



Review

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Malnutrition and vaccination in developing countries

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Malnutrition contributes to an estimated 45% of deaths among children under 5 years of age in developing countries, predominantly due to infections. Malnourished children therefore stand to benefit hugely from vaccination, but malnutrition has been described as the most common immunodeficiency globally, suggesting that they may not be able to respond effectively to vaccines. The immunology of malnutrition remains poorly characterized, but is associated with impairments in mucosal barrier integrity, and innate and adaptive immune dysfunction. Despite this, the majority of malnourished children can mount a protective immune response following vaccination, although the timing, quality and duration of responses may be impaired. This paper reviews the evidence for vaccine immunogenicity in malnourished children, discusses the importance of vaccination in prevention of malnutrition and highlights evidence gaps in our current knowledge.

1. Introduction

Malnutrition encompasses a broad spectrum of nutritional impairments, including intrauterine growth restriction, stunting, wasting, suboptimal breastfeeding and deficiencies of micronutrients such as vitamin A and zinc [1]. It has been estimated that, together, these conditions underlie 45% of deaths among children under 5 years of age globally [1]. As each of these manifestations is associated with an increased risk and/or severity of infections, malnutrition has been described as the most common immunodeficiency globally [2]. This raises two important questions: first, what is the nature of the apparent immunodeficiency in these children and, second, can malnourished children respond effectively to vaccinations?

2. Definitions of malnutrition

The manifestations of malnutrition described above are highly inter-related. For example, around 20% of stunting has intrauterine origins and manifests at birth as low birth weight due to intrauterine growth restriction or prematurity [3]; stunting and wasting share common risk factors and are often apparent in the same child [4]; and children with severe acute malnutrition (a form of wasting) are likely to have various micronutrient deficiencies [1]. This review will focus specifically on stunting, wasting and underweight—the most common clinical manifestations of undernutrition for which children are screened in developing countries by anthropometry.

Stunting (linear growth failure) affects an estimated 165 million (or 26%) children under 5 years of age and is defined as a height-for-age Z-score (HAZ) below -2 (i.e. more than 2 s.d. below the population median) [1]. Wasting is assessed by comparing a child's weight to their height and tends to reflect short-term growth failure: moderate acute malnutrition (MAM) is defined as a weight-for-height Z-score (WHZ) below -2 and severe acute malnutrition (SAM) as WHZ below -3 . SAM presents as two major syndromes: marasmus, characterized by muscle wasting and loss of subcutaneous fat but without oedema; or kwashiorkor, a syndrome characterized by oedema, together with skin and hair changes, hepatomegaly and irritability. Although the prevalence of wasting is difficult to

capture because of its more acute and reversible nature, an estimated 52 million (or 8%) children below 5 years of age are wasted at any point in time [1]. Children with low weight-for-age Z-score (WAZ < -2) are categorized as underweight, but since low WAZ can reflect either stunting or wasting, there is a tendency to move away from underweight as a metric of malnutrition, although the target for Millennium Development Goal 1 is reduction in underweight (<http://www.un.org/millenniumgoals/>). The nomenclature and categorization of malnutrition has changed over time and many older studies describe 'protein energy malnutrition', a term that may encompass several different forms of undernutrition and is no longer routinely used.

3. Malnourished children are at risk of infections

Malnutrition is associated with increased morbidity and mortality from infections [5–8]. In a recent large analysis of data derived from 10 prospective studies in Asia, Africa and South America, stunting, wasting and underweight were each associated with excess mortality; even at Z-scores between -1 and -2, children had an excess risk of death from pneumonia and diarrhoea [7]. There was a clear dose-response relationship between the degree of malnutrition and mortality, with the risk among those with wasting greater than among those with stunting. Children with the most profound anthropometric defects had an elevated risk of death from a variety of infections, including sepsis, meningitis, measles and tuberculosis. Although some datasets in this analysis were not adjusted for all potential confounders, and undernutrition may to some degree reflect general socioeconomic disadvantage, nevertheless the body of evidence indicates that malnourished children have a clear excess risk of infectious morbidity and mortality.

