Review Article

The risk of infectious pathogens in breast-feeding, donated human milk and breast milk substitutes

Katherine Blackshaw[1],†, Peter Valtchev[1],†, Nooshin Koolaji[1], Nina Berry[2], Aaron Schindeler[1,4] , Fariba Dehghani[1] and Richard B Banati[3,5,6],*

[1]School of Chemical and Biomolecular Sciences, Faculty of Engineering, University of Sydney, Camperdown, NSW 2006, Australia: [2]School of Public Health, University of Sydney, Camperdown, NSW 2006, Australia: [3]Mother's Milk Bank Charity and Australian Breast Milk Bank Consortium (Human Milk Emergency Reserve Project), Bilinga, QLD 4225, Australia: [4]Bioengineering and Molecular Medicine Laboratory, The Children's Hospital at Westmead, Westmead, NSW 2145, Australia: [5]Faculty of Medicine and Health, Brain and Mind Centre, University of Sydney, Camperdown, NSW 2006, Australia: [6]Australian Nuclear Science and Technology Organisation, Lucas Heights, NSW 2234, Australia

Abstract

Objective: This review collates the published reports that focus on microbial and viral illnesses that can be transmitted by breast milk, donor milk and powdered infant formula (PIF). In this context, we attempt to define a risk framework encompassing those hazards, exposure scenarios, vulnerability and protective factors.
Design: A literature search was performed for reported cases of morbidity and mortality associated with different infant feeding modes.
Setting: Exclusive breast-feeding is the recommended for infant feeding under 6 months, or failing that, provision of donated human milk. However, the use of PIF remains high despite its intrinsic and extrinsic risk of microbial contamination, as well as the potential for adverse physiological effects, including infant gut dysbiosis.
Results: Viable pathogen transmission via breast-feeding or donor milk (pasteurised and unpasteurised) is rare. However, transmission of HIV and human T-cell lymphotropic virus-1 is a concern for breast-feeding mothers, particularly for m others undertaking a mixed feeding mode (PIF and breast-feeding). In PIF, intrinsic and extrinsic microbial contamination, such as *Cronobacter* and *Salmonella*, remain significant identifiable causes of infant morbidity and mortality.
Conclusions: Disease transmission through breast-feeding or donor human milk is rare, most likely owing to its complex intrinsically protective composition of human milk and protection of the infant gut lining. Contamination of PIF and the morbidity associated with this is likely underappreciated in terms of community risk. A better system of safe donor milk sharing that also establishes security of supply for non-hospitalised healthy infants in need of breast milk would reduce the reliance on PIF.

National and international health authorities recommend infants breastfeed to the exclusion of all other foods and fluids for the first 6 months of life and continue breast-feeding as part of a mixed diet well into early childhood[1,2]. This remarkable unanimity recognises breast-feeding as necessary for physiological growth and development and immune protection during the amount of time that the infant is immune incompetent[3]. Increasingly, it is recognised that the immunological resilience conferred through breast-feeding has lasting effects throughout life. Nevertheless, it is estimated that worldwide less than 40 % of infants under 6 months of age are exclusively

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†These authors contributed equally to this work.

Corresponding author: Email richard.banati@sydney.edu.au

breastfed[4]. In Australia, although 96 % of mothers initiate breast-feeding, by 3 months only 39 % are still breast-feeding and only 15 % continue to 5 months[5]. Powdered infant formula (PIF) is commonly used as a replacement for breast-feeding. The normalisation of its use has seen its change from a last resort intervention for infants who cannot be breastfed or fed with donor milk to a routine infant feeding practice[6,7]. However, there is an unavoidable risk of intrinsic and extrinsic bacterial contamination with PIF use, in addition to the risks associated with the removal of the protective factors in breast milk that should be taken into consideration when deciding upon infant feeding mode.

Many structural and societal factors contribute to low breast-feeding rates. These include insufficient awareness of breast milk as a complex functional food; the lack of availability of donor milk, including pasteurised donor human milk (PDHM); little information about the comparative risks across all infant feeding modes; a poor appreciation of the intrinsic and extrinsic pathogen risks of PIF use and, no less important, gender discriminatory work and employment practices. Information on pathogen risk and morbidity associated with PIF use and recalls of PIF products due to microbial contamination are not always made available or easily accessible to the public. As a result, it is challenging for mothers to make a fully informed choice between the different infant feeding methods. Our systematic analysis of the scientific literature compares the reported pathogen risks of breast-feeding, PDHM, expressed breast milk (unpasteurised) and PIF use by collating available infant morbidity and mortality data. This review is intended as a comparative overview of the reported microbial risks involved across all the main feeding modes for infants, rather than an in-depth analysis of any particular risk. Human milk fortifiers (derived from sterilised human milk, where processing practices are not fully disclosed[8] and bovine milk) were not included in this review.

Factors affecting pathogen risk in infant feeding

A hazard is any source or cause of potential damage. In regard to PIF use and breast milk feeding, the main hazard is the possible presence of pathogens and/or a reduced resilience against pathogens. Risk can be expressed as a product of hazard, exposure and vulnerability (Fig. 1). A hazard only becomes a risk to a target *if* it is exposed to that hazard *and* it is vulnerable. Risk may be mitigated by minimising exposure to the hazard or by reducing the target's vulnerability. By including the latter, the assessment of risk also considers factors inherent to the milk, the processes required to produce and deliver it (Fig. 2[9–13]) and factors inseparable from the feeding mode that mitigate hazards (e.g., antimicrobial properties of human milk) or reduce the infant's vulnerability (e.g., immunological properties of human milk) (Table 1). Table 1 attempts to list the known hazards and mitigation factors. Non-biological hazards are

Hazard	A property inherent to an agent or process with the capacity to cause harm
Exposure	Contact with a hazard
Vulnerability	A property of a target that makes it capable of being harmed by a hazard
Resistance	A concept included in the vulnerability. Measures taken to prevent loss
Resilience	A concept included in the vulnerability. The ability to recover to a prior state of health

$$Risk = hazard \times exposure \times vulnerability$$

Fig. 1 Risk equation and definitions of terms. Risk is an expression of the probability that exposure to a hazard will cause harm to a vulnerable organism or group. Resistance and resilience are both factors included in the broader definition of vulnerability

mentioned for the sake of completeness (Table 1) but are beyond the scope of this review that focuses on infectious pathogens.

