IBOM MEDICAL JOURNAL
Vol.19 No.1 | January - March 2026 | Pages 220-232
www.ibommedicaljournal.org

Micronutrient-Driven Immunomodulation Against *Streptococcus Pneumoniae*: The Role of Vitamins and Minerals in Pulmonary Defense

Noor Alhuda A. K[1], *Marwa Jewi*[2], *Khaldoon Jasim Mohammed*[3]

[1]*Institute of Medical Technology, Baghdad, Iraq*
[2]*AL-Mustansiriyah University, College of Basic Education, Iraq*
[3]*Department of Chemistry, College of Sciences for Girls, University of Babylon, Babylon, Iraq*

Abstract

Context: *Streptococcus pneumoniae* is a leading cause of community-acquired pneumonia, disproportionately affecting children under five, the elderly, and immunocompromised individuals. Although vaccines and antibiotics are available, issues such as drug resistance and variable vaccine efficacy present ongoing challenges, which may be mitigated by support measures that enhance lung-stimulating immune function.
Objective: This review examines the immunological effects of essential dietary vitamins and minerals in defending against *S. pneumoniae* and how they may serve as nutritional support to reduce disease severity and improve clinical outcomes in high-risk populations.
Materials and Methods: Scientific studies were reviewed on the impact of key micronutrients like vitamins A, D, C, E, and minerals such as zinc, selenium, iron, and copper on cellular and humoral immune responses related to *S. pneumoniae*. Data from experimental models, human cell studies, and clinical trials were compiled to provide a comprehensive overview.
Results: Vitamin D activates vitamin D receptor (VDR), stimulates the production of antimicrobial peptides such as LL-37, strengthens the epithelial barrier, and reduces inflammation. Vitamin C acts as an antioxidant, promotes phagocytosis and T cell differentiation, and lowers NF-κB activity. Zinc and selenium regulate oxidative balance, enhance immune cell activity, and modulate cytokine gene expression. Iron and copper support immunity but also nourish bacteria, so their levels require careful regulation. Clinical trials have shown improvements in inflammatory markers, reduced hospital stay duration, and better recovery rates in patients receiving nutritional supplements, especially those with pre-existing deficiencies.
Conclusion: Micronutrients have shown a promising potential to modulate the immune response against *S. pneumoniae*, particularly in high-risk groups. However, issues such as optimal dosages, bioavailability, and drug interactions need to be addressed on an individual basis and through standardized examinations in the future. Integrating micronutrients into current treatment regimens could be a strategic step toward enhancing pneumonia outcomes and reducing the global disease burden.

Keywords: *Streptococcus Pneumoniae*, Vitamin C, Pulmonary defense, Zinc, Vitamin D

1. Introduction

Streptococcus pneumoniae ranks as one of the most feared bacterial infections globally, causing significant community-acquired pneumonia and other invasive diseases such as meningitis and bacteremia. *S. pneumoniae* is a Gram-positive, encapsulated diplococcus with remarkable ability to colonize the human nasopharynx, invade host tissues, and evade immune responses.[1] These properties make it highly virulent and persistent. According to the World Health

Corresponding Author:
Khaldoon Jasim Mohammed
Department of Chemistry, College of Sciences for Girls, University of Babylon, Babylon, Iraq
sci945.kaldun.jasem@uobabylon.edu.iq

DOI: 10.61386/imj.v19i1.936

Organization, pneumonia is the leading infectious cause of death in children under five years old, with *S. pneumoniae* responsible for a significant percentage of these deaths. Pneumococcal infections also cause high morbidity and mortality rates among the elderly and immunocompromised individuals.[2]

Although pneumococcal vaccines and antimicrobial treatments are widely available, challenges remain that hinder effective disease control. The emergence of antibiotic-resistant strains, inconsistent serotype coverage of current vaccines, and limited access to immunization in resource-poor regions further threaten global health. Moreover, the complex interactions between host immune systems and pathogen adaptability highlight the need for exploring alternative strategies to boost pulmonary immunity, especially among vulnerable population.[3,4]

Host response to *S. pneumoniae* involves multiple steps and factors, incorporating both innate and adaptive immunity. Defense mechanisms rely on alveolar macrophages, neutrophils, dendritic cells, and cytokine signaling pathways that promote phagocytosis and bacterial lysis. Adaptive immunity enhances protections through the production of pneumococcal-specific antibodies and memory T cells. However, this immune defense can weaken due to nutritional deficiencies, chronic disease, or age-related immune decline, leaving individuals susceptible to severe disease outcomes.[5,6]

In recent decades, increasing attention has been given to the role of micronutrient-rich foods, particularly vitamins and minerals, in regulating immune system functions and increasing resistance to respiratory infections. Micronutrients such as vitamins A, D, C, and E, along with trace elements like zinc, selenium, iron, and magnesium, are vital for maintaining immune homeostasis.[7,8] These nutrients influence numerous biological functions, including epithelial integrity, antioxidant defenses, gene expression, and leukocyte activity. Deficiencies can impair host defenses, increasing susceptibility to respiratory pathogens like *S. pneumoniae.*[9]

Micronutrient-driven immunomodulation represents an emerging paradigm in infectious diseases management, suggesting that nutritional supplements could complement conventional pharmacological treatments. Understanding the specific roles of vitamins and minerals in pulmonary immunity can help searchers and clinicians develop comprehensive approach to strengthen innate defenses.[10] This review focuses on the importance of essential vitamins and minerals in boosting immune protection against *S. pneumoniae*. It examines the complex interactions between nutrition and immunity, including how various vitamins and minerals support cellular and humoral defenses in the respiratory tract. By reviewing existing research, the paper seeks to support the hypothesis that targeted nutritional interventions could severe as effective supplementary measures in reducing the global burden of pneumococcal pneumonia.

2. Biological characteristics of *Streptococcus pneumoniae*

S. pneumoniae is a Gram-positive, alpha-hemolytic bacterium characterized by lancet-shaped diplococcal bodies, which are usually covered with a polysaccharide-rich capsule. This capsule is a key virulence factor that aids in evading the immune system and protecting against phagocytosis.[11] Over 90 different capsular serotypes have been identified, each distinguished by its unique antigenic and pathogenic features. The bacteria are facultative anaerobes and tend to form characteristic streptococcal chains during culture, assisting in their identification and classification.[12] Its metabolic properties and structural stability contribute to its role as a major cause of pneumococcal pneumonia, as well as other invasive diseases such as meningitis and septicemia.

