Meta-Analysis

High-dose oral vitamin D supplementation for prevention of infections in children aged 0 to 59 months: a systematic review and meta-analysis

Janet Adede Carboo*, Robin Claire Dolman-Macleod, Linda Malan, and Martani Johanni Lombard

Centre of Excellence for Nutrition (CEN), North-West University, Potchefstroom, North West Province, South Africa
*Correspondence: *J.A. Carboo*, Centre of Excellence for Nutrition, North-West University, Private Bag X6001, Potchefstroom 2520, South Africa.

Context: *Vitamin D plays an important role in immune function, and the deficiency thereof has been associated with several infections, most notably respiratory tract infections. However, data from intervention studies investigating the effect of high-dose vitamin D supplementation on infections have been inconclusive.* ***Objective:*** *The aim of this study was to evaluate the level of evidence regarding the efficacy of vitamin D supplementation above the standard dose (400 IU) in preventing infections in apparently healthy children < 5 years of age.* ***Data Sources:*** *PubMed, Scopus, Science Direct, Web of Science, Google Scholar, CINAHL, and MEDLINE electronic databases were searched between August 2022 and November 2022. Seven studies met the inclusion criteria.* ***Data Extraction:*** *Meta-analyses of outcomes in more than one study were performed using Review Manager software. Heterogeneity was evaluated using the I^2 statistic. Randomized controlled trials in which vitamin D was supplemented at > 400 IU compared with placebo, no treatment, or standard dose were included.* ***Data Analysis:*** *Seven trials that enrolled a total of 5748 children were included. Odds ratios (ORs) with 95%CIs were calculated using random- and fixed-effects models. There was no significant effect of high-dose vitamin D supplementation on the incidence of upper respiratory tract infection (OR, 0.83; 95%CI, 0.62–1.10). There was a 57% (95%CI, 0.30–0.61), 56% (95%CI, 0.27–0.07), and 59% (95%CI, 0.26–0.65) reduction in the odds of influenza/cold, cough, and fever incidence, respectively, with daily supplementation of vitamin D > 1000 IU. No effect was found on bronchitis, otitis media, diarrhea/gastroenteritis, primary care visits for infections, hospitalizations, or mortality.* ***Conclusion:*** *High-dose vitamin D supplementation provided no benefit in preventing upper respiratory tract infections (moderate certainty of evidence) but reduced the incidence influenza/cold (moderate certainty of evidence), cough, and fever (low certainty of evidence). These findings are based on a limited number of trials and should be interpreted with caution. Further research is needed.*

Systematic Review Registration: *PROSPERO registration number CRD42022355206.*

Key words: *children, infections, pneumonia, upper respiratory tract infection, vitamin D supplementation.*

https://doi.org/10.1093/nutrit/nuad082

INTRODUCTION

Vitamin D, also known as calciferol, is a fat-soluble vitamin known primarily for its classical role in enhancing bone health. It also plays a role in immune function by modulating the expression of several genes involved in the differentiation, activation, and proliferation of immune and inflammatory cells. The benefit of vitamin D in immune function and inflammation remediation is explained by the expression of vitamin D receptors (VDRs) in various cells of both the innate and acquired immune system.[1]

There are two forms of vitamin D: D_3 and D_2. Vitamin D_3 (cholecalciferol) is synthesized mainly from 7-dehydrocholesterol in the skin upon exposure to ultraviolet B radiation of approximately 290 to 315 nm wavelength.[2] Cutaneous synthesis of vitamin D_3 contributes a large proportion of vitamin D_3 in the body. Vitamin D_3 is also found naturally in animal foods such as fatty fish and egg yolk and can be obtained from fortified dairy products and dietary supplements. However, this only provides a small proportion of vitamin D_3 in blood. Vitamin D_2 (ergocalciferol), in contrast, is present in plant food sources such as mushrooms grown under ultraviolet light.[3]

Vitamin D_2 and D_3 act as prohormones and produce the same biological effects.[4] To convert vitamin D_2 and vitamin D_3 into their active states, both are sequestered by vitamin D–binding protein in the liver, where they are converted to 25-hydroxyvitamin D (25[OH]D), also known as calcidiol, by the enzyme 25-hydroxylase (CYP2R1).[5] Although calcidiol is inactive, it is the major form of vitamin D in the body, and thus calcidiol serum concentrations are measured to assess vitamin D status clinically.[6] Calcidiol is converted to the active hormone 1α,25-dihydroxyvitamin D (1α,25$[OH]_2$D), also known as calcitriol, in the kidney by the enzyme 1α,hydroxylase (CYP27B1) and is subsequently released into the blood circulation. Calcitriol exerts its biological effect by binding to VDRs found in the nuclear membrane of various target tissues and cells. These VDRs have been found in the pancreas, brain, placenta, colon, respiratory tract, and tissues of the immune, cardiovascular, and neurological systems.[3,5] Calcitriol bound to VDRs in cells of the innate and adaptive immune system activates the expression of anti-inflammatory cytokines and antimicrobial peptides.[1]

Vitamin D deficiency is emerging as a common problem worldwide and has been associated with both infectious and noncommunicable diseases.[7] According to the American Academy of Pediatrics and the Institute of Medicine, vitamin D sufficiency is defined as a serum concentration of calcidiol greater than 20 ng/mL (50 nmol/L). However, the Endocrine Society defines sufficiency as a calcidiol concentration of 30 ng/mL (75 nmol/L) or more.[8,9] Globally, the prevalence of vitamin D deficiency varies, ranging from approximately 30% to 60% in Europe, to 42% in the United States, and up to 80% in Middle Eastern countries.[10,11] In Africa, the prevalence of serum calcidiol below 20 ng/mL and below 30 ng/mL has been reported as 34% and 60%, respectively.[12] This prevalence is higher than expected, considering the availability of abundant sunshine on the continent.