Literature review methodology

Search criteria
The databases Scopus and Web of Science were selected to retrieve peer-reviewed scientific publications. The search through the Web of Science databases comprised the Web of Science Core Collection, BIOSIS previews, CABI: CAB Abstracts®, Chinese Science Citation Database[SM], Current Contents Connect, KCI-Korean Journal Database, MEDLINE®, Russian Science Citation Index, SciELO Citation Index and Zoological Record. Initial search terms included ('HIV' or 'Human immunodeficiency virus') and ('Human milk' or 'breastmilk' or 'breast milk') and 'Transmission'; ('HTLV' or 'human T-lymphotropic virus' or 'human T-cell lymphotropic virus' or 'human T-cell leukemia-lymphoma virus') and ('Human milk' or 'breastmilk' or 'breast milk') and 'Transmission'; ('*Cronobacter sakazakii*' or '*Enterobacter sakazakii*' or '*salmonella*' or 'salmonellosis') and ('PIF' or 'powdered infant formula' or 'infant formula' or 'milk substitute' or 'replacement formula'); and ('donated milk' and pathogen or morbidity).

For each topic, papers from all sources were integrated with duplicates removed and the final list curated by the lead author removing irrelevant publications based on title, abstract and finally full paper text in a three-step process (online Supplemental Fig. 1). After the initial search was completed, the reference list was expanded by including the term 'donor milk' as a more common term. Additional literature was extracted from the reference lists of publications retrieved through the search terms of the initial search.

Inclusion and exclusion criteria
Publications were only included in the review if they provided quantitative data of morbidity or mortality and
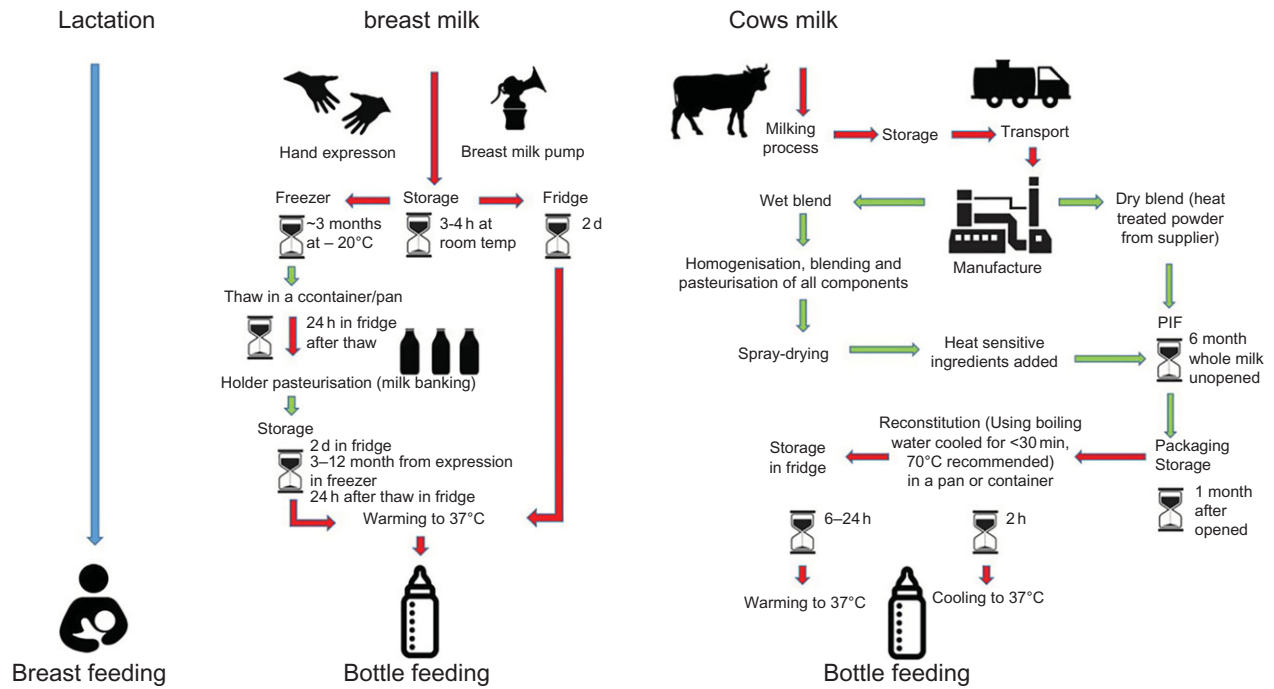
Fig. 2 Flow diagram of infant feeding pathways. While in breast-feeding (blue) there is minimal external entry of pathogens other than from the maternal skin, all other modes of infant feeding have numerous entry points for pathogens from the environment[9–11]. Red indicates those steps in which the food preparation and feeding processes are particularly prone to entry and/or growth of pathogens. Recommended safety steps for handling powdered infant formula (PIF) as set out by WHO[12] (not included in this diagram) should also be taken into consideration. The schematic is based on information taken from FAO 2004[13]

specifically traced the source of the pathogen. Publications on pathogens known to be associated with PIF but without an examination or comment on the association with PIF in the reported specific case were excluded. Likewise, publications that did not specify the feeding mode were excluded as were publications on potential disease transmission through breast-feeding if the infant feeding mode was insufficiently specified, for example, breastfed exclusively, or mixed.

Pathogen risks associated with breast-feeding

Exclusive breast-feeding is not normally associated with any risk, even in the case of maternal infection (online Supplemental Table 1). The main hazards of breast-feeding are exposure to the maternal viral pathogens HIV and human T-cell lymphotropic virus-1 (HTLV-1). However, for both of these pathogens the actual transmission risk is not fully understood[14]. Other viruses or pathogens may be present in breast milk but are rarely associated with subsequent infection in the infant (online Supplemental Table 1). This may be due to the concurrent presence of specific antibodies and antimicrobial factors in the breast milk[15]. Breast-feeding has been described as a form of natural, broad-spectrum immunisation as it can, apart from passive immune transfer, elicit antigen-specific immune responses in the infant, boosting immunity to infectious

diseases long-term[16]. Consequently, the WHO recommends exclusive breast-feeding, except in the presence of a very limited number of pathogens as listed in online Supplemental Table 1.