The initial pathogenic step involves colonization or attachment to the upper respiratory tract, particularly the nasopharyngeal epithelium. In this process, adhesion molecules like choline-binding proteins (e.g., CbpA), pneumococcal surface adhesin A (PsaA), and phosphorylcholine in teichoic acids play roles.[13] These factors facilitate close attachment to epithelial cells and mucus layers of the host. Successful colonization leads to invasion, which involve stimulating host-cell receptors such as platelet-activating factor receptors to breach epithelial barriers and reach deeper lung tissues. The virulence of *S. pneumoniae* enhances this invasion, allowing it to multiply efficiently within the nutrient-rich alveolar spaces, especially when the host's immune defenses are weakened.[14]

The bacterium's ability to modulate local immune responses promotes replication within the lungs. It also induces inflammatory cascades, which increase vascular permeability to grant better access to nutrients in the host.[15] Concurrently, pneumococcal autolysins facilitate cell remodeling and lysis,

releasing intracellular virulence factors that exacerbate tissue destruction and inflammation. The lung environment, high in oxygen and iron, further supports rapid bacterial growth unless effectively countered by a robust immune response.[16]

A major harmful effect of *S. pneumoniae* infection is its release of pneumolysin, a pore-forming toxin that destabilizes epithelial and immune membranes, leading to cytolysis and compromised barrier function. Pneumolysin also upregulates compliment pathways and cytokine release, amplifying inflammatory responses and aiding bacteria spread. Besides pneumolysin, other secreted factors such as hydrogen peroxide and neuraminidases contribute to the host cell damage and nutriment acquisition.[17,18]

Another critical aspect of pneumococcal survival and immune evasion is biofilm formation. In the respiratory tract, *S. pneumoniae* develops biofilms—structured communities of bacteria encased in extracellular polymeric substances—which confer resistance to antibiotics and host defenses.[19] Biofilms enable persistent colonization and serve as reservoirs for chronic infections, especially in individuals with long-stranding lung diseases. The bacterium's capacity to switch from planktonic to biofilm phenotype demonstrates its versatility and resilience, driven by quorum sensing and environmental cues.[20] The complex biological features of *S. pneumoniae* are summarized in Figure 1. This pathogen evades immune responses by forming a protective capsule, producing binding proteins, and multiplying within the lungs. It secretes potent toxins and forms biofilms, making it a formidable respiratory pathogen. These features offer potential avenues for adjunctive therapies. Manipulating micronutrient availability could help bolster the host's defenses and reduce disease severity.

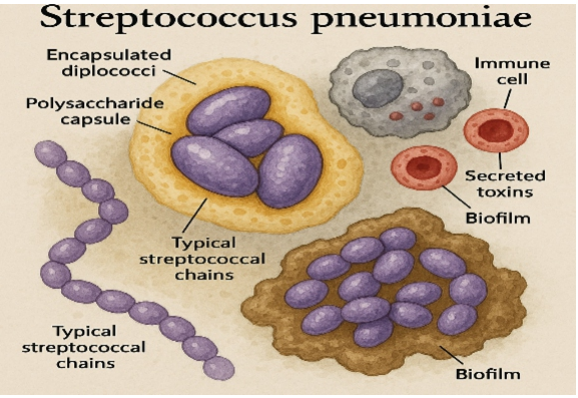

Figure 1: Morphological, structural components, and virulence attributes of *Streptococcus pneumoniae*

3. The immune response against *S. pneumoniae*

The innate immunity against *S. pneumoniae* is complex, involving a rapid innate response that is then extended by a tailored acquired response. Such a multilayered response is essential to control the infection, prevent colonization, and minimize lung damage. The interaction between host immunity and bacterial virulence factors ultimately determines the outcome of pneumococcal infection.[21]

Once the respiratory tract is invaded, *S. pneumoniae* first encounters the innate immune system. Epithelial cells, alveolar macrophages, and dendritic cells serve as first-line defenders by recognizing of pathogen-associated molecular patterns (PAMPs) via toll-like receptors (TLRs), especially TLR2 and TLR4.[22,23] This recognition triggers intracellular signaling pathways, leading to the activation of nuclear factor-kappa B (NF-kB), which in turn induces the production and release of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and interferon-gamma (INF-γ). These cytokines promote the recruitment of neutrophils and monocytes to the infection site, enhancing inflammation and microbial clearance.[24]

Control of pneumococcal proliferation relies on phagocytosis by alveolar macrophages and neutrophils. These cells destroy bacteria through oxidative burst and lysosomal degradation. However, the polysaccharide capsule of *S. pneumoniae* presents a major challenge by hindering opsonization and subsequent phagocytosis. To overcome this, the bacterium's surface must be tagged with opsonins such as complement component C3b and natural antibodies to improve recognition and clearance.[25,26]

As infection progresses, adaptive immunity becomes crucial for long-term protection and eradication of the pathogen. Activated B lymphocytes secrete serotype-specific immunoglobulins particularly IgG and IgA, which neutralize pneumococcal antigens and activate the complement systems. IgA plays a vital role in mucosal immunity by preventing colonization and invasion in the respiratory pathways.[27] Concurrently, CD4+ T helper cells coordinate immune responses that support B cells activity and secrete cytokines that enhance macrophage activation and antibody production. Additionally, a subset of CD4+ T cells, known as Th17 cells, are critical in the recruiting

neutrophils to the mucosal epithelium and strengthening epithelial barriers.[28]

The immune response to *S. pneumoniae* various greatly depending on the strain, which can trigger either a harmless or a deadly immune reaction. *S. pneumoniae* exhibits extensive genetic and antigenic diversity, with over 90 known serotypes.[29] Some strains produce higher levels of the cytotoxic protein pneumolysin, which damages immune cells and disrupts pulmonary epithelia integrity. Strains with dense capsules or enhanced biofilm formation ability can evade immune recognition, allowing survival within host tissues. This capsular diversity influences both pathogenicity and the host's ability to mount an effective immune response, thereby affecting disease severity and vaccine efficacy.[30]

Furthermore, host factors such as age, nutritional status, and prior exposure can influence the immune landscape. Both innate and adaptive immune responses can be compromised by immunosenescence in order adults or micronutrient deficiencies in vulnerable groups, increasing susceptibility and worsening outcomes. Understanding how host immunity interacts with pneumococcal biology through complex crosstalk is essential for developing targeted interventions to boost resistance and reduce infection burden. Figure 2 illustrates the synergistic effects of innate and acquired immunity in response to pneumococcal infection, factoring in strain diversity and host conditions such as age and nutrition.

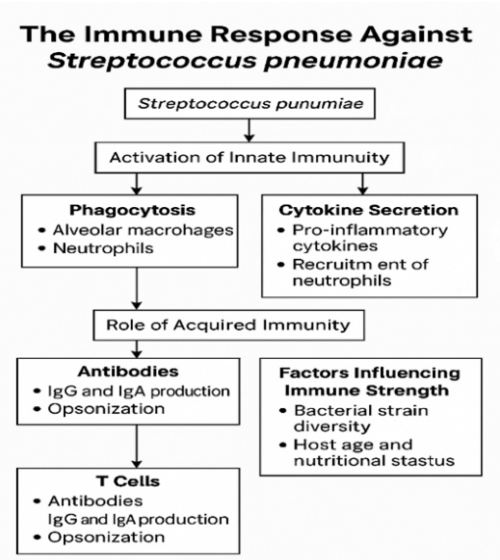

Figure 2: A diagram illustrating the stages of the immune response against *Streptococcus pneumoniae* and their influencing factors.

