



# Micronutrient Resilience, the Immune System and the Gut Microbiome

## The Critical Role of Micronutrients in Immune Function

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### Summary

The immune system is a complex network that protects the body from pathogens and reduces the risk of diseases for which nutrition plays a crucial role. Every component of the immune response depends on the presence of certain vitamins and minerals, which operate both individually and in combination. Micronutrients such as vitamins A, B6, B12, C, D, and E, folate, zinc, copper, iron, and selenium are essential for optimal immune function. Deficiencies in individual or a combination of micronutrients, reduce the ability of the immune systems to fight off pathogens. The human gut is a major site of micronutrient absorption and immune activity. And the microbiome, the complex ecosystem of microbes residing in the gut, helps “train” the immune system, and is a key determinant of immune development and function. In many places and situations people’s diets are not adequate in micronutrients to assure adequate immune response, which leads to a self-perpetuating cycle of infection, gut dysfunction, and worsening of nutrition and immunity. Several factors, including poor diet and sanitation, can negatively influence the microbiome, further augmenting this detrimental cycle. Research points to some specific benefits from specific micronutrients and other interventions. Recent findings show that very early interventions are required to help newborns develop healthy immune systems and that micronutrient supplements may be needed to support immunity in older adults. Nonetheless, further research is vital to help determine the optimal timing, dosages, and vehicles for micronutrient interventions and the populations at risk for each life stage to maximize people’s immunity and resilience in the face of challenges to their health.

# Introduction

A well-functioning human immune system fits the very definition of resilience: the capacity to recover from shocks. In this case, the shocks include a whole range of pathogens—harmful microbes—to which humans are continually exposed over the course of their lives. It is the job of the immune system to recognize these pathogens, such as bacteria, viruses and parasites, and take action against them to prevent disease or reduce its severity.

The immune system is a complex web of cells, tissues, organs, and substances about which much is known and

much remains to be learned. How this system functions, and the role of nutrition in its operation, have been the subject of extensive ongoing research that has produced a stream of new insights in recent decades.

It is now clear that nutrition has a direct effect on all aspects of people’s immune response. By acting on what is known so far about nutrition and the immune system, and by urgently pursuing answers to the many questions that remain, we can begin to apply nutrition interventions in ways that will help break the cycle of malnutrition and disease.

## Nutrition and the Immune System: Feeding the Pathogen Fighters

The human immune system has two main types of immunity: innate and adaptive. Innate immunity—the immune system that is present at birth and lasts life long—is the body’s rapid first line of defense against pathogens. It includes barriers like skin, mucus, stomach acid, and enzymes in sweat and tears, as well as immune system cells like macrophages and natural killer cells.

Adaptive immunity, which develops over time, is a system that learns to recognize, attack, and destroy pathogens. Specialized cells like T cells and B cells create antibodies specific to the pathogen they are fighting and can remember it, so they are even more efficient at destroying it if they encounter it in the future. The immunizing benefits of vaccinations rely heavily on adaptive immunity.<sup>1</sup>

How well the immune system overall works to fend off pathogens depends on a range of factors, including age, chronic diseases, stress, and environmental toxins, but nutrition plays a key role. Each of the many components of the immune response depends on the presence of certain vitamins and minerals, which operate both individually and in combination to, among other things, contribute to the integrity of physical barriers like skin, support the proliferation of immune cells, antimicrobial activity, and antibody production.<sup>2-4</sup> The body’s immune system and inflammation are regulated by nutrition, and deficiencies in certain micronutrients can compromise immune function. One key aspect of this is thanks to enterocytes, cells in the intestinal barrier, acting as detectors that can sense harmful substances and send a signal to the immune system to trigger an immune response to fight them off.<sup>5</sup> For example, a deficiency in Vitamin A can compromise immune function,<sup>6</sup> while its supplementation has been shown to reduce inflammation.<sup>5</sup>

Among the most vital micronutrients for the immune system are vitamins A, B6, B12, C, D, and E, folate, zinc, copper, iron, and selenium.<sup>4</sup>