Limited sunlight exposure is recognized as a major cause of low serum vitamin D.[13,14] Dark skin pigmentation (melanin shields the skin against ultraviolet radiation and limits vitamin D synthesis) and variations in the genetic expression and activity of key enzymes involved in the metabolism of vitamin D have been identified as biological risk factors for vitamin D deficiency.[15,16] Pathological risk factors for vitamin D deficiency include, among others, impaired intestinal absorption due to gut inflammation or bile salt malabsorption; liver cirrhosis and renal failure (compromise vitamin D metabolism); chronic infection (increases vitamin D utilization and turnover); and long-term use of certain medications (eg, anticonvulsants, rifampicin, nifedipine, clotrimazole, and antiretroviral agents, which induce hepatic CPY450 enzymes that increase the degradation of vitamin D).[17–20] In children, exclusive breastfeeding is an additional risk factor, as breast milk is not a good source of vitamin D and its concentration is dependent on maternal intake.[21] Moreover, sunlight exposure (the primary source of vitamin D) is limited or inhibited in children because of urbanization as well as the association of ultraviolet light with skin cancer.[22,23] Poor nutrition in children is a also contributor to low serum vitamin D concentrations.[23] In low-income countries, where the availability of fortified foods might be limited, the dietary contribution of vitamin D in children may be minimal.[12]

Vitamin D deficiency in children has become a challenge in both high-income and low-income countries. A pooled analysis of vitamin D deficiency in children from several African countries, including Algeria, Botswana, Egypt, Ethiopia, Kenya, Nigeria, South Africa, Tanzania, and Tunisia, showed a prevalence of approximately 23%.[12] In Ghana, Oteng[24] observed the prevalence of vitamin D deficiency in healthy schoolchildren to be 49.1%. In Middle Eastern countries such as Iran,[25,26] Lebanon,[27,28] Jordan,[29,30] Saudi Arabia,[31–33] Qatar,[34] and the United Arab Emirates,[35] a tremendously high prevalence of vitamin D deficiency, up to 97%, has been reported among children. The situation is no different in high-income countries. The estimated prevalence of vitamin D deficiency and insufficiency among

children is up to 69% in the United States[36] and up to 92% in Denmark.[37]

To ensure sufficient vitamin D intake for the maintenance of bone health, most pediatric guidelines are unanimous in recommending the standard dose of 400 IU and 600 IU of vitamin D daily, respectively, for healthy infants (0–1 year) and children (1–18 years).[8,38,39] However, it is not clear whether this recommendation is sufficient to provide all the potential nonskeletal health benefits of vitamin D to maximize immune function and reduce susceptibility to infection.[8] According to the Endocrine Society, to maintain a blood calcidiol concentration consistently above sufficient levels (30 ng/mL), a daily dose of 1000 IU is required.[8] For correction of vitamin D deficiency, higher dosages of 2000 IU/d or 50 000 IU/wk may be needed for at least 6 weeks to achieve concentrations above 30 ng/mL, followed by a maintenance dosage of 400 to 1000 IU/d. Vitamin D is generally safe, although toxicity with hypercalcemia following inappropriate self-administration or prescription by physicians can occur at extremely high daily doses ranging from 50 000 IU to 2 604 000 IU.[40]

Description of the intervention

The role of vitamin D in bone mineralization is well documented, and vitamin D has been used over several decades for the prevention and treatment of nutritional rickets.[1] Recent studies, however, have reported the benefits of vitamin D in optimizing immune function.[1] Observational studies have shown independent associations between vitamin D deficiency and increased susceptibility to and incidence of acute respiratory tract infections.[41–45] This observed link between vitamin D deficiency and respiratory infections originated in the 19th century, when it was discovered that sunlight exposure was beneficial for the treatment of tuberculosis.[46] In the mid-1980s, the relationship between vitamin D levels and the susceptibility to tuberculosis was reported.[47,48] In the same era, it was observed that metabolites of vitamin D inhibited the proliferation of *Mycobacterium tuberculosis* in human macrophages.[49,50]