As an example, human cytomegalovirus may also be transmitted via breast-feeding and infants can test positive. However, the vast majority of infants with cytomegalovirus remain asymptomatic. Symptomatic cytomegalovirus infection is usually only a concern for preterm infants (<32 weeks), and the approach to management remains controversial. One group has suggested that preterm infants receive pasteurised mothers milk[17], while others note that post-partum cytomegalovirus produces negligible severe outcomes and that the benefits of pasteurisation may not be justified by the risks or cost[18].

Hazard: HIV in breast milk

It is increasingly recognised that when infants are exclusively breastfed by an HIV positive mother, the infant usually remains HIV negative. However, an accurate transmission risk is difficult to obtain as studies designed to investigate this risk often either do not control for mixed feeding (combinations of breast-feeding and PIF and/or solid foods) or allow for variable amounts of mixed feeding even in the designated exclusive breast-feeding groups, which is a potential compounding hazard in its own right[19–22].

HIV transmission through breast-feeding is mainly seen in endemic areas, such as sub-Saharan Africa[23] with its

Table 1 Hazards and mitigation factors related to breast-feeding, donated breast milk (PDHM) and PIF

Infant feeding modes	Potential hazards	Exposure effects	Vulnerability effects
Breast-feeding The process of feeding human milk to an infant, directly from the breast of a woman, usually the biological mother of the child. The milk is delivered directly from the mother's mammary anatomy to the infant's alimentary canal	• HIV • HTLV-1 • HCMV • Some other maternal viruses (see 'Risk involved in breast-feeding and cross feeding') • Persistent (fat soluble) environmental pollutants • Orally bioavailable drug residues with small atomic weights	• Maternal viral load • Maternal environmental pollutant load • Maternal excretion of environmental pollutants • Protective and bioactive substances including antimicrobials such as Ig, lactoferrin, lysozyme, peptides and carbohydrates • Entero-mammary pathways	• Duration of breast-feeding (in some cases – see HTLV section) • Absence of antibody in the breast milk • Non-exclusive breast-feeding (i.e., when other solids or liquids are introduced before 6 months)
PDHM and expressed breast milk PDHM is expressed human milk that is refrigerated; transported; possibly frozen and defrosted; pooled (mixed together); pasteurised (Holder pasteurised – 62·5°C for 30 min); frozen; possibly transported; defrosted and warmed in preparation for feeding. The milk is either delivered to the infant's alimentary canal from a container fitted with a rubber or silicone teat, or delivered through a tube if the infant is <32 weeks Expressed breast milk is the same as above but not usually pasteurised and is not handled by the milk bank	• HIV • HTLV-1 • HCMV • Persistent (fat soluble) environmental pollutants • Orally bioavailable drug residues • Bacterial contamination • Chemical or other contamination • Foreign proteins (e.g., when mixed with other milks such as cow milk)	• Donor under-screening • Donor environmental pollutant load • Degradation of protective and bioactive factors through pasteurisation including antimicrobials, for example, Ig, lactoferrin, lysozyme and peptides • Pooling effect (i.e., colostrum, transitional and mature milk are pooled) • Storage chain integrity (temperature; duration; sanitation) • Quality assurance testing • Adulteration of donor milk with non-human milk	• Decrease in beneficial microbial colonies • Decrease in active and passive immune properties • Absence of entero-mammary pathways
PIF A modified animal (usually bovine or goat) milk-based partial or total replacement for human milk. The constituents of these products vary, even while their nutritional profiles are strictly prescribed. These are powdered milk products that must be reconstituted and are usually delivered to the infant's alimentary canal from a container fitted with a rubber or silicone teat	• Bacterial contamination • Survival of bacterial spores in powdered products • Chemical contamination • Sustained nutritional excess/deficiency (through over – or under-dilution) • Non-human-sourced components • Contaminated water • Residues from agrochemical and veterinary exposure (hormones, antibiotics, pesticides, etc.) • Milk sources from non-human species • Compositional degradation from processing • Overheated water for reconstitution	• Manufacturing process • Faulty batch testing • Packaging material • Storage chain integrity • Hygiene standards of preparer and reconstitution process • Storage duration before and after reconstitution • Water temperature during reconstitution (e.g., loss of nutrients) • Adulterations	• Mucosal injury • Pathological gut pH • Atopic sensitisation • Inflammation • Nutritional bioavailability • Sustained nutrition inadequacy (through over dilution of PIF) • Failure to seed/sustain beneficial microbial colonisation • Absence of maternal immune system influence (passive immune components and active response through entero-mammary pathway) • Scalding of mouth and digestive tract from overheated water during reconstitution PIF (increased infection risk)

high background prevalence of infant mortality and maternal under-nutrition.

In areas where HIV is endemic, the risk of HIV transmission through breast-feeding must be compared with the risks associated with PIF feeding, which include malnutrition, diarrhoea or pneumonia[24]. This is illustrated well by an outbreak in Botswana in 2006. In an area where PIF use was high due to endemic HIV infection, heavy rains caused an outbreak of diarrhoea that disproportionally affected PIF-fed infants, regardless of HIV status. Of the 153 children hospitalised with diarrhoea, 88 % were not breastfed; of the thirty-three infants who died, twenty-seven were not breastfed. Non-breastfed infants were often undersupplied with PIF and therefore malnourished, an additional contextual determinant of the overall health outcome[25]. Where PIF feeding cannot be done safely, breast-feeding is critical to infant survival, regardless of HIV status[25,26]. Where HIV is endemic, lifelong maternal antiretroviral therapy is recommended for HIV positive mothers, and exclusive breast-feeding to 6 months and continued breast-feeding to at least 12 months is recommended as these measures are associated with a lower risk of infant morbidity and mortality then mixed or PIF feeding[24,27]. Despite this recommendation, PIF use is common in heavily HIV-affected areas.

A meta-analysis was performed in all publications specifically reporting transmission rates for mother-to-child transmission rate of HIV. Across those sixteen studies, estimates of transmission were 6·2 % for exclusively breastfed infants, 15·3 % for mixed breastfed/PIF-fed infants and 12·7 % for exclusively PIF-fed infants (Table 2). In some reports, the definition of exclusive breast-feeding allowed for some solids or PIF to be used for short periods of time[21,28,34], which confounds interpretation. Additionally, while most reports had a study duration starting at 6 weeks of life, others started the study duration from birth, which may not clearly delineate between congenital and postnatal transmission (Table 2). The presence of HIV transmission in exclusively PIF-fed infants may indicate unsuccessful HIV testing for congenital transmission, or undisclosed occasional breast-feeding, which was noted in at least one of the studies, but is likely common[28].