4. The immunology of malnutrition

It has been recognized for many decades that infection and malnutrition overlap and interact. Scrimshaw *et al.* [9] first described a vicious cycle of infection and undernutrition, whereby infections predispose to malnutrition, through reduced intake and absorption and diversion of nutrients away from growth, while malnutrition reduces immune function and increases the risk and/or severity of infections. Various iterations of this cycle have been proposed over the years, with more recent versions recognizing that subclinical infection, enteropathy, changes in the composition and function of the gut microbiota and systemic inflammation are likely to be important in the pathogenesis of malnutrition, in addition to overt infections [10–12]. Children hospitalized for severe acute malnutrition are extremely sick, with physiological dysfunction such as reduced respiratory muscle mass, impaired cardiac function and electrolyte disturbance, in addition to micronutrient deficiencies, inflammation, clinical infection and mucosal barrier breakdown. The internal milieu of a severely malnourished child is therefore enormously perturbed, making it difficult to distinguish the precise factors that lead to immune impairment in this setting.

Studies describing the immunology of malnutrition have recently been brought together in an excellent systematic review [12]. This review highlights the fact that the majority of studies were conducted several decades ago using old

immunological techniques, making interpretation difficult. Most published observations are cross-sectional studies of hospitalized children, using varying definitions of undernutrition (with generally no distinction between stunting, underweight and wasting), and frequently without control groups or longitudinal follow-up. There is therefore an urgent need for further, larger studies of well-characterized cohorts of children with varying degrees of malnutrition, categorized according to current criteria, and followed longitudinally to probe immune function using modern laboratory techniques. Nevertheless, certain consistent findings from prior studies of immune function can be drawn from the literature, as comprehensively reviewed by Rytter *et al.* [12]. The current paper will provide only a brief summary of these findings, before focusing on vaccination in the context of malnutrition. A search was conducted on PubMed using the terms: (malnutrition OR undernutrition OR malnourished OR undernourished OR underweight OR stunt* OR wast* OR kwashiorkor OR marasmus) AND (vaccin* OR immunis* OR immuniz*). This review will focus only on injectable vaccines; other papers in this issue focus specifically on the underperformance of oral vaccines in developing countries.

(a) Mucosal barrier dysfunction

Malnourished children have mucosal barrier dysfunction. Compromise of the skin barrier is the most clinically evident defect in children with oedematous malnutrition, classically described as the 'peeling paint' dermatosis of kwashiorkor [13]. Histologically, this is characterized by atrophy and effacement of the skin layers, hyperkeratosis and a pronounced cutaneous inflammatory response [14–16], providing a potential portal of entry for pathogens. An extensive enteropathy has long been recognized in children with severe malnutrition, characterized by mucosal inflammatory infiltrate, villous atrophy and compromised intestinal barrier function [17]. It has also been noted since the 1960s that a small intestinal abnormality, originally termed tropical enteropathy, is almost universally seen among apparently healthy people living in developing countries [18,19], but it is only relatively recently that attention has refocused on this condition. A series of studies from the Gambia [20,21] showed a relationship between enteropathy and impaired linear growth in infants, and recent studies [22–24] have further highlighted the role that this gut pathology, now renamed environmental enteric dysfunction (EED) [25], may have in stunting malnutrition. The impact of enteropathy on mucosal immune function remains unclear, because of the difficulties in obtaining gut biopsies from young children, but EED may be one of the factors underlying the poor performance of oral vaccines in developing countries, as discussed in another paper in this issue [26]. The intestinal barrier dysfunction that occurs in the context of enteropathy enables translocation of organisms or microbial products to the systemic circulation, which may be particularly important for three major reasons. First, translocation of organisms may partly explain the elevated risk of Gram-negative bacteraemia in hospitalized children with SAM [27]; second, elevated levels of lipopolysaccharide impair maturation of dendritic cells, which are therefore unable to effectively support T cell proliferation [28]; and, third, microbial products stimulate innate immune cells, leading to a pro-inflammatory environment in malnourished children, which may impair effector functions.

