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Perinatal nutrition and immunity to infection

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Abstract

Epidemiological data provide strong evidence for a relationship between undernutrition and life-threatening infection in infants and children. However, the mechanisms that underlie this relationship are poorly understood. Through foetal life, infancy and childhood, the immune system undergoes a process of functional maturation. The adequacy of this process is dependent on environmental factors, and there is accumulating evidence of the impact of pre- and post-natal nutrition in this regard. This review outlines the impact of nutrition during foetal and infant development on the capacity to mount immune responses to infection. It provides an overview of the epidemiologic evidence for such a role and discusses the possible mechanisms involved.

Keywords

malnutrition; foetal nutrition disorders; neonatal immunity, maternally acquired; immunity; mucosal; immune disorders

The neonatal immunodeficiency

Upon delivery, the developing neonatal immune system is transferred from the relatively sterile confines of the uterus to an environment teeming with countless antigenic challenges. It must quickly gain competence in identifying and destroying pathogens, whilst maintaining tolerance to self tissues, and to a huge range of harmless food and environmental antigens. At birth, neonates are susceptible to infection because of a functional immaturity of the immune system that spans most areas of host defence.

Mucosal and epithelial surfaces form the first line of defence against infection but are less developed in the neonatal period (1). Antigen-presenting cells in lymphoid accumulations in the foetal gut express markers of maturation and costimulatory molecules from as early as

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14–16 wk gestation. They are seen in close apposition with T cells within lymphoid accumulations in the small intestine, which exhibit capping of receptors, suggesting that primary sensitization is occurring (2, 3). However, the ontogeny of the gut-associated lymphoid tissues is structurally incomplete, and its further development is highly dependent on microbial colonization in the early post-natal period (4, 5).

Several factors severely compromise the neonatal innate immune system's response to pathogenic challenge. Circulating levels of complement proteins are low, and neutrophils display impaired chemotactic, phagocytic and microbicidal capabilities (6, 7). Macrophage activation by cytokines and Toll-like receptor (TLR) ligands is also impaired (8), although NK cells, which are present in large numbers in cord blood samples, express high levels of activating receptors, implying effector functions that may be in excess of adult levels (9).

It has long been recognized that in the neonatal period, the antimicrobial effector function of the adaptive arm of the immune system is attenuated. The system adopts a fundamentally tolerogenic posture so as to avoid inappropriate reactivity to common and harmless antigens during the experiential acquisition of antigen-specific memory (10). Consequently, cell-mediated immunity to infectious pathogens is inefficient in the neonatal period (11, 12). However, this is not because of some intrinsic immaturity in lymphocyte function. Indeed, whilst low baseline expression of T-cell receptor (TCR), adhesion molecules and CD40L, and inefficient cytokine generation certainly diminish T-cell responsiveness (13), neonatal T cells are able to demonstrate a relatively complete repertoire of effector functions (14). As early as 28 wk gestation, the foetus is able to mount an antigen-specific CD8+ response to intrauterine viral infection, although these cells may not have a full repertoire of effector functions (15, 16), and antigen-specific T-cell proliferation has been demonstrated at similar gestational ages in response to environmental allergens (17). The inadequate response to pathogenic challenge is partly explained by a bias towards Th2-type responses at the expense of Th1 effector mechanisms important in fighting infection. This bias is crucial for continued maternal acceptance of the foetus and is partly mediated by placental factors (18). It also helps to facilitate the proper acquisition of tolerance to innocuous antigens and resolves gradually through infancy and childhood, as the adaptive immune system becomes more competent at fighting infection (19). Th2 dominance is supported by differences in antigen presentation and in the balance of regulatory lymphocytes. Antigen presentation by circulating cells is inefficient at birth, with cord blood monocytes, macrophages and dendritic cells expressing low levels of costimulatory molecules and demonstrating inefficient TLR-mediated signalling alongside abnormalities in maturation and cytokine production (20). Additionally, foetal blood, thymus and lymphoid organs contain large numbers of functional Treg cells, which exhibit a powerful suppressant effect over the foetal immune system (21).

