Maternal nutritional status during pregnancy and infant immune response to routine childhood vaccinations

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To systematically review the association between maternal nutritional status in pregnancy and infant immune response to childhood vaccines. We reviewed literature on maternal nutrition during pregnancy, fetal immune system and vaccines and possible relationships. Thereafter, we undertook a systematic review of the literature of maternal nutritional status and infant vaccine response, extracted relevant information, assessed quality of the nine papers identified and present findings in a narrative format. From limited evidence of average quality, intrauterine nutrition deficiency could lead to functional deficit in the infant's immune function; child vaccine response may thus be negatively affected by maternal malnutrition. Response to childhood vaccination may be associated with fetal and early life environment; evaluation of programs should take this into account.

Routine childhood vaccination prevents many child deaths and has contributed substantially to improvements in survival up until, at least, the age of 5 years [1]. However, routine childhood vaccination programs do not reach all children [2], and concern has been expressed that even where children receive vaccines, some may not be fully protected and may still be at risk of infectious disease [3–6].

Fetal and early development is intricately associated with maternal health; the impact of maternal genetic, nutritional and environmental factors already starts preconception and continues through pregnancy and after birth [7], possibly irrevocably programming the developing fetal systems, including immunological development [8]. Compromised programming can negatively impact thymus size and function and the number of thymus-derived T cells [7,9]. Malnutrition has been put forward as the primary cause of immunodeficiency worldwide [10]. Maternal nutritional status, and exposure during fetal life to an inadequately nurturing environment, could thus impact fetal immune development [3,4], in particular, micronutrients including zinc, iron, vitamin A and protein energy malnutrition (PEM). Dietary macronutrients are the ultimate sources of energy substrates during fetal growth [11]; energy in the form of adenosine triphosphate is required for physiological processes in the fetus and mother, including nutrient transport, cell motility and synthetic pathways [12]. Nutritionally essential microminerals that the body cannot synthesize must be provided in the diet, because they are essential for fetal development, acting directly as second messengers in cell signaling, maintenance of the plasma, electron transport, membrane polarity or indirectly as cofactors for enzymes or components of metalloproteins [11].

Findings from epidemiological and experimental studies have shown that a poorly developed fetal immune system, increased risk of infectious diseases in infancy and its sequelae in adulthood can result from lack of energy, protein and other nutrients during fetal life [11,13]. Suboptimal infant immune development, as a result of a nutrient-deficient fetal environment, may lead to reduced antibody response to routine childhood vaccines due to the inadequate ability of the infant to mount an immune response.

Very little is known about the association between maternal nutritional status, as it pertains to the fetus, and infant response to routine childhood vaccines. In this review, we first provide a brief overview of maternal nutrition

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Table 1. Key maternal nutrition/nutrients and their potential effect on fetal immunity and vaccine response.

Nutrient	Role in immunity	Fetal immune deficit	Vaccines that may be affected
PEM	– Building blocks of proteins and peptides – Precursors for the synthesis of nitrogenous hormones – Substrates for the production of numerous substances, including DNA, neurotransmitters, vasodilators and signaling molecules – Major metabolic fuels for the small intestine and cells of the immune system	– IUGR causing reduced fetal thymic function – Neurological damage – Anemia – Impaired blood flow	All vaccines
Zinc	– Fetal growth and development, regulation of food – Intake, development of immune system	– Thymic atrophy – Distortion of the cell-mediated immune response – Impaired mucosal integrity	All vaccines
Vitamin A	Maintaining the integrity of mucosal surfaces, cell-mediated and humoral immune responses	Weakened mucosal integrity	Oral vaccines like rota and oral polio more affected than nonoral vaccines
Vitamin D	– Promotion of Th2 and Treg signaling – Cell-mediated and humoral immune responses	Impaired absorption of dietary calcium and phosphorentus to support fetal growth and developm	More effect on live attenuated than killed vaccines
Vitamin C	Connective tissue growth and development protect mother and fetus from oxidative stress	– IUGR – Subcutaneous hemorrhage – Defective collagen structure	All vaccines
Folate	– Cell proliferation, central nervous system cell repair – Appropriate epigenetic expression of the genome – Immune development – Formation of red blood cells	– Impaired immune system – Neural defects	Live vaccines
Iodine	Production of thyroid hormones	Poor immune response	All vaccines
Iron	– Oxygen binding, transport, storage and sensing metabolism of nutrients including proteins, lipids and glucose – Mitochondrial electron transport and ATP production DNA synthesis, antioxidative reactions, immunity	– IUGR – Impaired immune system	All vaccines

IUGR: Intrauterine growth retardation; PEM: Protein energy malnutrition.

during pregnancy, fetal immune system development and routine childhood vaccines, and additionally present a systematic review of the literature on the association between maternal nutritional status and infant immune response to routine childhood vaccinations. We found no systematic review on this subject and conducted this review using an unpublished protocol.

Background
Maternal nutrition in pregnancy

Fetal and early life present an important and vulnerable period for optimal development, where the developing human system is programmed for life and functional capacity is fixed for life [14,15]. Developmental origins of health and disease research has shown the critical importance of fetal life when maternal malnutrition and other environmental factors have the potential to permanently alter the human mechanism, leading to future adverse effects on health and increased risk of chronic diseases [14,15]. The fetal immune system depends on adequate maternal nutritional intake of macro- and micronutrients [16]. Macronutrients involved include carbohydrates, lipids and proteins, while key micronutrients include minerals such as zinc, selenium, copper, iodine and iron, and vitamins like vitamin A, C, D, E and folate.