### Key Micronutrients in Various Components of the Immune Response<sup>2</sup>

- **Integrity of physical barriers (such as skin and gastrointestinal tract):** Vitamins A, D, C, E, B6, B12, folate, iron, zinc
- **Oxidative burst and self-protection:** Vitamins C, E, iron, zinc, copper, selenium, magnesium
- **Regulation of inflammation:** Vitamins A, C, E, B6, zinc, iron, copper, selenium, magnesium
- **T-cell proliferation, differentiation, and function:** Vitamins A, D, C, E, B6, B12, zinc, iron, copper, selenium
- **Innate immune cell proliferation, differentiation, function, and movement:** Vitamins A, D, C, E, B6, B12, folate, zinc, iron, copper, selenium, magnesium
- **Inhibitory actions:** Vitamins D, E, B6
- **Antimicrobial activity:** Vitamins A, D, C, zinc, iron, copper, selenium
- **Antibody production and function:** Vitamins A, D, C, E, B6, B12, folate, zinc, copper, selenium, magnesium
- **Cell-mediated immunity:** Vitamins A, D, C, E, B6, B12, folate, zinc, copper, selenium

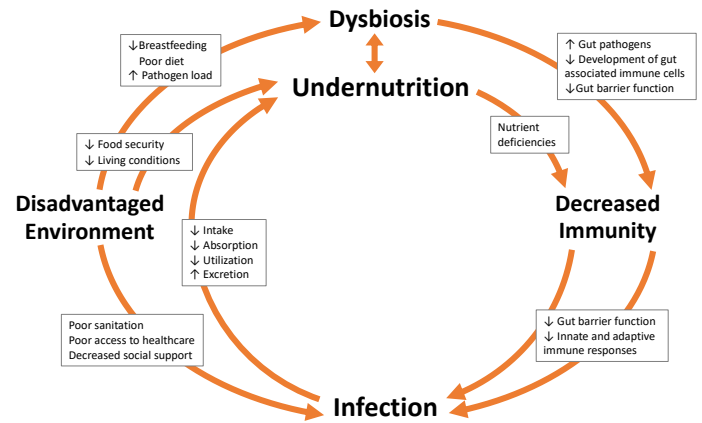
The human gut is where nutrition and immunity converge. Most immune cells in the human body—about 70 percent—are found in the gastrointestinal tract, strategically located near the greatest concentration of microbes in the body, found in the lumen of the gut. The gut microbiome consists of trillions of microorganisms, including viruses, and fungi, and especially bacteria. Many of these bacteria are microbes which help digestion, including the synthesis of micronutrients, such as B vitamins and vitamin K. However, the greatest impact of the human microbiome is that of shaping the response of immune cells.

A balanced microbiota is composed of beneficial non-pathogenic bacteria but also includes some less beneficial and some occasionally pathogenic bacteria. This bacterial ecosystem helps to “train” and stimulate immune cells to respond appropriately. However, poor nutrition and environmental factors can lead to an unbalanced microbiota, termed *dysbiosis*, with less beneficial bacterial species, and often with a predominance of bacterial pathogens, which can lead to inadequate immune responses and higher risk for infections. Thus, the microbiota is central to all of the functions of the gut: digestion, nutrient absorption, and the immune response.

It is ever clearer that immune dysfunction is both a cause and a consequence of malnutrition.<sup>3</sup> When people suffer from deficiencies in individual micronutrients or in combinations of micronutrients, their immune systems become less able to fight off pathogens and their inflammation response is disrupted. The result can be a cycle of malnutrition and

disease, in some cases exacerbated by poverty, and disadvantaged environments, in which undernutrition reduces immunity, leading to increased infection, which can in turn worsen undernutrition (Figure 2).

**Figure 2. The cycle of malnutrition and disease**

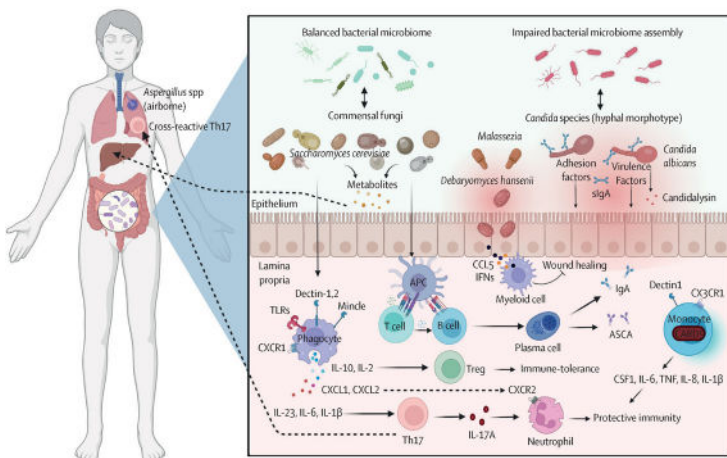


Source: Jose M. Saavedra.