Breast milk and immunity to infection

The neonatal immune system is considerably bolstered by factors present in breast milk (see Figure 1). Epidemiological studies have demonstrated lower infant mortality for breastfed infants in both the Developing and Developed World, with less morbidity from diarrhoeal disease, respiratory infections, otitis media and urinary tract infections, effects which are consistent in small for gestational age babies as well as those of normal birthweight (22). There are very few instances in which breastfeeding is absolutely contraindicated, although rates of breastfeeding continuation – especially in the developed world – are often far below the WHO target of exclusive breastfeeding for the first 6 months of life (23, 24).

Breast milk contains a range of substances that demonstrate direct antimicrobial activity. These include lactoferrin, which chelates iron and has bacteriostatic and bactericidal

activities, lysozyme, which causes bacterial cell wall lysis and binds endotoxin, defensins, soluble CD14, antiviral lipids and complement proteins. It also contains a variety of factors that are anti-inflammatory in nature, including antioxidants such as vitamins A and C, protease inhibitors and anti-inflammatory cytokines. This mixture facilitates the activity of a wide range of antimicrobial factors at the infant's mucosal surface independently of their own mucosal immune system, providing broad protection from enteric infection whilst suppressing immune activation in the mucosa itself, where a fine balance of pathogenic and tolerogenic influences direct the development of a mature and experienced immune system. This multifunctional role is reinforced by directly immunoactive factors in breast milk such as hormones, IL-10, interferon and epithelial growth factor (EGF). EGF has been demonstrated to act directly on gut epithelium, decreasing permeability to infectious agents (25). Breast milk is also rich in nucleotides and nucleosides. These have been shown to augment infantile NK cell activity and humoral responses in some cases and may confer limited protection against diarrhoea (26).

In the first few months of life, the neonatal immune system is supported by maternal IgG, which is actively transported across the placenta during the third trimester and often reaches higher levels in cord blood than in the maternal circulation. During breastfeeding, this passive 'adaptive' arm of the immune system is further supplemented by activated leucocytes and secretory immunoglobulin (27). By virtue of the maternal mucosal immune system, a proportion of these immune constituents will be directed against known environmental and enteric antigens, and thereby give dynamic and environmentally specific immune protection (28, 29).

Consideration of the nutritional status of lactating mothers is important, as the concentration of some micronutrients in breast milk, notably the B vitamins, vitamin A and iodine, are directly correlated with maternal values (30). Maternal deficiencies can be demonstrated to contribute to specific deficiencies in their infants (31). Micronutrient deficiencies can lead to compromise in immune function, as will be discussed later. In addition, maternal undernutrition is associated with differential levels of breast milk antimicrobial factors, and with decreased IL-7 levels, which may impact on the development of the infant's immune capabilities (32).

Immunity and intestinal flora

Soon after delivery, the sterile infant intestinal tract becomes colonized by bacteria, mostly from maternal faecal flora (33). The balance of this colonization is affected by the mode of delivery and the infant's diet. Caesarean section delivery denies the neonate the inoculum of organisms from the maternal gut. In breastfed babies, *Bifidobacteria* and *Lactobacilli* quickly become dominant, whereas in formula-fed babies, *Bacteroides* species are present in large numbers, alongside other bacteria known to be enteric pathogens (34, 35). Breast milk contains high concentrations of oligosaccharides, which ferment in the bowel and promote the growth of *Bifidobacterium* gut commensals. Other nutrients have similar pre-biotic effects, including casein, alpha-lactalbumin, lactoferrin and nucleotides (22, 35). Non-pathogenic commensal bacteria are protective against infection via a number of mechanisms including competitive inhibition of epithelial binding by enteropathogenic bacteria and effects on tight junctions (36). In the neonate, a healthy gut flora may also be critical to the development of a properly functioning mucosal immune system. Crosstalk between enteric bacteria and TLRs in the intestinal mucosa can modulate the level of immune activation in the gut and direct towards either Th1 or Th2 type responses (37, 38). *Lactobacilli* prime dendritic cells to drive the development of Treg cells and to promote mucosal tolerance to non-pathogenic antigens (39).