Protein energy malnutrition

Maternal PEM is one of the main causes of intrauterine growth retardation (IUGR) (Table 1) [17]. During the Dutch famine (November 1944–May 1945), malnutrition of women in the second and third semesters of pregnancy resulted in reduced birth weight, length and head circumference [11]. Further, cohort studies from the Gambia have

demonstrated that being born in the season of food insufficiency, when levels of maternal malnutrition were high, was associated with reduced thymic size and function [18], and elevated levels of CD8$^+$ T cells and NK cells throughout the first year of life were independent of current nutritional status [19].

In murine studies, a period of maternal malnutrition during gestation was shown to lead to permanent immunodeficiency in the offspring that was not corrected by adequate feeding during infancy [20,21]. Human infants with IUGR were more likely to have evidence of significant and prolonged impairment of both cell-mediated and humoral immunity [22] than infants born appropriate for gestational age. IUGR-associated immune deficiency at birth would most likely result in the infant being unable to optimally mount an immune response to both live and killed vaccines.

Overall, evidence obtained from human and murine studies suggests that PEM during pregnancy may lead to IUGR, with affected infants having a less developed immune system and lower response to childhood vaccines than normal birthweight infants.

Micronutrients

Several micronutrients (minerals or vitamins) are known to be important in fetal immune system development and child immune response to vaccines. Table 1 summarizes findings relevant to immune functioning (zinc, vitamin A, D, folate, iodine and iron).

Zinc is obtained from the consumption of meat and legumes and has an important role in nutrient metabolism, the structure of DNA and protein [23]. During pregnancy, zinc is needed for the regulation of nutrient metabolism, DNA and protein synthesis, antioxidative reactions, neurological function, immunity, growth and development [24,25]. Zinc is stored, as such zinc from food or supplements need to be part of the regular diet [26]. Lack of zinc has been shown to weaken overall immune function and impair resistance to infection, inhibit thymic function, T-lymphocyte development, lymphoproliferation and T-cell-dependent B-cell functions in animals and humans [27].

Findings from eight randomized, controlled intervention trials performed in resource-limited settings showed that maternal zinc supplementation had a beneficial effect on neonatal immune status, early neonatal morbidity and infant infections [28], with two of these trials showing an indirect relationship, with infants of zinc-supplemented mothers having a decreased rate of infectious morbidity.

Dietary sources of vitamin A include whole milk, liver, eggs, dark colored fruits and vegetables [11]. In fetal development, the role of vitamin A has been related to general embryonic and fetal survival, regulation of hematopoiesis and fetal growth. Vitamin A is fat soluble and can be stored, but is potentially teratogenicity at high intake [11]. Vitamin A is essential in maintaining the integrity of mucosal surfaces, which are important for oral vaccine immune responses such as to rotavirus and oral polio [29]. Further, vitamin A is needed in the development and functioning of the cell-mediated and humoral immune systems, with deficiency at birth potentially reducing the infant's response to vaccines. Vitamin A when co-administered with measles vaccine was shown to enhance seroconversion (84%), with potentially improved overall response to vaccination, and be of particular importance in tropical countries where seroconversion to measles vaccine after routine immunization was suboptimal (63%) [30]. There is no information on the association between maternal vitamin A status during pregnancy and infant immune response.

Vitamin D has numerous key immunologic actions, including the promotion of Th2 and Treg signaling, increased macrophages and monocytes antimycobacterial effects [31]. Immune response to live vaccines like oral polio, measles, BCG, mumps, rotavirus, rubella, varicella and yellow fever is known to be dependent on optimal levels of these cell-mediated T cells. Fetal vitamin D stores have been found to be highly dependent on maternal nutritional levels [32].

Folate, one of the B complex vitamins, was shown to be crucial for cell proliferation [33], central nervous system cell repair [34], appropriate epigenetic expression of the genome [35] and for immune development [36]. This is why folate may play a role in live vaccines like oral polio, BCG and measles.

Iodine is necessary for the production of thyroid hormones, which in turn play an essential role in the central nervous system during fetal and early postnatal life. Evidence now suggests that the immune response is modulated by thyroid hormones [37]. The lack of iodine may have a general effect on fetal immune development leading to inability of the child to respond adequately to vaccines. Iodine facilitates absorption of dietary calcium and phosphorus to support fetal growth and development [11].

Iron is one of the most abundant essential minerals and is required in optimal amounts for normal functioning of several biological and chemical activities in the body [38,39]. Mainly, it is present in blood as hemoglobulin, in

Table 2. Vaccines routinely used in the first year of life.		
Vaccine	Type	Mechanism of action
Polio vaccine	– Live (oral) – Killed (inactivated)	– Induces the formation of serum IgG, mucosal IgG and IgA antibodies – Induces the formation of serum and mucosal IgG
Rotavirus	Live attenuated	Induces the formation of mucosal IgA
BCG	Live mycobacterium	The mechanisms of action of BCG remains poorly understood. This vaccine contains several substrains that differ in geno- and phenotypes. May induce CD4 and CD8 T cells
DPT	– Diphtheria toxoid – Tetanus toxoid – Pertussis killed	Induces the formation of circulating protective levels of neutralizing serum IgG
Measles	Live attenuated	Induces antibodies (serum IgG) and CD8 cells that protect against measles virus
Pneumococcal	Polysaccharide and polypeptide	Induces serum and Mucosal IgG
Hepatitis B	Protein	Induces serum IgG
Hemophilus influenza type B	Polysaccharide and protein	Induces serum and mucosal IgG

muscles as myoglobulin and in heme, iron sulfur and other iron containing enzymes [39]. Normal blood levels of iron are needed in several biochemical processes including oxygen binding, transport, storage and sensing; protein, lipids and some other nutrients metabolism; integrated electron transport; DNA synthesis; mounting of immune response; and antioxidative reactions [11]. Lack of adequate levels of iron may cause impaired immune function, anemia, hypoxia, increased risk for maternal morbidity and mortality, preterm birth and IUGR babies [39,40]. The number of circulating T cells and *in vitro* response to mitogens were found to be significantly reduced in children with iron deficiency and anemia [41–43]. In experimental situations, irreversible immune impairment was found in offspring whose mothers had high iron deficiency in pregnancy [44].

