Review Article

Vaccine and malnutrition: A narrative review

Saroj K. Tripathy[1], Sarthak Das[1], Archana Malik[2]

[1]Department of Pediatrics, All India Institute of Medical Sciences, Deoghar, Jharkhand, India, [2]Department of Pulmonary Medicine, All India Institute of Medical Sciences, Deoghar, Jharkhand, India

Abstract

Nearly 45% of under 5 mortality is directly or indirectly linked to malnutrition. Infection adds to the increased mortality and morbidity in these groups. Vaccination is very important in these undernourished children protecting against life-threatening infections. The goal of vaccination is to produce long-term protection by generating memory cells and the generation of antibodies. Since malnutrition is a state of immunodeficiency, the immune response to vaccines in these children is a matter of concern. We did an exhaustive search to gather more recent studies and corroborated previous findings. Oral Polio Vaccine (OPV), Pneumococcal Polysaccharide Vaccine, Haemophilus influenza vaccine, rabies, and cholera vaccine showed normal response to immunization. Measles and rotavirus vaccines were found to elicit lower seroprotection and lower efficacy in undernourished children. Data regarding response to vaccination against BCG, DPwT, Hepatitis B, pneumococcal conjugate vaccine, and meningococcal vaccine was inconclusive. Although most of the studies show a normal immune response to different vaccines, excluding other confounding factors and effect modifiers had not been easy to interpret. However, with the advances in the understanding of vaccine physiology with newer immunological techniques, good-quality studies might explore the gray areas that remain untouched.

Keywords: Immune response, malnutrition, vaccination, vaccine

Introduction

Malnutrition is the imbalance in the intake of energy and/or nutrients, which includes both undernutrition and overnutrition. However, for all practical purposes, we consider it undernutrition. The WHO classifies undernutrition into being underweight, wasting, and stunting. Underweight is low weight for age (≤2SD) as per WHO growth standards. Wasting is the weight for height less than minus 2SD (≤2SD), and stunting is length or height for age less than minus 2 SD (≤2SD) as per WHO growth standards.[1] In 2018, stunting and wasting accounted for 21.9% and 7.3% of under 5 children globally.[2] Two-thirds of stunted children and three-fourths of wasted children under 5 years of age live in low- and middle-income countries.[2] Nearly 45% of under 5 mortality is directly or indirectly linked to malnutrition. Malnutrition not only robs the children of their future but also keeps their lives hanging in balance. Among the potential complications of malnutrition, one of the most important complications is an infection that adds to the increased mortality and morbidity in these groups. Vaccination is very important in these undernourished children protecting against life-threatening infections. Since malnutrition is a state of immunodeficiency, the immune response to vaccines in these children is a matter of concern. The majority of the Indian population lives in rural belt and is primarily dependent on primary and secondary health centers for healthcare needs and vaccination. A sound knowledge of the effect of individual vaccines on malnutrition will help in the augmentation of the vaccination drive and address important queries and concerns. There is no definite recommendation for vaccination for malnutrition to date. In this paper, we will discuss the immune dysfunction in malnutrition and individual vaccine response.

Address for correspondence: Dr. Sarthak Das, Department of Pediatrics, All India Institute of Medical Sciences, Deoghar - 814 152, Jharkhand, India.
E-mail: sarthak.ped@aiimsdeoghar.edu.in

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Immune system in malnutrition

It is well known that malnutrition and infection are correlated and overlap with each other. It was in 1968 when Scrimshaw *et al.* first described undernutrition and infection as a vicious cycle in which infection can precipitate undernutrition and malnutrition increases the risk of infection.[3] Increased susceptibility to infection is due to immune dysfunction. We will briefly discuss the immune abnormality in this population.

