

Respiratory Tract Infections and Antibiotic Resistance: A Protective Role for Vitamin D?

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Abstract

Upper and lower respiratory tract infections are amongst the most common infections globally, and in the United Kingdom they account for about half of all oral antibiotics prescribed. Antibiotic overuse and the emergence of “superbugs” that are resistant to their effects is a global problem that is becoming a serious concern. Considering this, the potential role of immunonutrition as a “prehabilitation” in helping to tackle bacterial infections and reduce over-reliance on antibiotic usage is gaining interest. This narrative mini review summarizes current knowledge on the roles of certain nutrients in helping to modulate immune function, with particular focus on vitamin D. Vitamin D supplementation appears to reduce the risk of acute respiratory tract infections and thus could have a valuable to play in reducing over reliance on antibiotics. Investment in high-quality trials is needed to further explore this field.

Introduction

There has been an upsurge of novel bacterial, viral, and fungal respiratory pathogens which are becoming increasingly challenging to treat, with respiratory tract infections (RTIs) being exacerbated by antibiotic resistance of Gram-positive and Gram-negative bacteria [1]. Acute respiratory tract infections (ARTIs), which include upper respiratory infections (URTIs), are, amongst adults, the most common cause of antibiotic prescription [2]. In the United Kingdom, an examination of over 8 million patient records from 587 general practices showed that URTIs accounted for around 31% of oral antibiotic prescriptions and lower respiratory tract infections (LRTIs) around 19% [3].

The very first antibiotic, salvarsan, was developed in 1910 whilst penicillin discovery by Alexander Fleming followed in 1928 [4]. Multiple antibiotics have been discovered since then, but now, after about 100 years of the “antibiotic era”, fewer new antibiotics are being identified and significant antibiotic resistance has emerged [4]. The World Health Organisation considers that the unprecedented use of antibiotics and subsequent antimicrobial resistance (AMR) is currently one of the largest threats to global health, food security and human development [5; 6].

In 2016, ARTIs were responsible for approximately 2.38 million deaths globally [7; 8]. Within the European Union 25,000 people have been estimated to die annually because of AMR with resultant societal costs of around 1.5 billion euros annually [9]. By 2050 it has been estimated that some 10 million people globally could die annually as a result of AMR – with 390,000 Europeans estimated to be affected and even larger proportions of Asian (4,730,000 and) African (4,140,000) populations [6]. It has been further predicted that standard antibiotic treatments may no longer work, subsequently making infections more difficult to treat and control [10].

Giving the high prevalence of ARTIs coupled with rising rates of AMR, novel approaches are needed for the future. The concept of “prehabilitation”, including the role of immunonutrition, could play a pivotal role in helping to both prevent and offset RTIs should these occur. Prehabilitation has been well defined elsewhere as: *“interventions that can help to improve patient’s health in advance of being exposed to a physiological stressor so they are then better able to cope with that stress”* [11]. This narrative mini review describes how immunonutrition could become a valuable tool in conventional medicine. It focuses on ARTIs and vitamin D for which there is an expanding body of evidence.

Nutrition, infection, and immunity

The roles of nutrients in supporting the function of the immune system are numerous and varied, with an adequate and balanced supply of nutrients being required if a suitable immune response is to be mounted [12]. The immune system protects the body against infectious agents and is comprised of innate responses – the body’s first lines of defence - and adaptive responses which generate immunological memory [13]. It is known that a bidirectional relationship exists between nutrition, infection, and immunity with changes in one impacting on each of the others [14]. Micronutrients (vitamins and minerals) have extended roles influencing and supporting every stage of the human immune response [13]. Subsequently, deficiencies in one or more

micronutrients can impact on both innate and adaptive immunity, resulting in immunosuppression and exacerbating susceptibility to infections [13].

A host of nutrients have been implicated as being essential for immunocompetence, including vitamins A, B2, B6, B9 (folic acid), B12, C, D, E, and iron, zinc, selenium, copper, and magnesium [14]. Vitamins A, C, D, E and zinc are important for the structural and functional integrity of the body's external and mucosal barriers to invading pathogens [15]. Cellular processes of both innate and adaptive immunity, such as cell differentiation and proliferation, phagocytosis, respiratory burst, killing activity, cytokine production and antibody production are all dependent on suitable amounts of vitamins A, D, C, E, B6 and B12, folate, iron, zinc, copper, selenium, and magnesium [15].