4. Vitamins with an immunomodulatory effect against *S. pneumoniae*

Micronutrients regulate the host immune response, and among them, vitamins D, C, E, and A have been found to provide significant immunoregulatory effects that can predispose individuals to infection with *S. pneumoniae*. These compounds are not only involved in the basic processes of participate life but also actively control molecular mechanisms, enhance cellular responses, and preserve lung tissues integrity—all of which are crucial in fighting pneumococcal colonization and disease development.[31]

The importance of certain vitamins, especially vitamin D, must be highlighted because of its ability to regulate gene expression and strengthen the lung epithelial immune system. The biologically active metabolite 1,25-dihydroxyvitamin D 3PS acts as a ligand or activator of the vitamin D receptor (VDR). 32 VDR governs various genes, primarily those for antimicrobial peptide genes such as cathelicidin (LL-37) and defensins. These peptides directly kill *S. pneumoniae* and support restructuring of the epithelial barrier. Vitamin D also influences junctional protein expression in airway epithelial cells, reinforcing the physical barrier against pathogen invasion. Additionally, it prevents harmful inflammation by inhibiting NF-kB signaling and regulating pro- and anti-inflammatory cytokines in immune cells, lowering of pro-inflammatory responses while increasing anti-inflammatory effects. These combined properties help the lungs prevent and control pneumococcal infections.[33,34]

Ascorbic acid (vitamin C) is another vital micronutrient with immune-protective properties. As a potent antioxidant, vitamin C inhibits reactive oxygen species (ROS) generated during phagocytosis, thus maintaining immune cells viability and function. It also enhances the chemotaxis and phagocytic activity of neutrophils, which are essential during early defense against pneumococcus. Vitamin C promotes T lymphocyte growth and activity, aiding adaptive immune responses.[35,7] Furthermore, it modulates inflammatory pathways by regulating transcription factors like NF-kB, preventing excessive lung inflammation typical of severe pneumococcal pneumonia. This dual action of stimulating microbial clearance while reducing tissue damage emphasizes the therapeutic importance of

Table 1: Immunological functions of key vitamins against *S. pneumoniae.*

Vitamin	Targeted immune pathways	Affected immune cell types	Cytokine regulation	Immunological and clinical outcomes
Vitamin D	- Binds to VDR to activate gene transcription - Stimulates antimicrobial peptides (e.g., Cathelicidin LL-37, Defensins)	- Epithelial cells - Alveolar macrophages - Regulatory T cells	- ↓ IL-6, TNF-α (anti-inflammatory) - ↑ IL-10 (anti-inflammatory)	- Strengthens pulmonary barrier immunity - Reduces inflammatory damage - Limits bacterial colonization
Vitamin C	- Potent antioxidant reducing oxidative stress - Enhances chemotaxis and phagocytosis	-Neutrophils - CD8+ and CD4+ T lymphocytes	- ↓ NF-κB (dampens inflammation) - ↑ IFN-γ (boosts cellular response)	- Accelerates bacterial clearance - Mitigates tissue injury - Supports T cell differentiation
Vitamin E	- Protects cellular membranes from lipid peroxidation - Stimulates cell-mediated immunity	- Th1 cells - Antigen-presenting cells	- ↓ PGE2 (reduces immune suppression) - ↑ IL-2 (promotes T-cell proliferation)	- Enhances immune surveillance - Improves lung tissue resilience during infection
Vitamin A	- Regulates epithelial differentiation and mucosal integrity - Promotes mucosal antibody production	- Regulatory T cells - IgA-producing B cells	- ↑ TGF-β (immune modulation) - ↑ IgA in mucosal surfaces	- Reinforces mucosal immunity - Improves mucociliary clearance - Prevents bacterial adherence

vitamin C.[36]

Vitamin E, fat-soluble antioxidant, primarily protects cell membranes from oxidative damages in the inflamed lung environment. It sustains immune cell membranes and bolsters T-cell mediated immunity, which is critical for targeting *S. pneumoniae*. Vitamin E also improves alveolar macrophage function, aiding in eliminating pathogens from lung tissue.[37,38]

Vitamin A is vital for mucosal immunity and epithelial cell growth. Its active form, retinoic acid, regulates the expression of genes involved in epithelial differentiation, mucin synthesis, and immune cell trafficking[39]. Vitamin A encourages the differentiation of regulatory T cells and increases IgA production, strengthening mucosal defenses against pneumococcal colonization. Deficiency in vitamin A linked to higher risks of respiratory infections, barrier damage, and impaired in antibody production.[40]

As shown in Table 1, these vitamins collectively serve as modulators of immune resilience: they serve other purposes not just nutrition. They work synergistically to support epithelial defense, combat oxidative stress, modulate cytokine responses, and enhance cellular immunity. Consequently, they hold potential as adjuvants in the presentation and treatment of pneumococcal infections, particularly in groups with micronutrient deficiencies.

5. The role of minerals in resisting *S. Pneumoniae*

To contain the effects of *S. pneumoniae* infection, minerals play crucial roles as cofactors in immune regulation and lung defense, since they activate various pathways that support resistance against infection. Zinc, selenium, iron, and copper are key micronutrients with dual function: sustaining host immunity and modulating bacterial pathogenesis. They participate in enzyme activity, oxidative stress response, cell signaling, and immune cell functions, acting as vital defenders in fight against respiratory infections.[28,41]

Zinc is essential for structure and function of the innate and adaptive immune systems. As a cofactor for over 300 enzymes, it coordinates cellular processes, such as phagocytosis, oxidative burst activity, and cytokine production. Zinc enhances microbial killing by neutrophils and macrophages by promoting NADPH oxidase assembly and lysosomal activity.[42] Low zinc levels are also linked to impaired phagocytic clearance of *S. pneumoniae* leading to prolonged infection and tissue damage. Additionally, zinc modulates inflammatory signaling by inhibiting nuclear factor-kappa B (NF-kB) activation and regulating cytokine profiles. It boosts anti-inflammatory mediators like IL-10 while suppressing pro-inflammatory cytokines such as TNF-α and IL-6. Maintaining this immunoregulatory balance is critical to prevent excessive lung inflammation that can cause tissue injury during pneumococcal pneumonia.[42,43]

Selenium is a key antioxidative incorporated into selenoproteins like glutathione peroxidases and thioredoxin reductases. These enzymes play vital roles in quenching reactive oxygen species and preserving cell integrity during immune responses. During pneumococcal phagocytosis, excessive ROS production can damage lung tissues; therefore, selenium supplementation enhances redox balance, reinforces epithelial barriers, and supports T cell and cytotoxic lymphocyte proliferation.[44] It also aids in the maturation and function of dendritic cell, optimizing antigen presentation and activating the adaptive immune response. Selenium deficiency is associated with increased susceptibility to respiratory infection and infections weekend vaccine responses, highlighting its importance in mucosal defense.[45]

The relationship between iron and copper in host-pathogen interaction is complex. These minerals are essential for immune cells; iron promotes DNA synthesis and cellular respiration in lymphocytes, while copper enhances macrophage activation and IL-2 production.[46] However, their levels must be carefully regulated since they are also utilized by

