANA 2015; UKAMB 2003). Under the Australian Therapeutic Goods Order No. 88 potential donors of human blood and blood components, human tissues and human cellular therapy products are ineligible to donate for a period of 4 weeks after receiving a live attenuated bacteria or virus vaccine (except smallpox which has a 8 week ineligibility period).

Evaluation of uncertainty

There is uncertainty around the presence and transmissibility of live attenuated vaccines in human milk.

Pooling of human milk from multiple donors is common practice amongst many human milk banks, and would dilute the viral or bacterial 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

For several of the vaccines - MuV, PV, rotavirus, *S.* Typhi and VZV - there is a lack of evidence of their presence in human milk, or human milk as a route of transmission. Therefore there is a very low likelihood of exposure to these vaccines via human milk.

There is a low likelihood of exposure to the MeV vaccine strain. Although the vaccine has been detected in human milk, there are no reports of transmission of MeV vaccine to infants via human milk.

There is a medium likelihood of exposure to the rubella vaccine strain as there is some evidence of the virus being detected in human milk and transmission to infants occurring. However, infants potentially infected with the rubella vaccine through human milk were asymptomatic or had mild symptoms.

There is a low likelihood of exposure to the YFV vaccine strain as there is limited evidence of transmission of the YFV vaccine through human milk. However in the CDC case report (2010a), YFV vaccine caused severe disease that was potentially life threatening.

Therefore the live attenuated vaccines for MeV, MuV, PV, rotavirus, rubella, *S.* Typhi and VZV in imported human milk and human milk products do not present a potential medium or high risk to public health and safety.

However, the live attenuated YFV vaccine in imported human milk and human milk products presents a potential medium or high risk to public health and safety.

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