This mini review focuses on vitamin D, due to the growing body of evidence favouring a role for vitamin D in preventing ARTIs. Vitamin D augments host barrier epithelial integrity by reinforcing intercellular junctions [16]. It has also been found to trigger antimicrobial peptide production which exhibits direct pathogen-killing capacity [17]. The vitamin D receptor is expressed on many immune cell types including B-cells, T-cells and antigen-presenting cells [18; 19; 20]. Furthermore, some immune cell types, including macrophages and dendritic cells, can synthesise the active form of vitamin D, 1,25-dihydroxyvitamin D₃ [21]. These two observations suggest a high importance for vitamin D within the immune system. Indeed, vitamin D deficiency results in impaired localized innate immunity and a defective antigen-specific cellular immune response, correlated with a higher susceptibility to infections [22]. Vitamin D metabolites have also been found to influence the expression and secretion of pro-inflammatory chemokines and cytokines [23], and vitamin D promotes the production of antimicrobial peptides such as cathelicidin [21; 24].

An established body of evidence now shows that 1,25-dihydroxyvitamin D₃ influences endothelial membrane stability and acts on multiple parts of the innate and adaptive immune responses [21]. Low levels of 1,25-dihydroxyvitamin D₃ correlate with an increased risk of developing several immune-related disorders including respiratory infection and COVID-19 [21]. Vitamin D has further been found to be involved in pulmonary angiotensin-converting enzyme 2 expression and has the ability to reduce lung surface tension in COVID-19 [25]. Other work suggests that vitamin D may induce progesterone-induced blocking factor and exert

inhibitory effects on inflammation including the cytokine IL-6 which tend to be elevated in COVID-19 infections [26].

Vitamin D and Respiratory Tract Infections

A growing number of studies have investigated the role vitamins D on the occurrence of ARTIs. Table 1 summarises evidence from meta-analyses and Table 2 evidence from RCTs, published in the last 5 years with a focus on adulthood, although some meta-analyses included extended age ranges.

Two meta-analyses focused on observational research [27; 28] and four focused on evidence from RCTs [29; 30; 31]. Those collating observational findings found inverse relationships between serum 25-hydroxyvitamin D levels and risk and severity of ARTIs [27] and risk of community-acquired pneumonia [28]. Meta-analyses pooling evidence from RCTs focused on findings from vitamin D supplementation programmes represent a higher level of evidence since they can establish a cause-and-effect relationship. The largest meta-analysis included data from 45 RCTs (n=73,384 subjects) concluding that daily dosing regimens providing 400-1000 IU (10-25 µg) of vitamin D were most effective at protecting against ARTIs [29]. Earlier meta-analyses reported similar findings: that vitamin D supplementation lowered ARTI risk [30], particularly amongst those with profound 25-hydroxyvitamin D deficiency at baseline [30]. Focusing on vitamin D supplementation, a separate meta-analysis (15 RCTs, n=7,053) observed a 6% risk reduction of clinical RTIs but this was not statistically significant and heterogeneity amongst the included studies was high (I-squared 57%) [31].

Evidence from individual RCTs has reported similar findings. Five studies reported that vitamin D supplementation reduced the incidence [32; 33; 34], duration and severity [35], and symptoms [36] of RTIs. Amongst asthmatic patients, Ramos-Martinez *et al.* observed that vitamin D reduced RTIs, an effect which correlated with higher sputum levels of IL-10, IFN-γ and cathelicidin LL-37 [34]. Vitamin D dosages used among the different studies were highly variable, ranging from just 10 IU (0.25 µg daily) [34] up to 4,000 IU (100 µg daily) [33]. Similarly, durations of RCTs were also wide-ranging with the shortest being 4 weeks [36] and the longest, conducted in health-care residents, being over a 12-month period [33].

Regarding pathological cause of infection only four studies clearly specified whether these were bacterial [31; 34; 37] or viral [32]. The remaining studies focused on the location, duration and/or severity of RTIs but their source was not clearly defined nor diagnosed.