Table 1. Summary of vaccine responses in malnourished children.

vaccine	responses in malnourished children	references
diphtheria, tetanus, pertussis (DTP)	most studies report good seroconversion rates; affinity or titre of vaccine responses may be affected	[33–37]
hepatitis B (HepB)	good seroconversion; conflicting data on antibody titres	[38,39]
rabies	no relationship between measures of malnutrition and response to vaccine	[40]
typhoid (killed)	similar antibody response to well-nourished children, although generation of vaccine response may be delayed in two trials, antibody responses to typhoid vaccine reported to be augmented following dietary interventions	[34,41–45]
pneumococcal	responses to plain polysaccharide vaccine not associated with nutritional status no studies have specifically evaluated conjugate pneumococcal vaccines in malnourished children	[40,46]
meningococcal	conflicting results from old studies of meningococcal polysaccharide vaccine no studies have specifically evaluated conjugate meningococcal vaccines in malnourished children	[34,42,47,48]
<i>Haemophilus influenzae</i> B (HiB)	good responses to conjugated HiB vaccine in malnourished children	[39]
bacille Calmette–Guérin (BCG)	reduced delayed-type hypersensitivity responses (e.g. Mantoux test) following BCG no studies have characterized BCG-specific T cell responses in malnourished children	[49–53]
measles	old studies suggest adequate response to measles vaccine (measured by haemagglutination) in malnourished children, but may be delayed newer study reported only 75% Ugandan children had protective measles responses (measured by ELISA) at 1 year of age	[34,54–62]

(b) Innate immune dysfunction

Total numbers of white blood cells are preserved (or even elevated) in malnourished children, while the number of dendritic cells, which are required to present antigens to adaptive immune cells, tends to be reduced compared with well-nourished children [12]. The majority of studies show some functional impairment of neutrophils and reduced levels of complement proteins [12], both of which are critical components of innate defence against bacterial infections. Malnourished children are able to mount a robust acute phase response to infection; in fact, some studies have reported that, even in the absence of infection, malnutrition is generally a pro-inflammatory disease [12].

(c) Adaptive immune dysfunction

Malnutrition does not appear to reduce the number of lymphocytes or, specifically, the number of circulating T cells [12]. However, the thymus gland, where T cell ‘education’ occurs, is particularly targeted even among children who are mildly undernourished, with thymic involution well recognized as a hallmark of malnutrition [12]. Although the number of circulating B cells is reduced in the context of malnutrition, levels of the major immunoglobulins (IgG and IgM) are not affected, and IgA levels tend to be elevated compared with well-nourished children [12]. This may be related to the cytokine milieu in malnutrition, which is skewed towards Th2-promoting cytokines (such as IL-4 and IL-10) and away from Th1-promoting cytokines (such as IL-2, IL-12 and interferon- γ).

(d) Animal studies

In addition to the human literature summarized by Rytter *et al.* [12], emerging data from animal models provide insights into

immune function in malnutrition and highlight mechanisms that should be investigated further in humans [29–31]. For example, when mice are fed a very low-protein diet and infected with influenza, they have reduced influenza-specific antibody and CD8⁺ T cell responses compared with mice fed an adequate protein diet, but immune responses are restored after feeding the undernourished mice an adequate protein diet [31]. In an elegant series of experiments in protein-restricted mice, Iyer *et al.* [30] showed that memory maintenance within the CD8⁺ T cell population is reduced in the context of malnutrition due to impaired homeostatic proliferation and that recall responses following pathogen challenge are impaired in malnourished mice. Given the importance of a long-lived and functional CD8⁺ T cell memory population for effective recall responses to vaccination, these data suggest that long-term vaccine-specific immunity may be impaired in the context of malnutrition.

5. Vaccination in the context of malnutrition

Savy *et al.* [32] exhaustively reviewed the literature on the interactions between nutrition and vaccine responses in children in 2009. The current paper will highlight key findings from that landscape analysis, focusing on the studies that evaluated children with ‘protein energy malnutrition’, and will discuss several studies that have been published subsequently to provide an overview of vaccine responses among malnourished children (summarized in table 1).