Natural defense system

The skin and mucosal surface serve as the first line of defense in the body. The integrity of skin and mucosa is breached in malnutrition, which is pronounced in patients with severe malnutrition. In patients with severe malnutrition with edema (Kwashiorkor), skin peeling, darkening, and crackling (flaky paint dermatosis) occurs, which acts as a portal of entry for pathogens.[4] Extensive enteropathy described in children with malnutrition is characterized by intestinal atrophy along with inflammation.[5,6] Loss of the intestinal barrier leads to the translocation of the microbe and its products to systemic circulation causing bacteremia and inflammation.[7] Secretory Ig A was found to be reduced in saliva, tears, and nasal secretions in patients with severe malnutrition.[8]

Innate immunity

Total leukocyte count (TLC) remains normal in children with malnutrition. Few studies report increased granulocyte count in malnourished children.[9] Chemotaxis of granulocytes is reduced in malnutrition. There is an increased acute phase response in malnutrition associated with infection. Complement protein C3 level is reduced in malnutrition.[9]

Adaptive immunity

Lymphoid tissue, particularly the thymus undergoes atrophy even in children with mild-to-moderate malnutrition.[9] Total lymphocyte and T-cell counts were found to be normal in malnutrition, but B cell counts were reduced.[10] Cell-mediated immunity response as assessed by delayed type of hypersensitivity to the Mantoux test is reduced in malnutrition. T_H1 cytokines (IL 2, IL 12, IFNγ) are reduced. It was observed that total immunoglobulin, IgM, and IgG levels were normal in malnutrition. However, serum Ig A level was elevated in malnutrition.[9]

The pathophysiology behind immune dysfunction in undernutrition is still unclear. It is difficult to explain it by only deficiency of calories and protein because many immune parameters are elevated in malnutrition. Infection and epigenetic modifications also play a role in immune abnormality in these children. Animal studies suggest dyshormonogenesis as the cause of immune dysfunction.

Growth hormones, leptin, and prolactin help in thymic growth whereas cortisol and adrenaline induce thymic atrophy. It was observed that cortisol levels were high, and leptin, growth hormone, and prolactin levels were low in malnutrition.[11-13] Another group of researchers proposed the "Tolerance hypothesis" to explain the immunology in malnutrition.[14] Undernutrition is a catabolic state, so there is a possibility of the release of self-antigens leading to autoimmunity. To prevent this, there occurs depression of cell-mediated immunity as an adaptation. However, the validity of the hypothesis was never tested. Immune dysfunction in malnutrition is summarized in Table 1.

Immunology of vaccination

Vaccines are the greatest discoveries of medical science that have the potential to save 2–3 million lives each year.[15] An ideal vaccine should be able to trigger both innate and adaptive immunity.[16] Vaccines activate cellular immunity by expressing an antigen to a subset of T cells and humoral immunity by binding to B lymphocytes. The goal of vaccination is to produce long-term protection by generating memory cells and the generation of antibodies.[17,18] There are two types of antigens: T cell-dependent and T cell-independent. T cell-dependent antigens are usually proteins that produce memory B cells and long-term immunity. T cell-independent antigens usually have short-lived immunity. Polysaccharide vaccines are T cell-independent antigens whereas conjugate vaccines are T cell-dependent antigens. Similarly, live attenuated vaccines mimic natural infection and usually produce lifelong immunity after 1 or 2 doses. Inactivated and subunit vaccines have a less immune effect and therefore may need multiple doses to boost immunity. Toxoid vaccines target toxins and need booster doses for protection.[18]

Vaccine response in malnutrition

Since malnutrition causes immune dysfunction, there is a need to know its effect on vaccine response. Most of the studies on vaccine response were from more than two decades ago. We did an exhaustive search to gather more recent studies and corroborated previous findings. We are briefly discussing individual vaccines and their effect on undernutrition.