Exposure effects
Exposure to antiretroviral therapy for both the infant and mother during pregnancy and breast-feeding has been shown to reduce the risk of transmission[35], as this reduces the viral load. Mixed feeding is also associated with higher rates of HIV transmission (Table 2[19–23,28–33]).

Vulnerability effects
Breast milk contains antimicrobial substances that support host defence[36] and protects against infections through entero-mammary pathways[37]. Secretory IgA, an anti-inflammatory antibody, is the first line of defence against pathogens gaining entry through the mucosal lining of the gut[3]. During the first few months of life where the

infant's secretory immune system (production of antibodies) is deficient, and the mucosal gut barrier is not established adequately[38], the infant is reliant on the supply of antibodies from breast milk[39]. Therefore, the absence of breast milk can disrupt the mucosal barrier. Breast milk colonises the gut with *Bifidobacteria* for which breast milk oligosaccharides provide the favourable growth conditions[40]. In contrast, infants fed with reconstituted PIF or prematurely with solid foods show an increased gut pH and altered microbiota[41,42]. This dysbiosis, along with increased disruption of the mucosal barrier[3] and increased gut permeability, may result in translocation of luminal contents[43] and make the infant more vulnerable to pathogens[44]. Altered gut mucosal lining and permeability may be particularly important in HIV transmission[45], which could explain in part the increased HIV transmission under mixed feeding conditions.

Hazard: HTLV-1 in breast milk
HTLV-1 is a retrovirus that causes life-long infection. It is transmitted sexually or through an iatrogenic route in adults or through breast milk. While infants remain largely asymptomatic, about 10 % of adult HTLV-1 carriers develop adult T-cell leukaemia[46]. Adult T-cell leukaemia has a high mortality rate and is linked to mother-to-child transmission of HTLV-1 (rather than adult infection of HTLV-1)[46]. At least 5–10 million people are living with HTLV-1. Areas of high prevalence are found in parts of Africa, Peru, Iran, Brazil, Japan[46] and central Australia[47], although the true prevalence of HTLV-1 is unknown[48]. The exact portion of infection globally that comes from mother-to-child transmission is not known and varies regionally[46]. Our meta-analysis included all publications reporting morbidity and mortality thought to be due to mother-to-child transmission of HTLV-1. Across eleven retrieved studies, the overall transmission rates were 5·9, 14·1, 23·7 and 4·3 % for infants breastfed for <6, <12, >12 months and PIF-fed infants, respectively (Table 3[49–59]). Two reports were excluded in these overall rates due to incidence rates being reported without sufficient information about the duration of breast-feeding[49,50].

Exposure effects
The mechanism of transmission during breast-feeding is not well understood[46]. Mechanisms for both transmission through disrupted and intact epithelium have been reported[60]. The transmission rate is lower when the duration of breast-feeding is shorter than 6–12 months[46,59]. Since these studies do not specify whether 'breast-feeding' refers to exclusive or mixed modes, it is not known whether and how much a 'mixed feeding mode' might increase the risk of HTLV-1 transmission. In some regions of high prevalence, breast-feeding mothers lacking screening and education are unaware of their HTLV-1 status and may transmit the virus unknowingly[47]. Increased proviral load[59,61] increases transmission, irrespective of

Table 2 Vertical postnatal HIV transmission data (2000–2018) separated by the infant feeding modes (breastfed, mixed-method and PIF-fed infants)*

Year (country)	Exclusive breast-feeding definition in study	Exclusive breast-feeding Incidence/total number of infants in study	%	Mixed breast-feeding Incidence/total number of infants in study	%	PIF feeding Incidence/total number of infants in study	%	Antiretroviral therapy Incidence/total number of infants in study	%	Study duration	References
2000 (South Africa)	No liquids/solids introduced	15/103	14·6	69/288	24·1	29/156	18·8	No		1 d–3 months	(19)
2005 (Uganda)	Only breast milk was received with no other concomitant fluid or feed. Infants who were switched to PIF before 4 months were still included in the EBF group	19/119	16	10/49	20·4	4/108	3·7	Short-term courses of zidovudine or nevirapine for mothers		Birth-6 months	(28)
2005 (Zimbabwe)	No liquids/solids or non-human milk except for vitamins or prescribed medicines for at least 3 months. One lapse in EBF was allowed as long as the non-breast milk item was not non-human milk	8/156	5·1	PBF 35/490 MBF 156/1414	7·1 11	Not reported		No		6 weeks-18 months	(20)
2007 (South Africa)	No liquids/solids except for vitamins or drugs (but up to 3 d of PIF feeding allowed in the EBF group)	55/362	15	MBF > 14 weeks 89/322, MBF < 14 weeks 61/239	27 26	2/287	7	Single-dose nevirapine provided for mothers and infants		6–26 weeks	(21)
2010 (Nigeria)	Not defined	5/27	18·8	32/47	68	11/228	4·8	231/304 mother and infant/ only mother or only infant received ART	76	6 weeks–17 months	(29)
2014 (Tanzania)	Not defined	43/497	8·7	6/22	27·3	4/40	10	469/561 received chemoprophylaxis	86	4 weeks–18 months	(f)
2014 (Nigeria)	Not defined	3/94	3·2	10/63	15·9	6/426	1·4	431/583 received ART	73·9	6 weeks-18 months	(23)
2017 (Kenya)	Not defined	10 364/167 166	6·2	3600/23 682	15·2	3672/ 27 856	9·7	68 % mother and child or mother only received some form of prophylaxis. 14 % prophylaxis status unknown		Birth-24 months	(31)
2018 (Cameroon)	No added supplements except vitamins. Feeding options described for the first 3 months only	11/405	2·7	3/14	21·4	25/658	3·8	All mothers received zidovudine		6 weeks-24 months	(22)
2018 (Ethiopia)	Not defined	15/691	3·3	3/10	37·5	4/63	7·5	407/764 mothers on prophylaxis 353/764 mothers on HAART 736/764 infants on prophylaxis	53·3 46·3 97·9	Birth–18 months	(32)
2018 (Nigeria)	Not defined	1/29	3·4	0/8	0	1/7	14·3	2/44 mother-infant pairs received ART	95·2	1–18 months	(33)
Total	n/a	10 539/169 549	6·2	4074/26 648	15·2	3758/ 29 829	12·6	n/a		n/a	n/a

PIF, powdered infant formula; MBF, mixed breast-feeding; PBF, predominantly breast-feeding; EBF, exclusively breast-feeding; EFF, exclusive formula feeding; ART, antiretroviral therapy; HAART, highly active antiretroviral therapy.
*This review records the incidence in each study of vertical HIV transmission, the total number of infants in the study and the percentage of the transmission rate. It should be noted that some of the included studies began their study from birth, which may not differentiate accurately between congenital and postnatal transmission.