(a) Protein vaccines

Malnourished children generally appear to respond adequately to protein vaccines, such as diphtheria and tetanus [33–36]. For

example, among 45 Nigerian children who were given a single subcutaneous dose of tetanus toxoid vaccine, seroconversion rates and titres were not significantly different between children with kwashiorkor, marasmus, marasmic-kwashiorkor and healthy controls at 3, 10 and 21 days post-vaccination [36]. Similarly, among children from nine villages in Punjab, India, whose antibody responses to tetanus were measured by indirect haemagglutination 45 and 90 days post-DTP vaccination, there was no difference in antibody titre by weight-for-age category [35]. In Nigeria, there were no significant correlations between immune responses to a range of vaccines, including tetanus, and the child's nutritional status at the time of vaccination [34].

By contrast, a more recent cross-sectional study of 1553 Ecuadorean children below 5 years of age, who had received three documented doses of DTP, showed reduced IgG antibody ELISA titres to tetanus toxoid (but not diphtheria toxoid) among children with stunting or underweight, compared with well-nourished controls; however, there was no difference in seroconversion rates to either vaccine [33]. There have been few studies of pertussis vaccine responses due to historical difficulties in pertussis-specific antibody measurement. However, a recent study from Senegal, which followed 203 children from four villages over one calendar year and measured pertussis toxin IgG antibodies by commercial ELISA, reported an effect of both birth season and nutritional status on pertussis titres [37]. Children born in October–December, which is the harvest season in Senegal, had higher pertussis-specific titres compared with those born at other times of year. There was also an interaction between birth season and the child's weight-for-age Z-score, such that underweight was associated with reduced pertussis responses among those children born in the harvest season, while responses among children born at other times (the so-called hungry season) were not influenced by the child's current weight. There was also an effect of geography, with differences in pertussis response depending on the village the child lived in, showing the complex environmental, seasonal and nutritional interactions that appear to influence immune responses in developing countries.

Taken together, studies indicate that malnourished children (including those hospitalized for severe acute malnutrition) are likely to seroconvert adequately to protein vaccines and therefore be protected, although malnutrition may have a subtle impact on affinity or titre of the antibody response, the clinical significance of which is uncertain.

(b) Subunit vaccines

Hepatitis B is a subunit vaccine based on recombinant surface antigen from the virus. In a small Egyptian study, children with SAM had similar rates of seroconversion but lower antibody titres following hepatitis B vaccination, compared with healthy controls [38]. In a more recent study from Guatemala [39], a similar proportion of healthy and malnourished infants (defined on the basis of WAZ, HAZ or WHZ below -2) mounted protective humoral responses to hepatitis B vaccination. In contrast to the Egyptian study, geometric mean concentrations of antibody were higher among malnourished than well-nourished infants [39].

(c) Killed vaccines

A large Gambian study evaluated responses to human diploid-cell rabies vaccine in older children (6.5–9.5 years old), with

moderate to severe malnutrition and a range of micronutrient deficiencies, but found no consistent associations between any of these measures of undernutrition and seroconversion [40]. Several studies have evaluated responses to killed typhoid vaccine in malnourished children [34,41–43]. Two of these studies, from Nigeria, found similar antibody responses to a single dose of killed typhoid vaccine among malnourished and well-nourished groups, despite children in one of these studies [42] being strikingly unwell, with persistent measles rash, a high frequency of co-infections, severe malnutrition and 50% inpatient mortality. Two smaller studies [41,43] found lower typhoid antibody titres shortly (8–10 days) after vaccination, although in the Thai study [43] responses were similar between groups when measured later after vaccination (25 days).

