International Journal of Immunology
2024, Vol. 12, No. 3, pp. 38-47
https://doi.org/10.11648/j.iji.20241203.11

Review Article

The Significance of Prebiotics and Immuno-Nutrients for Assuring the Developmental Milestones in Toddlerhood

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Abstract

The immune system development of children is influenced by the mother's nutritional state throughout pregnancy as well as the nutrients the unborn kid is exposed to through nursing and other meals. Micronutrients that are important for the development of the immune system in neonates include iron, zinc, and vitamins A, C, D, and E. both probiotics and prebiotics are essential for maintaining a healthy gut microbiota and a robust immune system. While probiotics directly add beneficial bacteria to the gut, prebiotics serve as food for these bacteria, enhancing their growth and activity. Together, they play a vital role in supporting immune function and overall health. Prebiotics also play a significant role in this process by acting as fertilizers to encourage the growth of healthy bacteria in the stomach. Micronutrient deficiencies (MNDs) have an effect on the developing immune system; therefore, a meeting of specialists was arranged to talk about preventative and mitigating strategies. Immunological responses are largely determined by nutrition, and malnutrition is the leading cause of immunodeficiency worldwide. Protein-energy deprivation is associated with a significant decline in cell-mediated immunity, phagocyte activity, complement system, secretory immunoglobulin an antibody concentration, and cytokine production. Certain nutrient deficits cause altered immune responses, even in cases when the deficiency is fairly mild. The immune responses are significantly influenced by micronutrients such as folic acid, zinc, selenium, iron, copper, and vitamins A, C, E, and B-6. Additionally, overeating and obesity reduce immunity. Low birth weight babies' cell-mediated immunity is permanently compromised; this can be somewhat restored by adding more zinc to their diets. Prebiotics are inactive dietary ingredients that, when combined with immuno-nutrients, benefit the host by encouraging the growth and/or activity of a certain kind of bacteria in the colon. Government, development partners, non-governmental organizations, and academia must collaborate to increase the availability of basic and effective nutrition interventions, as well as those that address more stifling issues. These interventions include exclusive breastfeeding, appropriate supplemental feeding, micronutrient supplementation for children, adolescents, pregnant women, and lactating women, managing severe acute malnutrition and deworming, and hygiene interventions. The entire healthcare system needs to be revitalized in order to get over the obstacles that exist at the levels of policy, governance, and service delivery and to create demand for the services at the household level. Priority should also be devoted to stabilizing food prices and managing nutrition following natural disasters.

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Received: 27 June 2024; **Accepted:** 15 July 2024; **Published:** 6 August 2024

Keywords

Immunity, Micronutrients, Macronutrients, Prebiotics, Nutritional Problems, Maternal Nutrition, Child Nutrition

1. Introduction

The immune system consists of both innate immunity and adaptive immunity. [1, 2] The yolk sac is where the first hematopoietic cells begin to form as the immune system develops throughout embryogenesis. While the construction of the bone marrow begins during the twentieth week of pregnancy, the growth of the thymus, a vital organ of the natural defenses, begins throughout the seventh week. [3, 4] T lymphocytes, natural killer (NK) cells, and various dendritic cells (DCs) develop in the thymus, while B lymphocytes, monocytes, granulocytes, and certain DCs grow in the bone marrow. The lymphoid system is not completely developed at birth, despite this. Because their immune systems are still growing and not yet completely developed, newborns are more susceptible to infections and have a lower ability to create a robust response. Nonetheless, babies are shielded from disease by passive immunity, which is provided by IgG and IgA antibodies that are passed from the mother through the placenta during the last trimester of pregnancy and through breastmilk during nursing, respectively. During the prenatal stage, the fetal immune system is vulnerable to changes in the environment, diet, infections, and inflammation. [4] A significant impact on the thymus's shape and/or function during pregnancy may result from severe exposure to any of these, and this might change the immune cell population over time and cause immunological deficiencies.

Research employing animal models has connected micronutrient deficiencies (MNDs) to detrimental effects on lymphocyte function, thymus size, and B lymphocyte size. Food insults during pregnancy therefore lead to detrimental alterations in immune programming, which increases the risk of infection in infancy and inflammatory illnesses in later life [5, 6, 22, 23]. These results highlight the need of an adequate and healthy diet for immune system development and a strong enough immune reaction during pregnancy and the early stages of lifespan.

