Symposium on ‘Nutrition and immunity’

Role of breast-feeding in managing malnutrition and infectious disease

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Breast-feeding policy tends to be an emotive issue. International agencies recommend exclusive breast-feeding for 4–6 months followed by continued partial breast-feeding into the second year of life in order to promote infant and child health and minimize the damage caused by the malnutrition–infection cycle. To what extent are these recommendations supported by the experimental evidence? Are they a simplification for emotional reasons or public health purposes? Breast-feeding is believed to benefit infants because breast milk contains the ideal mix of nutrients for infants, because it contains factors which promote development of the infant’s gut and immune system and which prevent pathogen invasion, and because exclusive breast-feeding prevents intake of pathogens in food or water. However, some apparently contradictory evidence exists. First, in environments which are not highly contaminated breast-fed infants tend to growth falter relative to those fed formula. Second, in such environments partial breast-feeding is not associated with significantly increased gut damage relative to exclusive breast-feeding, suggesting that active promotion of gut development by breast-feeding is more important than simple avoidance of pathogens from other foods. Third, many immune factors in breast milk are probably present primarily to protect the mother, not the infant. Finally, breast milk itself may contain bacteria or viruses. This problem has come to the fore with the human immunodeficiency virus epidemic, since it is clear breast-feeding is an important mode of mother-to-child transmission. The present review will examine these challenges to the basis of the international infant feeding recommendations and will suggest that the science does actually support the policy.

Breast-feeding is a key component of infant and child health programmes. The benefits in terms of preventing the malnutrition–infection cycle are especially great in less-developed countries (Brown et al. 1989), but infections are also less prevalent in breast-fed infants in industrialized countries (Howie et al. 1990; Wright et al. 1998). There is little need to explain to this audience the scientific bases for the international policy that all infants should be exclusively breast-fed, i.e. not given any other foods or liquids including water, for the first 4–6 months of life and partially breast-fed into the second year (World Health Organization, 1993). The information supporting these recommendations is well reviewed in WHO publications concerning breast-feeding (World Health Organization, 1993) and complementary feeding of infants (Brown et al. 1998). Breast-feeding is considered to decrease the incidence and severity of infection and malnutrition by three main mechanisms: (1) it is nutritionally ideal for infants, whereas weaning foods in poor communities are often of low energy density or lacking in micronutrients; (2) weaning foods may be contaminated and cause diarrhoea and gut damage; (3) breast milk contains factors which both passively prevent infection and actively promote the infant’s own immune function. The present review will consider recent evidence undermining these mechanisms and possibly challenging the recommendations. I hope to convince the audience that, in spite of apparently conflicting evidence, the infant feeding recommendations are truly based on science and are not being promoted merely for philosophical or emotional reasons.
Breast milk as the best source of nutrition for infants

Breast milk is considered the ideal food for infants for about the first 6 months of life, after which growth and status of certain micronutrients, particularly Fe, are improved by adding appropriate complementary foods to continued partial breast-feeding (Brown et al. 1998). Those agencies asserting the nutritional superiority of breast-feeding have recently had to deal with the unfortunate experimental evidence that both parts of the international recommendations, for early exclusive breast-feeding and prolonged partial breast-feeding, are associated with growth faltering relative to relevant controls. Breast-fed infants grow at least as well as the largely non-breast-fed cohort of the widely-used National Centre for Health Statistics/WHO standards during the period of exclusive breast-feeding (World Health Organization Working Group on Infant Growth, 1994). However, in areas where ambient infection is low, these infants growth falter compared with the standards in the second half of infancy when partially breast-fed. Children breast-fed for prolonged periods, defined variously as more than about 12–18 months, have often been shown to have poorer anthropometric indices than children given breast milk early but weaned by the time of measurement (Victora et al. 1984; Brakohiapa et al. 1988; Briend & Bari, 1989; Nube & Asenso-Okyere, 1996). The results are well acknowledged to be confounded by factors such as: (1) socio-economic status, which might result in the poorest who are least able to afford quality complementary foods continuing to breast-feed longer; (2) reverse causality, such that a mother might want to continue breast-feeding a child which was growth faltering or ill and unwilling to eat sufficient complementary foods; (3) early death of non-breast-fed children in poor households (Briend & Bari, 1989), so that they do not contribute to anthropometric data later. However, when such confounders are accounted for statistically, children breast-fed for prolonged periods still have significantly poorer growth (Victoria et al. 1984; Nube & Asenso-Okyere, 1996).