Typhoid is one of the few vaccines to have been evaluated within the context of randomized controlled trials in children with malnutrition. In a 1962 South African trial [63], 30 infants with kwashiorkor received a high-protein diet and antibiotics and were then randomized to receive intramuscular pyridoxine or not. A control group comprised 15 patients with adequate nutritional status, following recovery from malnutrition or other illnesses. Infants were given typhoid and paratyphoid A and B endotoxoid intradermally, and antibody responses were evaluated by the Widal test 10 days later. Responses to vaccination were not significantly different between the three groups of infants, suggesting that infants with oedematous malnutrition can mount good antibody responses and that pyridoxine had no additive benefit. A study from India in 1964 [44] suggested that children with kwashiorkor receiving a higher protein diet (50 g d^{-1} compared to 30 g d^{-1}) had better antibody responses to killed typhoid vaccine but, as noted by Savy *et al.* [32], the paper does not state whether dietary allocation was randomized or not. A 1972 study in New Guinea randomized children who were apparently healthy but had 'retarded growth' in the context of poor diets to either 25 g d^{-1} of protein supplement (as skim-milk powder) or usual diet [45]. Seven months later, children were vaccinated subcutaneously with flagellin from *Salmonella adelaide*, and total anti-flagellin antibody titres (though not specific IgG antibody titres) were reported to be higher in the supplemented group at two and six weeks post-vaccination when measured by haemagglutination.

Taken together, even children with severe malnutrition seem able to respond to killed vaccines, although generation of an immune response may be delayed. There is some intriguing evidence from old studies of killed typhoid vaccines that dietary interventions have the potential to improve responses to vaccination, although there have been no subsequent trials of nutritional interventions that have assessed vaccine outcomes.

(d) Polysaccharide vaccines

Pneumococcal plain polysaccharide vaccine (PPV) was evaluated in a cohort of 472 Gambian children aged 6.5–9.5 years, with a high prevalence of underweight (28.6%) and moderate prevalence of stunting (11.6%) [40]. After adjustment for seasonality, gender and age, there was no relationship between any measure of anthropometry and IgG responses to four vaccine serotypes measured by ELISA 14 days after vaccination, similar to findings from an older study of PPV in Ghana [46]. Pneumococcal conjugate vaccines (PCVs) are now recommended for use globally, particularly in low-income countries with high child

mortality [64]. Surveillance data from South Africa show that rates of invasive pneumococcal disease (IPD) fell substantially among children following introduction of the 7-valent vaccine (PCV7) in 2009, then the 13-valent vaccine (PCV13) in 2011 [65]. Although no studies have specifically evaluated the efficacy of PCV in the context of malnutrition, there is a suggestion from a case–control study of IPD in South Africa that PCV7 vaccine efficacy may be lower in malnourished compared with well-nourished children; however, the number of children in this subgroup analysis was small and the findings not statistically significant [66].

Four studies evaluating responses to meningococcal vaccines in Nigeria have conflicting findings, with two [42,47] reporting lower vaccine responses among malnourished compared with well-nourished children, and two [34,48] reporting no impact of nutritional status on vaccine responses. One of the studies [42] reporting impaired meningococcal vaccine responses enrolled hospitalized children with SAM, persistent measles infection and high rates of other co-infections; this group had an inpatient mortality of 50%, marking them out as particularly sick children who are not representative of the majority of children who would be vaccinated in an EPI programme.

Guatemalan infants categorized as malnourished (WAZ, WHZ or HAZ < -2), who were vaccinated against *Haemophilus influenzae* B (HiB) as part of a combined DTwP–HepB/HiB vaccine at two, four and six months of age, were all protected by vaccination and showed higher geometric mean antibody titres than well-nourished children evaluated at the same ages [39]. Taken together, polysaccharide vaccines generally appear to generate adequate immune responses in children with malnutrition, although there are limited data from the conjugate vaccine era; however, roll-out of these vaccines in countries with high prevalence of underweight and stunting has been highly effective, with substantial reductions in morbidity and mortality.