The mother's nutritional status throughout pregnancy and nursing has a major effect on the programming of the developing organ systems and homeostatic pathways in the kid. The first trimester of pregnancy is a time of rapid growth and proliferation of the immune system and related organs. As a result, the immune system keeps developing during the first few years of life [5, 6, 22, 23]. Maternal malnutrition or a reduction in food intake can also directly affect the development of the fetus's immune system by affecting placentation and the subsequent transfer of immunological components through the placenta and nursing. An unsatisfactory nutritional status in a fetus affects organogenesis, growth, and fetal programming. [5, 6, 22, 23] A child's early immune system development is significantly impacted by postnatal environmental shocks in addition to the nutrition they receive from breast milk, breast milk substitutes, and supplementary meals. [6, 7] During the postnatal period, foods have an impact on the development of immune cells and innate immune signal transduction pathways. These mechanisms impact early allergy sensitivity, encourage tolerance to ingested antigens and the development of gut microbiota, and establish patterns of host defense against infections.

Table 1. *Innate vs. adaptive immunity.*

Innate immunity	Adaptive immunity
Provides first line of defence	Serves as second line of defence
Activated as soon as an antigen is encountered	Triggered for secondary elimination of infectious agents
Comprises neutrophils, macrophages, monocytes, and dendritic cells	Comprises T cells and B cells
Has no immunologic memory	Has immunologic memory

Malnutrition or undernutrition is associated with impaired immunity because it heightens susceptibility to infections and cytokine activation. [8] Immunonutrient deficits may affect the immune system at the cellular level, thereby impeding the immunological response by affecting cell function, the mucosal barrier, etc. Research indicates that acute malnourishment may influence the thymus's development, hence influencing immunity. On the other side, infection can also lead to malnutrition. Infection sets off a series of inflammatory cascades in the immune system that further stress the immature immune system. Thus, the dietary level of the host influences the course of a disease.

2. Prebiotics Lowers the Risk of Diarrheal Disease

Probiotics have been shown to reduce upper respiratory tract infection frequency and duration, as well as the risk of diseases such infectious diarrhea. [9] Probiotics have been shown to improve the absorption of zinc, calcium, and vita-

min B12 and reduce the risk of anemia [9, 10]. As a result, they may aid in the promotion of newborn growth by warding off infections and micronutrient deficiencies. Fermentation is a commonly utilized and accepted practice worldwide, particularly in Asia and Africa, where rural populations consume a significant amount of fermented foods. [11] Since many African countries widely use the fermentation technology to prepare supplemental meals, fermented foods are essential for the nutrition of babies and children. [12] In 1995, the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) jointly organized a workshop to study the possible application of fermented food to enhance newborn and early child nutrition. [13] The process of fermentation is cost-effective. Consequently, it is feasible to reach the target population and enhance children's growth on a big scale and at a cheap cost by using locally produced/culturally accepted probiotic products [14]. There are just two systematic studies that have examined the effect of probi-otics on weight gain, even with this awareness. [15, 16] Steenhout et al. (2009) evaluated the effects of bifidobacterium lactis in babies under six months of age, whereas reviews by Million et al. evaluated the influence of lacto-bacillus species on weight growth in healthy humans and animals [17]. Nonetheless, the focus of both evaluations was on specific probiotic strains for the target audiences. Non-digestible oligosaccharides, often known as prebiotics, can reduce a child's risk of allergy diseases by promoting the growth and metabolism of advantageous commensal microorganisms in the infant's stomach. Probiotics, or living bacteria, work with the gut microbiota when consumed in sufficient proportions to provide positive effects.