In recent years, several studies have provided evidence of the antimycobacterial properties of vitamin D in controlling tuberculosis infection.[51–54] However, in India, Jubulis et al[55] found no association between vitamin D deficiency and the risk of tuberculosis in children younger than 5 years. Neonates with vitamin D deficiency at birth had a 6-fold increased risk of developing respiratory syncytial virus bronchiolitis in the first year of life compared with neonates whose cord blood calcidiol levels exceeded 30 ng/mL.[56] Camargo et al[57] observed a relationship between sufficient vitamin D levels in neonates and a decreased risk of respiratory infection by 3 months of age and a decreased risk of wheezing by 15, 36, and 60 months of age. Additionally, the magnitude of vitamin D deficiency in children has been associated with the severity of acute lower respiratory tract infection, as children who had acute lower respiratory tract infections and severe vitamin D deficiency were more likely to require intensive care admission.[58] Furthermore, evidence points toward vitamin D deficiency increasing the risk of community-acquired pneumonia.[59] Some intervention studies have also shown that vitamin D supplementation may have a protective effect by decreasing susceptibility to respiratory infections. Supplementation of schoolchildren with 1200 IU of vitamin D per day reduced the incidence of influenza A, with a subgroup of asthmatic participants obtaining greater benefit from the intervention.[60] Similarly, in another trial in which children received either unfortified milk or milk fortified with 300 IU of vitamin D for 7 weeks, those who received fortified milk reported having fewer acute respiratory tract infections.[61] Martineau et al,[62] in a systematic review and meta-analysis of 25 human studies that evaluated the overall effect of vitamin D supplementation on the risk of acute respiratory tract infections, showed that vitamin D supplementation is protective against acute respiratory tract infections, with daily and weekly doses being more effective than bolus doses. On the contrary, Murdoch et al[63] and Li-Ng et al[64] observed no benefit of vitamin D supplementation at dosages of 100 000 IU/mo and 2000 IU/d, respectively, in reducing the incidence or severity of upper respiratory tract infections (URTIs) in healthy adults.

Due to the immune modulatory effect of vitamin D, its deficiency may influence susceptibility to infections, especially respiratory tract infections. Vitamin D deficiency has been associated with systemic infection[65] as well as greater severity of critical illness and longer length of hospital stay.[66,67] Furthermore, evidence from a prospective study of schoolchildren showed that vitamin D deficiency is linked with increased rates of diarrhea, vomiting, and ear infections.[68] However, quarterly supplementation with 100 000 IU of vitamin D showed no effect on the risk of recurrent diarrheal episodes or diarrheal diseases.[69] Vitamin D insufficiency and deficiency have also been associated with recurrent *Staphylococcus aureus* skin and soft tissue infection in children.[70] A growing body of evidence indicates an interaction of vitamin D in immune modulation and susceptibility to infections, especially respiratory infections. However, evidence from intervention trials of the role of vitamin D in preventing infections generally has been inconclusive.

How the intervention might work

The biological effect of vitamin D is produced when vitamin D binds to VDRs on specific target cells. The VDR functions as a gene transcriptional factor, such that the calcitriol-VDR complex regulates the expression of over 900 genes in several target cells.[71,72] These VDRs have been discovered in cells of the immune system, which substantiates the role of vitamin D in immune function and its potential to reduce susceptibility to infections. Additionally, immune cells also possess CYP27B1 activity, which enables the local production of calcitriol.[1] It is well known that the calcitriol-VDR complex modulates the expression of several genes involved in regulating the activation of immune cells.[1,4]

The active role of vitamin D in protecting against pathogenic invasion has been documented. In the innate immune system, the activated calcitriol-VDR complex regulates pattern recognition signaling of monocytes and neutrophils in epithelial cells by inducing the production of antimicrobial peptides, including β-defensin 2 and cathelicidin, in response to bacterial, viral, and parasitic infection.[73,74] Vitamin D also induces the expression of the Toll-like co-receptor CD14 (cluster of differentiation 14), which is a pattern recognition molecule in the innate immune system that detects microorganisms and exogenous and endogenous stress factors. It further induces the production of cytokines for the killing of microorganisms.[73,75] In the adaptive immune system, calcitriol suppresses T-cell–driven inflammation and enhances the effects of regulatory T cells.[76] In activated B cells, calcitriol upregulates the expression of interleukin 10 and also inhibits the expression of immunoglobulin E, which causes allergic reactions.[77]

In human epithelial cells treated with calcitriol, Dimitrov and White[78] observed that the capacity of the cells to generate antimicrobial activity against *Escherichia coli* and the lung pathogen *Pseudomonas aeruginosa* was augmented. This finding is further buttressed by evidence from a double-blind controlled trial that showed vitamin D supplementation significantly improved the antimicrobial activity of airway surface liquid.[79] Vitamin D has also been shown to enhance autophagy in macrophages, thus controlling viral infections by destroying viruses, regulating inflammatory responses, and promoting antigen presentation.[80,81] Multiple lines of evidence from observational studies and randomized controlled trials (RCTs) show that vitamin D may play a role in the prevention, incidence, and severity of infectious diseases, despite reports of some conflicting evidence.[60,62,82]

Rationale for this systematic review

Infectious diseases remain the leading cause of mortality and morbidity worldwide in children under age 5, particularly in sub-Saharan Africa and Southern Asia. Globally, infectious diseases are the primary cause of death in children, with pneumonia having the highest mortality, accounting for 15% of all deaths in children under age 5 in 2018.[83] It is estimated that, in 2015, 138 million episodes of clinical pneumonia were recorded in children under age 5, which led to 921 000 deaths.[84] Similarly, in 2016, 1.1 billion episodes of diarrheal disease occurred in children younger than 5 years, resulting in 446 000 deaths.[85] Aside from these diseases, thousands of children die each year from other infectious diseases such as tuberculosis, malaria, HIV, and intestinal infections, among many others.[86–88]