Table 2: Immunological functions of key minerals against *S. pneumoniae.*

Mineral	Targeted immune pathways	Affected immune cells	Cytokine regulation	Immunological & clinical outcomes
Zinc	- Enhances phagocytosis - Supports NADPH oxidase activation - Maintains redox balance	- Neutrophils - Macrophages - Regulatory T cells	- ↓ TNF-α, IL-6 (anti-inflammatory) - ↑ IL-10 (immune modulation)	- Promotes bacterial killing - Reduces lung inflammatory damage - Strengthens pulmonary barrier
Selenium	- Antioxidant via selenoproteins (e.g., GPx) - Controls oxidative stress - Supports T cell differentiation	- Cytotoxic T cells - Antigen-presenting cells - Epithelial cells	- ↑ IFN-γ, IL-2 (enhanced immunity) - ↓ ROS (limits oxidative inflammation)	- Improves antigen presentation - Minimizes pulmonary tissue injury - Enhances vaccine efficacy
Iron	- Supports mitochondrial function and cellular proliferation - Critical for enzyme activity	- T and B lymphocytes - Macrophages - Epithelial cells	- ↑ IL-6 when excess (pro-inflammatory) - ↑ Hepcidin for regulation	- Balanced levels: boost immunity - Excess: supports bacterial growth - Deficiency: weak immune response
Copper	- Antimicrobial action within phagosomes - Catalyzes oxidative enzymes (e.g., cytochrome oxidase)	-Macrophages - Helper T cells	- ↑ IL-2, TNF-α at optimal levels - ↑ ROS when excessive	- Facilitates intracellular killing of *S. pneumonia* - Excess may induce oxidative stress

bacteria. *S. pneumoniae* depends on iron for growth and virulence, and excess iron can facilitate bacteria proliferation and weaken host resistance. The host counters this through strategies like producing of hepcidin and lactoferrin to sequester iron and deprive pathogens.[48] Copper exhibit antimicrobial activity in phagosomes by causing oxidative damage to bacteria, but excess copper can disrupt host cell function and induce oxidative stress. Proper management of iron and copper homeostasis is therefore essential for effective immunity without adding bacterial survival.[49]

As summarized in Table 2, these critical minerals help maintain a balance between immune defense and limiting pathogen viability. Understanding their individual and combined effects can lead to micronutrient-based adjunct therapies to enhance pulmonary immunity, especially among populations at risk for mineral deficiencies and recurrent infections.

6. Mechanisms of micronutrient influence on immunity

Micronutrients, including essential vitamins and trace elements, play a crucial role in supporting immune defenses against respiratory diseases such as *S. pneumoniae*. They influence more than just metabolic functions; they also directly affect immune cell activities, gene expression, and cytokine networks regulation. Micronutrients determine the effectiveness, specificity, and resolution of host defense mechanisms by interacting with immune cell receptors, modulating gene expression of interleukins and antimicrobial proteins, and balancing different T-helper cell subsets.[50]

6.1. Interaction with immune cell receptors

One of the main ways micronutrients acts is by interacting with the receptors on immune cells. For example, vitamin D binds to VDR, which is expressed in monocytes, dendritic cells, and activated T cells. This interaction lead to the heterodimerization of VDR-RXR and their movement into the nucleus, where they initiate transcriptional programs that promote the production of antimicrobial peptides and reduce hyperinflammatory responses.[51] Similar, vitamin A works through retinoic acid by binding to retinoic acid receptors (RARs) and retinoid X receptors (RXRs), both of which play roles in immune cell differentiation and strengthening mucosal immunity. Although not mediated through classic receptors, trace minerals like zinc and selenium influence signaling pathway by stabilizing receptor protein structures, activating kinases, and providing redox-sensitive sensor functions, thereby effectively modulating immune responses.[52]

6.2. Modulation of gene expression of interleukins and defense proteins

Micronutrients are essential in regulating of gene transcription for the production of cytokines and innate effector molecules. Genomic signaling by vitamin D promotes the transcription of cathelicidin (LM-37) and the gene for 8-y-defensin, both crucial in breaching bacterial membrane and fighting *S. pneumoniae*. Simultaneously, it inhibits the transcription of various pro-inflammatory cytokines like IL-6, TNF-alpha, and IL-17, which help reduce tissue damage in the lungs.[53.54] Zinc controls the expression of IL-2, a T-cell proliferation stimulant, and also modulates the regulation of NF- kappaB, balancing inflammation through cytokine gene regulation. Selenium affects intracellular redox status via selenoproteins, thereby modulating factors such as STATs and NF-kappaB that influence the levels of IL-10 and IFN-gamma. These transcriptional adjustments optimize immune efficiency while preserving tissue architecture during infection.[55]

6.3. Impact on the Th1/Th2 balance

Vitamins significantly influence the polarization of CD4+ T-helper cells, including a bias in the immune

system toward either Th 1 (cell-mediated) or Th 2 (humoral) responses to immunization. Vitamin D tends to promote a regulatory phenotype (Tregs) and reduce excessive Th1 production, thereby limiting unchecked inflammation.[56] However, at healthy ratios, it can facilitate balanced Th1 responses to eliminate intracellular pathogens. Vitamin A has a dual role because retinoic acid favors regulatory and Th2 differentiation and supports mucosal tolerance, whereas deficiency may shift the balance toward harmful effects. Zinc enhances Th1 dominance by increasing the production of IL-2 and IFN-gamma, which are essential for stimulating macrophage and cytotoxic T cells. Higher selenium levels help rebalance the Th1/Th2 ratio during oxidative stress and immune dysfunction.[57,58]

Overall, micronutrients are dynamic immunomodulators that affect receptor signaling, gene transcription, and T-cell lineage commitment. Their mechanisms are crucial for developing balanced and effective pulmonary immune responses against *S. pneumoniae*. Impairments in these nutrients can tilt the balance toward increased susceptibility pathogenicity of infections.[59] Figure 3 illustrates how micronutrient impact immunity through mechanisms such as interaction with immune cell receptors, regulation of defensin and cytokine gene expression, and modulation of the Th1 and the Th2 responses. The figure highlights how vitamins D and A activate nuclear receptors to promote the expression of immune regulatory factors, leading to a balanced and effective defense against infection.

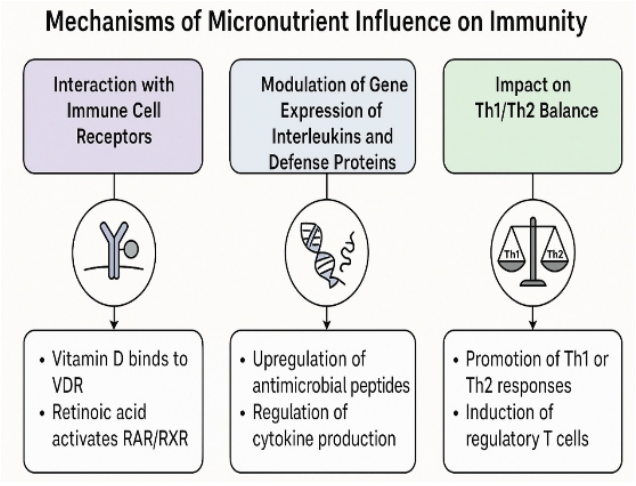

Figure 3: Immune mechanisms regulating the body's response via micronutrients: the role of nuclear receptors and the Th1/Th2 balance.