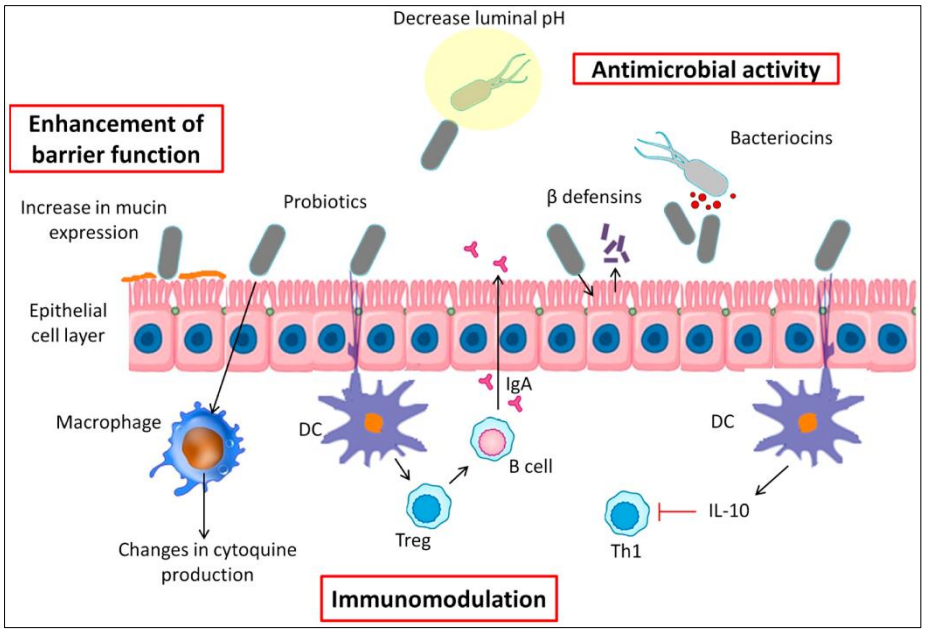

Figure 1. *Probiotics Activity [26].*

They strengthen the stomach's barrier function and control the immune system [Figure 1]. Probiotics also influence immune system cells, particularly dendritic cells, and enhance the functionality of regulatory T cells. For a source to be categorized as a prebiotic, it must demonstrate that it benefits the host [15]. One well-known class of prebiotics is fermentable prebiotics made from xylans and fructans [16]. Since 4-10% of the starch in mixed meals has been found to reach the large intestine, resistant starch from starchy foods has historically been the greatest known source of prebiotics in the diet [17]. Africans on a traditional diet consumed 38 grams of resistant starch per day, according to a research [18].

In 1995, when the idea of prebiotics was initially proposed, Bifidobacteria and Lactobacillus were the major emphasis. [15-17] Prebiotic targets have grown to include a greater variety of microorganisms, including Roseburia species, Eu-bacterium species, Akkermansia species, Christensenella species, Propionibacterium species, and Faecalibacterium species, as a result of enhanced mechanistic methodologies in recent years [18]. Due to their potential benefits for improving the host's digestion (including but not limited to enhancing mineral absorption) and the efficiency and intrinsic strength of the immune system, these bacteria have been identified as essential probiotics and good gut bacteria. [19]

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advancements in mechanistic approaches [18]. These bacteria may help the host in several ways, such as digestion (including but not limited to boosting mineral absorption) and the efficiency and intrinsic strength of the immune system. For these reasons, they have been identified as essential probiotics and beneficial gut bacteria. [19]

3. Nutritional Status During and After Pregnancy: Impact on the Newborn's Immune System

The mucous membranes of the skin and other mucous tissues, phagocytic cells, mucus, cilia, lysozyme, interferon, and other humoral components are examples of nonspecific defenses. These innate mechanisms are part of the infectious pathogen and are not impacted by previous infection exposure. They serve as the initial line of defense and stop the spread of overt illness. The T cell system for cell-mediated immunity and the B cell system for the generation of antibodies are two examples of antigen-specific systems. These processes are both adaptive and essential since they are particular responses set off by an earlier encounter with the bacterium and its antigenic determinants. They work well to destroy the intruder and stop the illness from spreading.

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Furthermore, PEM results in the loss of lymphoid cells in the paracortical splenic regions, which depend on the thymus for lymphocyte production. Most of the host defense systems in PEM are weak. Both memory and freshly formed de-layed-hypersensitivity cutaneous responses elicited by antigens experience significant inhibition. It is common for a battery containing several antigens to be fully charged. These alterations are also seen in mild deficits. After receiving the proper nutritional therapy for a few weeks or months, the skin reacts properly. Moreover, a decrease in serum thymic factor activity helps to partially explain the decrease in fully differentiated mature T cells. Leukocytes also exhibit an increase in deoxy-nucleotidyltransferase activity.