To deal with these potential arguments against international feeding recommendations, WHO is developing new growth standards based on growth of infants fed according to the recommendations. While such action may seem to involve circular logic and a manipulation of growth curves to fit a particular philosophy of infant feeding, it is worth remembering that the aim of maximal and rapid growth comes largely from agriculture, and what is optimum for an animal raised for meat is not necessarily so for a human infant. The importance of maximal growth is especially debatable among populations prone to obesity. The immunological (Goldman, 1993) and possible cognitive (Anderson et al. 1999) benefits of breast-feeding are more important for human infants. Finally, it should be remembered that the growth differential favouring non-breast-fed infants may be erased in areas where the lack of safe nutritionally adequate complementary or alternative foods results in severe growth faltering or death of non-breast-fed infants. Although breast-fed Bangladeshi children, 12–35 months old, had slightly lower weight-for-age than completely-weaned children, the former had much lower risk of dying and breast-feeding was most protective for the most malnourished children (Briend & Bari, 1989).

Complementary or alternative foods and gut integrity

The inevitable need to wean means that in communities without access to clean water, the prevention of the malnutrition–infection cycle by exclusive breast-feeding eventually will end. The weaning period is the time of greatest risk of infection and stunting. Do weaning foods themselves cause this situation or is it some other aspect of reducing the proportion of dietary intake from breast milk? Especially in resource-poor countries weaning foods may be nutritionally inadequate in terms of low energy density and high bulk, and deficiencies in many micronutrients (Brown et al. 1998). Furthermore, consumption of other foods is more affected by illness-induced anorexia than is consumption of breast milk (Brown & Perez, 1992). Breast-feeding during acute diarrhoea reduced the amount of oral rehydration fluid required and improved recovery in Burmese infants (Khin-Maung-U et al. 1985). Breast-milk consumption during acute diarrhoea reduced the risk of developing persistent diarrhoea, although with the small number of patients the difference was not significant (Sazawal et al. 1992). Persistent diarrhoea carries a high risk of mortality, so its prevention is of great clinical importance. Thus, continued partial breast-feeding can make up for the nutritional shortcomings of many complementary foods during periods of both health and illness.

Weaning foods may be a source of pathogens and cause diarrhoea. Recent work has shown that breast milk may overcome the risk of gut damage from weaning foods. Numerous nutrients, e.g. nucleotides (Uauy et al. 1990) and vitamin A (Warden et al. 1997), and growth factors (Donovan & Odle, 1994) present in milk promote gut integrity and repair of tissue damaged by infection so that minor inflammation does not progress to major pathology. In a large cross-sectional study breast-fed Guatemalan infants had lower intestinal permeability, as measured by dual-sugar absorbance tests, than did non-breast-fed infants (Goto et al. 1999). Such permeability changes are probably of physiological importance, since they have been shown in Gambian infants to be correlated with lactose maldigestion (Northrop-Clewes et al. 1997) and growth faltering (Lunn et al. 1991). Although cows’ milk or other foods may damage the gut mucosa, it is also possible that the permeability differences are due to positive actions of breast milk for promoting gut integrity. In Guatemala permeability was negatively correlated with the age of cessation of breast-feeding but not with the amount of time since cessation, which suggested the positive effects of breast milk were paramount (Goto et al. 1999). We have recently conducted a longitudinal study of gut function of infants of human immunodeficiency virus (HIV)-infected South African women in an area where most of the population had access to piped water from the city supply. Infants given no breast milk had increased intestinal permeability, but permeability did not differ between exclusively and partially breast-fed infants (NC Rollins, SM Filteau, KE Uebel, A Coutousois and A Tomkins, unpublished results). This study...
provides further evidence that in areas where water supplies and sanitation are not too bad, complementary foods are not themselves the major problem, and it is the active role of breast milk which is primary for maintaining gut integrity. Thus, although we may have overestimated the damage caused by weaning foods, we may have underestimated the gut protective effects of breast milk.