Even though there have been great advances in developing highly effective antimicrobial agents, the benefits of prevention outweigh cure. Preventive measures such as vaccination, vector control programs, and health education have contributed largely to the reduction of the infectious disease burden in children over the years.[89] Nonetheless, there is opportunity for further improvement. Finding effective and low-cost prevention strategies is imperative to further reduce infectious diseases and their economic burden. Considering the role of vitamin D in immune modulation, the use of supplemental vitamin D could confer a preventive benefit against the mortality and morbidity of infections in children, thereby reducing the associated costs. However, evidence from intervention trials of the role of vitamin D supplementation above the standard dose of 400 IU in preventing infections in children generally has been inconclusive. Therefore, the objective of this review was to determine and estimate the effectiveness of vitamin D supplementation above the standard dose of 400 IU in preventing the incidence of infections in healthy children under 5 years of age.

METHODS

The methodology and findings of this systematic review are reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[90] (see Appendix S1 in the Supporting Information online). The protocol for this systematic review was registered in PROSPERO (CRD42022355206) and approved by the North-West University Health Research Ethics Committee (NWU-00237–21-A1).

Eligibility criteria

The criteria for inclusion of studies in this review were based on the PICOS (Population, Intervention, Comparison, Outcomes and Study design) framework described in Table 1.

Literature search

The following electronic databases were searched for RCTs of vitamin D supplementation for infection prevention in children: PubMed, Scopus, Science Direct, Web of Science, Google Scholar, CINAHL, and MEDLINE. The MeSH (Medical Subject Headings) terms used in the search strategy are available in Appendix S2 in the Supporting Information online. The search of databases commenced August 24, 2022, and ended November 11, 2022. The reference lists of relevant primary studies, reviews, and meta-analyses identified through the electronic search were explored for the identification of additional relevant studies. No language or publication date restrictions were applied in the search.

Data extraction and risk-of-bias assessment

Two investigators (J.A.C. and M.J.L.) independently performed the assessment of studies for inclusion. Articles were first screened by title to exclude nonrelevant studies, after which potentially eligible articles were screened by abstract (Figure 1). Next, J.A.C. and M.J.L. independently reviewed the full texts of potentially relevant articles using a predesigned screening form based on the inclusion criteria. Differences in opinion about the eligibility of a study were resolved by discussion with the other authors (R.C.D-M. and L.M.). Data were extracted independently by two investigators (J.A.C. and M.J.L.) using an electronic data extraction spreadsheet. The following data were extracted for each trial: study identification (author, date, setting, and registration), study design, eligibility criteria, randomization method, participant characteristics (sample size, age, sex, and comorbidities), intervention characteristics (number of intervention groups, type of vitamin D, dosage, frequency of administration, duration, and cointervention), comparator, outcomes (measurement time point, definitions by authors, loss to follow-up), adverse outcomes, and conclusions by authors. For any missing information, corresponding authors were contacted by email to obtain additional data or clarification. When relevant data could not be obtained from the authors, it was identified as missing or unclear. Any disagreements regarding extracted data were resolved through consensus with all authors. Final data were

Table 1 **PICOS criteria for inclusion of studies**

Parameter	Inclusion criteria	Exclusion criteria
Population	Healthy children aged 0–59 months	Studies including children born preterm or with low birth weight or diagnosed with any inflammatory disease, infection, or metabolic or genetic disorder
Intervention	Vitamin D supplementation above the standard dose of 400 IU, irrespective of frequency or duration	
Comparison	Placebo, no treatment, or standard treatment (400 IU) Studies that compared higher vs lower doses. Vitamin D > 400 IU + nonpharmacological intervention vs identical nonpharmacological intervention (ie, vitamin D–rich foods, fortification, education)	Vitamin D administered as part of a combination treatment or multivitamin compared with placebo or no intervention as control
Outcomes	Primary: Incidence of upper respiratory tract infections and pneumonia Secondary: Incidence of other infections reported by authors, number of hospitalizations due to infections, number of primary care visits due to infections, duration of infections, clinical signs and symptoms indicating the presence of infection (ie, fever, diarrhea, nausea, vomiting, headache, sore throat), antibiotic use, serum vitamin D concentration (25[OH]D/calcidiol concentration in ng/mL, measured with immunoassays or chromatographic methods, with "sufficiency" defined according to the current cutoff values recommended by the Endocrine Society [United States]), and case-specific mortality Studies that reported at least one of the outcome measures were included.	
Study design	Randomized controlled trials, cluster randomized trials, or open-label trials (with random allocation applied); only studies that obtained ethics approval and informed consent from participants were included.	Studies without full report available