7. Scientific evidence from clinical and experimental studies

The effect of immunomodulation by micronutrients, vitamins, and minerals can be summarized through a body of scientific research on the enhanced host defense response against *S. pneumoniae*. This evidence includes both controlled laboratory studies and real-world clinical trials, which provide valuable insights into how micronutrient supplementation can improve molecular and physiological functions. However, there remains a significant challenge in translating these findings into standardized clinical practice.[60,61]

7.1. Animal experiments and cell models

The effects of micronutrients on immunity are initially understood through preclinical studies. Vitamin D supplementation in murine models has shown to have significant effects on the upregulation of antimicrobial peptides like cathelicidin LL-37, enhancing bacterial clearance and reducing lung inflammation after exposure to *S. pneumoniae*. Rodents that received vitamin D had lower bacterial loads and higher survival rates than infected controls.[62] Similarly, cellular studies, including those with human bronchial epithelial cells, have demonstrated that zinc improves the ability of macrophages to phagocytize substances, regulates NF-kappa B activity, and increases IL-10 production, which helps keep inflammatory responses in check. The antioxidant properties of selenium are also supported by experimental evidence. High levels of oxidative stress markers and reduced T-cell activation were observed in selenium-deficient mice challenged with *S. pneumoniae*, but these levels normalized when the mice were supplemented with selenium and their immune cells. Iron and copper researches provide subtler results.[63] Although necessary during the proliferation of immune cells were activated. Research on iron and copper shows more nuanced results. Although iron is essential for the proliferation of immune cell, excessive availability of iron in animal models has encouraged bacterial growth and reduced pulmonary pathology. Copper has been shown to enhance bacterial killing by macrophages when used in regulated doses; however, at higher levels—above those naturally occurring or in supraphysiological states —toxicity emerged. This suggests that dosing of these nutrients cannot be generalized.[64]

7.2. Effects of supplements in patients with pneumonia

Some of these experiment results have been replicated in clinical trials. Community-acquired pneumonia Elderly patients with community-acquired pneumonia have shown shorter hospital stays and lower inflammatory markers, including C-reactive protein, when supplemented with vitamin C. In a randomized controlled trial of zinc therapy in children with pneumonia, recovery times were shorter, severity scores decreased, and the incidence of treatment failure—mainly in children with zinc deficiency at baseline —was reduced.[65] The studies involving vitamin D have produced mixed results. Although supplementation has been linked to a lower risk of upper respiratory tract infections and improved epithelial barrier functions in selected cohorts, interventional research targeting on *S. pneumoniae*-specific pneumonia has shown inconsistent outcomes, likely due to variations in dosage, timing, and baseline vitamin D levels. The role of selenium is also promising in immunocompromised groups, including patients with HIV or chronic obstructive pulmonary disease, where supplementation has positively impacted antioxidant protection and immune responsiveness.[67]

Table 3: Scientific evidence on micronutrient effects against *S. pneumoniae.*

Micronutrient	Experimental/Cellular Model Findings	Clinical impact in pneumonia patients	Challenges in clinical application
Vitamin D	- Induces LL-37 and defensins in lung tissue - Reduces inflammation in infected animal models	- Decreases hospitalization duration in some studies - Potential preventive effects in elderly and pediatric groups	- Response varies by dosage and baseline levels - Individual differences complicate standardization
Vitamin C	- Enhances macrophage phagocytic activity - Reduces oxidative stress and boosts IFN-γ production	- Lowers inflammatory markers (e.g., CRP) - Speeds recovery in elderly patients	- Limited high-quality trials - Optimal therapeutic dose remains unclear
Zinc	- Promotes neutrophil and macrophage activity - Regulates IL-10 and NF-κB signaling	- Reduces treatment failure in children - Improves pulmonary symptom scores	- May interfere with copper absorption - Most effective in patients with existing deficiency
Selenium	- Restores T-cell function and redox balance - Enhances antioxidant enzyme activity	- Boosts immunity in immunocompromised groups (HIV, COPD) - Associated with better vaccine responsiveness	- Toxicity risk with high intake - Bioavailability varies by formulation
Iron	- Supports immune cell proliferation - Excess levels promote bacterial growth	- Excess iron linked to worsened infection outcomes - Deficiency impairs cellular immunity	- Tight regulation needed to balance immune support and bacterial risk - Requires individualized dosing
Copper	- Enhances intracellular bacterial killing in macrophages - Stimulates IL-2 production	- Limited direct studies in pneumonia patients - Preliminary animal results show promise	- Difficult to regulate safe levels - Toxicity possible without proper monitoring

7.3. Challenges in standardization and clinical translation

However, even though the evidence shows great promise, integrating micronutrient interventions into standard pneumonia treatments faces several challenges. Variability in study design, patient populations, baseline nutritional status, dosage regimens, and other factors makes it difficult comparative results. Interactions between micronutrients, other medications, and underlying conditions are likely to confound outcomes, requiring stratified approaches.[68] Additionally, identifying optimal therapeutic windows and safe supplementation doses is not straightforward. Overconsumption of minerals like iron and copper can worsen infections or cause toxicity. The variability in bioavailability due to differences in formulation, route of administration, and genetic factors of recipients further emphasizes the need for personalized treatment.[69] As in Table 3, experimental and clinical trials highlight the potential of micronutrients to modulate immunity against *S. pneumoniae*. However, to translate these findings into practice, systematic investigation and precise, care-based systems are essential.

8. Clinical applications and recommendations

With more clinical focus being placed on the potential of micronutrient-based immunomodulation as a tool for prevention and management *S. pneumoniae* infections, especially among vulnerable groups such as children, the elderly, and immunocompromised patients, increasing evidence from both interventional studies and observational research highlights the efficacy of specific nutritional supplements in boosting immune resilience and improving pulmonary outcomes. This evolving field combines the worlds of nutrition, immunology, and personalized medicine, paving the way for the integration of holistic care in the treatment of respiratory diseases.

8.1. Effectiveness of nutritional supplements in prevention and treatment

In vitamin D supplementation studies, randomized trials have shown improved epithelial barriers and reduced incidence of acute respiratory infections. However, this is inconsistent with other studies in

different cohorts due to variations in baseline levels and dosage protocols. The antioxidative and immunoprotective properties of vitamin C are believed to shorten recovery times and lower inflammatory biomarkers in patients with pneumonia.[70] Supplementation with zinc, especially in zinc-deficient children, has also been effective in reducing the duration and severity of respiratory infections, and leading quicker recovery and fewer complications. Although micronutrients cannot replace current treatments such as antibiotics or vaccines, they can serve as adjuncts that modify disease progression, decrease inflammatory tissue damage, and improve clinical outcomes. Future research should explore the synergetic effects of micronutrient therapy combined with conventional treatments to establish evidence-based approaches.[71]

8.2. Nutritional guidelines for at-risk groups

Practical implementation requires setting nutritional guidelines specific to at-risk groups. The World Health Organization and other national health authorities support the idea of regular micronutrient status evaluation, especially in areas with high rates of malnutrition or respiratory diseases. For example, children under five years old, the elderly, and individuals with chronic lung diseases should undergo regular screening to detect deficiencies in vitamin D, zinc, selenium, and iron.[71]