Specific variations in intestinal flora have been shown to be associated with differential development of atopy (40, 41), but the role of artificially modulating the infant's intestinal microbiome through the use of pro- or pre-biotic supplements to effect immunological outcomes is unclear. Whilst both probiotic and pre-biotic supplementations for formula-fed infants has been shown to lead to 'healthier' gut flora, rich in *Bifidobacteria* and depleted of known pathogenic enterobacteria (42-44), clinical outcomes have been inconsistent.

Probiotic supplementation in infancy results in shorter and less frequent episodes of diarrhoea (45-48), as well as a reduction in the incidence of lower respiratory tract infections (49, 50). However, the effects are small, and results of other trials have been inconsistent (51). The possibility that probiotic supplements may influence the development of atopy is still contested (52). Maternal probiotic consumption around birth can modify infantile gut flora (53-55), and supplementation alters immunomodulatory properties of breast milk (56), although effects on the foetal and neonatal immune system may be limited (57).

A single trial of pre-biotic-enriched complementary food in Peru failed to demonstrate a reduction in episodes of infectious diarrhoea, utilization of healthcare resources, or vaccine responsiveness (58). However, another study has demonstrated that pre-biotic supplementation leads to increased levels of sIgA in stool – more so than probiotic supplementation (59), and two recent trials of pre-biotic supplemented milk in European infants have demonstrated decreased incidence of gastrointestinal and recurrent upper respiratory tract infections (60, 61). Maternal consumption of pre-biotic oligosaccharides modified maternal gut flora but failed to alter that of the neonate and did not lead to significant differences in neonatal immune status as demonstrated by *in vitro* cord blood immunological parameters (62).

Pre- and perinatal nutrition

Childhood malnutrition (or protein-energy malnutrition, PEM) is associated with increased incidence and case fatality rates of common illnesses such as diarrhoea and pneumonia, and amongst children, this malnutrition-attributable risk of infection accounts for more than half of global mortality (63, 64). Malnutrition and infection exist in a vicious cycle, with infectious episodes contributing directly to growth faltering and the diversion of essential nutrients (65), whilst malnutrition impedes immune responsiveness by a number of different pathways. Mucosal barrier function, the first line of host defence is inefficient, leading to ingress of pathogens and systemic inflammation (66). Complement activation is reduced, phagocytic cells are compromised, and antibody production is deficient (67). The number of circulating lymphocytes is low, T cells express low levels of activation markers and the proportion of T cells with a memory phenotype is reduced (68). The number of circulating dendritic cells is also reduced, and a recent study demonstrated reduced dendritic cell IL-12 production in half of a cohort of severely malnourished children (69).

The relationship between maternal nutrition and foetal growth is complex. Foetal growth is modulated by a large range of factors including maternal metabolic and endocrine function, placental function, as well as the availability of nutrients (70). However, maternal PEM during pregnancy can lead to low birthweight (71, 72) via effects on gestational length and, especially, through the association with delivery of small-for-gestational-age babies (SGA), who may be thought of as an analogue of malnourished infants and share their increased infection risk (73-75) (see Figure 2). In the West, SGA infants typically experience a phase of rapid catch-up growth over the first few weeks of life but whether or how this is manifest in the context of dietary insufficiency is unclear. Understanding the links between maternal malnutrition, SGA and infantile malnutrition is hampered by an inadequate evidence base. Notably, there are no published anthropometric criteria for severe malnutrition under 6

months of age, and little research has been carried out on the treatment of malnutrition in this age group. A large retrospective analysis of growth rates amongst children in Developing World found that 'wasting' did not occur until late in infancy, but faltering in terms of length occurs from birth (76). However, the clinical correlates of this pattern are unclear. In 2004, a WHO technical review committee found that 'no new research was identified pertaining to the optimum dietary management of severely malnourished infants aged <6 months. The evidence base for defining the most advantageous formulations for feeding this age remains weak' (77).

Whilst the burden and immediate impact are largely unknown and current clinical management is unstructured, there is evidence that malnutrition during infancy may lead to permanent structural and functional changes in the developing immune system (79, 80). Cohort studies from the Gambia have demonstrated that being born in the 'hungry season' is associated with reduced thymic size and function (32), with elevated levels of CD8+ve T cells and NK cells that persist through the first year independent of current nutritional status (81), and is strongly associated with risk of death from infection in adolescence and early adulthood (79). Similarly, correlations between birthweight and functional responses to vaccines administered in adolescence have been described in Pakistan and in the Philippines (82, 83), although such observations have not been universal (84).