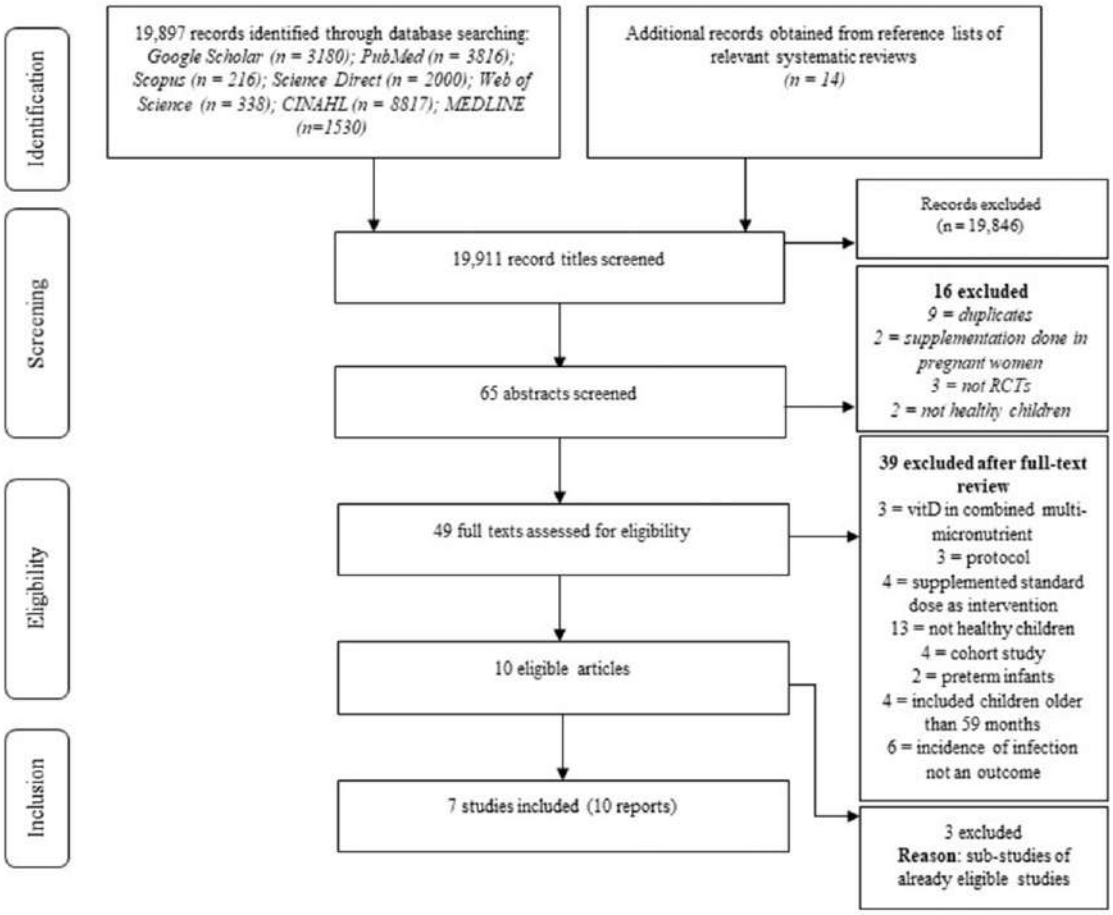

Figure 1 **Flow diagram of the literature search process.**

exported into Review Manager (RevMan) software for analysis.

For each study, the level of bias was independently assessed by two authors (J.A.C. and M.J.L.), using the Cochrane risk of bias 2 assessment tool (RoB 2).[91] The risk of bias for each included study was assessed and judged as *low risk*, *some concerns*, or *high risk*. The RoB 2 comprises 5 domains to assess risk of bias from the following: (1) the randomization process, (2) deviations from the intended interventions (intention-to-treat effect), (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result. For each of the domains, there were signaling questions according to which each trial was evaluated for a response of *yes*, *probably yes*, *no*, *probably no,* or *no information*. Based on a mapping of the responses to the signaling questions, each domain was judged as *low*, *some concerns*, or *high*. The overall risk of bias for each study was then assessed and judged as *low risk of bias* (ie, low risk of bias for all 5 domains), *some concerns* (ie, some concerns in at least 1 domain), or *high risk of bias* (ie, high risk of bias in at least 1 domain or some concerns in multiple domains). The RoB 2 assessment of each included study is presented in Appendix S3 in the Supporting Information online. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework was used to assess the overall quality of the included studies.[92] GRADE Pro GDT (Grade Profiler Guideline Development Tool) software was used to summarize the quality of the evidence.

Data analysis

RevMan version 5.4.1 was used to perform meta-analyses.[93] All analyses were performed using fixed- or random-effects models. Comparable binary outcome data were summarized as odds ratios (ORs) with 95%CIs by applying intention-to-treat analysis results from the included trials. Continuous outcome data reported as arithmetic means and standard deviations (SDs) in the included trials were summarized using mean differences and 95%CIs. For continuous data presented as medians and 25th and 75th percentiles, the mean and SD were estimated.[94] If a trial's outcome data could not be pooled, they were described narratively.

All tests were two-tailed, and $P \leq 0.05$ was considered significant. Heterogeneity across studies was evaluated by visually inspecting the forest plots and the I^2 statistic value. $I^2 \geq 50\%$ with a significant χ^2 test indicated considerable heterogeneity in this meta-analysis,[95] and the random-effects model was then applied. When considerable heterogeneity was observed, prespecified subgroup analysis was performed to ascertain the effect of different doses (ie, daily doses of < 1000 IU vs > 1000 IU vs > 2000 IU), duration of intervention (ie, < 3 months vs > 3 months), daily/weekly vs bolus supplementation, and baseline vitamin D status (ie, calcidiol ≤ 20 ng/mL vs calcidiol > 20 ng/mL).