BCG: Studies evaluating response to BCG vaccination used delayed hypersensitivity reaction to purified protein

Table 1: Immune dysfunction in malnutrition

Type of defense mechanism	Immune dysfunction
Natural defense system	Loss of integrity of skin and mucosa
	Enteric dysfunction
	↓Secretory Ig A in saliva, tears, and nasal secretion
Innate immunity	N/↑ Granulocyte count
	Reduced chemotaxis
	↑Acute phase reactants
	↓C3 complement
Adaptive immunity	Thymic atrophy
	Normal T cells and total lymphocytes
	B cells reduced
	T-cell hypo responsiveness
	↓ TH1 cytokines (IL 2, IL 12, IFNγ)
	Normal IgM and IgG
	↑ Serum Ig A

derivative (PPD). Previous studies have reported reduced response to PPD in malnourished children.[19-23] Subsequently, a mice model study revealed that protein-energy malnutrition (PEM) during vaccination causes immediate impairment in CD4 T-cell function, which was reversible after protein supplementation.[24] PEM did not change the number of CD4 T cells rather it caused the loss of antigen-specific CD4 T cells with increased effector T cells expressing tumor necrosis factor α and γ interferon. Reconstitution of protein during infection promoted adequate T-cell response and the protective effect of the vaccine against *Mycobacterium tuberculosis* infection.[24] The latest study from Nigeria involving 6,928 children indicated poor uptake of BCG in stunted children adding to the conflicting results.[25] PEM during TB infection not only impairs response to BCG vaccination but also causes a flare of the disease.

OPV: Four observational studies were done in the past to look for OPV response in malnutrition out of which three studies did not find any significant difference in immune response in undernutrition.[26-29] A study in Bangladesh in 2014 found lower OPV three titer following immunization in patients with malnutrition, diarrhea, and reduced breastfeeding.[30] An RCT conducted in Pakistan found no difference in immune response between the normal and malnourished groups.[31] The largest prospective cohort study "malnutrition and the consequences of child health and development (MAL-ED)," which assessed the impact of malnutrition on vaccination was recently published. The study was conducted with 1862 children in eight low- and middle-income countries. Analysis was done in children who received at least three doses of OPV. Blood samples were collected at 7 months and 15 months of age and neutralizing antibody assays were done for OPV serotypes 1 and 3. It was found that undernutrition was not strongly associated with vaccine response.[32]

Rotavirus vaccine: The effectiveness of the rotavirus vaccine in developed countries against severe diarrhea is 80–90%. In developing and underdeveloped regions like Africa and Southeast Asia efficacy is 30–50% where it is needed the most.[33-37] The low immunogenicity of the rotavirus vaccine in developing countries might be due to transplacental antibodies, breastfeeding, genetics, enteric dysfunction, and malnutrition.[38] A study by Schael *et al.* found that malnutrition alone may not impair the efficacy of rotavirus vaccination.[39] A similar finding was also observed in a study involving mice. Overall, the efficacy and effectiveness of the oral rotavirus vaccine were found to be more in well-nourished children as compared to malnourished children.[40]

Measles: Measles is an important cause of mortality and morbidity in low-income countries. Malnutrition and measles are interrelated; therefore, measles vaccination plays an important role in these children. Most of the studies on the efficacy of the measles vaccine in malnutrition date back to the1980s. Although maximum studies reported no differences in immune response as compared to healthy infants, very few studies reported reduced/delayed immune response.[41] However, it is questionable since the sample size in these studies were very small and the methods of assessment of immune response were less accurate. However recently, an observational study from Entebbe, Uganda was done with 711 children to assess their response to measles vaccination. It was noted that children with wasting had fewer measles-specific IgG antibodies.[42] Low seroprevalence of measles-specific IgG antibodies was found in Mexican underweight children.[43]

DPwT: A total of six observation studies were done out of which four studies found adequate seroprotection against diphtheria and tetanus toxoid. Two studies found less immune response to diphtheria and tetanus toxoid in the context of malnutrition.[41] A longitudinal survey was done in Senegal to look for pertussis vaccine response to nutrition. It concluded that nutrition plays an important role in children's response to pertussis following natural infection or vaccination.[44]