**Immunological factors in breast milk**

Breast milk contains a wide range of immunologically active factors which both passively protect the infant against infection and actively stimulate development of its immune system. Older research has focused mainly on passive protection mediated by defined molecules such as secretory IgA, lactoferrin, lysozyme and oligosaccharides. Milk also passively protects by virtue of its wide range of anti-inflammatory factors which serve to minimize gut damage. This work has been reviewed elsewhere (Goldman, 1993; Filteau & Tomkins, 1994; Grazioso & Buescher, 1996; Newberg, 1997; Filteau, 2000) and will not be further discussed here.

Additional less-immunologically-specific passive protection is provided by milk fat globules. This area has been little investigated, but is probably a key part of the mechanism whereby breast milk protects infants from infection. Fat globules can bind potential pathogens and prevent their attachment to infant cells, a first step in infection (Peterson et al. 1998). Fat globules may sequester and thus protect specific milk immune factors during passage through the infant stomach (Garofalo et al. 1995; Filteau et al. 1999a; Schroten et al. 1999). Once hydrolysed from triacylglycerols, milk fatty acids can damage bacteria by disrupting their cell membranes (Hamosh, 1998).

Recent research has investigated cytokines in milk, in part because they may be responsible for some of the active immune stimulation, rather than passive protection, of the infant. Some immunological differences between breast-fed and formula-fed infants which are not easily explained by passive protection or avoidance of inflammation are shown in Table 1. For investigation of which milk components are key immunostimulants it is not sufficient, as most of us have usually done, to simply demonstrate the presence of a particular factor in milk. It is also necessary to consider whether the amounts in milk are adequate for biological activity, whether there co-exist factors in milk which inhibit the function of the postulated immunoenhancer (especially important for cytokines) and whether the factor is able to survive passage through the infant stomach to the intestine for either absorption or interaction with gut leucocytes or epithelial cells.

The extent to which cytokines survive passage through the infant stomach is largely unknown, but recent work has suggested that some hormones and cytokines may be sequestered and protected until they reach the intestine. Erythropoietin (Kling et al. 1998) and granulocyte colony-stimulating factor (Calhoun et al. 1999) are stable in milk when subjected in vitro to infant gastric secretions and low pH typical of the infant stomach. Similar studies with other cytokines would be useful. Milk macrophages contain sIgA which they cannot themselves synthesize (Crago et al. 1979), and may possibly be serving as carriers of sIgA past the stomach. Although this possibility has not been investigated, cytokines may be similarly transported in milk and released by lysis of the macrophages in the gut. Measurable concentrations of both interleukin (IL)-10 (Garofalo et al. 1995) and transforming growth factor-β (Filteau et al. 1999a) increased in milk after treatment of the samples with bile salts, suggesting these cytokines may be sequestered in the lipid globule and released in the infant intestine. Transforming growth factor-β is the cytokine for which perhaps the best evidence exists for its survival and indeed, activation, during passage through the infant gut (Ishizaka et al. 1994; Letterio et al. 1994). Transforming growth factor-β may promote immunoglobulin A synthesis (Defrance et al. 1992) and oral tolerance (Lundin et al. 1999), and decrease inflammation and promote healing of intestinal cells damaged by cytokines or infection (Dignass & Podolsky, 1993; Planchon et al. 1994).