Fetal immune system

During fetal life, the immune system starts its development and maturation, which continues through infancy and early childhood, but there are periods when the immune system can be especially adversely affected by environmental factors including malnutrition [16]. One early vulnerable period is when tissues are being seeded by precursors of immune cells (4–7 weeks for myeloid-derived cells and 8–18 weeks for lymphoid cells) [45]. The immune system is composed of innate and acquired immunity, both of which are needed in the defense against infectious diseases [46,47]. Innate immunity is mostly the first general line of defense; the cell types involved are macrophages, neutrophils and NK cells [46]. Acquired immune responses are initiated following pathogen antigen uptake and presentation to T and B cells [46], and usually involve antibody production to specific pathogens [48]. The performance of the innate cell-mediated immune response will be affected by deficient T-cell function [46]. Antibody responses, as part of the acquired immune response, can be detected in the neonatal period, even though the immune system (both innate and acquired) at delivery is not yet fully functional [46], but such antibody responses are then most likely to represent passively acquired antibodies of maternal origin.

Routine childhood vaccines

Childhood vaccination, in global public health programs, prevents 2–3 million child deaths annually [49]; currently, 27 vaccines are approved by the WHO for global use according to regional epidemiological profiles, with the traditional six childhood diseases vaccines (polio, BCG, DPT and measles) mandatory for all children. Any deficiencies in infant immune response to vaccines will have negative implications for global child health and wellbeing. The adaptive immune system, made up of the humoral and cell-mediated immune system, is involved in child vaccine immune response [29], with generally, live attenuated vaccines mostly inducing the cell-mediated immune system and killed attenuated vaccines potentiating their effect most of the times in the humoral immune system (Table 2) [29].

The most widely used polio vaccine is a trivalent vaccine, with each of the vaccine serotype strains having a high probability of inducing protective immune responses against each of the three serotypes following three doses of vaccine [4]. The vaccines induce an immune response in serum IgG and mucosal IgG but only the oral type produces a local mucosal IgA response (Table 2) [29]. Polio vaccine results in a local immune response in the lining

Table 3. Search method and results

Serial number	Database	Search terms	Publication dates	Number of articles
1	Medline Ovid	Maternal nutrition AND (child OR infant) AND (vaccine OR immune response)	Oldest article in database to 19 May 2017	68
2	Scopus	–	–	206
3	CINAHL	–	–	25
4	Web of Science	–	–	862
5	Popline	–	–	278
Total no. of articles: 1439 - 38 duplicates = 1301				

of the intestines, which is the primary site for poliovirus replication, and systematically in the production of serum IgG [50–53].

Rotavirus is a major cause of diarrheal mortality in children below 2 years of age and accounts for about 40% of all hospitalized gastroenteritis cases globally with relatively similar rates of disease in developed and developing countries [3,54–55]; more than 85% of deaths occur in Africa and Asia [56]. There are several types of rotavirus vaccines available, all induce a mucosal IgA immune response [29]; all are live attenuated, with major differences being the number of strains covered.

BCG is a live mycobacterium vaccine for the prevention of tuberculosis, given at birth. The mechanisms of attenuation of BCG remain poorly understood. BCG comprises a number of substrains that differ in genotypes and phenotypes, recruiting CD4 and CD8 T cells as a response to protective mycobacterial antigens [29]. DPT vaccine, made up of diphtheria toxoid, tetanus toxoid and killed pertusis, induces the formation of circulating protective levels of neutralizing serum IgG diphtheria toxoid also induces mucosal IgG [29].

Measles vaccine is a live attenuated vaccine inducing antibodies (serum IgG) and CD8 cells, which protect against measles virus [29].

Pneumococcal conjugate vaccine is a polysaccharide with polypeptide vaccine, which induces the serum and mucosal IgG [29].

Hepatitis B vaccine is a protein, which induces serum IgG [29].

Hemophilus influenza type B (Hib) vaccine is a polysaccharide and protein vaccine, which induces IgG in the mucosal and serum [29].

Maternal nutritional status & infant immune response to routine childhood vaccination

Although there is some literature on the link between particular nutrients and fetal development, and the mechanism of action may be understood to an extent, there is no clear understanding of the association between maternal nutritional status and infant immune response to routine childhood vaccinations. We thus undertook a systematic review of the literature to inform our understanding of this association.

Methods

Identification of information sources, study search, selection and inclusion, paper quality assessment and narrative synthesis were all overseen by both authors.

CINAHL, Medline, Popline, Scopus and Web of Science databases were searched for articles published in English by 19 May 2017. Searches were done using free text to identify materials having the words maternal, nutrition, child, infant, vaccine and immune response. Table 3 shows the search methods and results. Findings are reported according to the PRISMA guideline [57].

Eligible for inclusion in the review were studies reporting on associations between maternal malnutrition in pregnancy and infant (0–2 years) immune response to childhood vaccination; experimental/interventional (randomized and nonrandomized controlled trials), observational cohort (case control, longitudinal and case series) and reviews; published in a peer review journal or conference proceedings; published in English language; and related to human populations.