## Nutrition, the Microbiome, and Immunity in Early Life

Providing necessary micronutrients to all infants is a *sine qua non* for normal growth and development, as deficiencies will impair physical, cognitive, and behavioral development with long term consequences. However, various nutrient deficiencies, such as vitamin A and zinc are particularly significant as related to infant and children’s immune function, and a major global cause of infectious disease morbidity and mortality.

**Figure 1. The relationship between the immune system and the composition of the gut mycobiome.**



Source: Zhang, Fen et al. “The gut mycobiome in health, disease, and clinical applications in association with the gut bacterial microbiome assembly”, *The Lancet Microbe* (2022) 3e969-e983DOI: (10.1016/S2666-5247(22)00203-8)

The gut microbiome in early life is also a major determinant of immune response. This complex ecosystem develops starting at birth. Infants are born with very few bacteria in the gut lumen, which is colonized by trillions in the first days of life. The composition of this developing microbiota will depend on several factors, but primarily on how the infant is born and their diet.

Infants delivered vaginally pick up their first helpful microorganisms, including maternal microbiota, as they pass through the birth canal, whereas infants delivered via cesarean section often develop dysbiosis, and tend to lack the strains of gut bacteria found in healthy children and adults.<sup>7</sup> Breastfeeding is the other critical factor in this process. Breast milk passes along a wealth of microorganisms, as well as growth factors that specifically support the growth of health-promoting bacteria, which in turn help to build the infant’s immune system and protect from pathogens.<sup>8</sup>





## Nutrition and Immunity in Adolescence and Adulthood

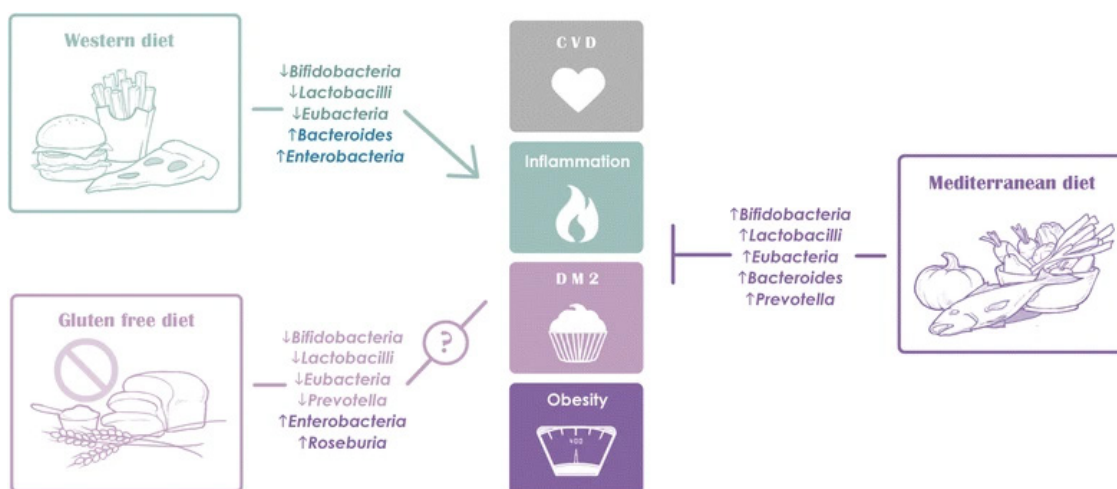
The immune system matures during adolescence, and young, nonpregnant adults in general can be well equipped to cope with challenges to the immune system.<sup>11</sup> Yet for billions of people, diets in adulthood do not supply all of the micronutrients needed for healthy functioning of the immune system. As mentioned above, specific micronutrients are key to all aspects of immune function, particularly the adaptive immune response. Recent data show that two in three women of reproductive age suffer from at least one micronutrient deficiency.<sup>12</sup> Deficiencies in, for example, iron, vitamin A, vitamin D, and zinc—all of which are vital to the immune system—appear to be widespread globally.<sup>13</sup>