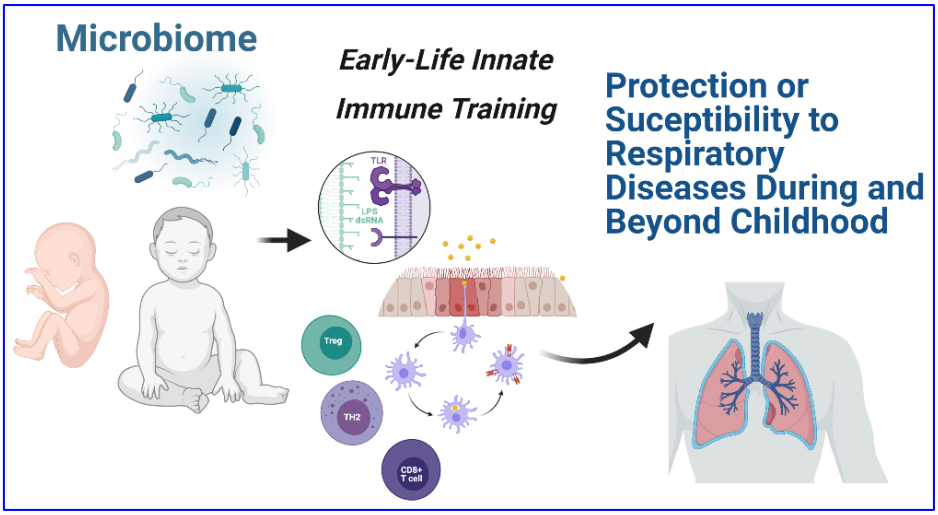

Figure 2. *The Immunity System [23].*

The mother's nutritional status throughout pregnancy and nursing has a major effect on the programming of the developing organ systems and homeostatic pathways in the kid. The first trimester of pregnancy is a time of rapid growth and proliferation of the immune system and related organs [Figure 2]. As a result, the immune system keeps developing during the first few years of life [5, 6, 22, 23]. Maternal malnutrition or a reduction in food intake can also directly affect the development of the fetus's immune system by affecting placentation and the subsequent transfer of immunological components through the placenta and nursing. An unsatisfactory nutritional status in a fetus affects organogenesis, growth, and fetal programming [5, 6, 22, 23]. The postnatal environmental shocks that children experience and the nourishment they receive from breast milk, breast milk substitutes, and additional meals have a significant impact on the development of

the immune system in early life [23, 24]. Foods have an effect on immune cell development and innate immunological signal transduction pathways during the postnatal period. These processes influence early sensitivity to allergens, promote tolerance for ingested antigens and forming gut microbiota, and create host defense patterns against infections.

A vital element in the immune system's development is breast milk. Breast milk is an essential medium for the transfer of the mother's immunological memory to the child because it is the first meal to which infants are exposed [23]. It contains immune-modulating compounds that enhance both active and passive immunity during the formative years of life, as well as several physiologically active antimicrobial peptides (AMPs), such as defensins and cathelicidin [23-25]. The AMP cathelicidin (which is present in the inactive proform of neutrophil granules) causes the production of cathelin after neutrophil degranulation. Several effects of cathelicidin, including as wound healing, chemotactic, angiogenic, and endotoxin neutralization, indicate its role as a mediator between innate and adaptive immunity [25]. Breast milk contains oligosaccharides and probiotics that support the formation of the infant's gut microbiota, which is critical for the immune system's maturation. Research indicates that the content of breast milk carries genetic information from mother to child that influences the child's immune system.