Furthermore, limited data suggest that nutritional status can exert transgenerational effects. In murine studies, a period of maternal malnutrition during gestation leads to permanent immunodeficiency in the offspring that is not amenable to correction by optimal feeding during infancy. The offspring of these mice also demonstrate abnormalities in immune function, especially if grandmaternal malnutrition incorporates zinc deficiency (85, 86). Some observational studies of famine-exposed populations have shown a similar effect (87), and there is growing interest in the role of foetal and prenatal programming of immune function. Such transgenerational phenomena have been well documented in other areas, as grandmaternal smoking during pregnancy is associated with increased levels of asthma irrespective of maternal smoking status (88). They may represent modulation by epigenetic mechanisms and are a source of significant interest at present (89).

Micronutrient malnutrition

Alongside protein-energy nutrition, micronutrient status is an important determinant of immune function. Different micronutrients have numerous roles in immune responses, and individual micronutrient deficiencies can lead to immunocompromise in infants.

Iron deficiency is associated with impairment of neutrophil and NK cell-mediated killing and T-cell proliferative responses and tends to bias the immune response towards the Th2 type (90). However, iron supplementation for infants and children remains controversial. Iron is an essential nutrient for pathogens as well as humans. Bacterial proliferation is impaired by environmental iron depletion, for example because of the actions of lactoferrin in the gut, and mild iron deficiency may be protective against malaria (91). In two large recent studies of routine iron and folate supplementation for children younger than 3 yr old, supplementation was associated with an increased risk of infectious morbidity and mortality confined to those living in an area of intense malarial transmission (92, 93). In non-malarial areas, routine supplementation carried no such increased infection risk, and in the Pemba trial, it was probably confined to a subgroup who were already iron replete at enrolment (94). In populations with high levels of anaemia, routine supplementation has been associated with positive effects on cognitive performance and other long-term outcomes (95). However, the evidence points to a degree of risk associated with routine iron supplementation and with the early administration of iron to subjects who may have

infection as well as malnutrition (96). Current WHO guidelines restrict iron supplementation in malnourished children until a course of broad-spectrum antibiotics has been instituted, and appetite has started to return. During pregnancy, it is recognized that iron delivery to the foetus is preserved even in the face of maternal iron-deficient anaemia, allowing sufficient stores to be established to last until weaning. However, maternal iron deficiency during pregnancy has been associated with an increased risk of deficiency in the infant at 6 and 9 months (97), and strategies to optimize iron nutriture during infancy remain the subject of investigation (98).

Zinc deficiency is associated with lymphopenia and impaired lymphocyte function including a bias towards Th2 responses, thymic atrophy and distortion of the cell-mediated immune response, which are corrected by appropriate zinc supplementation (90, 99). Zinc deficiency is probably very common, affecting up to a third of the World's population, especially in the context of protein-energy malnutrition (99), and it has proved an important nutrient for immunity in children. A recent systematic review of zinc supplementation amongst children with diarrhoea demonstrated a significant reduction in length of the diarrhoeal episode (100), and supplementation is recommended as part of routine diarrhoea management by WHO. However, in infants < 6 months old, the benefits are less clear, and a recent trial even demonstrated increased diarrhoeal duration (101). Amongst children with pneumonia, there are conflicting data on the effect of zinc supplementation, with two trials demonstrating hastened recovery, but the most recent showing no effect – and a possibility of harm for those children with the most severe infections (102-104). Routine supplementation with zinc has failed to show significant effects on mortality in infants less than a year old (105-107), although there are probably beneficial effects in decreasing incidence of infections (108), which may be especially important amongst children born at low birthweight (109). Zinc homoeostasis in the infant is affected by gestation, birthweight and feeding method, but accurately predicting zinc status based on the current evidence is difficult (110). Other recent work from Africa has emphasized that effects observed in Asia, where many zinc trials have been carried out, may not be uniform across different Developing World communities (111).