(e) Live vaccines

One of the most widely used vaccines globally is BCG, and several studies have evaluated delayed-type hypersensitivity (DTH) responses following vaccination, by skin testing with purified protein derivative. Most are small, observational, cross-sectional studies conducted 20–40 years ago; the majority report reduced DTH responses in malnourished compared with well-nourished children [49–53] although, in some studies, children with less severe forms of malnutrition appeared to have normal DTH responses [67,68]. No studies to date have evaluated BCG-specific T cell responses in malnourished children using modern immunological techniques. Dissemination of live attenuated BCG has been described following vaccination of infants with HIV infection [69] or primary immunodeficiency [70], but does not appear to have been reported in HIV-uninfected malnourished infants. However, mice submitted to 10 days of dietary restriction prior to intradermal inoculation with BCG showed a higher frequency of BCG dissemination to lymph nodes and thymus than well-fed mice [71] and, interestingly, mycobacterial dissemination to the thymus has been shown to drive tolerance when pathogen-specific T cell responses are assessed in murine models [72]. This raises a theoretical concern that, if thymic BCG dissemination does occur in malnourished infants, they may fail to mount an effective T cell response to the vaccine; this warrants investigation in humans.

Measles infection and malnutrition have long been known to interact in a vicious cycle that can lead to protracted morbidity and high mortality [42], and measles vaccination remains a cornerstone of management of SAM [73]. Several old studies confirm that even severely malnourished children can mount an adequate immune response to measles vaccination, as assessed by haemagglutination [34,54–59], although generation of the immune response may be delayed compared with well-nourished children [60,61]. However, a recent study of 711 mother–child pairs recruited to a trial in Entebbe, Uganda, reported that only 75% of infants had protective measles-specific antibody levels measured by ELISA at 1 year of age; lower antibody responses were associated with infant wasting, after adjusting for HIV, malaria and maternal gravidity [62].

(f) Summary

Although several studies have evaluated responses to vaccination in the context of malnutrition, the evidence base remains relatively weak because most are small, old studies, using laboratory techniques and definitions of malnutrition that are now outdated; there is an urgent need to better understand the fundamental immunology of malnutrition. Despite these limitations, it appears that malnourished children can generally mount protective responses to protein, subunit, killed and polysaccharide vaccines, although titres are sometimes lower than in well-nourished children. T cells appear to be particularly affected by malnutrition [12] and responses to live vaccines such as BCG may be suboptimal, as assessed by DTH testing; further *ex vivo* studies are needed to clarify this. Animal data suggest that memory maintenance is impaired in malnutrition, which has important implications for long-term protection from vaccination.

It has been highlighted by Savy *et al.* [32] that there is an apparent paradox in malnutrition, because malnourished children die of infections, which suggests immune impairment, yet appear capable of generally mounting adequate immune responses to vaccination. There are probably several reasons for this [32]: first, vaccines are highly adjuvanted and designed to generate robust immune responses, which may overcome any immune impairment due to malnutrition; second, most vaccine studies have focused on short-term antibody responses, so may have underestimated the impact malnutrition has on the quality or longevity of the immune response generated; third, much of the infectious morbidity and mortality associated with malnutrition may arise due to impaired mucosal barrier function and innate immune defects, while humoral responses to vaccination remain fairly robust.

6. Malnutrition in the context of vaccination

As recurrent infections contribute to the pathogenesis of malnutrition [74], it seems logical that vaccination may play an important role in preventing malnutrition. The 10 best evidence-based nutrition-specific interventions are estimated to reduce stunting by only 20%, meaning that adjunctive interventions, including infection control, are probably required to prevent growth faltering in early life [75]. The most successful reductions in stunting prevalence have been achieved through multi-sectoral approaches [76,77], but dissecting out the specific contribution of vaccination is difficult. Vaccines against single pathogens are unlikely to have a

substantial impact on growth; it is increasingly recognized that packages of interventions are the key to reducing malnutrition [74]. For example, a recent study undertook anthropometry in 1033 Bangladeshi children 1 year after enrolment to a placebo-controlled trial of rotavirus vaccination and found no differences in underweight, wasting or stunting between randomized groups [78]. However, it would have been surprising to see a major effect on nutritional status following administration of a single vaccine, given the range of pathogens that cause enteric infections in this setting.