Table 3 Vertical postnatal HTLV-1 transmission data (1984–2018) separated by the infant feeding modes and duration of breast-feeding (breastfed for <6 months, >6 months, mixed-method and PIF-fed infants)

Year (country)	Breast-feeding <6 months		Breast-feeding >6 months		Mixed feeding		PIF feeding		Study duration	References
	Incidence/total number of infants in study	%	Incidence/total number of infants in study	%	Incidence/total number of infants in study	%	Incidence/total number of infants in study	%		
1986 (Japan)	Not reported		13/16 (BF duration not specified)	25	Not reported		Not reported		Birth-18 months	(49)
1987 (Japan)	Not reported		BF (duration not specified) 11/24	46	Not reported		1/11		Tested at 12 months	(50)
1987 (Japan)	Not reported		12 months 5/8 –18 months 5/18	63 28	12 months 2/7 18 months 3/29	29 10	Not reported		Tested at 12 months and 18 months	(51)
1990 (Japan)	Not reported		17/44	39	5/49	10	0/10	0	Retrospective study of 1–13 year olds	(52)
1991 (Japan)	<6 months 4/90	4·4	>7 months 20/139	14·4	Not reported		9/158	5·7	Tested every 3 months for 1 year, then 6 months for 2 years	(53)
1991 (Japan)	<3 months 2/39 <6 months 5/22	5·1 22·7	<12 months 6/23 >12 months 5/13	26·1 38·5	Not reported		2/12	16·7	Tested every 6 months	(54)
1996 (Gabon)	<6 months not reported		>8 months 4/34	11·8	Not reported		Not reported		Tested every 6 months until 2/4 years old	(55)
1997 (Japan)	<6 months 2/51	3·9	>6 months 13/64	20·3	Not reported		4/162	2·5	Infant s > 30 months were tested	(56)
1997 (Jamaica)	<6 months not reported		<12 months 8/86 >12 months 19/60	9 32	Not reported		Not reported		Birth–24 months	(57)
1999 (French Guyana)	<3 months 1/35 4–6 months 1/17	2·9 5·9	7–9 months 1/13, 10–12 months 7/68 >12 months 9/70	7·7 10·3 12·9	Not reported		0/23	0	Retrospective study of 0–12 year olds	(58)
2018 (Brazil)	Not reported		<12 months 7/145 >12 months 34/143	4·8 23·8	Not reported		Not reported		Birth–until BF stopped	(59)
Total	15/254	5·9	<12 months 88/624 >12 months 72/304	14·1 23·7	10/85	11·8	16/376	4·3	n/a	

*This review records the incidence in each study of vertical HTLV-1 transmission, the total number of infants in the study and the percentage of the transmission rate (incidence/total number of infants in study (%)). It should be noted that no definitions were found for feeding modes; therefore, it is not known if breast-feeding was strictly exclusive or if other solids and/or liquids were allowed. Therefore, all HTLV-1 reports must be viewed as potentially having some PIF exposure.

breast-feeding duration[61]. Additional independent variables for increased transmission also include more than one child with HTLV-1 and mothers who are >26 years old[59]. No clinical trials have been undertaken to test the efficacy of antiretroviral therapy for HTLV-1 positive mothers, which may help to reduce viral loads and transmission[46].

Vulnerability effects

The major factor in the infants' vulnerability to HTLV-1 seems to be the protective presence of the maternal HTLV-1 antibody in the milk for the first 6–12 months[46,53,54]. Although there has been a strong focus on the effects of mixed feeding on HIV transmission, no such studies have been conducted for HTLV-1. The integrity of the infant gut may be a factor in transmission of HTLV-1. However, no reports were found where mixed feeding was included as a variable.

Pasteurised donor human milk and expressed breast milk

In this review, PDHM refers to donor milk that is handled by staff in milk banks following prescribed processes, that is, low temperature long time heat treated (Holder pasteurisation). Expressed milk refers to milk that is expressed for either the mother's own child or unofficially shared with other mothers and handled in an unregulated manner and is not pasteurised[17]. Holder pasteurisation is generally recognised as a necessary step for donor milk to ensure compliance with microbiological safety standards[62]. The current pasteurisation standards are based on the destruction in cows' milk of *Coxiella burnetii*, the cause of Q fever[63]. The temperature and time established for the pathogen control *C. burnetii*, however, significantly reduces the protein, lipid and lactose content compared with unpasteurised breast milk[64], as well as reducing protein function, antibody content, antioxidants, vitamin C, B_{12}, growth factors[65] and the natural microbiota present in milk[66]. For this reason, milk banks in Norway rely on donor screening rather than pasteurisation, and the provision of unpasteurised human milk has not been associated with any increase in infant morbidity[67]. Limited supply of donated milk in milk banks usually limits PDHM to premature infants in hospitals[9]. Despite the prevalence of bacterial contamination present in expressed breast milk and PDHM before and after pasteurisation (up to 25 % being discarded as a result)[68,69] clinically significant infection events associated with either of these feeding modes are rare (online Supplemental Table 2).

Hazards: transmissible maternal viral pathogens and opportunistic pathogens

The main hazards include maternal pathogens present in the breast milk and contamination with a pathogen after expression. In PDHM, the main isolates before and after pasteurisation are *Staphylococci* and the spore-forming, heat resistant *Bacillus cereus*, respectively[68,70]. The presence of *Staphylococcus aureus* pre-pasteurisation may produce heat resistant enterotoxins, and these may still be present after pasteurisation[71]. The presence of heat stable enterotoxins or bacteria (*Bacillus cereus*) emphasises the importance of post-pasteurisation checks[70].