RESULTS

Literature search

The initial database search yielded 19 897 titles. Additionally, 14 titles were obtained from the reference lists of relevant systematic reviews. After the initial screening, 65 titles were selected for abstract screening. Forty-nine abstracts were selected for full-text screening. Ten articles met the inclusion criteria, of which 3 were excluded for being substudies of already included studies. In total, 7 RCTs (with a total of 10 articles) were included in this review and meta-analysis. Figure 1 shows the detailed study selection process.

Study characteristics

Table 2[96–102] shows the characteristics of each included trial. The GRADE summary of findings table is provided in Appendix S4 in the Supporting Information online. The trials, published between 2012 and 2022, were conducted in 7 different countries and included 5748 children under 5 years of age. Six of the trials were double-blinded[96–101] and one was open-labelled.[102] Three trials compared higher daily doses of vitamin D (ie, 1200 IU–2000 IU/d) with the standard dose of 400 IU/d.[96,100,102] Three trials compared various doses, ranging from 1000 IU/d to 100 000 IU quarterly, with a placebo.[98,99,101] One trial compared a high daily dose (800 IU) with the standard dose and a placebo.[97]

Two trials reported the incidence of URTI as an outcome.[96,97] Other respiratory tract infection outcomes reported included pneumonia,[98,102] influenza,[96,97,101,102] bronchiolitis,[97] bronchitis,[97] and wheezy lower respiratory tract infection.[97] Additionally, two trials reported diarrheal disease incidence.[98,100] Three trials reported the number of hospitalizations,[97,98,100] and 3 reported the number of primary care vists.[96,97,100] All included trials reported postsupplementation serum calcidiol concentrations.[96–102] Only one trial reported mortality as an outcome.[98] One trial reported the incidence of enterovirus infection.[101] Hueniken et al[103] and Aluisio et al[69] are substudies of Aglipay et al[96] and Manaseki-Holland et al,[98] respectively, hence their data were extracted and included in the analysis. The Grant et al[97] trial included two additional articles from the same trial[104,105] and consisted of 3 study arms (high-dose, standard-dose, and placebo) from which data were extracted and included in the meta-analysis. For the purposes of this review, the comparison between the high-dose arm and the placebo arm was designated as Grant 2015a, whereas the comparison between the high-dose arm and the standard-dose arm was identified as Grant 2015b.

Risk of bias in included studies

The risk-of-bias summary is presented in Figure 2[96–102]. The assessment and justification of each trial are presented in Appendix S3 in the Supporting Information online. Four trials were judged to have a low risk of bias[96–98,100] and two a high risk of bias.[99,102] One trial was judged as having some concerns, as there was no clarity on how allocation concealment was performed (domain 1).[101] Marchisio et al[99] provided no information on loss to follow-up or missing outcomes. Zhou et al[102] provided no clear details of the allocation sequence generation and concealment (domain 1), and the intervention was not blinded to the participants, study personnel, or assessors, and not all the participants randomized into the study were included in the primary analysis (domains 2 and 4).

Incidence of URTI and pneumonia

Incidence of URTI and pneumonia were the primary outcomes of this review. Two trials, Aglipay et al[96] and Grant et al,[97] reported URTI incidence. Aglipay et al[96] reported the number of all-cause laboratory-confirmed cases of viral URTI in the 2000 IU/d vs 400 IU/d supplementation groups. Grant et al[97] reported the number of URTI diagnoses among the groups that received 800 IU/d vs placebo (Grant 2015a) and 800 IU/d vs 400 IU/d (Grant 2015 b). The pooled analysis of these two trials showed no significant difference in the incidence of URTI with daily high-dose supplementation compared with standard-dose supplementation or placebo (OR = 0.83; 95%CI, 0.62–1.10; $P = 0.19$) (Figure 3[96,97]). The quality of this evidence was graded as moderate because of the variation in the dose of supplemental vitamin D between the two trials (ie, 2000 IU/d vs 800 IU/d). However, statistical heterogeneity between the studies was low ($I^2 = 0\%$, $P = 0.68$). Aglipay et al[96] further compared the average time to