Preventive measures include diversifying diets, focusing on immune-boosting foods such as oily fish (vitamin D), citrus fruits (vitamin C), nuts and seeds (vitamin E and zinc), and leafy greens (iron and folate). Treatment supplementation should be individualized for cases of confirmed deficiency or high risk, considering substance dosage, duration, and potential interactions among nutrients. For patients with comorbidities or impaired, intravenous or lipid-based products may be used to enhance bioavailability.[72]

8.3. Interaction between dietary factors, genetics, and future immunotherapy

These genetic polymorphisms, which contribute to nutritional immunomodulation, interact with nutrient metabolism, immune receptor sensitivity, and cytokine expression. Differences in genes encoding VDR, to give one example, may influence the response to supplements as well as the secondary effects on downstream immunological responses. The mapping of nutrigenomics offers a platform for precision nutrition to identify individuals who can derive the most benefit from value specific nutrient-related diets.[73,74]

Future advances in nutritional immunotherapy could involve combining micronutrient therapy with bioengineered nanoparticles or incorporating targeted gene controls or vaccine adjuvants. This may enhance immune activation or tolerance, particularly against resistant pneumococcal strains and chronic inflammation. The integration of nutrition science with molecular immunology and genetic technologies promises a revolutionary approach to pneumonia prevention and therapy.[75]

9. Conclusion

The nutritional status of micronutrients and immune competence play a key role in protecting the host against *Streptococcus pneumoniae*. The focus is on the role of essential vitamins and minerals, including D, C, E, and A, as well as zinc, selenium, iron, and copper, in modulating innate and adaptive immune responses. These nutrients improve epithelial barrier integrity, reduce oxidative stress, promote antimicrobial peptide secretion, and coordinate cytokine signaling, all of which are vital for pulmonary immunity. The immunomodulatory mechanisms of these nutrients affect gene expression, receptor signaling, and cellular differentiation, contributing to infection outcomes. Deficiency has been associated with increased susceptibility to pneumococcal colonization, heightened inflammatory toxicity, poor vaccine responses, and vulnerability in certain populations. Micronutrient supplementation can be effective as an adjunct in both preventive and therapeutic settings. Future studies should address challenges related to standardizing dosage, improving bioavailability, understanding nutrient-drug interactions, and considering genetic variability in nutrient metabolism.

Conflict of Interest

The authors declare no conflicts of interest.

References

1. Martín-Cerezuela M, Aseginolaza-Lizarazu M, Boronat-García P, Asensio-Martín MJ, Alamán-Laguarda G, Álvarez-Lerma F, et al. Severe community-acquired Streptococcus pneumoniae meningitis: Clinical and prognostic insights from intensive care units. Crit Care 2023;27:72.

https://doi.org/10.1186/s13054-023-04347-3
2. Crotty M, Devall H, Cook N, Fischer F, Alexander J, Hunter L, et al. Short versus long antibiotic duration in Streptococcus pneumoniae bacteremia. Open Forum Infect Dis 2024;11(9):ofae478. https://doi.org/10.1093/ofid/ofae478
3. Schellenberg JJ, Adam HJ, Baxter MR, Karlowsky JA, Golden AR, Martin I, et al. Serotype coverage of PCV21 and epidemiology of unique Streptococcus pneumoniae serotypes in Canadian adults. J Antimicrob Chemother 2025;80(5):1377–1385. https://doi.org/10.1093/jac/dkaf085
4. Atıcı S, Güneşer D, Kepenekli E, Söyletir G, Soysal A. Serotype distribution and antibiotic susceptibility of Streptococcus pneumoniae strains: Five-year surveillance post-PCV13. BMC Pediatr 2025;25:244. https://doi.org/10.1186/s12887-025-05593-w
5. World Health Organization. Guideline on management of pneumonia and diarrhoea in children up to 10 years of age. Geneva: WHO; 2024. https://www.who.int/publications/i/item/9789240103412
6. Abioye AI, Bromage S, Fawzi W. Effect of micronutrient supplements on influenza and other respiratory tract infections among adults: A systematic review and meta-analysis. BMJ Glob Health 2021;6(1):e003176. https://doi.org/10.1136/bmjgh-2020-003176
7. Mohammed KJ, Imran AF, Rubat SK. Association of vitamins and minerals with COVID-19: A mini review. Asia Pac J Mol Biol Biotechnol 2024;32(3):11–20.
8. Majumdar A, Saraf SK, Sahu C, Verma K, Vishwakarma P. Malnutrition and immunomodulators: Bridging nutritional deficiencies and immune health. Future J Pharm Sci 2025;11:50. https://doi.org/10.1186/s43094-025-00804-8
9. Calder PC, Carr AC, Gombart AF, Eggersdorfer M. Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. Nutrients 2020;12(4):1181. https://doi.org/10.3390/nu12041181
10. Pecora F, Persico F, Argentiero A, Neglia C, Esposito S. The role of micronutrients in support of the immune response against viral infections. Nutrients 2020;12(10):3198. https://doi.org/10.3390/nu12103198
11. Nishimoto AT, Rosch JW, Tuomanen EI. Pneumolysin: Pathogenesis and therapeutic target. Front Microbiol 2020;11:1543. https://doi.org/10.3389/fmicb.2020.01543
12. Moscoso M, García E, López R. Biofilm formation by Streptococcus pneumoniae: Role of choline, extracellular DNA, and capsular polysaccharide. J Bacteriol 2006;188(22):7785–7795. https://doi.org/10.1128/JB.00673-06
13. Paton JC, Trappetti C. Streptococcus pneumoniae capsular polysaccharide: Structure, regulation, and role in pathogenesis. Microbiol Spectr 2019;7(2):GPP3-0019-2018. https://doi.org/10.1128/microbiolspec.GPP3-0019-2018
14. Chao Y, Marks LR, Pettigrew MM, Hakansson AP. Streptococcus pneumoniae biofilm formation and dispersion during colonization and disease. Front Cell Infect Microbiol 2015;4:194. https://doi.org/10.3389/fcimb.2014.00194
15. Weinberger DM, Trzciński K, Lu YJ, Bogaert D, Brandes A, Galagan J, et al. Pneumococcal capsular polysaccharide structure predicts serotype prevalence. PLoS Pathog 2009;5(6):e1000476. https://doi.org/10.1371/journal.ppat.1000476
16. Martner A, Dahlgren C, Paton JC, Wold AE. Pneumolysin released during Streptococcus pneumoniae autolysis activates intracellular oxygen radical production in neutrophils. Infect Immun 2008;76(9):4079–4087. https://doi.org/10.1128/IAI.01747-07
17. Domenech M, García E, Moscoso M. Insight into the composition of the intercellular matrix of Streptococcus pneumoniae biofilms. Environ Microbiol 2012;14(3):1044–1058. https://doi.org/10.1111/j.1462-2920.2011.02684.x
18. Reid SD, Hong W, Dew KE, Winn DR, Pang B, Watt J, et al. Streptococcus pneumoniae forms surface-attached communities in the middle ear of experimentally infected chinchillas. J Infect Dis 2009;199(6):786–794. https://doi.org/10.1086/596736
19. Paixão L, Oliveira J, Veríssimo A, Vinga S, Lourenço EC, Ventura MR, et al. Host glycan sugar-specific pathways in Streptococcus pneumoniae: Galactose as a key sugar in