Exposure effects

For PDHM, donor screening is used to reduce exposure risk, although there are no global regulatory frameworks for milk banking in place[72]. Therefore, screening and processing practices differ and are based on screening requirements for blood and tissue donation[9] and processing techniques used in the dairy industry as a basis[73]. This results in a variable product and therefore has variable risks and benefits[74]. The entry points for bacterial contamination for both PDHM and expressed milk include unhygienic expression (improperly washed hands or breast pump), unhygienic storage (incorrect temperature or storage duration), non-compliant pasteurisation, improperly sterilised feeding equipment (parenteral tube, enteral tube, bottle or cup) and through contamination during fortification of donated milk for premature infants[69,75].

The majority of cases of infant morbidity collected for this review were associated with unpasteurised milk (not sourced through milk banks) and expressed with both manual and electric breast pumps (online Supplemental Table 2). However, if expressed milk is handled properly, there is little evidence for any significant risk to infants, in contrast to PIF use, which is associated with a direct intrinsic and extrinsic pathogen risk as well as substantial intolerance reactions. Health authorities routinely advise against the use of expressed milk, notably if shared informally between mothers, due to the lack of regulatory control and lack of pasteurisation. However, with appropriate hygiene, there is no strong evidence that under share arrangements without monetary incentives, the quality and microbial contamination is systematically different between supervised, formally or informally shared milk[76]. It thus appears that it is specifically the education in appropriate handling and storage of expressed milk, rather than necessarily pasteurising milk (with its potential lowering of quality), that yields the greatest health benefits and that sharing as such does not increase the risk above that of bottle feeding with own milk.

Vulnerability effects

Thermal pasteurisation, as generally practiced, significantly reduces the milk's nutritional and bioactive components[77], as well as most beneficial bacteria naturally present[66]. Despite a partial loss of function, PDHM is still associated with better clinical outcomes than reconstituted PIF in the protection against opportunistic pathogens. Studies have found that feeding preterm infants with PDHM (rather than reconstituted PIF) significantly reduces

the incidence of necrotising enterocolitis[78–80], late onset sepsis[81] and bronchopulmonary dysplasia[82]. However, not all studies have found a difference in necrotizing enterocolitis rates between PDHM and reconstituted PIF-fed infants[83]. There are a number of reasons why PDHM might not show the expected beneficial effects. Over-treatment of PDHM may aggravate the loss of biological functions still present in expressed raw milk. Also, prolonged storage of expressed milk in a fridge (>72 h)[84] or freezer (>3 months)[85] reduces bactericidal activity. Increased vulnerability might also result from the absence, as with any form of bottle feeding, of the entero-mammary transfer of beneficial microbiota through breast-feeding[37] and the missing adaptive responses of the maternal immune system in the wake of breast-feeding[3].

Risks associated with powdered infant formula

Pathogen risk is inherent to PIF use as the manufacturing process itself introduces direct, albeit small, pathogen risks that cannot be completely eliminated[86]. Contamination risks are associated with both dry and wet blending methods[10]. Although dry blending tends to have a lower contamination risk due to the dry environment[10], batch testing of dried milk samples does not always detect contamination due to uneven distribution[87]. Recall of PIF due to either later-detected contamination or increased infant morbidity is a regular occurrence (online Supplemental Table 4).

In addition to the risks associated with manufacturing, PIF reconstitution also yields sources of contamination. Potential extrinsic pathogen entry points include reconstitution water, utensils, bottles and teats, the preparers' hygiene practices or the storage duration/conditions. Contamination of reconstituted PIF with faecal bacteria and inadequate sterilisation of the bottle and teat is common[11]. Some feeding bottles designed with a silicone straw inside are particularly difficult to clean according to WHO recommendations, which recommend scrubbing all internal and external surfaces with hot soapy water[12] and are thus prone to biofilm formation.

PIF are mostly based on modified bovine milk with added vegetable oils, vitamins, minerals and processing agents. Due to the heat processing of bovine milk, PIF contains a range of pro-inflammatory advanced glycation end-products[88].

Use of reconstituted PIF is associated with an increased risk of gut inflammation, alteration of the gut microbiome and disruption of the epithelium barrier[42], all of which may increase the risk of pathogen entry into the bloodstream[89], thus increasing the infant's vulnerability. Some infant formulas are supplemented with probiotics[90], and some with a synthetic human oligosaccharide[91]. It should, however, be noted that there are over 200 interactive human oligosaccharides present in breast milk[92] and that the health benefits of probiotics in infant formula are reported in comparison with conventional infant formula and not benchmarked against donor milk. Thus, the reported effects are primarily a mitigation of the detrimental effects of un-supplemented infant formula.

There are a wide range of pathogens that have been linked to contamination of PIF (online Supplemental Table 3), including bacterial spores[93] and bacteria that resist desiccation[94]. *Salmonella* and *Cronobacter* are the two most critical genera based on prevalence and health impact reported in the literature. While both pathogens are regularly detected in batches of PIF (online Supplemental Table 4), morbidity is mostly associated with *Salmonella enterica*. However, there may also be an underappreciated link between contamination of PIF with spores and infant morbidity[95].

Hazard: Salmonella enterica

Salmonella enterica are non-spore forming gram-negative *Enterobacteriaceae*, with a growth range of 5·2–46·2°C, are able to survive desiccation and, in certain circumstances, are able to survive freezing and some heat treatments[96]. Although there is no dose-specific model for infants <9 months, existing data suggest a very low infective dose (possibly as low as <10 CFU)[97]. *Salmonella* contamination of milk substitutes is associated with non-typhoidal *S. enterica*[10]. It affects both term and premature infants and, based on reports in the literature, is generally associated with large outbreaks (although the true incidence rates are not known). The natural reservoirs of *Salmonella* are foods of animal origin including raw milk, human contact with animals, the faecal-oral route or exposure to other infants with diarrhoea[97]. Non-typhoidal *Salmonella* infection can lead to gastroenteritis, diarrhoea, fever and vomiting, or more serious and potentially fatal conditions in premature infants including bacteremia, meningitis or severe levels of dehydration[98]. This is particularly pertinent in resource-poor settings where medical attention and clean water are not readily available. While the detection of *Salmonella* is by far the most commonly identified reason for morbidity associated with contaminated PIF, no reports could be found for the overall morbidity or mortality rates for *Salmonella* associated with PIF contamination[99]. While reports of *Salmonella* outbreaks associated with PIF exist for resource-rich settings, no such reports could be found for resource-poor settings, despite high levels of *Salmonella* infection in infants in these regions[100,101]. It remains a common cause of neonatal sepsis in Africa and is thought to be associated with unhygienic conditions in the home environment[102]. However, the association with PIF is unknown and calls for urgent research into the prevalence and incidence of *Salmonella* infections in PIF-fed infants. Our meta-analysis included all reports commenting on either morbidity or