Table 2 **Characteristics of the 7 trials included in the systematic review**

Reference	Methods		Participants			Baseline	Intervention		Outcomes
	Study location	Study design	Sample size and sex	Age	Inclusion and exclusion criteria	Mean 25(OH)D	Dose, duration, no. of participants	Control	
Aglipay et al (2017)[96]	Toronto, Ontario, Canada	Randomized, double-blind clinical trial	n = 703 57.7% male	1–5 y	*Inclusion*: Healthy children aged 1–5 y *Exclusion*: Gestational age < 32 wk Chronic illness (other than asthma) Children whose siblings participated in the trial	35.9 (± 12.3) ng/mL in high-dose group 36.9 (± 11.8) ng/mL in standard-dose group 31.6% had serum 25(OH)D < 30 ng/mL at baseline	2000 IU/d 4–8 winter months n = 349	400 IU/d 4–8 winter months 354	*Primary outcome*: Number of all-cause laboratory-confirmed viral URTIs *Secondary outcomes*: Time to first laboratory-confirmed case of influenza; total number of parent-reported and laboratory-confirmed cases of influenza and non-influenza URTIs; serum 25(OH)D; URTI severity; frequency of outpatient physician visits; number of emergency department visits; number of antibiotic prescriptions for URTI
Grant et al (2015)[97]	Auckland, New Zealand	Randomized, double-blind clinical trial	n = 260 mother/infant pairs 48.6% male infants	Birth to 18 mo	*Inclusion*: 26–30 wk of gestation and singleton pregnancy *Exclusion*: VitD supplementation > 200 IU/d Any serious pregnancy complication History of renal stones or hypercalcemia	26 ng/mL in high-dose group 13 ng/mL in placebo group 24 ng/mL in low-dose group	800 IU/d Birth to 6 mo + 18 mo of follow-up n = 86 mother/infant pairs in 2000/800 IU groups	400 IU or placebo Birth to 6 mo + 18 mo follow-up 87 mother/infant pairs in 1000/400 IU group 87 mother/infant pairs in placebo group	*Primary outcomes*: Proportion of infants achieving serum 25(OH)D > 30 ng/mL during the first 6 mo of infancy; incidence of hypercalcemia *Secondary outcomes*: Number of primary care visits for ARI; number of primary care visits for ARI reported by parent; time to first ARI primary care visit; number of primary care visits for respiratory illnesses due to cold, otitis media, URTI, croup, asthma, bronchitis, bronchiolitis, a wheezy lower RTI, or fever and cough; number of children hospitalized; sensitization to airborne allergens

(continued)

Table 2 **Continued**

Reference	Methods		Participants			Baseline	Intervention		Outcomes
	Study location	Study design	Sample size and sex	Age	Inclusion and exclusion criteria	Mean 25(OH)D	Dose, duration, no. of participants	Control	
Huang et al (2022)[101]	Taipei, Taiwan	Randomized controlled trial	n = 248 54.8% male	2–5 y	*Inclusion*: Healthy preschool children *Exclusion*: Not clearly stated	Not reported	2000 IU/d for 1 mo Monthly follow-up for 6 mo n = 135	Placebo for 1 mo Follow-up: monthly for 6 mo 113	*Primary outcome*: Incidence of influenza and enterovirus infection
Manaseki-Holland et al (2012)[98]	Kabul, Afghanistan	Randomized, double-blind, placebo-controlled community-based trial	n = 3046 52.2% male	1–11 mo	*Inclusion*: Infants aged 1–11 mo residing in the study districts *Exclusion*: Families expecting to move to another town within 18 mo Diagnosis of rickets or treatment with vitD in the previous 3 mo Clinical diagnosis of kwashiorkor or marasmus	Not reported	100 000 IU every 3 mo 18 mo n = 1524	Placebo 18 mo 1522	*Primary outcome*: First or only episode of radiologically confirmed pneumonia *Secondary outcomes*: Incidence of first or only episode of pneumonia; incidence of repeat episodes of pneumonia; proportion of children with a first episode of pneumonia; mean serum 25(OH)D level; number of hospital admissions; all-cause mortality; time to first diarrheal episode; risk of first and recurrent diarrheal illness; incidence of diarrheal episodes
Marchisio et al (2013)[99]	Milan, Italy	Randomized, double-blind, placebo controlled trial	n = 116 55.2% male	1–5 y	*Inclusion*: History of recurrent AOM (ie, at least 3 episodes in the last 6 mo or at least 4 episodes in the last 12 mo, with the most recent episode in the previous 2–8 wk). At time of enrollment, children had to be free of AOM	26.5 ng/mL in vitD group 25.8 ng/mL in placebo group	1000 IU/d 4 mo n = 58	Placebo 4 mo 58	*Primary outcome*: Serum vitD concentration *Secondary outcomes*: Total number of AOM episodes; number of complicated and uncomplicated AOM episodes; risk of developing complicated or uncomplicated AOM; correlation between serum vitD level and risk of AOM

(continued)

Table 2 **Continued**

Reference	Methods		Participants			Baseline	Intervention		Outcomes
	Study location	Study design	Sample size and sex	Age	Inclusion and exclusion criteria	Mean 25(OH)D	Dose, duration, no. of participants	Control	
					Exclusion: Severe atopy, acquired or congenital immunodeficiency, cleft palate, a chronically ruptured eardrum, craniofacial abnormalities or obstructive adenoids, sleep apnea syndrome, or the placement of tympanostomy tubes				
Rosendahl et al (2018)[100]	Helsinki, Finland	Randomized double-blind clinical trial	n = 975 50.3% male	2 wk to 24 mo	*Inclusion*: Healthy infants born at term, birth weight within 2 SDs of the mean for gestational age, Northern European *Exclusion*: Infants requiring IV glucose, antibiotics, nasal continuous positive airway pressure treatment for > 1 day, phototherapy for- > 3 days, or NGT feeding for- > 1 day, and infants with seizures	32.57 (± 9.62) ng/mL in high-dose group 32.73 (± 11.14) ng/mL in standard-dose group Only 4.3% had 25(OH)D < 20 ng/mL at baseline	1200 IU/d 24 mo n = 486	400 IU/d 24 mo 489	*Primary outcome*: Bone strength *Secondary outcomes*: Incidence of parent-reported infections at 24 mo, ie, URTI, conjunctivitis, gastroenteritis, nonspecified viral infection, bacterial infection