With the use of a specially designed Excel sheet, data were extracted from identified studies. The final consensus on study inclusion was based on extractions with information on study designs, maternal nutrition status, childhood vaccines and infant response to vaccinations. A PRISMA flowchart shows this process in Figure 1.
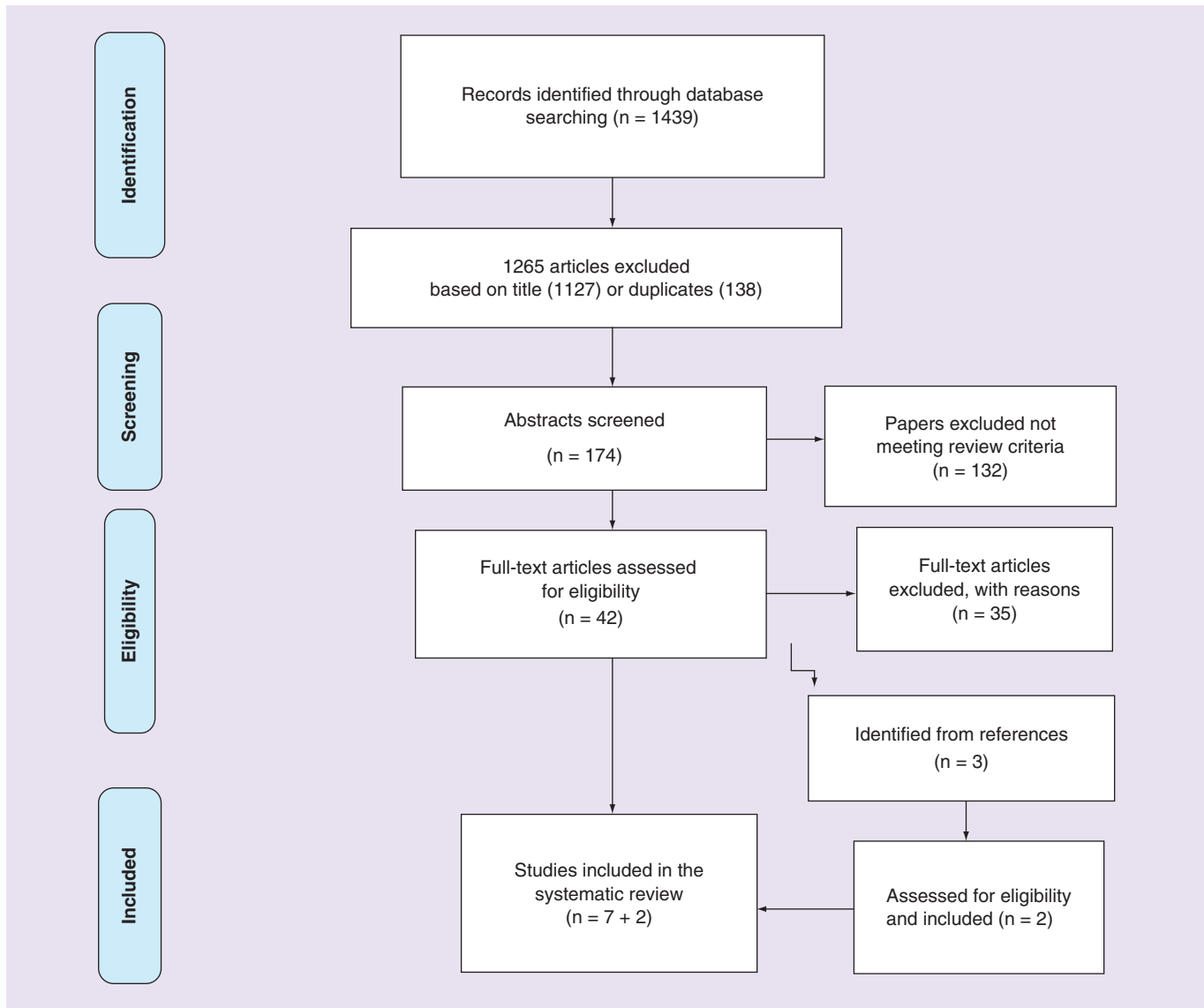
Figure 1. Flowchart of literature screening process.

Findings are presented in a narrative format. Key findings are summarized in tables. Meta-analyses could not be performed due to heterogeneity in methodology between studies: of the nine included papers three were reviews, two were longitudinal studies, one was a retrospective cohort and three were observational studies nested in a controlled trial. The quality of the research evidence for this systematic review was assessed with the use of the critical appraisal skills program (CASP), which appraises validity, importance and practicality of the study findings [58,59].

The three review papers [3–4,22] were appraised using the CASP systematic review checklist which has ten questions [60]: did the review address a clearly focused question; did the authors look for the right type of papers; were all the important, relevant studies included; did the review's authors do enough to assess the quality of the included studies; if the results of the review were combined, was it reasonable to do so; what were the overall results of the review; how precise were the results; can the results be applied to the local population; were all important outcomes considered; and were the benefits worth the harms and costs. A star was awarded for each point. Nine of the questions (question 5 was excluded as not applicable) were applied with the highest scoring study, Sack *et al.* [4] having four stars, while the others had two each.

The two longitudinal papers [61,62], the three observational studies nested within controlled trials [5,63–64] and the retrospective cohort study [6] were assessed with the use of the CASP cohort study checklist with 12 questions [65]:

Table 4. Associations between maternal nutritional status during pregnancy and infant immune response to routine childhood vaccines.