Table 4 Salmonella outbreaks attributed to contamination of PIF

Year	Country	Symptomatic/ deaths	Source of the contamination	Outbreak	Recall	References
1968	USA	12/0	Manufacturing environment (spray driers)	Yes	?	(104)
1987	UK	46/1	Manufacturing environment (hole in inner liner of spray drier)	Yes	Yes	(105)
1993	Spain	3/0	Manufacturing environment (production equipment)	Yes	Yes	(106)
1996	Spain	45/0	Source not identified but attributed to the supplier of ingredients for the PIF brand	Yes	Yes	(107)
1998	UK and France	17/0	Manufacturing environment implicated through isolation in one brand of PIF	Yes	Yes	(108)
2002	USA	11/0	PIF mixed by the hospital	Yes	Yes	(109)
2003	Australia	7/0	Manufacturing environment (spray driers)	Yes	Yes	(110)
2004	Korea	28/0	Attributed to infected staff mixing PIF at NICU	Yes	Yes	(111)
2008	France	136/0	Traced back to one production line and two brands	Yes	Yes	(112)
2008	Spain	31/0	Manufacturing environment implicated through isolation in one brand of PIF	Yes	Yes	(113)
2017	France/Europe	39/0	Traced back to one production line and several brands	Yes	Yes	(114)
2018	France/Europe	32/0	Manufacturing environment implicated through isolation in one brand of PIF	Yes	Yes	(115)
n/a	n/a	407/1	n/a	n/a	n/a	Total

NICU, neonatal intensive care unit.

mortality traceable to a *Salmonella* contamination of PIF. Based on the reports found, there were 407 cases of *Salmonella* infant infection from twelve unrelated outbreaks that could be attributed to contaminated PIF in the past 50 years. From the compiled data, one was fatal (0·2 %) (Table 4[103–114]). These morbidity and mortality rates for *Salmonella* infection from contaminated PIF may well represent a substantial under-reporting. Non-typhoidal *Salmonella* is a common foodborne pathogen worldwide and is the most frequently isolated enteric bacterial pathogen in children under 5 in the USA[115]. The source of the infection is often difficult to find and is frequently not even investigated.

Exposure effects
All outbreaks of *Salmonella* infections caused by contamination of PIF were either traced back to manufacturing equipment or the raw milk product[103,105,106,109,116,117] or isolated from unopened tins of PIF, implicating the manufacturing environment. The only exception was an outbreak in a neonatal intensive care unit in 2001, which was attributed to infected staff[108]. Small amounts of *Salmonella* may grow to an infectious dose through unhygienic reconstitution, storage and feeding conditions[104].

Vulnerability effects
As previously noted, PIF feeding can increase vulnerability to bacterial pathogens due to gut microbiome dysbiosis[41,44] or lack of passive maternal immune protection[3].

Hazard: Cronobacter sakazakii
Cronobacter are an opportunistic gram-negative *Enterobacteriaceae* with a growth range from 5 to 47°C, are able to survive desiccated conditions for up to 2 years and, once ingested, can pass through the blood-brain barrier[118].

Cronobacter sakazakii (or *Enterobacter sakazakii* prior to 2007)[118] is a ubiquitous pathogen that rarely causes disease except in vulnerable populations, including infants and the elderly[118]. *Cronobacter* infection is almost exclusively associated with premature infants, or term infants within the first 2 months of life[119], and has not been associated with large outbreaks. Although the natural reservoir is not known, *Cronobacter* infection in infants is usually associated with PIF use[119]. Morbidities associated with *Cronobacter* include meningitis, necrotising enterocolitis, bacteremia and sepsis, all of which can lead to fatality or permanent sequelae[118]. Mortality rates are estimated to be between 33 and 80 %[120]. The infectious dose for neonates is estimated to be between 1×10^3 CFU and 1×10^4 CFU in a single feed[97] which is most likely subject to the degree of vulnerability of the infant.

Estimates of invasive *Cronobacter* infection incidence in infants in the USA from 2003 to 2009 were 0·66 per 100 000[121]. This is likely underestimated as *Cronobacter* is not notifiable in all states of the USA or in most countries, even in resource-rich settings[97]. Data for the incidence of *Cronobacter* infection outside of resource-rich settings could not be found.

A meta-analysis of all the reports containing comments on *Cronobacter*-associated morbidity or mortality identified fourteen reports of *Cronobacter* outbreaks or cases in neonates where the source was investigated and attributed to PIF use. Of the sixty-two cases in these reports, thirty-eight cases were invasive (61·2 %) and eleven were fatal (17·7 %); eight of fourteen studies were considered to be outbreaks (Table 5[122–135]).