Discussion and Conclusions

Presently, vitamin D guidelines in the United Kingdom have been set at 10 µg daily from October to March to keep bones, teeth and muscles healthy [38]. However, given updated meta-analytical evidence and a growing number of RCTs, combined with the global COVID-19 pandemic, it seems timely that this advice should be updated to encompass respiratory health with the required supplemental dose being re-evaluated. Clearly, vitamin D intakes should conform to recommended upper safety limits established by expert authorities with the European Food Safety Authority setting an Upper Limit of 100 µg/day for adults, including pregnant and lactating women [39]. Equally, supplementation should always be in addition to the consumption of a healthy, varied, and well-balanced diet. Nevertheless, a more desirable level of intake of vitamin D taking the latest evidence into account would be 2000 IU (50 µg) daily to reduce the risk of ARTIs [40]

Regarding antibiotic use, more clinical studies evaluating the impact of vitamin D are needed as an outcome alongside ARTI incidence, symptoms, and severity. One Cochrane review evaluated evidence from seven studies where vitamin D was used as an adjunct to antibiotics to treat pneumonia, but findings were inconclusive [41]. In Sweden, vitamin D3 supplementation (1500-1600 IU (37.5-40 µg) daily over 12 months) was found to significantly reduce antibiotic usage – from 20 to 15 days per person [42]. Equally future studies should clearly define the origin of pathological RTIs. It is possible that different vitamin D dosing regimens may be warranted for viral and bacterial infections but there is presently not enough evidence to draw firm conclusions on this.

AMR poses a threat to future global health and the current COVID-19 pandemic is highly damaging to health, societies and economies. Urgent responses are needed. Supporting the immune system of the population in advance of exposure to infections (i.e. “immune prehabilitation”) would reduce the number and severity of infections and reduce use of antibiotics. Vitamin D has multiple roles in supporting the immune system [21; 43; 44] and evidence from RCTs demonstrates that supplemental vitamin D reduces risk of acquiring RTIs [32; 33; 34] as well as their duration and severity [35; 36] and may reduce antibiotic use [42].

There is also evidence that individuals with better vitamin D status are less likely to develop COVID-19 and severe COVID-19 [45; 46; 47]. Given these observations, guidance of vitamin D intake should consider immune health, in addition to bone, tooth and muscle health. Higher vitamin D intake in the population would reduce infections, result in infections being less severe and reduce use of antibiotics. The RCTs that form the current evidence base have highly variable designs including substantial differences in dose of vitamin D used, regularity of dosing and duration of dosing. Thus, further clinical trials and meta-analytical approaches are warranted to clarify matters of dose, dosing regimen and the precise relationship between vitamin D status and immune and respiratory health in different groups of the population including older people and different ethnicities.

Table 1: Summary of meta-analyses of Vitamin D and RTIs with a focus on adults.

Author(s)	Details of studies included	Study Type	Infection Definition/ Form	Publication focus	Main findings
Meta-analysis publications					
Jolliffe <i>et al.</i> (2020) [29]	45 RCTs (n = 73,384)	Meta-analysis (Update: additional RCTs added to Martineau <i>et al.</i> (2019) meta-analysis)[30]	ARTIs - The definition of ARI encompassed URI, LRI and ARI of unclassified location (i.e., infection of the upper and/or lower respiratory tract). Form: Not Specified	RCTs of vitamin D supplementation	Protective effects against ARTIs were seen in trials where vitamin D was given: <ul style="list-style-type: none"> ○ Via a daily dosing regimen (OR 0.75, 95% CI 0.61-0.93) ○ at daily dose equivalents of 400–1000 IU (OR 0.70, 95% CI 0.55 to 0.89) ○ for a duration of ≤12 months (OR 0.82, 95% CI 0.72-0.93)
Pham <i>et al.</i> (2019) [27]	14 studies of ARTI risk (n = 78,127) 10 studies for trend analysis (n = 69,048) 5 studies ARTI and vitamin D concentration (n = 37,902)	Systematic review and meta-analysis of observational studies	ARTI, defined as an acute infection of the respiratory tract in either the lower or upper airway or with the location not specified. ARTI was either self-reported or clinically confirmed. Form: Not Specified	Vitamin D status	Serum 25(OH)D concentrations were inversely associated with risk and severity of ARTI (pooled OR 1.83, 95% CI 1.42-2.37 and OR 2.46, 95% CI 1.65-3.66 comparing the lowest with the highest 25(OH)D category, respectively)
Zhou <i>et al.</i> (2019) [28]	8 studies (n = 20,966)	Meta-analysis of observational studies.	Pneumonia infection. Form: Not Specified	Vitamin D status	Community-acquired pneumonia patients with vitamin D deficiency (serum 25(OH)D levels <20 ng/mL) experienced a significantly increased risk of pneumonia (OR 1.64, 95% CI 1.00 - 2.67)
Martineau <i>et al.</i> (2019) [30]	25 eligible RCTs (n =11,321; individuals aged 0 to 95 years)	Meta-analysis of RCTs	Classified as an upper respiratory tract infection, lower respiratory tract infection, and acute respiratory tract infection of unclassified location. Form: Not Specified	RCTs of vitamin D supplementation	Vitamin D supplementation lowered ARTI risk among all participants (OR 0.88 95% CI 0.81-0.96); effects were greater amongst those more deficient at baseline
Vuichard <i>et al.</i> (2016) [31]	15 RCTs (n = 7,053)	Meta-analysis of RCTs	The first episode of clinical RTI was reported as cold/influenza-like illness and laboratory confirmed by standard microbiological methods. Form: Bacterial	RCTs of vitamin D ₃ supplementation	There was a 6% risk reduction of clinical RTIs with vitamin D ₃ supplementation but this was not statistically significant (RR 0.94; 95% CI 0.88 to 1.00)