Much work on milk cytokines has been done by dairy researchers who have little interest in calf health and are concerned about the cow. Since mastitis is a major problem in the dairy industry, resulting in substantially decreased milk production, controlled studies of the cytokine mediators of mastitis have been conducted. Comparison of mastitis severity with cytokine concentrations and of time-courses of cytokine production with key features of the disease (mammary epithelial permeability and neutrophil recruitment) suggest important roles for IL-1, IL-6, IL-8 and tumour necrosis factor-α (Shuster et al. 1993, 1995, 1996; Waller et al. 1997; Barber & Yang, 1998). The work also supports previous suggestions from the human lactation literature that the main role of milk neutrophils is in maternal protection, and that once secreted neutrophils are ‘used’ and capable of only minimal further activation and function (Buescher & McIlheran, 1988, 1993; Keeney et al. 1993). Finally, even classical immune factors protecting infants may also serve to protect the mammary gland. Gambian women with mastitis in one breast had lower levels of sIgA, complement component C3, and lactoferrin in milk from their unaffected breast than was found in milk samples from women in the community without mastitis, suggesting that low levels of these immune factors may have predisposed these women to mastitis (Prentice et al. 1985).

### Table 1. Evidence for active promotion of immune system development by breast-feeding

<table>
<thead>
<tr>
<th>Difference in breast-fed relative to formula-fed</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Increased urinary IgA</td>
<td>Prentice (1987), Goldblum et al. (1989)</td>
</tr>
<tr>
<td>Lymphocyte subpopulation profile</td>
<td>Hawkes et al. (1999)</td>
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<tr>
<td>Larger thymus size</td>
<td>Hasselbalch et al. (1996, 1999)</td>
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<tr>
<td>Protection from <em>Hemophilus influenzae</em> even after complete weaning</td>
<td>Silfverdal et al. (1997)</td>
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<tr>
<td>Increased antibody response to <em>Hemophilus influenzae</em> B vaccine</td>
<td>Pabst &amp; Spady (1990)</td>
</tr>
<tr>
<td>Increased antibody response to oral polio vaccine</td>
<td>Hahn-Zoric et al. (1990), Pickering et al. (1998)</td>
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IgA, immunoglobulin A.
Thus, possibly many immune factors do not need to get through the infant gut intact since they have already done their job in the mother.

The importance of women’s health

The studies on mastitis remind us of the importance of considering women’s health when trying to understand the benefits of breast-feeding. Most work on the subject has investigated the effects of maternal undernutrition on milk volume and energy (Rasmussen, 1992; Perez-Escamilla et al. 1995; Gonzalez-Cossio et al. 1998) and immune factors (Miranda et al. 1983; Chang, 1990; Herias et al. 1993). The work on immune factors is confounded by the fact that undernourished women often live in areas of high microbial contamination, which tends to increase the concentration of some milk immune factors (Lonnardal et al. 1976; Prentice et al. 1983) and which could obscure effects of maternal undernutrition. For example, a randomized controlled trial of vitamin A supplementation of deficient Bangladeshi women showed no effects on milk concentrations of sIgA, lactoferrin, lysozyme and IL-8, at least partly because these concentrations were normal, even in the placebo-treated women (Filteau et al. 1999b).

There have been relatively few studies of the effect of infection on milk quantity and quality. Peruvian women with established lactation who suffered an acute febrile infection exhibited no changes in milk volume or concentrations of protein, casein, lactoferrin or trace metals despite the expected acute-phase changes in serum proteins and minerals (Zavaleta et al. 1995). Maternal fever and clinical symptoms of infection in the first 48 h post partum also did not adversely affect initiation of lactation (as indicated by full lactation by day 14 post partum) or protein or mineral contents in colostrum and early milk, although lactoferrin concentration was decreased (Lonnardal et al. 1996). This study did not investigate milk volume, whereas other work from this group has shown that a very stressful labour and delivery can result in delayed initiation of lactation and decreased milk production on day 5 post partum (Chen et al. 1998).