Study (year)	Direct evidence		Indirect evidence		Ref.
	Infant immune response to vaccines	Maternal nutrition status in pregnancy	Infant immune response to vaccines	Maternal nutrition status in pregnancy	
Review papers					
Chandra (1979)	✓			✓	[22]
Qadri *et al.* (2013)			✓	✓	[3]
Sack *et al.* (2008)			✓	✓	[4]
Observational studies					
Osendarp *et al.* (2006)	✓			✓	[64]
Grindulis *et al.* (1984)	✓			✓	[5]
Hur *et al.* (2014)	✓			✓	[62]
Neumann *et al.* (1998)	✓			✓	[61]
Xiao *et al.* (2015)	✓	✓			[6]
Ahmad *et al.* (2016)	✓			✓	[63]
✓ = Yes					

were the results of the study valid; was the cohort recruited in an acceptable way; was the exposure accurately measured to minimize bias; was the outcome measured to minimize bias; were confounders handled appropriately; was follow-up process described; were the results of the study presented clearly; how precise the results were; whether the results are believable; whether the results were applicable to the local population; did the results of this study fit with other available evidence; and what were the implications of this study for practice, with a star for each criteria. The quality of this group of papers ranged from 7–9 stars, with Ahmad *et al.* [63] and Hur *et al.* [62] studies scoring the highest.

Findings

Overall, there was no evidence of a quantified dose–response relationship between maternal malnutrition during pregnancy and a reduced immune response to routine immunization by the infant. However, children whose fetal environment was nutrition deficient were less likely to respond to immunization than those whose fetal environment was nutritionally adequate. Evidence of maternal nutritional status was either direct (by measurement of nutrient level) or indirect (as measured by season of birth, supplementation, micronutrient deficiency, birth outcome in the form of IUGR and low birth weight [LBW]). The following assumptions were made for indirect evidence: IUGR and LBW was most likely due to maternal malnutrition, maternal micronutrient supplementation in pregnancy may have corrected pre-existing intrauterine nutrient deficit and the rainy season in Africa is the period of hunger with more cases of intrauterine malnutrition.

Five studies focused on the infant response to BCG vaccine [5,22,61–62,64], two papers [6,63] investigated the infant response to Hepatitis B vaccine, reviews by Sack *et al.* and Qadri *et al.* synthesized evidence on oral vaccines and response to Hib vaccine was investigated in one study [64]. Only Osendarp *et al.* explored responses to two injectable vaccines (BCG and Hib), while each of the other eight studies focused on oral vacccines or a single injectable vaccine.

Seven of the studies [5–6,22,61–64] provided direct evidence (antibodies, reaction to purified protein derivatives [PPDs], cytokine/chemokine signatures and scar formation) of the infants' response to vaccines. In eight studies, maternal nutrition status was determined indirectly because it was not quantified, quantification not stated or not available (Table 4) [3–5,22,61–64].

Direct evidence of a link between maternal nutritional status, measured by specific nutritional components, on the infant's antibody response to routine vaccinations came from the study by Xiao *et al.* Results from the large study population of 3666 Chinese infants [6], who had completed their routine childhood vaccination of Hepatitis B at 0, 1 and 6 months, showed that maternal calcium deficiency and anemia during pregnancy was not associated with infant's immune response to the vaccine, but that maternal folic acid supplementation during pregnancy was associated with an increased vaccine immune response (p = 0.03) [6].

Indirect evidence of the association between maternal nutritional status (assumed from having IUGR and LBW babies, micronutrient supplementation in pregnancy and critical periods of pregnancy during the rainy season), and the infant's immune response to routine vaccinations was found in six studies [5,22,61–64]. Neumann *et al.*'s study in Kenya [61], where two groups of IUGR (birthweight – group I ≤2500 g and group III ≥2501–2799 g) infants were compared with normal infants (group III ≥2800 gram), showed that the IUGR group I total lymphocyte count was significantly higher than in the normal birth weight group III infants [61]. Further, response to BCG given at birth differed significantly when immune response to PPD was measured at 6 months of age, with the mean induration for groups I, II and III, respectively, being 5.3, 10.6 and 11.3 mm, implying a reduced ability to respond in the most birth weight retarded group [61]. Reviewed literature on nutritional deficiency and susceptibility to infection showed that LBW infants had a reduced tuberculin conversion and decreased lymphokine production following BCG vaccination [22]; both suggesting a link between newborn nutritional status and immune response at birth. A total of 149 children of Asian mothers, who had taken part in a controlled trial of protein energy supplement in Birmingham, who had been administered BCG vaccine shortly after birth, were assessed at 22 months for immune response to the vaccine using a Mantoux test and recorded evidence of scar formation [5]. About 25% of these young children had no scar and half of those who developed a scar responded negatively to 10 TU (Mantoux). Infants without scar were smaller for gestational age, thinner at birth with fewer of their mothers in the supplementation groups compared with their peers with scars [5]. A study involving 30 Malawian infants assessing seasonal variation in 42 immune (cytokine, chemokine and growth factors) responses to BCG at 3 months postvaccination showed that 3 responses were significantly higher in infants born in the dry season while 1 was significantly higher in the rainy season and the remaining 28 responses did not statistically differ between seasons [62]. In a maternal zinc supplementation study, a higher negative response to PPD skin test at 22 weeks following BCG vaccination at birth in LBW compared with normal birth weight infants was found to be statistically significant [64]. The analyses of only LBW infants showed that more infants whose mothers were in the placebo group had no skin response to PPD compared with infants from the zinc supplemented group, but the difference did not reach significance, possibly due to limited sample size [64].

This indirect evidence of the association between maternal nutritional status and the infant's immune response is not limited to BCG vaccine. A study on the effects of maternal zinc supplementation in pregnancy on the infants' immune response at 24 weeks of age, following the administration of three doses of Hib conjugate, found no significant difference in the immediate and long-term antibody protective titres between the infants whose mothers were in the supplemented and placebo groups [64]. Results from a large study population of 3666 Chinese infants who had completed their routine childhood vaccination of Hepatitis B at 0, 1 and 6 months showed that maternal calcium deficiency and anemia during pregnancy was not associated with infant's immune response to the vaccine, while maternal folic acid supplementation during pregnancy was associated with an increased vaccine immune response [6]. Infants of zinc supplemented mothers had a higher antibody response to the three routine vaccination doses of Hepatitis B vaccine at the age of 6 months compared with peers whose mothers had placebo supplements, but this finding was not statistically significant [63].