Vitamin A has a diverse range of roles in effective immune responses. It is important in maintaining the integrity of mucosal surfaces, and deficient states are associated with increased rates of invasive respiratory, gastrointestinal and ocular infections. Deficiency also interferes with phagocytic and NK cell function, and with both Th1 and, especially, Th2 responses. Routine supplementation trials have demonstrated improvements in measles and diarrhoeal disease morbidity (112-114) and decreased incidence of malaria (115), although they have largely failed to demonstrate a positive effect on respiratory disease morbidity, and supplementation may even increase the rate of respiratory infection (116). Studies assessing the survival benefit of supplementation have suggested that modest benefit exists, although it may be highly time dependent; routine supplementation for infants <6 months appears to be expeditious only in the very early neonatal period, and benefit in African populations is less apparent than in those from south Asia (117).

Vitamin D has diverse immunologic effects, including the promotion of Th2 and regulatory T-cell signalling as well as increasing the antimycobacterial properties of monocytes and macrophages (118). It has long been recognized that children with rickets have increased susceptibility to respiratory tract infections, and recent epidemiological work has hinted at the importance of subclinical deficiency in this regard, with several studies reporting increased pneumonia incidence associated with vitamin D insufficiency (119). In a very large retrospective cohort analysis, vitamin D levels were inversely correlated with self-reported recent respiratory infection (120). Vitamin D was used as a treatment for tuberculosis (TB) in the pre-antibiotic era, and interest in its anti-TB properties has recently

been revived. A study of adult TB contacts in London found that a single dose of oral vitamin D significantly improved antimycobacterial whole blood innate immune indices (121), contributing to an accumulating evidence base for the use of vitamin D supplementation in active TB (122). Whilst a recent trial of supplementation in Guinea Bissau showed no overall effect, it may have suffered from underdosing the supplement (123). Subclinical vitamin D deficiency is probably very common in all parts of the World, and infants are highly vulnerable. Foetal vitamin D stores are highly dependent on maternal nutritional sufficiency, and breast milk is poor in vitamin D even from vitamin replete mothers (124). At present, the scale of the problem of subclinical vitamin D deficiency in infants is not clear, and the potential roles of supplementation both in routine care and as an adjunct to TB or pneumonia treatment have not been tested.

Other micronutrients have important effects on the developing immune system. Selenium deficiency is associated with the development of atopic features and of poor cell-mediated immunity including increased risk of viral infections and rapid progression of HIV (125-127). Copper, manganese, the antioxidant vitamins C and E and other nutritional factors are also important for immune function.

The relative clinical importance of different micronutrient deficiencies is difficult to ascertain. Subsistence diets in low or middle income countries where the effects of nutritional deficiencies are most pressing are often deficient in multiple micronutrients. These multiple deficiencies are likely to have a cumulative effect on immunity to infection that is difficult to control for in trials of the supplementation of single micronutrients. Additionally, single micronutrient deficiencies or excess can impact on the absorption and bio-availability of other micronutrients, and there are many examples of how dietary supplementation can inadvertently have negative impacts on global micronutrient status. An additional problem in assessing the clinical importance of different deficiencies is that interventional studies have not typically incorporated detailed assessment of individual subjects' nutritional status at either initiation or completion because of logistical and ethical concerns, and the generalizability of outcomes across different populations is questionable.

The effect of these problems is that clear dose–response relationships for the effect of individual micronutrients on immune function have proved impossible to ascertain, and their relevance to real-world scenarios in which a complex web of nutritional deficiencies co-exist is questionable. As a result, the research agenda and public policy discourse are shifting towards the provision of balanced multiple micronutrient supplementation. There has been particular interest in the development of a balanced micronutrient supplement for use during pregnancy (128). Pregnancy constitutes a significant metabolic and nutritional burden for women, especially those in the Developing World, and the foetus is sensitive to micronutrient depletion, leading to low birthweight independent of protein-energy status (129, 130). So far, the effects of such supplementation remain controversial.