Mastitis, i.e. localized mammary infection or inflammation, appears to have greater effects on lactational performance than does maternal systemic infection. Subclinical mastitis, although long recognized as decreasing milk production in cows (Peaker, 1974; Shuster et al. 1995), has only recently been investigated in human subjects and appears to be very common (Filteau et al. 1999a,b; Willumsen et al. 2000). Subclinical mastitis lacks symptoms but otherwise shares many features with clinical mastitis, i.e. both are often unilateral and are associated with raised milk Na, pH and inflammatory cytokines (Willumsen et al. 2000). We use raised milk Na:K, which is easy and cheap to measure in spot milk samples, to diagnose subclinical mastitis. The opening of paracellular pathways between mammary epithelial cells during this local inflammation results in elevated concentrations of most immune factors which have been measured, i.e. immunoglobulins, lactoferrin, IL-8 and transforming growth factor-β (Prentice et al. 1985; Filteau et al. 1999a,b; Semba et al. 1999b). Lysozyme was not increased concurrently with subclinical mastitis (Filteau et al. 1999b; Semba et al. 1999b), and was increased in clinical mastitis only 1 week after diagnosis (Prentice et al. 1985).

Subclinical mastitis has been associated with poor weight gain of Bangladeshi (Filteau et al. 1999b) and American (Morton, 1994) infants. Milk stasis may be the cause of the inflammation, but may also become a consequence. The raised Na imparts a salty taste which the infant may refuse (Connor, 1979). An infant refusing the breast may encourage the mother to give additional foods, thus further decreasing milk volume, and resulting in further stasis and possibly cessation of lactation. Other likely causes of subclinical mastitis are maternal systemic infection or deficiencies of antioxidant micronutrients (Filteau et al. 1999a). The problem of local clinical or subclinical mastitis can usually be treated by encouraging women to continue breast-feeding or to express milk from the affected breast, although in serious cases antibiotics or surgery may be required (Thomsen et al. 1984). Similarly, intensive lactation counselling before subclinical mastitis had a chance to occur reduced the prevalence of the condition among Bangladeshi women (M Flores & SM Filteau, unpublished results).

In addition to milk quality and quantity, another potential problem with breast-feeding by mothers with local or systemic infections is the transmission of the infection to the infant. Bacteria can frequently be cultured from breast milk, especially since milk is rarely expressed under sterile conditions and may contain skin bacteria (Thomsen et al. 1984). Nevertheless, even among women who were themselves infected in the early post-partum period, most milk bacteria were non-pathogenic (Narayanan et al. 1984). In this study, an unusual trial of infections in high-risk Indian infants randomized to receive raw or pasteurized breast milk, with or without additional formula, the infants receiving raw human milk suffered fewer infections than infants receiving pasteurized milk (Narayanan et al. 1984). Infants receiving formula in addition to raw or pasteurized milk had more infections than the respective groups receiving breast milk alone. The results indicate that immune factors in milk, some of which are heat labile and destroyed by pasteurization, outweigh the extra risk to an infant of infection caused by receiving pathogen-contaminated breast milk. Thus, maternal bacterial infection, whether systemic or in the mammary gland, should not preclude breast-feeding.

Human immunodeficiency virus

Maternal viral infections may be a different case. There is evidence that several viruses, including HIV (Leroy et al. 1998; Miotti et al. 1999), hepatitis C (Kumar & Shahul, 1998) and cytomegalovirus (Vochem et al. 1998), can be transmitted by breast-feeding, with possible detriment to the infant. The HIV epidemic in Africa, where breast-feeding is crucial to child survival, has intensified research in this area. Prolonged breast-feeding may be advisable for most mothers, but among HIV-infected mothers prolonged breast-feeding increases the risk of breast-milk transmission of HIV to the infant, particularly if the mother first becomes HIV-infected while lactating (Dunn et al. 1992). Even if the
infant itself escapes HIV infection, it may grow up in a family where the adults are too ill and stressed to be maximally economically productive or involved in child care, or where family resources are depleted by medical expenses. Thus, although breast-feeding is an acknowledged risk factor for mother-to-child HIV transmission, these high-risk infants may particularly need the health benefits of breast-feeding. It is difficult and expensive to determine at birth which infants are already infected and which are still at risk of infection from breast-feeding, so infant feeding advice directed towards HIV-infected women needs to maximize the health benefits to all their infants. The advice must not undermine support for the international policy for the uninfected women in the area, a difficult problem since most women do not know their HIV-infection status.