colonisation and infection. PLoS One 2015;10(3):e0121042. https://doi.org/10.1371/journal.pone.0121042
20. Im H, Chembilikandy V, Dmello A, Pearson M, Tettelin H, Orihuela CJ. Alterations in nutrient availability in the lungs during Streptococcus pneumoniae-induced pneumonia. bioRxiv 2025. https://doi.org/10.1101/2025.07.14.664699
21. Brooks LRK, Mias GI. Streptococcus pneumoniae's virulence and host immunity: Aging, diagnostics, and prevention. Front Immunol 2018;9:1366. https://doi.org/10.3389/fimmu.2018.01366
22. Hien YE, Nikiema AR, Kima D, Kambiré D, Ouedraogo O, Ouedraogo G, et al. Innate and adaptive immunity against Streptococcus pneumoniae infection with emphasis on complement system. Curr Trends Immunol 2021;22:1–12. http://www.researchtrends.net/tia/article_pdf.asp?in=0&vn=22&tid=36&aid=6798
23. Koppe U, Suttorp N, Opitz B. Recognition of Streptococcus pneumoniae by the innate immune system. Cell Microbiol 2012;14(4):460–466. https://doi.org/10.1111/j.1462-5822.2011.01746.x
24. Gil E, Noursadeghi M, Brown JS. Streptococcus pneumoniae interactions with the complement system. Front Cell Infect Microbiol 2022;12:929483. https://doi.org/10.3389/fcimb.2022.929483
25. Spelmink L. Streptococcus pneumoniae and the host: Activation, evasion and modulation of the human innate immune system dissertation. Karolinska Institutet; 2016. https://openarchive.ki.se/articles/thesis/Streptococcus_pneumoniae_and_the_host_activation_evasion_and_modulation_of_the_human_innate_immune_system/26909101
26. Wilson RJ. Natural adaptive immunity to Streptococcus pneumoniae lung infection dissertation. University College London; 2013. https://discovery.ucl.ac.uk/id/eprint/1417184/
27. McNeela EA, Burke A, Neill DR, Baxter C, Fernandes VE, Ferreira D, et al. Pneumolysin activates the NLRP3 inflammasome and promotes proinflammatory cytokines independently of TLR4. PLoS Pathog 2010;6(11):e1001191. https://doi.org/10.1371/journal.ppat.1001191
28. Eijkelkamp BA, Morey JR, Neville SL, Tan A, Pederick VG, Cole N, et al. Dietary zinc and the control of Streptococcus pneumoniae infection. PLoS Pathog 2019;15(8):e1007957. https://doi.org/10.1371/journal.ppat.1007957
29. Flatby HM, Ravi A, Damås JK, Solligård E, Rogne T. Circulating levels of micronutrients and risk of infections: A Mendelian randomization study. BMC Med 2023;21:80. https://doi.org/10.1186/s12916-023-02780-3
30. Berger MM, Shenkin A, Schweinlin A, Amrein K, Augsburger M, Biesalski HK, et al. ESPEN micronutrient guideline. Clin Nutr 2022;41(6):1357–1424. https://doi.org/10.1016/j.clnu.2022.02.015
31. Gombart AF, Pierre A, Maggini S. A review of micronutrients and the immune system–working in harmony to reduce the risk of infection. Nutrients 2020;12(1):236. https://doi.org/10.3390/nu12010236
32. Bishop EL, Ismailova A, Dimeloe S, Hewison M, White JH. Vitamin D and immune regulation: Antibacterial, antiviral, anti-inflammatory. JBMR Plus 2021;5(1):e10405. https://doi.org/10.1002/jbm4.10405
33. Musa FA, Salim DK, Shalgam DO, Mohammed KJ. Bacteria and viruses in gene therapy: An evidence-based review. Asia Pac J Biol Biotechnol 2024;32(4):160–171.
34. Salehi Z, Askari M, Jafari A, Ghosn B, Surkan PJ, Hosseinzadeh-Attar MJ, et al. Dietary patterns and micronutrients in respiratory infections including COVID-19: A narrative review. BMC Public Health 2024;24:1661. https://doi.org/10.1186/s12889-024-18760-y
35. Doaei S, Mardi A, Zare M. Role of micronutrients in the modulation of immune system and platelet activating factor in patients with COVID-19: A narrative review. Front Nutr 2023;10:1207237. https://doi.org/10.3389/fnut.2023.1207237
36. Erickson KL, Medina EA, Hubbard NE. Micronutrients and innate immunity. J Infect Dis 2000;182(Suppl 1):S5–S10. https://doi.org/10.1086/315922
37. Marcos A. Editorial: A review of micronutrients and the immune system—working in harmony to reduce the risk of infection. Nutrients 2021;13(11):4180. https://doi.org/10.3390/nu13114180
38. Gombart AF. Regulation of antimicrobial peptide gene expression by vitamin D. In Antimicrobial Peptides: Role in Human Health and Disease.