Key: ARTIs, acute respiratory tract infection; CI, confidence interval; LRTI, lower respiratory tract infection; OR, odds ratio; RTI, respiratory tract infection; URTI, upper respiratory tract infection.

Table 2: Summary of recent RCTs investigating the effect of vitamin D supplementation on RTIs in adults.

<i>Author(s)</i>	<i>Study Population</i>	<i>Study Type</i>	<i>Intervention</i>	<i>Infection Definition/Form</i>	<i>Main findings</i>
Arihiro <i>et al.</i> (2019) [32]	n = 223 patients with inflammatory bowel disease	6-month multicentre double-blind, placebo-controlled RCT	500 IU (12.5 µg) vitamin D or control daily	Influenza infection diagnosed using influenza virus test kits. Form: Viral	Incidence of URTI was significantly lower in the vitamin D group (RR 0.59; 95% CI, 0.35–0.98)
Slow <i>et al.</i> (2018) [48]	n = 60 vitamin D group, n = 57 placebo	6-week randomised, double-blind, placebo-controlled trial	Single high-dose vitamin D3 (200,000 IU)	Pneumonia that has been acquired outside of a hospital or health care setting. Form: Not specified	Vitamin D increased the complete resolution of pneumonia in participants with baseline vitamin D levels <25 nmol/L (OR 17.0, 95% CI 1.40–549.4) but this was of modest statistical significance ($p=0.043$)
Jung <i>et al.</i> (2018) [36]	n = 25 male taekwondo athletes aged 19–22 years	4-week double-blind, placebo-controlled RCT	5000 IU (125 µg) vitamin D ₃ or control daily	The Wisconsin Upper Respiratory Symptom Survey-11 (WURSS-11) was used Form: Not specified	Serum 25(OH)D levels increased by 256% and were inversely associated with total URTI symptoms ($r = -0.435, p = 0.015$).
Ramos-Martinez <i>et al.</i> (2018) [34]	n = 86 patients with asthma aged 18–50 years	6-month double-blind, placebo-controlled RCT	10 IU (0.25 µg) calcitriol (1,25-(OH) ₂ D ₃) or control daily	Respiratory infections in asthmatic patients. Form: Bacterial	Vitamin D supplementation reduced RTIs and reduced airways colonization by pathogenic bacteria
Shimizu <i>et al.</i> (2018) [35]	n = 428, aged 45–74 years	16-week double-blind, placebo-controlled RCT	400 IU (10 µg) vitamin D or control daily.	The Japanese version of Wisconsin Upper Respiratory Symptom Survey-21 (WURSS21) was used Form: Not specified	Vitamin D reduce the duration of URTI, the physical severity of URTI, and the quality of life when suffering from URTI
Ginde <i>et al.</i> (2017) [33]	n = 107 longer term care residents, aged over 60 years	12-month double-blind, parallel group, randomized controlled phase II trial	High dose (3,000–4,000 IU/75–100 µg day) or standard dose (400–1,000 IU/10–25 µg day).	Measured both upper (common colds, sinusitis, pharyngitis, otitis media) and lower (acute bronchitis, influenza, pneumonia) ARIs that required medical attention Form: Not specified	The high dose group had 0.67 ARIs per person-year compared to 1.11 in the standard dose group (incidence rate ratio 0.60; 95% CI 0.38–0.94; $p=0.02$)
He <i>et al.</i> (2016) [37]	n = 39 athletes during winter training	14-week placebo-controlled RCT	5000 IU (125 µg) vitamin D or control daily	Measured changes in antimicrobial peptides. Form: Bacterial	Blood and salivary analyses showed that serum 25(OH)D levels increased by 130% and vitamin D increased SIgA and cathelicidin which could improve resistance to respiratory infections

Key: UPTI, upper respiratory tract infection; CI, confidence interval; OR odds ratio.

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