Although HIV-infected women who have uninterrupted access to safe breast-milk substitutes should probably avoid breast-feeding, this problem leaves many women and health workers in Africa with a serious dilemma. Recent evidence suggests that advocacy of exclusive breast-feeding to these women may be possible as well as being appropriate for women of negative or unknown HIV status. Mother-to-child HIV transmission by 3 months of age was not different between South African infants given no breast milk and infants exclusively breast-fed, whereas infants receiving breast milk and other foods were more often infected (Coutsoudis et al. 1999). Recently we have been investigating mechanisms for this observation in the same cohort (JF Willumsen, SM Filteau, A Coutsoudis, ML Newell, AM Tomkins, unpublished results).

Subclinical mastitis has been associated with increased milk viral load among HIV-infected South African (Willumsen et al. 2000) and Malawian (Semba et al. 1999a) women, and with higher mother-to-child HIV transmission (Semba et al. 1999a). These findings further the work on clinical mastitis or other overt breast pathology, such as cracked nipples, which increase the risk of infant HIV infection (Nicoll et al. 1995). It is likely that during clinical or subclinical mastitis the virus enters the milk either with leucocytes recruited into the milk under the influence of inflammatory cytokines, or non-specifically through the leaky mammary epithelium. In a cross-sectional study of South African women not screened for HIV, mixing breast milk with formula was associated with higher milk Na:K than was exclusive breast-feeding. A similar, but non-significant, trend was seen among the HIV-infected cohort (JF Willumsen, SM Filteau, A Coutsoudis, ML Newell and AM Tomkins, unpublished results).

Another possible mechanism whereby adding other foods to breast milk may have increased HIV transmission in the South African cohort is by increasing infant gut permeability. However, gut permeability was not increased in mixed-fed infants (NC Rollins, SM Filteau, KE Uebel, A Coutsoudis and A Tomkins, unpublished results). It is possible that HIV transmission rate would be even higher in mixed-fed infants in an area without a piped water supply and where addition of other foods may cause greater damage to the infant gut.

Another mechanism which is at present largely speculative is that the amount of milk protective factors, e.g. sIgA or immunoglobulin M against HIV (Van de Perre, 1995), lactoferrin (Harmsen et al. 1995), or gp120-binding glycosaminoglycan (Newberg et al. 1995) was sufficient in exclusively breast-feeding infants, but not in those receiving other foods and probably less breast milk, to prevent free HIV from infecting the infant. This finding would be analogous to raw human milk being more protective than pasteurized milk, and milk alone being more protective than milk supplemented with formula (Narayanan et al. 1984).

In the South African trial the feeding groups were not chosen randomly (Willumsen et al. 2000) and it is probably unwise to speculate as far as I have on the mechanisms and the public health importance of the protective effect of exclusive breast-feeding for HIV transmission. The key question for an individual woman and her health care worker is whether lactation support, especially of women experiencing problems, can reduce her milk viral load. The key public health question is whether widespread advocacy and uptake of exclusive breast-feeding can reduce mother-to-child HIV transmission in Africa. Until further research is conducted, this situation remains one where advocacy of exclusive breast-feeding is probably based more on philosophy than science.

In conclusion, I suggest that we can, as scientists, support the international infant feeding policy as long as we broaden our support for women. Our support needs to go beyond lactation counselling and include reducing undernutrition, improving status of antioxidant micronutrients, and providing widespread advice and support to decrease the number of women becoming HIV-infected.

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References


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