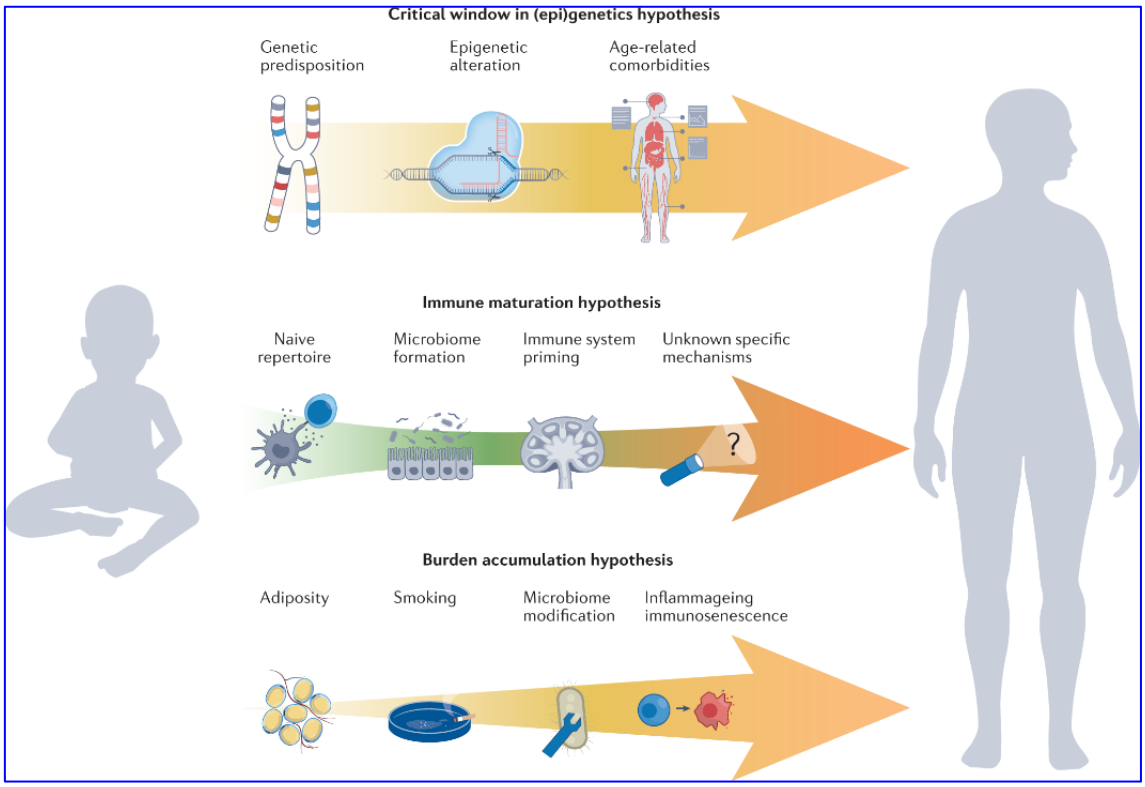

Figure 3. *Immune System During First 6 Years [26].*

4. The Value of a Healthy Diet for Young Children

A toddler's development increases dramatically between birth and age six, requiring a shift in dietary habits. Research indicates that a child's food throughout the first six years of life can have a significant impact on their future health [Figure 3]. Early nutrition has an effect on the development of the immune system, brain, and eyes. At this age, your child's immunity is developing swiftly, so it's critical to provide him with the best start possible through appropriate nutritional assistance. Additionally, since the child's brain is developing during this crucial period, it's necessary to provide them with the nutrients they need to support that growth, including LCPs, which are not present in adult milk [Figure 4].