Hepatitis B: Out of four studies done for assessing response to Hep B vaccination, three studies found good seroconversion after immunization although there were conflicting reports of antibody titers.[45-47] One study was from Egypt where the immunogenicity of the recombinant Hepatitis B vaccine was assessed in normal and chronically ill children. It was surprising to find that 55.6% of patients with malnutrition were nonresponders (anti-Hbs Ag <10 Miu/ml) whereas 16.7% had a low protective level needing a booster dose. It could have been caused by low immunoglobulin levels and low antibody titers in these children.[48]

Polysaccharide vaccines: Pneumococcal polysaccharide vaccine efficacy was tested in two studies in Ghana and Gambia. It was observed that there was no association between vaccine response to nutrition.[49,50] Pneumococcal conjugate vaccine (PCV) is currently recommended in children as a routine vaccination to prevent invasive pneumococcal infection. Studies on PCV in malnutrition are lacking except in Kenya, which were published in 2017. Children were administered Deca valent PCV (PCV 10), and immune response was assessed in the context of parasitic infection and undernutrition. Children with malnutrition showed hypo responsiveness to the PCV.[51]

Meningococcal vaccine response in malnutrition had conflicting results with three studies showing a normal response and two studies showing a reduced immune response.[41,52]

Children with malnutrition who received Haemophilus influenza B (HiB) vaccine as a pentavalent vaccine mount a good immune response against HiB infection.[53]

Other vaccines: Rabies vaccine showed a good immune response in undernutrition as observed in the Gambian study.[49] Results of two small studies report no difference in cholera vaccine response between normal and malnourished children.[53,54] Data regarding the immunogenicity of other vaccines in malnutrition are limited or lacking.

Immune response to different vaccines in undernutrition is summarized in Table 2.

Limitation of the review

Among the studies we have reviewed, we found many shortcomings of the studies. (1) Definition of malnutrition varied in different studies. Some studies consider any type of malnutrition and some studies considered only severe malnutrition. (2) Deficiency of specific micronutrient deficiencies, which were expected to affect the immune response, was considered separately in many studies (3) Sample size in many studies was very less (<10); so, it is difficult to interpret the findings. (4) Many factors play a role in vaccine response and are interrelated. Direct evidence of malnutrition affecting vaccine efficacy after adjusting for other factors is lacking in most of the studies. (5) Parameters taken to account to assess the efficacy of vaccines were not uniform and standardized. (6) Data baring BCG, OPV, measles, rotavirus, DPT, and Hepatitis B are either lacking or limited. Moreover, most of the studies done on a vaccine concerning for to nutrition were from the 20th century. (7) Vaccination schedule is different in different studies would have been a potential confounding factor altering the outcome.

Conclusion

Despite several studies evaluating the association of vaccines with nutrition, the outcome is still inconclusive. Rotavirus vaccine showed low efficacy and measles vaccines elicited low seroprotection from the majority of studies. Although most of the studies show a normal immune response to different vaccines, excluding other factors like infection and enteric dysfunction had not been easy to interpret. However, with the advances in the understanding of vaccine physiology with newer immunological techniques, good-quality studies might explore the gray areas that remain untouched. Till then primary care physicians and family physicians should continue to encourage routine vaccination at the scheduled date with the same dose without any delay regardless of the nutritional status of the child.

Table 2: Summary of vaccine response to malnutrition

Individual vaccine	Response to immunization (Seroprotection and/or vaccine efficacy)
BCG	Inconclusive[19-25]
OPV	Normal response[26-32]
Measles	Possible low seroprotection[41-43]
Rotavirus	Low vaccine efficacy[33-40]
DPwT	Inconclusive[41,44]
Hepatitis B	Inconclusive[45-49]
Pneumococcal polysaccharide vaccine	Normal response[49,50]
PCV	Inconclusive[51]
Meningococcal vaccine	Inconclusive[41,52]
H. Influenzae B vaccine	Normal response[53]
Rabies vaccine	Normal response[49]
Cholera vaccine	Normal response[53,54]

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Conflicts of interest

There are no conflicts of interest.

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