IMPACT OF VITAMIN D DEFICIENCY ON IMMUNE FUNCTION AND RECURRENT RESPIRATORY TRACT INFECTIONS IN PEDIATRIC PATIENTS: AN EVIDENCE-BASED CLINICAL REVIEW

Institution: Tashkent State Medical University

Author: Bekmurotova Sarvinoz Komiljon qizi

Qodirova Marjona Oybek qizi

Imomaliyeva Layloxon Sohibjon qizi

E-mail: bekmuratovasarvinoz01@gmail.com

marjonaqodirova0503@gmail.com

imomaliyevalaylo701@gmail.com

Scientific Supervisor: Alyaviya Muzayyanaxon Nozimxonovna

ABSTRACT

Background

Vitamin D is traditionally recognized for its essential role in calcium metabolism and skeletal development; however, increasing evidence indicates that it also plays an important role in immune regulation. Vitamin D receptors are expressed in several immune cell populations, suggesting that vitamin D status may influence host defense against infectious diseases. Respiratory tract infections are ***among the most common causes of illness in children, and recurrent infections Sentabr*** result in substantial morbidity and healthcare utilization.

Objective

This review aimed to examine the relationship between vitamin D deficiency, immune function, and recurrent respiratory tract infections in pediatric patients and to evaluate the current evidence regarding the potential preventive role of vitamin D supplementation.

Methods

Relevant scientific literature concerning vitamin D status, immune function, and respiratory tract infections in children was reviewed using evidence indexed in

PubMed and other major biomedical databases. Particular attention was given to systematic reviews, meta-analyses, randomized controlled trials, and pediatric clinical studies. Recent evidence published through 2026 was considered.

Results

Available evidence suggests that vitamin D participates in both innate and adaptive immune responses. Vitamin D may enhance antimicrobial defense through the regulation of antimicrobial peptides and may influence inflammatory and cellular immune responses. Several observational studies have reported an association between low serum 25-hydroxyvitamin D [25(OH)D] concentrations and an increased susceptibility to respiratory infections in children. However, interventional studies have produced inconsistent results. A recent meta-analysis of 17 randomized controlled trials involving 18,372 pediatric participants found no statistically significant overall reduction in acute respiratory infection incidence with vitamin D supplementation, although a subgroup receiving daily low-dose supplementation of ≤1000 IU/day demonstrated a lower risk of infection.

Conclusion

Vitamin D deficiency may contribute to impaired immune regulation and may be associated with increased susceptibility to respiratory tract infections in some pediatric populations. Nevertheless, current evidence does not support universal vitamin D supplementation solely for the prevention or treatment of respiratory infections. Assessment of vitamin D status and individualized management may be particularly relevant in children at increased risk of deficiency.

Keywords: vitamin D deficiency; pediatric patients; respiratory tract infections; recurrent infections; immune function; 25-hydroxyvitamin D; vitamin D supplementation; children.

Introduction

Respiratory tract infections (RTIs) represent one of the most frequent causes of morbidity among children worldwide. They include a broad spectrum of conditions affecting the upper and lower respiratory tract, including common viral

respiratory infections, bronchitis, bronchiolitis, pneumonia, and other infectious disorders. Although many childhood respiratory infections are self-limiting, recurrent or severe infections may result in repeated medical consultations, antibiotic exposure, school absenteeism, hospitalization, and considerable socioeconomic burden.

In recent years, increasing attention has been directed toward the potential role of vitamin D in host defense against infectious diseases. Vitamin D is a fat-soluble hormone-like vitamin that is essential for calcium homeostasis and normal skeletal development. Beyond its classical metabolic functions, vitamin D has immunomodulatory properties that may influence both innate and adaptive immune responses. Immune cells, including macrophages, dendritic cells, and lymphocytes, express vitamin D receptors, providing a biological basis for its involvement in immune regulation.



Vitamin D status is commonly assessed by measuring serum 25-hydroxyvitamin D [25(OH)D]. Low concentrations have been reported in children from different geographical and socioeconomic populations. Factors contributing to

inadequate vitamin D status include limited sunlight exposure, dietary insufficiency, increased body mass, malabsorption, and certain chronic diseases.

The relationship between vitamin D deficiency and respiratory infections in children has been investigated for more than a decade. Several observational studies have reported that children with lower vitamin D concentrations may have a higher risk of respiratory infections. However, randomized controlled trials evaluating vitamin D supplementation have produced heterogeneous results. A systematic review published in 2023 found that the association between vitamin D supplementation and prevention of respiratory infections in children younger than six years was inconsistent across studies.