A recent systemic review of trials of supplementation during pregnancy failed to demonstrate an effect of multiple micronutrients on reducing the frequency of low birthweight or perinatal mortality more than the effect of iron and folate supplementation, which is WHO routine antenatal care (131). However, several more recent trials have reported reduced rates of low birthweight deliveries, raising hopes of improvements in neonatal health (132-135). Indeed, a large trial in Indonesia involving more than 30000 pregnancies of a micronutrient supplement during pregnancy and 90 days post-partum showed positive results: The mortality rate during early infancy was decreased by 18% in the multiple micronutrient group compared to iron and folate alone (136). However, two large trial cohorts in Nepal comparing antenatal multiple micronutrient supplementation versus iron and folate or other less complete supplements have demonstrated strikingly

different results. Both groups, based in Sarlahi district and Janakpur, respectively, reported modest improvements in birthweight with percentage decreases in the rate of low birthweight of 14% and 25% (137, 138), but a combined analysis showed significantly increased perinatal and neonatal mortality rates with multiple micronutrient supplementation, with relative risks of 1.52 and 1.36, respectively (139, 140). This effect may partly be explained by larger birthweights leading to increased levels of birth asphyxia, the rate of which was increased by 60% in the Sarlahi trial and which was associated with 8- to 14-fold increases in mortality at 6 months if it occurred alongside prematurity or sepsis (141). However, the Janakpur trialists have recently reported improvements in weight at 2.5 yr in the micronutrient intervention group, emphasizing the current uncertainty surrounding this area (142). A further similar study from China has also demonstrated a very modest increase in birthweight with micronutrients versus iron and folate, not associated with any improvement in neonatal mortality (143).

Lipid malnutrition

Dietary lipids have immunomodulatory effects, and there has lately been increasing interest in utilizing the immunoactive properties of the n-3 polyunsaturated fatty acids (PUFA) in a variety of clinical settings (144, 145). Animal models and clinical trials of supplementation with n-3 PUFA, which are present in oily fish, have demonstrated a diverse and sometimes contradictory range of effects on immune function. Most studies show them to be predominantly immunosuppressant, with impairment of NK cell function, delayed-type hypersensitivity reactions and T-cell (especially Th1) function, although some studies have shown an opposite effect with increases in lymphocyte responsiveness (146, 147). Competitive antagonism of the generation of arachidonic acid metabolites and the parallel formation of anti-inflammatory ‘resolvin’ molecules underlie some of these effects (148). In addition, the incorporation of n-3 PUFA into cell membranes alters membrane fluidity, and their disruption of lipid raft formation in T-cell membranes has been shown to correlate with T-cell signalling defects (149).

Most clinical interest in young children has focused on the potential impact of lipid status on atopic disease incidence and severity. The Childhood Asthma Prevention Study trialled n-3 PUFA-rich supplements for infants at risk of asthma and reported less wheeze episodes at 18 months of age (150, 151). However, there was no long-term effect on the children’s incidence of asthma despite sustained alteration of their plasma fatty acids (152). Maternal consumption during pregnancy has resulted in both clinical and laboratory evidence of slight benefit to infants at risk of allergy (153-155), and variations in n-3/n-6 PUFAs in breast milk have been found in allergic mothers, and these have had an impact on allergic outcome in their infants (156).

Some recent work has shown encouraging signs that fatty acid supplementation may impact on the immune response to infection as well. N-3 PUFA supplementation during late infancy led to increased production of IFN during lipopolysaccharide–stimulated whole blood culture, suggesting a more efficient immune response (157). Similar effects were seen when the lactating mother received supplements during early infancy, and these efficiency gains persisted for at least 2 yr (158). A recent trial of n-3 supplementation for Thai school children aged 9 to 12 resulted in significantly reduced frequency of infections (159). In adult studies, there is conflicting data, although some studies have shown improved outcomes during sepsis, possibly because of immunoregulatory effect that improves the efficiency of the immune response (160).

These results and the observation that some subsistence diets in the Developing World may have markedly unbalanced n-6 to n-3 ratios of more than 30:1 (161) raise the intriguing

question of whether subclinical lipid malnutrition could lead to increased risk of infective pathology and whether n-3 PUFA supplementation could impact on the global disease burden of malnutrition-associated infection. Further research is warranted in this area.