Findings from the two reviews on oral vaccines suggest that there is an association between maternal nutrition status in pregnancy and infant immune response to routine childhood vaccinations [3,4]. Evidence obtained from the study on determinants of responses to oral vaccines in developing countries raised the possibility of maternal malnutrition in pregnancy decreased infant's immune response to vaccines [4]. Qadri *et al.* concluded that for the young infant, maternal nutrition and maternal antibodies could likely be reasons for the decreased immune response to oral live vaccines seen in developing countries [3]. In addition, children from developing countries have been shown to respond less well to oral vaccines than children in developed countries [3], possibly related to maternal environment. In older children, beyond infancy, macro- and micro-nutrient deficiency, enteropathy resulting from bad hygiene, flora overgrowth in the intestine have been suggested as more relevant in explaining poor response to oral live vaccines [3].

Conclusion

Findings presented in this review suggest a complex interaction between maternal nutritional status, whether measured by season of birth, supplementation, micronutrient deficiency, birth outcome in the form of IUGR, or LBW, and infant response to routine vaccinations. However, there was little direct evidence of the impact of exposure, or lack thereof, of particular nutrients in fetal life on the infant's ability to response to routine childhood vaccination, and no association was quantified. However, overall the findings suggest, in line with knowledge about

mechanism of action of particular nutrients on immune functioning, that maternal malnutrition in pregnancy may leave the offspring with a less than optimal immune system at birth, with the likelihood of subsequent reduced immune response to routine childhood vaccination in the first year of life [8,11,62,64]. These findings add to the emerging literature on the developmental origins of health and disease concept, with the insult during fetal and early life having immediate consequences in the first year of life, which are likely to bear on subsequent health into adulthood.

Our systematic literature review identified only nine studies and their quality for this review was average overall. The indirectness of most results and the need to assume a link between maternal nutritional status and birth nutritional status limits our ability to understand and reliably quantify the association between maternal malnutrition and child immune response.

Although we were not able to show a direct cause–effect relationship between maternal malnutrition and child vaccine immune response, the synthesized evidence suggests that maternal lack of adequate levels of macro and micronutrients during pregnancy impairs fetal growth and development leading to the inability of the child's immune system to mount appropriate response to vaccinations. This impaired system, with lower than protective antibody levels against the disease, was found even in the presence of nutrient supplementation to persist beyond infancy.

Vaccination programs are usually evaluated on the basis of how many children have been seen vaccination program coverage, with little thought given to whether vaccinations received are adequately protecting the child. This review shows the importance of maternal nutrition in achieving the goal of achieving universal protection of children against vaccine preventable diseases. Our results suggest that attention now needs to be given to the broader issues, going beyond mere evaluation of uptake of immunization offer, to understanding which children respond to vaccination and which do not, and why. Without broadening the research agenda, achieving the United Nation's 2010–2020 decade of vaccine child immunization coverage's target may not provide the expected levels of protection in children and control of these vaccine preventable diseases.

Future perspective

This paper highlights a major likely cause of childhood immunization failure. Inability of a vaccinated child to resist the vaccine preventable diseases could cause loss of faith in vaccination programs by parents, caregivers and communities. An estimated third of children who experienced intrauterine malnutrition will not mount protect level immune response to vaccines, and these infants may need appropriate supportive interventions.

Executive summary

Background
- Routine vaccination saves an estimated 2–3 million children annually.
- However, not all children are vaccinated, and not all who have responded appropriately.

Methods
- Systematic review using PRISMA guideline.
- Quality of included papers assessed using critical appraisal skills program checklist.
- Narrative summary.

Findings
- Of the 1439 papers identified, 9 were included with 3 assessed to be of poor quality.
- Maternal malnutrition during pregnancy reduces the fetal immune system development.
- Children who had intrauterine malnutrition responded less to vaccines compared with children with adequate intrauterine nutrition environment.

Conclusion
- Adequate nutrition of mothers during pregnancy has a role in the normal development of the fetal immune system and the infant's ability to mount protective levels immune response to vaccines.

New addition to knowledge
- Identified maternal nutritional status to be a major likely cause of vaccination failure.
- Highlighted the need to explore intrauterine nutrition interventions to increase child's inability to optimally mount immune response to routine vaccination.
- There is very little evidence on this important aspect of vaccinology.

References

Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

1. Tao W, Petzold M, Forsberg BC. Routine vaccination coverage in low- and middle-income countries: further arguments for accelerating support to child vaccination services. *Glob. Health Action* 6, 20343 (2013).

2. Subaiya S, Dumolard L, Lydon P, Gacic-Dobo M, Eggers R, Conklin L. Global routine vaccination coverage, 2014. *MMWR* 64(44), 1252–1255 (2015).

3. Qadri F, Bhuiyan TR, Sack DA, Svennerholm AM. Immune responses and protection in children in developing countries induced by oral vaccines. *Vaccine* 31(3), 452–460 (2013).

4. Sack DA, Qadri F, Svennerholm AM. Determinants of responses to oral vaccines in developing countries. *Ann. Nestle* 66(2), 71–79 (2008).

5. Grindulis H, Baynham MI, Scott PH, Thompson RA, Wharton BA. Tuberculin response two years after BCG vaccination at birth. *Arch. Dis. Child.* 59(7), 614–619 (1984).

●   **Findings of the association between maternal nutrition in pregnancy and infant response to childhood vaccination was reported precisely (p-value).**

6. Xiao M, Qiu Q, Pang X *et al.* Immune response in infants after universal high-dose hepatitis B vaccination: a community-based study in Beijing, China. *Vaccine* 33(43), 5878–5883 (2015).