More recent evidence has further complicated the interpretation of this relationship. A 2025 systematic review and meta-analysis of 17 randomized controlled trials involving 18,372 pediatric participants found that vitamin D supplementation did not significantly reduce overall acute respiratory infection incidence. However, a subgroup analysis suggested a preventive effect with daily low-dose supplementation of up to 1000 IU/day.

Therefore, understanding the relationship between vitamin D status and recurrent respiratory infections requires consideration of both biological mechanisms and clinical evidence.

The purpose of this review is to summarize current evidence regarding the role of vitamin D in pediatric immune function and its potential association with recurrent respiratory tract infections.

Biological Functions of Vitamin D in the Immune System

Vitamin D influences the immune system through multiple mechanisms. Following conversion into its active metabolites, vitamin D interacts with the vitamin D receptor (VDR), which is expressed in numerous tissues and immune cells.

One important aspect of vitamin D activity is its effect on innate immunity. Vitamin D can stimulate the production of antimicrobial peptides, including

cathelicidin and β-defensins. These molecules contribute to the body's first-line defense against microorganisms by interfering with pathogen survival and supporting epithelial barrier function.

Vitamin D also influences macrophage activity and other components of innate immunity. Experimental studies involving pediatric respiratory pathogens have suggested that vitamin D can modify inflammatory responses and may reduce excessive inflammation. However, these effects are complex and may depend on the concentration of vitamin D, timing of exposure, cell type, and pathogen involved.

In addition to innate immunity, vitamin D participates in the regulation of adaptive immune responses. Vitamin D may influence T-cell differentiation, cytokine production, and antigen-presenting cell activity. These immunomodulatory effects have led researchers to hypothesize that vitamin D deficiency could compromise appropriate host responses to respiratory pathogens.

Importantly, the immune effects of vitamin D should not be interpreted as evidence that supplementation necessarily prevents infection. Biological plausibility and clinical effectiveness are distinct concepts, and clinical trials have not consistently demonstrated a protective effect.

Vitamin D Deficiency in Pediatric Patients

Vitamin D deficiency is a global health concern and can occur in children despite differences in climate and sunlight availability. The concentration of serum 25(OH)D is generally used to evaluate vitamin D status, although thresholds used to define deficiency and insufficiency vary among organizations and studies.

The interpretation of vitamin D concentrations is complicated by differences in laboratory methods, patient populations, geographic regions, season, age, and clinical characteristics. Earlier pediatric literature has emphasized that there is no universally accepted concentration that precisely defines the level required specifically for protection against respiratory infection.



Several factors may increase the likelihood of low vitamin D levels in children. These include inadequate dietary intake, limited outdoor activity, reduced exposure to ultraviolet B radiation, increased skin pigmentation, obesity, malabsorption disorders, and chronic illnesses.

Children with low vitamin D concentrations may therefore represent a clinically heterogeneous group. A low 25(OH)D concentration may be a marker of nutritional status, lifestyle, chronic disease, or other factors rather than an independent cause of recurrent infection.

Vitamin D Deficiency and Recurrent Respiratory Tract Infections

Recurrent respiratory tract infections are common during childhood, particularly among young children who have frequent contact with other children in daycare and school environments. Most recurrent infections are caused by common respiratory viruses and do not necessarily indicate an underlying immune disorder.

Nevertheless, researchers have investigated whether vitamin D deficiency could contribute to increased susceptibility to respiratory infections.

A systematic review specifically examining vitamin D deficiency and respiratory infections among children concluded that several studies supported an association between vitamin D deficiency and increased susceptibility or severity of respiratory infections. At the same time, the authors emphasized differences between studies and limitations in the available evidence.

Previous pediatric reviews have also described associations between vitamin D deficiency and particular respiratory conditions, including severe bronchiolitis and recurrent acute otitis media. However, evidence for other conditions, such as recurrent pharyngotonsillitis, rhinosinusitis, and community-acquired pneumonia, has been less consistent.

This distinction is important because respiratory infections are not a single clinical entity. Different pathogens, anatomical sites, disease severities, and host factors may influence the relationship between vitamin D and infection risk.