Evidence shows that early disruptions to the development of an infant’s healthy gut microbiome, such as delivery by C-section and lack of breastfeeding, are difficult to reverse, and contribute to increased risk of infections, as well as other immune and metabolic related problems long after birth. Although much remains to be learned about how to strengthen the gut microbiome in newborns and infants, recent evidence suggests that interventions must come very early to make a difference. Multiple large trials have found that giving newborns vitamin A can reduce infant mortality by ~13% in South Asia but not in Africa,<sup>9</sup> signalling a need for further research to understand and resolve this issue to guide potentially impactful programs. Additionally, factors that alter the microbiome may play a role. For example, probiotic supplements during this period appear to reduce mortality and sepsis in preterm and/or low-birth-weight babies.<sup>10</sup>

It is especially important to ensure that adolescents and adults have an adequate intake of antioxidants (such as vitamins A, C, and E) as well as components of antioxidant enzymes (such as zinc, copper, iron, and selenium). Even a marginal deficiency in zinc has been shown to increase risk of infection.<sup>11</sup> Polyphenols and other bioactive compounds found in fruits and vegetables may also play an important part in fighting inflammation and its damaging effects.<sup>14</sup>

More broadly, energy dense, nutrient poor diets which have become more common in many urbanizing areas around the world, are harmful to the health of the gut microbiome and in turn the immune system. These diets, typically high in sugar and trans and saturated fats but low in micronutrients, fiber, complex carbohydrates, and other bioactive molecules such as polyphenols and omega 3 fatty acids, are associated with chronic inflammation that

**Figure 3. Diets high sugar, trans and saturated fats and low in micronutrients and fiber consumption are linked to chronic inflammatory diseases.**



Source: Singh, R.K., Chang, HW., Yan, D. et al. "Influence of diet on the gut microbiome and implications for human health". J Transl Med 15, 73 (2017), doi.org/10.1186/s12967-017-1175-y

raises the risk of cardiovascular disease, stroke, type 2 diabetes, and other chronic diseases. In contrast, diets, rich in vegetables, fruits, nuts, legumes, fish, and healthy fats, such as the Mediterranean diet, are associated with a reduced risk of chronic diseases such as cardiovascular disease and cancer.<sup>14</sup>

### Nutrition and Immunity in Later Life

As people age, their innate and adaptive immunity typically declines. Immune cells decrease in number and become less effective. Skin and mucous membranes function less well as barriers against pathogens. Low-grade chronic inflammation becomes more common. As a result, older adults are more susceptible to infections—a situation that

came into stark relief during the COVID-19 pandemic, which affected disproportionately older people.<sup>4</sup>

Although people typically require fewer calories as they age, their need for micronutrients stays the same, so micronutrient deficiencies are common in older adults. An estimated 35 percent of people 50 years old or older in Canada, Europe, and the United States have a demonstrable deficiency in one or more micronutrients. And deficiencies in many of the vitamins and minerals critical to the immune system are widespread. Impaired immunity, often caused by multiple micronutrient deficiencies, is evident in the high incidence and severity of respiratory and other infections experienced by older people.<sup>11</sup>

## Nutrition to Strengthen Immunity

Nutrition clearly has a critical role to play in immunity. Given widespread micronutrient deficiencies that contribute to poor health and susceptibility to infection, nutritional interventions have the potential to contribute to people's resilience to pathogens and health shocks throughout the lifecycle. However, we need to learn much more about the best options for leveraging nutrition to strengthen people's immunity.

A healthy, diverse diet is presumably an important first step toward supporting people's immune response. In many places and situations, however, people may not have access to an adequate and varied supply of food. Even in industrialized countries, where healthy, nutritious foods may be more available, inadequate diets are common.<sup>11</sup> As a result, many people's usual diets may not be enough to assure a strong immune system.