●●   **Direct evidence that maternal nutritional status in pregnancy is associated with infant immune response to childhood vaccination.**

7. Moore SE, Prentice A, Wagatsuma Y *et al.* Early-life nutritional and environmental determinants of thymic size in infants born in rural Bangladesh. *Acta Paedtr.* 98(7), 1168–1175 (2009).

8. Gluckman PD, Hanson MA. The developmental origins of health and disease. In: *Early Life Origins of Health and Disease. Advances in Experimental Medicine and Biology.* Wintour EM, Owen JA (Eds). Springer, MA, USA, 573, 1–7 (2006).

9. Raqib R, Alam DS, Sarker P *et al.* Low birth weight is associated with altered immune function in rural Bangladeshi children: a birth cohort study. *Am. J. Clin. Nutr.* 85(3), 845–852 (2007).

10. Katona P, Katona-Apte J. The interaction between nutrition and infection. *Clin. Infect. Dis.* 46(10), 1582–1588 (2008).

11. Wu G, Imhoff-Kunsch B, Girard AW. Biological mechanisms for nutritional regulation of maternal health and fetal development. *Paediatr. Perinat. Epidemiol.* 26, 4–26 (2012).

●●   **Provided information on role of maternal nutrients in pregnancy and dietary sources.**

12. Jobgen WS, Fried SK, Fu WJ, Meininger CJ, Wu G. Regulatory role for the arginine-nitric oxide pathway in metabolism of energy substrates. *J. Nutr. Biochem.* 17(9), 571–588 (2006).

13. Abu-Saad K, Fraser D. Maternal nutrition and birth outcomes. *Epidemiol. Rev.* 32(1), 5–25 (2010).

14. Barker DJ. The origins of the developmental origins theory. *J. Intern. Med.* 261(5), 412–417 (2007).

15. Palmer AC. Nutritionally mediated programming of the developing immune system. *Adv. Nutr.* 2(5), 377–395 (2011).

16. Marques AH, O'connor TG, Roth C, Susser E, Bjorke-Monsen A-L. The influence of maternal prenatal and early childhood nutrition and maternal prenatal stress on offspring immune system development and neurodevelopmental disorders. *Front. Neurosci.* 7, 120 (2013).

17. Wu G, Bazer FW, Cudd TA, Meininger CJ, Spencer TE. Maternal nutrition and fetal development. *J. Nutr.* 134(9), 2169–2172 (2004).

18. Forchielli ML, Walker WA. The role of gut-associated lymphoid tissues and mucosal defence. *Br. J. Nutr.* 93(S1), S41–S48 (2005).

19. Collinson AC, Ngom PT, Moore SE, Morgan G, Prentice AM. Birth season and environmental influences on blood leucocyte and lymphocyte subpopulations in rural Gambian infants. *BMC Immunol.* 9, 18 (2008).

20. Chandra RK. Antibody formation in first and second generation offspring of nutritionally deprived rats. *Science* 190(4211), 289–290 (1975).

21. Beach RS, Gershwin ME, Hurley LS. Gestational zinc deprivation in mice: persistence of immunodeficiency for three generations. *Science* 218(4571), 469–471 (1982).

22. Chandra RK. Nutritional deficiency and susceptibility to infection. *Bull. World Health Organ.* 57(2), 167–177 (1979).

23. Murakami M, Hirano T. Intracellular zinc homeostasis and zinc signaling. *Cancer Sci.* 99(8), 1515–1522 (2008).

24. Yin J, Li X, Li D *et al.* Dietary supplementation with zinc oxide stimulates ghrelin secretion from the stomach of young pigs. *J. Nutr. Biochem.* 20(10), 783–790 (2009).

25. Merialdi M, Caulfield LE, Zavaleta N *et al.* Randomized controlled trial of prenatal zinc supplementation and fetal bone growth. *American J. Clin. Nutr.* 79(5), 826–830 (2004).

26. World Health Organisation. Zinc. In: *Trace Elements in Human Nutrition and Health*. WHO, Geneva, Switzerland, 72–104 (1996).

27. Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. *Am. J. Clin. Nutr.* 68(2), 447S–463S (1998).

28. Walker CF, Black RE. Zinc and the risk for infectious disease. *Ann. Rev. Nutr.* 24, 255–275 (2004).

29. Siegrist CA. Vaccine immunology. In: *Vaccines*. Plotkin SA, Orenstein WA, Offit PA (Eds). Saunders Elsevier, NY, USA, 5(1), 17–36 (2008).

••   **Provides information on vaccines and their mechanism of action.**

30. Bhaskaram P, Rao KV. Enhancement in seroconversion to measles vaccine with simultaneous administration of vitamin A in 9-months-old Indian infants. *Indian J. Pediatr.* 64(4), 503–509 (1997).

31. Bikle DD. Vitamin D and the immune system: role in protection against bacterial infection. *Curr. Opin. Nephrol. Hyperten.* 17(4), 348–352 (2008).

32. Kovacs CS. Vitamin D in pregnancy and lactation: maternal, fetal, and neonatal outcomes from human and animal studies. *Am. J. Clin. Nutr.* 88(2), 520S–528S (2008).

33. Zeisel SH. Importance of methyl donors during reproduction. *Am. J. Clin. Nutr.* 89(2), 673S–677S (2009).

34. Iskandar BJ, Rizk E, Meier B *et al.* Folate regulation of axonal regeneration in the rodent central nervous system through DNA methylation. *J. Clin. Invest.* 120(5), 1603–1616 (2010).

35. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. *Nat. Genet.* 33, 245–254 (2003).