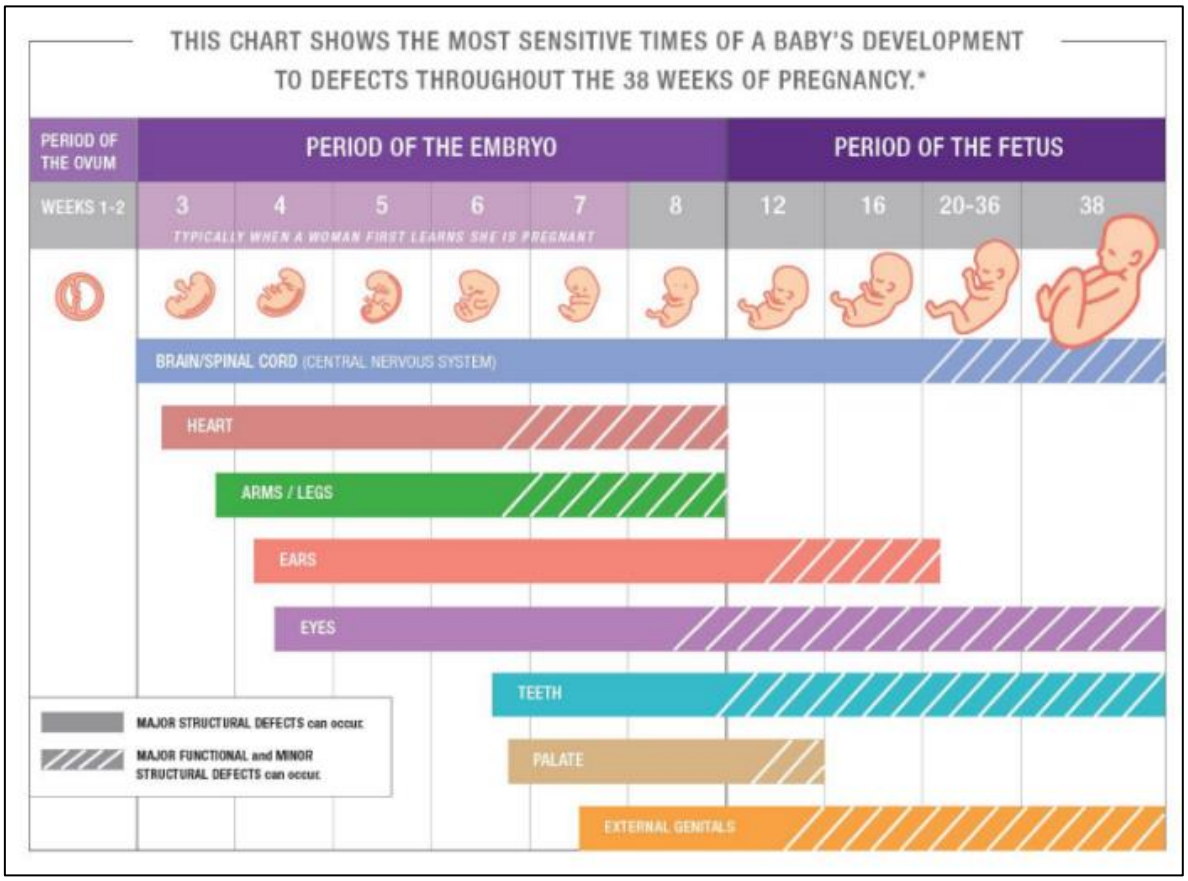

Figure 4. *Critical Period for Brain Development [23].*

5. The Immune Response's Role of Various Nutrients and the Effects of Their Deficiencies

5.1. Macronutrients

Because they regulate the generation of cytokines and antibodies, the activation of T, B, macrophage, and NK cells, lymphocyte proliferation, and gene expression, amino acids are essential for the immune system. [24] Research indicates that the bioactive peptide carnosine, which is included in meats and fish, may influence an individual's immune system in two ways: it may boost interleukin-1 b generation and reduce neutrophil death. [25] Because they maintain the integrity of cell membranes, regulate gene expression and signal transmission, and provide the building blocks for the creation of chemical mediators, LC-PUFAs are critical for immune cell responses. [26] Because neutrophils, lymphocytes, macrophages, and other immune cells have high metabolic needs, carbohydrates are required for a healthy immunological response.

5.2. Micronutrients & Immuno-nutrients

Micronutrients & Immuno-nutrients are essential for the development and expansion of Th1 and Th2 lymphocyte subsets, as well as for the regulation of the humoral antibody response, cell-mediated and innate immunity, and cytokine production. [27] Studies have shown that micronutrients including folic acid, iron, zinc, selenium, and vitamins A, C, D, and E are necessary for the immune system to operate correctly. [28] Other crucial micronutrients for immunomodulation include copper and chromium. Copper is critical for maintaining immunological competence because, according to animal research, a copper shortage inhibits T cell proliferation, which in turn affects humoral, cell-mediated, and non-specific immune responses. [25-28] Conversely, chromium alters immunostimulatory or immunosuppressive mechanisms, impacting the immune response that leads to hypersensitivity reactions. Additionally, it influences the production of macrophages, cytokines, and T and B cells.

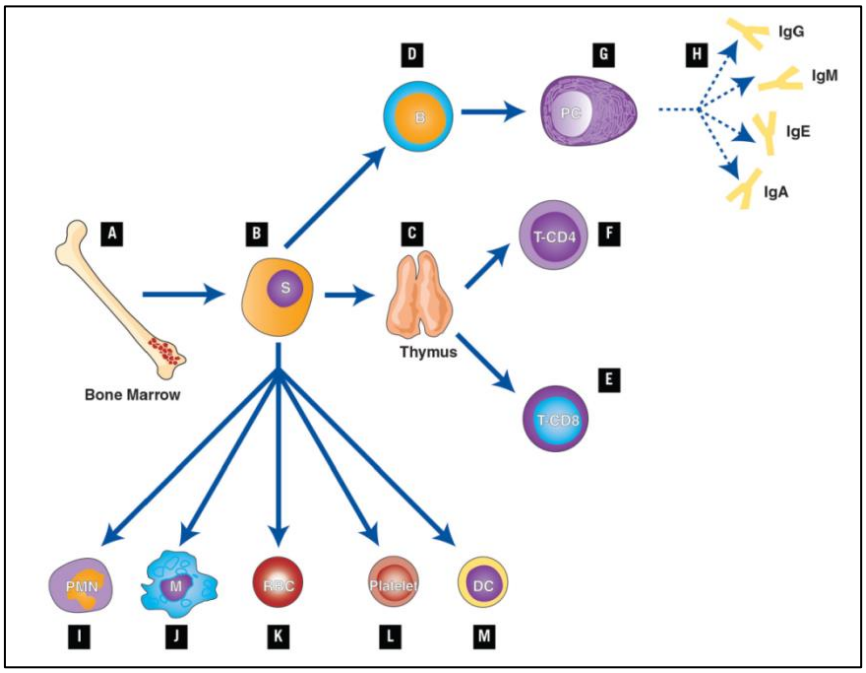

Figure 5. *Role of Micronutrients [32].*

Zinc deficiency, inherited or acquired, has been associated with lymphoid atrophy, delayed homograft rejection, Patients with a weakened immune system. Decreased delayed-hypersensitivity cutaneous reactions. It is also possible to show a reduction in T killer cell activation and a decrease in the quantity of antibody-forming cells in the spleen, which could corroborate these findings in experimental animals. a decrease in consumption. reduced phagocytosis as well [Figure 5].

Immuno- nutrient like Zinc is most likely involved in the activation of NADPH oxidase through its role as a cofactor for phospho-lipase A2 or phospholipase C. Zinc may stabilize arachidonic acid to prevent it from being oxidized by iron complexes. Complexes between zinc and oxygen may interact. manufacturing products that are very harmful to pathogens. Wound healing is hampered by zinc deficiency. Low zinc levels enhance infections in animals exposed to diverse species. Zinc deficiency accelerates the development of nematodes and modifies the features of their expulsion from the stomach, while spontaneous Otis cure is unaltered.