Exposure effects
Cronobacter contamination has been traced back to unopened tins of PIF[125,130,136], powdered milk[127] and

Table 5 Cases of *Cronobacter* in neonates attributed to contamination of PIF. Note that there are records of other *Cronobacter* infections in neonates; however, all cases where the source of contamination was not investigated were excluded

Year	Country	Exposure/symptomatic/death	Source of infection	Outbreak	Recall	References
1989	Iceland	4/3/1	Reconstituted PIF	Yes	No	(123)
1989	USA	4/4/0	Manufacturing environment	Yes	No	(124)
1990	USA	1/1/0	Blender	No	No	(125)
2001	Belgium	6/6/2	Reconstituted PIF+ unopened PIF	Yes	Yes	(126)
2001	Israel	5/2/0	PIF and blender	Yes	No	(127)
2001	USA	10/3/1	Reconstituted PIF + unopened powdered milk	Yes	Yes	(128)
2002	Belgium	1/1/1	PIF implicated	No	Yes	(129)
2004	New Zealand	5/1/1	Reconstituted PIF	Yes	No	(130)
1994	France	17/8/3	Reconstituted PIF + unopened PIF	Yes	No	(131)
2008	USA	1/1/0	Reconstituted PIF + unopened PIF	No	No	(132)
2010	Spain	1/1/0	Unopened PIF	No	No	(133)
2010	Mexico	2/2/0	Reconstituted PIF + unopened PIF	No	No	(134)
2011	USA	4/4/2	Reconstituted PIF + unopened PIF + nursery water	Yes	No	(135)
2016	USA	1/1/0	PIF	No	Yes	(136)
n/a	n/a	62/38/11	n/a	n/a	n/a	

once back to the manufacturing environment[123]. Several other studies on the incidence of bacteria in PIF found that it is common for there to be small amounts of bacterial contamination from the manufacturing environment.[137] Incidence of morbidity and mortality from *Cronobacter* infection is often associated with unhygienic practices during reconstitution and storage, including leaving reconstituted PIF for too long before consuming[122], improper cleaning of blenders[124,126] and reconstituting with water that is insufficiently heated[136]. A recent study demonstrated that the bacterial load on the hands of the caregiver may also pose a risk through the hand-spoon-PIF route and should also be considered in any risk assessment[138]. It is unclear whether the major source of the *Cronobacter* is the manufacturing environment or lies in the environment during reconstitution. Whatever the origin, if *Cronobacter* is present, unhygienic reconstitution conditions allow for growth to reach an infective dose[139].

Vulnerability effects

Cronobacter infection is highly specific to preterm and <2 months old infants, suggesting that the development of the immune system, presence of maternal immune components and a healthy microbiome in the infant gut (which may outcompete ingested *Cronobacter*)[118] are highly relevant to the degree of vulnerability of the infant. The absence of breast milk is associated with increased gut permeability and dysbiosis and therefore increased risk of pathogen translocation through the gut lining.

Outcomes and conclusions

This review collated cases of infant morbidity or mortality where the source of infection could be traced to breast-feeding, donor breast milk or PIF use, in an effort to better compare the risks associated with infant feeding modes. However, large gaps in the literature hampered this task. It is likely that issues such as PIF contamination remain significantly under-reported, making it challenging to gauge the risks associated with major hazards such as *Salmonella*. While the published peer-reviewed literature may give an incomplete picture of the different risks, important observations can still be made about each feeding mode.

The primary perceived risk associated with breast-feeding is maternal virus transmission, the greatest concern being HIV. However, when the mother is provided with antiretroviral therapy and exclusive breast-feeding is practiced, the transmission rate is very low. A mixed feeding mode appears to increase the transmission rate, which may be due to increased exposure of infants to the virus as a consequence of the damaging effects of PIF on the infant digestive system[140]. Moreover, mortality resulting from withholding breast milk is higher than the infant mortality rate due to HIV infection[25,26]. The design of future studies needs to pay greater attention to the definitions of exclusive (from birth) breast-feeding and the impact of early supplementation and later mixed feeding modes, which in many reports are frequently observed as confounding variables.

Proper management of breast-feeding for HTLV-1 positive mothers is complex. Although antenatal screening and strict withholding of breast-feeding for all HTLV-1 positive mothers have greatly lowered vertical transmission rates in Japan[141], this also carries its own risks and consequences associated with PIF use, which would be magnified in resource-poor settings. The risk of HTLV-1 transmission must be weighed against the risks associated with PIF use and the loss of the benefits associated with breast-feeding. Monitoring of the pro-viral load in the milk may be a feasible option to assess transmission risk.

Additionally, clinical trials should be conducted in order to assess the efficacy of antiretroviral therapy in lowering transmission risk. Finally, further research is needed to evaluate the effect of mixed feeding on transmission risk. An alternative practicable approach might also be the systematic provision of PHDM or pasteurisation of the mothers' own milk until the endemic presence of HTLV-1 in vulnerable communities has been removed.

Pathogen risk cannot be eliminated from the PIF manufacturing process. *Salmonella* is the pathogen of most concern as it has been repeatedly associated with large outbreaks traced back to PIF contamination. Recent assessments have concluded that final quality control measures may not be enough to ensure microbial safety[142]. The reconstitution from powder additionally introduces extrinsic pathogen risks from contaminated water[143], contaminated bottles, teats or utensils and improper storage conditions which allows for bacterial growth. While all of these risks may be adequately mitigated by strict adherence to hygienic practices (using 70°C water with sterilised equipment), the formula-fed infant will still be left more vulnerable due to the lack of protective and developmental components in PIF.

A full assessment of the true risk associated with infant feeding modes also needs to encompass indirect hazard mechanisms. This includes any delay or disturbance in gut maturation through PIF-induced gut dysbiosis[42] or through lack of the protective and developmental factors in breast milk[3], the involvement of (possibly sub-clinical) inflammation[42,144] and other immune responses. Presently, there are insufficient data on the frequency of hospitalised infant morbidity linked to PIF use, and non-hospitalised infants with infections are not captured systematically. Therefore, the true incidence of PIF with primary or secondary contamination leading to illness may be greatly underestimated. Better documentation and quantification of the impact of diarrheal disease and pneumonia in infants fed with reconstituted PIF is needed, and clinical trials of PIF need to be benchmarked against health benefits of breast-feeding or donor milk.

Ultimately, a wider availability of PDHM could be a highly valuable public health measure if it decreases reliance on PIF. The available published data indicate that the risk of infant infection through PDHM or expressed milk is low. Indeed, most cases of bacterial contamination can be attributed to unhygienic handling of donor milk, including handling errors during the pasteurisation process. Proper decontamination of collection equipment and user hygiene are, therefore, key preventative strategies. While Holder pasteurisation can limit opportunistic pathogens, challenges remain around heat-stable spores[68] and the potential impact of thermal treatment on milk quality. To resolve these issues, one solution would be to advance non-thermal pasteurisation methods. Alternatively, a greater emphasis could be placed on testing the functional integrity of the processed batches of milk and rigorously

comparing the advantages associated with unpasteurised donor milk on preterm infants with pathogen-related risks[145].

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Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1368980020000555

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