36. Kjer-Nielsen L, Patel O, Corbett AJ *et al.* MR1 presents microbial vitamin B metabolites to MAIT cells. *Nature* 491(7426), 717–723 (2012).

37. De Vito P, Incerpi S, Pedersen JZ, Luly P, Davis FB, Davis PJ. Thyroid hormones as modulators of immune activities at the cellular level. *Thyroid* 21(8), 879–890 (2011).

38. Winzerling JJ, Law HJ. Comparative nutrition of iron and copper. *Ann. Rev. Nutr.* 17(1), 501–526 (1997).

39. Beard JL. Iron biology in immune function, muscle metabolism and neuronal functioning. *J. Nutr.* 131(2), 568S–580S (2001).

40. Zimmermann MB. The influence of iron status on iodine utilization and thyroid function. *Annu. Rev. Nutr.* 26, 367–389 (2006).

41. Bhaskaram C, Reddy V. Cell-mediated immunity in iron-and vitamin-deficient children. *Br. Med. J.* 3(5982), 522 (1975).

42. Bhaskaram P. Micronutrient malnutrition, infection, and immunity: an overview. *Nutr. Rev.* 60(Suppl. 5), S40–S45 (2002).

43. Bhaskaram P. Immunology of iron-deficient subjects. *Nutr. Immunol.* 149 (1988).

44. Kochanowski B, Sherman A. Decreased antibody formation in iron-deficient rat pups – effect of iron repletion. *Am. J. Clin. Nutr.* 41(2), 278–284 (1985).

45. Dietert RR, Dietert JM. Potential for early-life immune insult including developmental immunotoxicity in autism and autism spectrum disorders: focus on critical windows of immune vulnerability. *J. Toxicol. Environ. Health B Crit. Rev.* 11(8), 660–680 (2008).

46. Kelly D, Coutts AG. Early nutrition and the development of immune function in the neonate. *Proc. Nutr. Soc.* 59(2), 177–185 (2000).

47. Medzhitov R, Janeway CA. Innate immunity: impact on the adaptive immune response. *Curr. Opin. Immunol.* 9(1), 4–9 (1997).

48. Jullien D, Stenger S, Ernst WA, Modlin RL. CD1 presentation of microbial nonpeptide antigens to T cells. *J. Clin. Invest.* 99(9), 2071 (1997).

49. WHO. Immunisation (2016). www.who.int/immunization/monitoring_survaillance/en/

50. Agarwal A, Sharma D, Khare S. Antibody response to three doses of standard and double dose of trivalent oral polio vaccine. *Indian Pediatr.* 28(10), 1141–1145 (1991).

51. John TJ, Jayabal P. Oral polio vaccination of children in the tropics: I. The poor seroconversion rates and the absence of viral interference. *Am. J. Epidemiol.* 96(4), 263–269 (1972).

52. Sutter RW, Suleiman AJM, Malankar P *et al.* Trial of a supplemental dose of four poliovirus vaccines. *N. Engl. J. Med.* 343(11), 767–773 (2000).

53. Triki H, Abdallah MOM, Aissa RB *et al.* Influence of host related factors on the antibody response to trivalent oral polio vaccine in Tunisian infants. *Vaccine* 15(10), 1123–1129 (1997).

54. Kawai K, O'brien MA, Goveia MG, Mast TC, El Khoury AC. Burden of rotavirus gastroenteritis and distribution of rotavirus strains in Asia: a systematic review. *Vaccine* 30(7), 1244–1254 (2012).

55. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR *et al.* Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N. Engl. J. Med.* 354(1), 11–22 (2006).

56. Parashar UD, Gibson CJ, Bresse J, Glass RI. Rotavirus and severe childhood diarrhea. *Emerg. Infect. Dis.* 12(2), 304–306 (2006).

57. Preferred reporting items for systematic reviews and meta-analysis (Prisma). PRISMA 2009 Flow Diagram (2009). www.prisma-statement.org

58. Akobeng AK. Principles of evidence based medicine. *Arch. Dis. Child.* 90(8), 837–840 (2005).

59. Yost J, Dobbins M, Traynor R, Decorby K, Workentine S, Greco L. Tools to support evidence-informed public health decision making. *BMC Public Health* 14(1), 728 (2014).

60. Critical Appraisal Skills Programme. Systematic Review Checklist (2017). www.casp-uk.net/

61. Neumann CG, Stiehm ER, Zahradnick J *et al.* Immune function in intrauterine growth retardation. *Nutr. Res.* 18(2), 201–224 (1998).

62. Hur Y-G, Gorak-Stolinska P, Lalor MK *et al.* Factors affecting immunogenicity of BCG in infants, a study in Malawi, the Gambia and the UK. *BMC Infect. Dis.* 14(1), 184 (2014).

•   **Findings of the association between maternal nutrition in pregnancy and infant response to childhood vaccination was reported precisely (p-value).**

63. Ahmad SM, Hossain MB, Monirujjaman M *et al.* Maternal zinc supplementation improves hepatitis B antibody responses in infants but decreases plasma zinc level. *Eur. J. Nutr.* 55(5), 1823–1829 (2016).

•   **Findings of the association between maternal nutrition in pregnancy and infant response to childhood vaccination was reported precisely (p-value).**

64. Osendarp SJ, Fuchs GJ, Van Raaij J *et al.* The effect of zinc supplementation during pregnancy on immune response to Hib and BCG vaccines in Bangladesh. *J. Trop. Pediatr.* 52(5), 316–323 (2006).

••   **Findings of the association between maternal nutrition in pregnancy and infant response to childhood vaccination was reported precisely (p-value) and response to two vaccines were studied.**

65. Critical Appraisal Skills Programme. Cohort Study checklist (2017). www.casp-uk.net/