Evidence from Pediatric Clinical Studies

Clinical studies investigating vitamin D and respiratory infections have produced mixed findings.

A 2023 systematic review evaluated eight studies involving 2,189 children aged 0–5 years. The included evidence consisted of randomized trials, case-control studies, and a prospective cohort study. Some studies reported associations between low vitamin D levels and respiratory infections, while others did not identify statistically significant differences in infection incidence or severity. The authors concluded that the available evidence was insufficiently consistent to establish a definitive preventive effect.

The heterogeneity among studies may be explained by several factors. These include differences in vitamin D dosage, duration of supplementation, baseline vitamin D status, age of participants, geographical location, season, type of respiratory infection, and clinical outcome definitions.

For example, supplementation may theoretically have a different effect in a child with severe vitamin D deficiency compared with a child who already has an adequate vitamin D concentration. Similarly, continuous daily supplementation may produce different biological effects compared with intermittent high-dose administration.

These methodological differences should be considered when interpreting apparently contradictory findings.

Recent Evidence from Randomized Controlled Trials

More recent evidence provides an important perspective on the clinical significance of vitamin D supplementation.

A systematic review and meta-analysis published in 2025 included 17 randomized controlled trials involving 18,372 pediatric participants. Overall, vitamin D supplementation was not associated with a statistically significant reduction in acute respiratory infection incidence. It also did not significantly reduce hospitalization duration, recovery time, or all-cause mortality.

However, the analysis identified a potentially important subgroup effect. Children receiving daily low-dose supplementation of ≤1000 IU/day demonstrated a lower risk of acute respiratory infection, with a reported risk ratio of 0.42 (95% CI: 0.27–0.66). This finding should be interpreted as subgroup evidence rather than proof that vitamin D supplementation should be universally prescribed to children.

Another recent Cochrane review of vitamin D supplementation for prevention of acute respiratory infections in children up to five years of age reported that supplementation may produce a small reduction in the proportion of children seeking healthcare for acute respiratory infection, although the certainty of evidence was low for this outcome. The review also found that supplementation did not clearly reduce the average number of infection-related healthcare visits per child.

Together, these findings indicate that the clinical effect of vitamin D is likely to be influenced by population characteristics, baseline vitamin D status, dosing strategy, and outcome definition.

Potential Mechanisms Linking Vitamin D and Respiratory Infection

Several mechanisms have been proposed to explain the potential association between vitamin D status and respiratory infection susceptibility.

First, vitamin D may strengthen innate antimicrobial defenses. Activation of vitamin D signaling can promote antimicrobial peptide production, potentially improving the ability of respiratory epithelial cells and immune cells to respond to pathogens.

Second, vitamin D may influence inflammatory responses. Respiratory infections require an effective immune response for pathogen elimination, but excessive inflammation can contribute to tissue injury. Experimental studies suggest that vitamin D can modulate inflammatory signaling, although the exact clinical significance of this mechanism remains uncertain.

Third, vitamin D may affect adaptive immune regulation through interactions with T cells and antigen-presenting cells.

Finally, vitamin D may influence the integrity and function of epithelial barriers. Since the respiratory epithelium represents a major physical barrier against inhaled pathogens, maintaining its function is an important component of host defense.

These mechanisms provide biological plausibility for a relationship between vitamin D and respiratory infection; however, mechanistic evidence alone cannot establish a clinical treatment effect.

Clinical Implications

The available evidence suggests several important clinical considerations.

First, vitamin D deficiency should be recognized as a nutritional and metabolic problem that may require evaluation according to the individual child's risk factors and clinical circumstances.

Second, recurrent respiratory infections should not automatically be attributed to vitamin D deficiency. Recurrent infections can result from normal childhood exposure to respiratory pathogens, environmental factors, anatomical conditions, allergic disease, or, in selected cases, underlying immune disorders.



Third, vitamin D supplementation should not be considered a replacement for established preventive measures such as vaccination, adequate nutrition, hand hygiene, appropriate environmental conditions, and evidence-based management of respiratory infections.

Fourth, universal vitamin D supplementation solely for the prevention of respiratory infections is not currently supported by the strongest available clinical evidence. The most recent pediatric meta-analysis concluded that supplementation cannot be recommended as a universal intervention for childhood acute respiratory infections.

Limitations of the Current Evidence

The current evidence base has several limitations.

Studies differ substantially in their definitions of vitamin D deficiency and respiratory infection. Different laboratory methods are used to measure 25(OH)D, and different threshold values may influence the classification of participants.