6. Methods to Avoid and Treat a Micronutrient Deficiency

6.1. Dietary Diversification

Dietary diversification or modification primarily involves increasing the consumption of a variety of foods from various food groups in order to maintain a balance of nutrients in the diet. Babies' diets should be high in energy and nutrients since calorie-dense foods increase the body's ability to absorb nutrients. The best and most efficient strategy to prevent MNDs is to change one's diet, however in poorer countries, it may be difficult to get or eat foods high in micronutrients due to a lack of resources. Furthermore, humans may be prohibited from eating foods derived from animals by some cultural or religious beliefs, which would reduce their dietary intake of particular nutrients.

6.2. Fortification

Given that universal access to adequate food is a major factor limiting the adoption of appropriate diverse dietary habits, food fortification offers the dual benefit of providing nutrients to large segments of the population without necessitating any changes in food consumption patterns. [29] Food fortification is considerably less expensive than other methods, and regular consumption of fortified foods contributes to the maintenance of steady body stores of the micronutrients. [30] More research is being done to determine how well fortification initiatives work to lower malnutrition in developing countries. Food titration was proposed by the Indian government in its 10th, 11th, and 12th Five-Year Plans as a way to improve nutritional status by utilizing already-existing government nutritional initiatives. [31] The World Health Organization recommends supplementing entire diets with iron or fortifying them with iron-containing micronutrient powders in order to increase iron status and lower the incidence of iron deficiency anemia in areas where the prevalence of anemia in children between the ages of two and five years is 20%. According to a Detzel study, the current intake of fortified infant foods (such as fortified cereals) in India has already decreased the annual burden of iron deficiency anemia, amounting to a 50% reduction in the health burden (measured

in years of life with a disability) and a 36% reduction in economic losses.

6.3. Supplementation

Providing children and expectant mothers with relatively large doses of micronutrients—which are necessary for growth and development—in the form of syrups or tablets is known as micronutrient supplementation. Studies reveal that just 13.8% of children between the ages of 6 and 59 months benefited. from the folic acid and iron supplements. It's also a population with pervasive impairments. Acute micronutrient deficiencies with clinical documentation necessitate corrective intervention and ought to be used as a temporary fix [32]. Dietary supplement programs face two key challenges: inadequate supplies and low compliance. There is evidence that fortification is more effective than dietary diversification and food supplements.

7. Nutrition and Immunity: Recent Advances and Upcoming Opportunities

Among the numerous systems that diet affects is the immune system. The organ system is both physically complex and has a wide range of functions. Both the qualitative and quantitative components of an immune response have an impact on immunity. Numerous variables, such as genetic predisposition, maternal stress, nutritional status, exposure to environmental toxins, infant nutritional adequacy (quantitative levels of macro & micronutrients), etc., might affect the growing fetal and neonatal immune system.

Even though the newborn immune system has a wide variety of biomarkers and proteomic indicators and is susceptible to shocks throughout the critical window of development, there is no one test that can consistently predict an infant's immunological status. The frequency, severity, and malnourishment of children's persistent illnesses may point to immune system damage brought on by deficiencies in certain micronutrients, malnourishment, and other associated variables. A newborn must receive early therapy for hidden hunger in order to reach their maximum potential for growth and development. Determining if a person is deficient may involve measuring their levels of important immune-supporting minerals including iron, zinc, vitamin B12, and vitamin D.

Iron used to be seen of as a micronutrient, but it is now considered a macronutrient because of its critical involvement in the development of the immune system, hematopoietic system, growth, and cognitive function in newborns and toddlers. Serum ferritin levels may be measured to show the need for iron supplementation, while hemoglobin levels can be used as a marker to diagnose iron deficiency anemia.

There is no consistent set of signs to identify immune system malfunction, making clinical prediction difficult. Examining a child's growth chart closely might be one of the clinically accessible indicators of a macronutrient deficiency. Unless there is severe malnutrition, a growth chart may not be useful for diagnosing nutritional deficiencies. Generally speaking, a child's growth inside the appropriate percentile on a growth chart may be a sign that they are getting adequate macronutrients from their food. Newborns should be fed a balanced diet with the necessary amounts of macro- and micronutrients as soon as supplementary feeding is started to maintain their general health and wellbeing.

Adequate nutrition is necessary for achieving good health, a high quality of life, and national productivity. The current low rate of undernutrition drop and the steep increase in rice and other necessity prices over the past couple of years raise concerns about the nation's food security and nutrition condition as well as the chances of attaining the MDG 1 nutrition objective. Bangladesh, which is rated in the bottom 25% of the Global Hunger Index, is expected to be particularly vulnerable to an increase in food costs. [10] The Household Food Security and Nutrition Survey found that 22% of families reduced health spending to offset the high cost of food, which is likely to have had a negative impact on health. The survey looked at how the price hike shock of 2007-2008 affected food security and nutrition. [31] But in the first half of 2011, the retail price of rice was 3% more than it peaked in 2008—the year of the food price shock—which implies that women and children are more at risk than they were in 2008 [32].

