Imported food risk advice

Extraintestinal pathogenic *Escherichia coli* 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

Escherichia coli is a facultative anaerobic Gram-negative, rod-shaped bacteria that belongs to the family *Enterobacteriaceae*. *E. coli* is commonly a harmless member of the normal commensal microflora of the intestinal tract of humans and other warm-blooded animals. However certain strains of *E. coli*, such as extraintestinal pathogenic *E. coli* (ExPEC), can cause illness in humans. Some pathogenic strains of *E. coli* cause relatively mild illness, however other strains, such as ExPEC, can cause severe, life-threatening disease (FDA 2012; FSANZ 2013; Mellata 2013; Meng et al. 2013).

Most *E. coli* strains are considered to be relatively heat sensitive (Li and Gänzle 2016).

Transmission

The primary reservoir of ExPEC is believed to be the human intestinal tract, where (like commensal *E. coli*) they do not cause gastroenteritis. The ExPEC strains carry virulence factors that allow them to translocate from their colonisation site (e.g. colon, vagina or oropharynx) and cause severe disease at sites outside of the gastrointestinal tract (Pitout 2012; Russo 2003; Smith et al. 2007). ExPEC can also be transmitted via person-to-person contact (e.g. sexual partners and possibly between household members), nosocomially (e.g. catheter associated) and potentially via consumption of contaminated food (Foxman 2002; Johnson et al. 1998; Manges et al. 2001; Poolman and Wacker 2016; Raymond et al. 2008). Mother-to-infant transmission of ExPEC can occur *in utero*, during delivery, or post-delivery (Mahjoub-Messai et al. 2011; Raymond et al. 2008).

E. coli has been detected in human milk from healthy women without underlying medical conditions or mastitis (Jiménez et al. 2008), as well as in milk from women presenting with acute mastitis (Patel et al. 2017). *E. coli* has also been isolated from swab samples from women's breasts (Ghuliani and Kaul 1995). The potential pathogenic nature of the *E. coli* detected in these studies was not reported. There are very few reports documenting human milk as a direct source of *E. coli* infection in infants.

In an *E. coli* outbreak of respiratory infection at a hospital Neonatal Intensive Care Unit, Nakamura et al. (2016) determined that the spread of *E. coli* occurred through the sharing of unpasteurised milk from a single donor (odds ratio of 49). The donor reported nipple pain in one of her breasts, which prevented her from sufficiently cleaning her nipple before and after lactation. Culture analyses of the expressed milk from both breasts showed that freshly expressed milk from the sore breast was exclusively contaminated with *E. coli*. The type of *E. coli* associated with this outbreak was not reported but was assumed to be ExPEC due to the extraintestinal nature of the infection.

Another report documented postnatally acquired *E. coli* sepsis in pre-term twins after receiving enteral feeds of their mother's expressed milk. The *E. coli* strain detected in the milk was the same as the strain detected in the infant's blood. In this report the mother did not have mastitis. However, transmission via direct handling by the mother

could not be ruled out (Widger et al. 2010). The type of *E. coli* detected in this study was not reported but again was assumed to be ExPEC due to the extraintestinal nature of the infection.

Disease severity

ExPEC causes severe disease that is potentially life threatening. ExPEC can cause urinary tract infection (UTI), sepsis, neonatal meningitis[1], and respiratory infections, as well as infections in other extraintestinal locations (Chmielarczyk et al. 2014; Mellata 2013; Smith et al. 2007). In young infants (and the general population) ExPEC can start as a localised UTI but this can lead to systemic infection (sepsis) which can be fatal (mortality rate for severe sepsis in children is 10%) (Angus et al. 2001; Mahjoub-Messai et al. 2011; Mellata 2013). Preterm neonates are more likely to develop sepsis and meningitis caused by *E. coli* compared with neonates born at full term (Krohn et al. 1997). ExPEC is the second most common cause of neonatal meningitis[1], which has a mortality rate of 10% in developed countries and 40-58% in developing countries (Furyk et al. 2011; Poolman and Wacker 2016). Sequelae of neonatal meningitis[1] can include developmental delay, hemiparesis[2], blindness and seizures (Klinger et al. 2000).

Infectivity

The infective dose of ExPEC in human milk is not known. However as other *E. coli* strains such as enterohaemorrhagic *E. coli* are very infectious (FDA 2012), it is assumed that ExPEC would similarly be very infectious and small quantities could cause infection.

Risk mitigation

Controls are required to minimise contamination of human milk with *E. coli*. As most *E. coli* strains are heat sensitive (D_{60} values of <1 minute) (Li and Gänzle 2016; Mercer et al. 2015), Holder pasteurisation (62.5^{o}C, 30 minutes) should inactivate ExPEC. However, ExPEC strains have been shown to encode the gene for a heat-stable enterotoxin (Maluta et al. 2016; Toval et al. 2014).

Human milk products should be produced from milk that has been subjected to Holder pasteurisation or an equivalent thermal treatment during processing to eliminate microbiological contamination. However, if human milk is heavily contaminated with microorganisms or if heat stable bacterial toxins are present, Holder pasteurisation used by international human milk banks may be ineffective. Therefore, pre- and post-pasteurisation microbiological criteria are used for human milk as described in international best practice guidelines to ensure the effectiveness of Holder pasteurisation and the microbiological safety of donor human milk (Bharadva et al. 2014; Hartmann et al. 2007; HMBANA 2015; UKAMB 2003). The United Kingdom Association for Milk Banking and other international human milk banks, such as in Australia, screen pre-pasteurised human milk for potential pathogens such as pathogenic strains that produce heat stable toxins and Enterobacteriaceae. Post-pasteurised human milk is screened for bacteriological growth, with any positive batches of human milk discarded (Hartmann et al. 2007; UKAMB 2003).

Evaluation of uncertainty

There is uncertainty around the transmissibility of ExPEC through human milk and the number of infectious particles required to cause illness for this potential method of transmission.

Pooling of human milk from multiple donors is common practice amongst many human milk banks and would dilute the 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).

Heat stable toxins produced by some pathogenic strains of *E. coli* may remain in the milk even after all viable bacteria have been destroyed by heating (UKAMB 2003), however it is unknown if this would be sufficient to cause illness in the absence of other virulence factors.

Risk characterisation

There is a low likelihood of exposure to ExPEC as there is limited evidence of transmission of ExPEC to infants through human milk. However, ExPEC can cause severe disease that is life-threatening, and ExPEC is assumed to be very infectious.

[1] Inflammation of the membranes of the brain or spinal cord

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[2] Weakness on one side of the body

Therefore in imported human milk and human milk products ExPEC presents a potential medium or high risk to public health and safety.

This risk advice was compiled in: March 2019, updated October 2019

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