Recommended dietary allowances (RDAs) exist for vitamins and minerals, but these recommended amounts are designed to avoid clinical or subclinical deficiencies in the majority of the healthy population. They are recommendations for healthy and well nourished people to stay healthy and well nourished, so they may not be adequate for maximizing many people's immune function. In fact, some research suggests that doses of vitamin C, vitamin D, and vitamin E, for example, may need to be significantly higher than RDAs to optimize immune protection.<sup>2</sup>

Research points to some specific benefits from specific micronutrients. In infants and young children, zinc supplements reduce illness and death from infectious diseases in developing countries, as do vitamin A supplements in



children with vitamin A deficiency. Zinc also has important effects against pneumonia, diarrhea, malaria, and the common cold in children. Vitamin C supplements reduce the severity and length of common cold symptoms in children and adults. In older adults, supplementation with zinc, vitamin C, and vitamin E have all been shown to have benefits for immunity.<sup>11</sup> So far, there is no evidence of direct benefits from micronutrient interventions in relation to COVID-19.

For infants, it seems clear that interventions to address disruptions to the immune system should start very early in life—within the first few days after birth. Avoiding unnecessary births by cesarean section, and exclusive breastfeeding are critical in establishing a healthy microbiota to support the infant’s immune system development. Such interventions should include maternal education in diet and nutrition, deworming, hygiene, and water sanitation. Strengthening the immune system in early life is likely to be critical to people’s long-term nutrition and health outcomes. Exclusive breastfeeding in early life and diverse nutritious diets, together with specific micronutrient supplementation at particular stages throughout the lifecycle can be key elements in developing and maintaining a robust immune system. Diet in later life, including adequate amounts of fiber and reducing intake of high amounts of sugar and refined carbohydrates can help maintain a healthy microbiome.

Still, there is much to learn. We need research to help define and identify specific at-risk groups that may benefit from targeted micronutrient interventions, to prevent and to manage micronutrient deficiencies at each life stage. This includes developing better biomarkers to track progress in people’s micronutrient status over time, better understand optimal intakes for each life stage, and better assessing micronutrient dietary intake. We need to better define the optimal timing, dosages, and vehicles for micronutrient

interventions. And we need to identify and define specific outcomes of micronutrient interventions, including those related to immune function and infectious disease outcomes. This is significant because a healthy immune system protects from infection, and also decreases the risk of allergies, cancer, and autoimmune and inflammatory diseases. Furthermore, an adequate immune response is the mechanism by which vaccines work to prevent bacterial and viral infectious diseases.

Given that the immune system depends on multiple micronutrients and that many people have deficiencies of several micronutrients, high-quality randomized controlled trials are needed to determine the role of specific and multiple micronutrient supplementation in treating and reducing the risk of infection. Finally, we need to better understand how diet, nutrition, and the gut microbiome interact to support immune health.

In a world where billions of people suffer from deficiencies of essential micronutrients, improving nutrition offers enormous potential to boost human resilience by strengthening people’s capacity to fight off pathogens and lead healthier lives. As new findings emerge, we are sure to gain further clarity about how diets and nutrition interact with the human immune system, opening the way to effective new nutrition interventions that can improve the health and resilience of people at all stages of life.

## Recommendations and priorities for research

The scientific community is in early stages of research on how healthy diets rich in micronutrients affect our immune and metabolic systems. This includes the diverse ways nutrients impact our immune system throughout the digestive tract. Such research could support evidence-based guidance on nutritional therapies to address inflammation and enhance the immune system. To further understand the biologic mechanisms by which diet, nutrition, and the gut microbiome interact to support immune health, future research priorities include:

- Further research on indicators of nutrient adequacy and biomarkers of nutrient status throughout the lifecycle
- Identification of at-risk groups for broad and specific targeted interventions, and when needed
- Further focus on optimal nutrient intake (individual and multiple nutrients) for healthy at-risk populations and those already affected by disease and/or nutrient deficiencies.
- Further research and understanding on outcomes at individual and population level of nutrient interventions.

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This white paper is part of a series designed to stimulate new thinking and discourse in advance of the Micronutrient Forum 6th Global Conference "Nutrition for Resilience (N4R): Ensuring Micronutrient Security in an Era of Complex Global Challenges," scheduled for 16–20 October 2023. This hybrid conference, with an in-person component in The Hague, Netherlands, will explore the interdependence of micronutrient nutrition and the resilience of individuals, communities and systems, within the context of a world where global crises are the new normal. **For more information, click [here](#).**