The NNP's lessons learned and current data must be included into the plan, along with any required alterations, in order to mainstream nutrition services throughout the health system. The adjustment should emphasize enhanced micronutrient status through food consumption and micronutrient supplementation, better complementary feeding, more effective behavior change communication, etc. Food supplements ought to be reserved for the most vulnerable individuals who live in areas of the nation with high rates of malnutrition and food insecurity. They are not meant to be used frequently. The supplement's quality and amount should be assessed to make sure it provides enough nourishment.

Children who are malnourished depend on animal-based foods and micronutrients, including milk, to thrive. The government plans to construct community clinics around the country, with one for every 6,000 citizens, in order to provide basic nutrition services at the local level.

In this model, a doctor working for the sub-district health complex would be the nutrition manager. The sub-district program would be overseen by the nutrition manager with support from field supervisors and community health workers. However, the community clinic must have at least one employee whose exclusive responsibility is to administer nutritional therapy. It is possible that other urgent health concerns will trump nutritional concerns. It will become evident that more qualified personnel must be enlisted. Addressing the enormous issue of undernutrition requires coordination amongst ministries. Coordination between multiple ministries

that are involved in health, nutrition, and food security, as well as with NGOs, the private sector, and international nutrition initiatives (Scaling up Nutrition, REACH, and Feed the Future) can only be ensured by a strong body within the Prime Minister's Office.

8. Extending the Range of Effective Nutritional Strategies

8.1. During Pregnancy and Lactation

1) Sufficient guidance on relaxation and nutrition during pregnancy, as well as guidance on suitable infant-feeding techniques in the latter half of the pregnancy;
2) Consistent use of iodized salt;
3) One precaution against anemia during pregnancy and lactation is to give women a dose of vitamin A (200,000 units) no later than six weeks after giving birth.

8.2. 0 to 5 Months

1) Raising awareness of breastfeeding through a range of initiatives, such as media coverage, adolescent girls' classroom talks, prenatal counseling, feeding assistance, and troubleshooting in the early hours and days following delivery.
2) Promoting exclusive breastfeeding for the first few years of life.

8.3. 1-63 Months

1) Encouragement of continuing nursing advising women on the use of nutrient-dense local foods such as cereals, vegetables, oil, lentils, and, when accessible, animal protein (meat, fish, or eggs) as supplemental feeding vitamin A supplementation every six months
2) Zinc therapy and ORT in the event of diarrhea
3) Observance of hygiene protocols, including hand washing and the use of various vitamin powders for food fortification at home
4) Adherence to WHO standards for deworming
5) The use of ready-to-use therapeutic meals made with regional ingredients in SAM treatment at the facility and community levels.

8.4. Teenage Girls and Recently Married Ladies

1) Iron-folic acid supplementation tablets
2) Education on nutrition and health
3) Inverting

Food security is crucial to enhancing nutrition since over 40% of the population cannot afford to consume the recommended daily intake of calories by mouth. For interventions that have an indirect impact on food security and nutrition, a multi-sectoral strategy should support pro-poor livelihood opportunities, such as direct cash transfers or transfers of productive assets, women's empowerment, girls' education, safe water, community infrastructure improvements, and so on.

9. Conclusion

The developmental milestones achieved during toddlerhood are crucial for long-term health and well-being. Adequate nutrition, particularly the inclusion of prebiotics and immuno-nutrients, plays a pivotal role in supporting this developmental phase. Prebiotics, through their ability to enhance beneficial gut microbiota, and immuno-nutrients, which are essential for robust immune function, collectively contribute to optimal growth and development.

Ensuring a balanced diet that includes a variety of nutrient-dense foods can prevent deficiencies and support the immune system, cognitive development, and overall health. Interventions that promote exclusive breastfeeding, appropriate complementary feeding, and supplementation where necessary, are vital strategies in combating malnutrition and enhancing immune competence.

A collaborative approach involving healthcare providers, policymakers, and caregivers is essential to promote nutrition education and ensure access to nutritious foods. By prioritizing the intake of prebiotics and immuno-nutrients, we can significantly contribute to the healthy development of toddlers, setting the foundation for a healthier future generation.

Abbreviations

LCP	Long-Chain Polyunsaturated Fatty Acids
PEM	Protein Energy Malnutrition
LC-PUFA	Long-Chain Polyunsaturated Fatty Acids

Conflicts of Interest

The authors declare no conflicts of interest.

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