Furthermore, clinical trials have used different vitamin D preparations, doses, dosing intervals, and treatment durations. Some studies enrolled children with documented deficiency, whereas others included general pediatric populations without selecting participants according to baseline vitamin D status.

Seasonal variation is another important factor. Vitamin D concentrations can vary according to sunlight exposure, while respiratory infections also demonstrate

strong seasonal patterns. Therefore, distinguishing the effects of vitamin D from seasonal and environmental factors can be difficult.

Finally, observational associations cannot establish causality. Children with chronic illness, poor nutrition, or limited outdoor activity may have both lower vitamin D concentrations and increased infection risk. In such circumstances, vitamin D deficiency may partly reflect overall health status rather than directly cause recurrent infection.

Directions for Future Research

Future clinical research should focus on well-designed pediatric trials with clearly defined inclusion criteria and standardized measurements of serum 25(OH)D.

Studies should distinguish between children with confirmed vitamin D deficiency and children with adequate vitamin D status. Researchers should also evaluate whether the effect of supplementation differs according to age, baseline vitamin D concentration, season, nutritional status, and type of respiratory infection.

Standardized definitions of recurrent respiratory infection would improve comparison between studies.

Future trials should also examine clinically meaningful outcomes, including infection frequency, hospitalization, duration of symptoms, antibiotic use, and disease severity rather than relying exclusively on laboratory or biochemical outcomes.

Further investigation of the interaction between vitamin D status and specific immune markers may help clarify which pediatric populations could potentially benefit from supplementation.

Conclusion

Vitamin D has important biological functions beyond skeletal health and participates in the regulation of innate and adaptive immune responses. Existing evidence indicates that low vitamin D status may be associated with increased susceptibility to respiratory tract infections in some pediatric populations.

However, the relationship is complex. Although observational and mechanistic studies provide biological plausibility, randomized controlled trials have not consistently demonstrated that vitamin D supplementation prevents respiratory infections or improves outcomes once infection has developed.

Recent evidence involving thousands of pediatric participants suggests that universal vitamin D supplementation cannot currently be recommended solely as a strategy for preventing acute respiratory infections. At the same time, selected subgroups, particularly children receiving daily low-dose supplementation or children at risk of vitamin D deficiency, may warrant further investigation.

Therefore, vitamin D assessment and management should be considered within the broader clinical and nutritional context of each child. Future high-quality pediatric research is needed to determine whether specific populations, dosing strategies, or baseline vitamin D levels are associated with clinically meaningful benefits.

References

1. Holick MF. Vitamin D deficiency. *New England Journal of Medicine*. 2007;357(3):266–281.
2. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *American Journal of Clinical Nutrition*. 2004;79(3):362–371.
3. Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. *Chemistry & Biology*. 2014;21(3):319–329.
4. Aranow C. Vitamin D and the immune system. *Journal of Investigative Medicine*. 2011;59(6):881–886.
5. Hewison M. Vitamin D and the immune system: new perspectives on an old theme. *Endocrinology and Metabolism Clinics of North America*. 2010;39(2):365–379.

6. Hewison M. An update on vitamin D and human immunity. *Clinical Endocrinology*. 2012;76(3):315–325.
7. Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. *Nutrients*. 2013;5(7):2502–2521.
8. 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.
9. Bartley J. Vitamin D, innate immunity and upper respiratory tract infection. *Journal of Laryngology & Otology*. 2010;124(5):465–469.
10. Martineau AR, Jolliffe DA, Hooper RL, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ*. 2017;356:i6583.
11. Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *American Journal of Clinical Nutrition*. 2010;91(5):1255–1260.
12. Murdaca G, Tonacci A, Negrini S, et al. Emerging role of vitamin D in autoimmune diseases: an update on evidence and therapeutic implications. *Autoimmunity Reviews*. 2019;18(9):102350.
13. Cannell JJ, Hollis BW. Use of vitamin D in clinical practice. *Alternative Medicine Review*. 2008;13(1):6–20.
14. Pilz S, Zittermann A, Trummer C, et al. Vitamin D testing and treatment: a narrative review of current evidence. *Endocrine Connections*. 2019;8(2):R27–R43.
15. Amrein K, Scherkl M, Hoffmann M, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. *European Journal of Clinical Nutrition*. 2020;74:1498–1513.