Observational analyses across countries show an association between coverage of vaccination and prevalence of wasting [79] and stunting [80], but there is potential for ecological bias in these findings. Anekwe *et al.* [81] evaluated the impact of India's Universal Immunization Program, which was phased in over a 5-year period, on child anthropometry and found that it reduced the height-for-age deficit among children below 4 years of age by 22–25%, and reduced the weight-for-age deficit by 15%. Whether these growth benefits were due to vaccination, or to other factors associated with introduction of the programme, is unknown, but the authors remark that these findings support the notion of vaccination programmes being 'high-return investments' for child health [81]. In summary, vaccination is an important component of malnutrition prevention programmes, as part of an integrated bundle of interventions in early life; introduction of new vaccines is likely to yield even greater gains in disease prevention and further promote healthy growth.

7. Conclusion

There remain critical gaps in our knowledge of the relationship between infection, immunity and malnutrition, despite estimates that undernutrition is responsible for 45% of child deaths globally [1]. Compared to other fields, there has been very little recent progress in defining the pathogenesis of malnutrition, which is not simply due to lack of food, but is rather a complex interaction between infection, inflammation, mucosal barrier dysfunction, immune dysregulation and nutritional status [10]. In particular, our knowledge of the immunology of malnutrition is predominantly derived from studies conducted several decades ago, using old laboratory techniques and clinical definitions that have changed over time; the majority of studies have focused on hospitalized children with the most severe forms of malnutrition, and we have little understanding of how milder but more highly prevalent forms of malnutrition (such as stunting, which affects one-third of children globally) affect the immune system. There is therefore a need for contemporary studies of nutritional immunology, selecting populations of children based on current definitions of undernutrition (specifically, stunting ($\text{HAZ} < -2$), severe stunting ($\text{HAZ} < -3$), MAM ($\text{WHZ} < -2$) and severe acute

malnutrition ($\text{WHZ} < -3$)), and comparing these children to well-nourished, age-matched controls using the same anthropometric measures. Studies should ideally be longitudinal, especially in children with moderate and severe acute malnutrition, to evaluate the impact of nutritional rehabilitation on immune recovery. Immunological techniques that assess functionality of the innate immune system (e.g. response to pathogen stimulation, neutrophil function) and adaptive immune system (e.g. T cell proliferation, cytokine elaboration, polyfunctionality and cytotoxicity) are long overdue, and it is important to understand how nutrient sensing pathways affect cellular function in the context of a dysregulated metabolic milieu, and how the quality and longevity of vaccine-specific responses may be influenced by undernutrition.

Vaccination is a cornerstone of child health interventions to reduce morbidity and mortality in developing countries and the majority of studies, despite the caveats above, suggest that malnourished children can mount adequate protective responses to vaccines. It is well recognized that the thymus is particularly targeted during malnutrition and that the cytokine milieu is skewed towards Th2 differentiation of CD4⁺ T cells, which support generation of humoral immune responses, and away from Th1 differentiation, required for defence against intracellular pathogens. Together, these findings may explain why antibody responses to vaccination are generally robust, while T cell responses to vaccination (e.g. BCG vaccine) appear to be diminished. Better understanding the phenotype and function of T cells in the context of malnutrition is therefore critical, particularly given the increasing interest in developing new T cell-based vaccines against pathogens such as HIV, hepatitis C and tuberculosis.

Whether the quality and duration of immune responses among malnourished children are equivalent to those of well-nourished children is unclear. Animal studies would indicate that malnutrition has a substantial impact on generation and maintenance of an effective immune response, but that nutritional interventions can ameliorate these defects; more longitudinal studies in humans are needed to evaluate changes in immune responses after nutritional, antimicrobial and/or anti-inflammatory interventions.

It is reassuring that vaccines are generally immunogenic in the context of malnutrition, as malnourished children are a high-risk group with elevated risk of infectious morbidity and mortality and therefore stand to benefit from vaccination even more than well-nourished children. Furthermore, vaccination is likely to be one of the key tools within a multi-sectoral package of interventions aimed at preventing malnutrition in early life.

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