Summary

Nutrition around the time of birth is an important determinant of the efficiency of neonatal immune responses to infection. The benefits of breastfeeding are clear and reinforce the public health imperative to improve breastfeeding rates across the World. Providing appropriate supplements for the pregnant and lactating mother could be useful methods to strengthen infant immune function, but their effectiveness, and even potential to cause harm, is unclear at present. The likely importance of malnutrition during infancy is not matched by a depth of mechanistic understanding of the associations between protein-energy, multiple micronutrient, and lipid malnutrition, and immunity to infection. A better understanding of the mechanisms behind these effects could generate biomarkers for use in clinical trials or practice, allowing complex nutritional interventions to be assessed over a shorter time period than is required to show significance under current circumstances. Further work quantifying the effects of nutrient supplementation on metabolism and stores will also be important, both looking in detail at trial participants' nutritional status at the start and end of an intervention and investigating maternal transfer of nutrients to the foetus. Without such information, questions regarding the optimum dose, delivery vehicle and combination of nutrients for routine supplementation are difficult to answer.

Nutritional research to date suggests that there will not be a simple or single nutritional intervention that dramatically reverses the association between malnutrition and infection. The importance of prenatal and infant malnutrition as determinants of global mortality necessitate more work in this area, but a focus on complex and relatively nutritionally 'complete' interventions may be indicated. A clearer mechanistic understanding of immunity during poor nutrition will be an important correlate of this approach and should be a priority for research.

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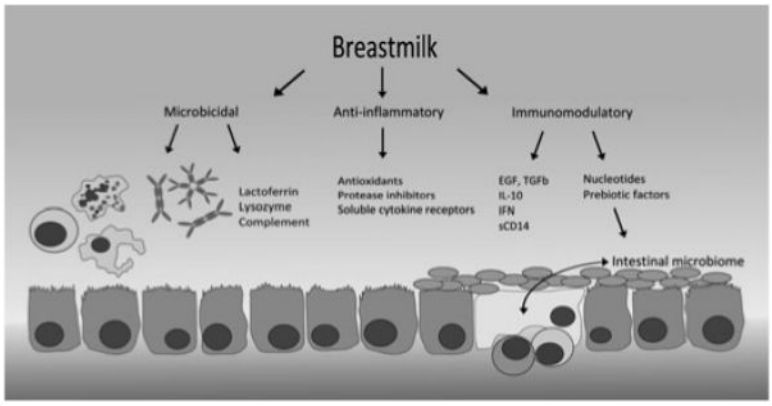

Fig. 1.

Breast milk is immunologically active at the infant's intestinal mucosa. Microbicidal factors include activated lymphocytes and phagocytes, secretory IgA and IgM, complement and other antimicrobial peptides and lipids, all of which provide broad immune activity against gut pathogens. Maternal IgG from cross-placental transfer provides further support, and the antimicrobial properties of breast milk are complemented by an anti-inflammatory activity, which downregulates damaging inflammation within the mucosa. Direct immunomodulatory factors include cytokines and growth factors, some of which interact directly with the mucosal epithelium, and others that have more distant targets (IL-7 targets the thymus – not shown). Pre-biotic factors including acidic and neutral oligosaccharides facilitate the growth of a healthy intestinal microbiome, and crosstalk between gut commensals, mucosal immune tissue (shown in yellow), and immunomodulators in breast milk help to drive tolerance to harmless antigens.

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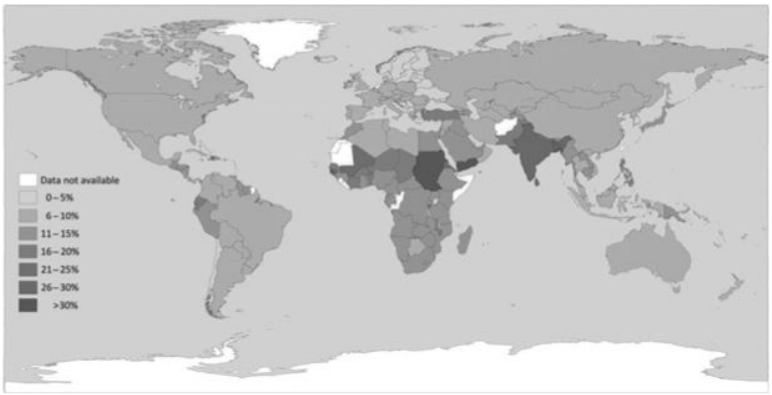

Fig. 2.
Percentage of low birthweight infants by country. Data from UNICEF/WHO (78).