Cham: Springer; 2015. p. 101–113. https://doi.org/10.1007/978-3-319-24199-9_7
39. Johnstone KF, Herzberg MC. Antimicrobial peptides: Defending the mucosal epithelial barrier. Front Oral Health 2022;3:958480. https://doi.org/10.3389/froh.2022.958480
40. Gozzi-Silva SC, Teixeira FME, Duarte AJS, Sato MN, Oliveira LM. Immunomodulatory role of nutrients: How can pulmonary dysfunctions improve? Front Nutr 2021;8:674258. https://doi.org/10.3389/fnut.2021.674258
41. Jarva H. Significance of zinc in innate immune defense against Streptococcus pyogenes. J Infect Dis 2014;209(10):1495–1496. https://doi.org/10.1093/infdis/jiu055
42. Başeğmez M. An overview of the antioxidant and anti-inflammatory activity of selenium. In: Selenium and Human Health. London: IntechOpen; 2023. p. 1–25. https://doi.org/10.5772/intechopen.111630
43. Belenichev IF, Gorchakova NO, Samura IB, Savchenko NV, Bukhtiyarova NV, Popazova OO. Pharmacological properties of selenium and its preparations: From antioxidant to neuroprotector. Res Results Pharmacol 2021;7(4):29–40. https://doi.org/10.3897/rrpharmacology.7.73051
44. Olivares-Trejo JJ, Alvarez-Sánchez ME. Proteins of Streptococcus pneumoniae involved in iron acquisition. In: Pneumonia. London: IntechOpen; 2022. p. 1–20. https://doi.org/10.5772/intechopen.101668
45. Romero-Espejel ME, González-López MA, Olivares-Trejo JJ. Streptococcus pneumoniae requires iron for its viability and expresses two membrane proteins that bind haemoglobin and haem. Metallomics 2013;5(4):384–389. https://doi.org/10.1039/c3mt20244e
46. Hoffmann PR. Mechanisms by which selenium influences immune responses. Arch Immunol Ther Exp 2007;55:289–297. https://doi.org/10.1007/s00005-007-0036-4
47. Salah I, Parkin IP, Allan E. Copper as an antimicrobial agent: Recent advances. RSC Adv 2021;11(30):18179–18186. https://doi.org/10.1039/D1RA02149D
48. Vincent M, Duval RE, Hartemann P, Engels-Deutsch M. Contact killing and antimicrobial properties of copper. J Appl Microbiol 2018;124(5):1032–1046. https://doi.org/10.1111/jam.13681
49. Gupta R, Bhatty M, Swiatlo E, Nanduri B. Role of an iron-dependent transcriptional regulator in the pathogenesis and host response to infection with Streptococcus pneumoniae. PLoS One 2013;8(2):e55157. https://doi.org/10.1371/journal.pone.0055157
50. Olliver M, Spelmink L, Hiew J, Meyer-Hoffert U, Henriques-Normark B, Bergman P. Immunomodulatory effects of vitamin D on innate and adaptive immune responses to Streptococcus pneumoniae. J Infect Dis 2013;208(9):1474–1481. https://doi.org/10.1093/infdis/jit355
51. Mohammed KJ. The impact of Toxoplasma gondii infection on vitamin D levels in pregnant women: A mini review. Microbes Infect Dis 2025. https://doi.org/10.21608/mid.2025.394084.2898
52. Skrobot A, Demkow U, Wachowska M. Immunomodulatory role of vitamin D: A review. In: Current Trends in Immunity and Respiratory Infections. Cham: Springer; 2018. p. 13–23. https://doi.org/10.1007/5584_2018_246
53. Singh B, Eshaghian E, Chuang J, Covasa M. Do diet and dietary supplements mitigate clinical outcomes in COVID-19?. Nutrients 2022;14(9):1909. https://doi.org/10.3390/nu14091909
54. Kidd P. Th1/Th2 balance: The hypothesis, its limitations, and implications for health and disease. Altern Med Rev 2003;8(3):223–246. https://altmedrev.com/wp-content/uploads/2019/02/v8-3-223.pdf
55. Mason P, Jenkins G. Nutrition and immune function: A science review of the role of micronutrients in the immune system. Nutr Food Technol Open Access 2021;8(1):NFTOA175. https://doi.org/10.16966/2470-6086.175
56. Pyka P, Haberek W, Więcek M, Szymanska E, Ali W, Cios A, et al. First-in-class selenium-containing potent serotonin receptor 5-HT6 agents with a beneficial neuroprotective profile against Alzheimer's disease. J Med Chem 2024;67(2):1580–610.
57. Rizwan M, Cheng K, Gang Y, Hou Y, Wang C. Immunomodulatory effects of vitamin D and zinc on viral infection. Biol Trace Elem Res 2025;203(1):1–7.
58. Sadler RA, Mallard BA, Shandilya UK, Hachemi MA, Karrow NA. The immunomodulatory effects of selenium: a journey from the environment to the human immune system. Nutrients 2024;16(19):3324.

https://doi.org/10.3390/nu16193324
59. Berger MM, Shenkin A, Dizdar OS, Amrein K, Augsburger M, Biesalski HK, et al. ESPEN practical short micronutrient guideline. Clin Nutr 2024;43(3):825–57.
60. Wang J, Xia C, Xia Z, Shen J. Disruption of zinc homeostasis reverses tigecycline resistance in Klebsiella pneumoniae. Front Cell Infect Microbiol 2025;15:1458945. https://doi.org/10.3389/fcimb.2025.1458945
61. Subramanian K, Bergman P, Henriques-Normark B. Vitamin D promotes pneumococcal killing and modulates inflammatory responses in primary human neutrophils. J Innate Immun 2017;9(4):375–86.
62. Liu X, Zeng W, Zhou W, Zheng D, Yang X, Liao W. Association between dietary fatty acid intake and preserved ratio impaired spirometry in US adults: a population-based cross-sectional study. Frontiers in Nutrition. 2025 Jul 30;12:1622795.
63. Mohammed KJ, Hasan MK, Imran AF. How do essential vitamins and minerals boost the immune system against tuberculosis?. Bull Pharm Sci Assiut Univ. 2025; https://doi.org/10.21608/bfsa.2025.387334.2567
64. Womack E, Alibayov B, Vidal JE, Eichenbaum Z. Endogenously produced H2O2 is intimately involved in iron metabolism in Streptococcus pneumoniae. Microbiol Spectr. 2024;12(1):e03297-23. https://doi.org/10.1128/spectrum.03297-23
65. Tan Y, Qiu L, Li D, Liu X, Gao P. Structural elucidation, antioxidant and neuroprotective features of Physalis pubescens L. polysaccharide and its selenium-modified product. Nat Prod Res. 2025:1–9.
66. Sun Y, Liu H, Jiang J, Hu L, Ma Q, Li S, et al. High-Calorie Diets Exacerbate Lipopolysaccharide-Induced Pneumonia by Promoting Propionate-Mediated Neutrophil Extracellular Traps. Nutrients. 2025 Jul 7;17(13):2242.
67. Hemilä H, Louhiala P. Vitamin C for preventing and treating pneumonia. Cochrane Database Syst Rev 2013;2013(8):CD005532. https://doi.org/10.1002/14651858.CD005532.pub3
68. Issae AR, Katakweba AS, Kicheleri RP, Chengula AA, Van Zwetselaar M, Kasanga CJ. Exploring pathogenic and zoonotic bacteria from wild rodents, dogs, and humans of the Ngorongoro district in Tanzania using metagenomics next-generation sequencing. Zoonotic Diseases. 2023 Sep 1;3(3):226-42.
69. Lenti MV, Hammer HF, Tacheci I, Burgos R, Schneider S, Foteini A, et al. European Consensus on Malabsorption—UEG & SIGE, LGA, SPG, SRGH, CGS, ESPCG, EAGEN, ESPEN, and ESPGHAN: Part 2: Screening, Special Populations, Nutritional Goals, Supportive Care, Primary Care Perspective. United European Gastroenterology Journal. 2025 Mar 15.
70. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: Systematic review and meta-analysis of individual participant data. BMJ 2017;356:i6583. https://doi.org/10.1136/bmj.i6583
71. Brown N, Kukka AJ, Mårtensson A. Efficacy of zinc as adjunctive pneumonia treatment in children aged 2 to 60 months in low-income and middle-income countries: A systematic review and meta-analysis. BMJ Paediatr Open 2020;4(1):e000662. https://doi.org/10.1136/bmjpo-2020-000662
72. Bermano G, Méplan C, Mercer DK, Hesketh JE. Selenium and viral infection: Are there lessons for COVID-19? Br J Nutr 2021;125(6):618–627. https://doi.org/10.1017/S0007114520003128
73. Wang C, Porta L, Yang TK, Wang YH, Wu TH, Qian F, et al. Optimal methods of vitamin D supplementation to prevent acute respiratory infections: A systematic review, dose–response and pairwise meta-analysis of randomized controlled trials. Nutr J 2024;23:92. https://doi.org/10.1186/s12937-024-00990-w
74. Mohammed KJ, Kenoosh HA, Akeel M. microbial enzymes in lipid metabolism: unveiling the key players in health and disease. Bull Pharm Sci Assiut Univ. 2024; 47(2): 1367-1378. https://doi: 10.21608/bfsa.2024.311734.2236
75. Guillin OM, Vindry C, Ohlmann T, Chavatte L. Selenium, selenoproteins and viral infection. Nutrients 2019;11(9):2101. https://doi.org/10.3390/nu11092101