(continued)

Table 2 **Continued**

Reference	Methods		Participants			Baseline	Intervention		Outcomes
	Study location	Study design	Sample size and sex	Age	Inclusion and exclusion criteria	Mean 25(OH)D	Dose, duration, no. of participants	Control	
Zhou et al (2018)[102]	Yongkang, China	Randomized, open, controlled clinical trial	n = 400 52.3% male	3 − 12 mo	*Inclusion*: No influenza or other respiratory tract infections within 1 month preceding enrollment; normal functioning of heart, liver, and kidneys; and normal baseline serum calcium and inorganic phosphorus levels *Exclusion*: History of vitD toxicity, coexisting serious diseases (cardiac, respiratory, liver, or renal dysfunction), or severe malnutrition	17.0 ± 2.4 ng/mL in high-dose group 17.4 ± 2.4 ng/mL in standard dose group	1200 IU/d 4 mo n = 200	400 IU/d 4 mo 200	*Primary outcome*: Number of children with symptoms of influenza A, including duration of fever, coughing, and wheezing *Secondary outcomes*: WBC count; CRP levels; influenza viral loads; safety of high-dose vitD, measured as serum levels of calcium, phosphorus, and 25(OH)D

Abbreviations: AOM, acute otitis media; ARI, acute respiratory infection; CRP, C-reactive protein; IV, intravenous; NGT, nasogastric tube; RTI, respiratory tract infection; SD, standard deviation; URTI, upper respiratory tract infection; vitD, vitamin D; WBC, white blood cell; 25(OH)D, calcidiol.

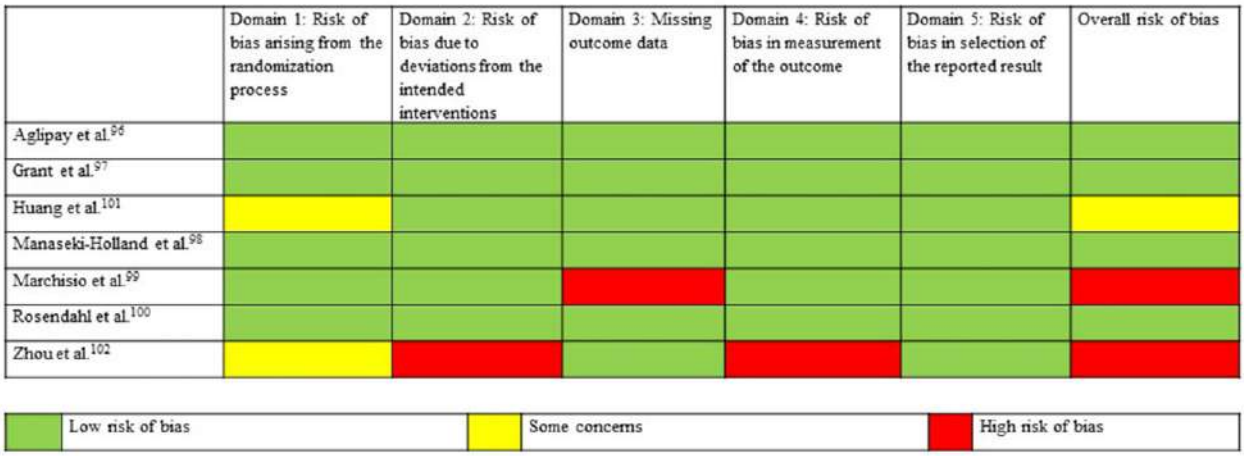

Figure 2 **Summary of the risk of bias of studies included in the systematic review.**

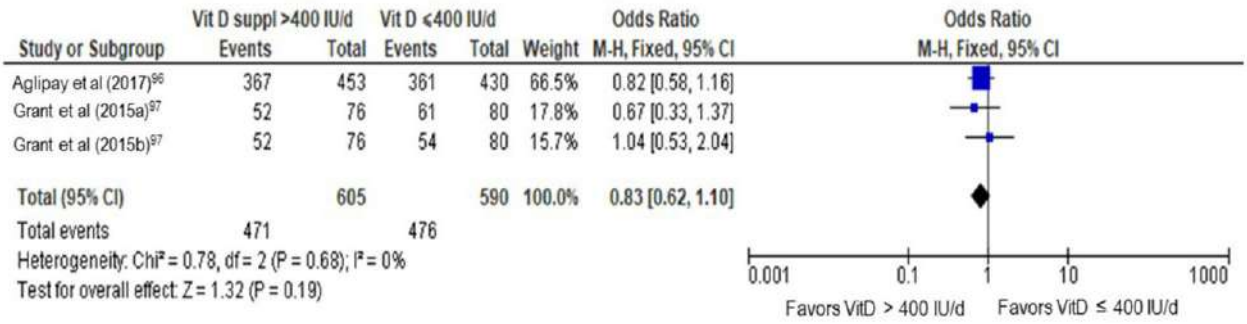

Figure 3 **Forest plot of the meta-analysis of the effect of vitamin D supplementation on the incidence of upper respiratory tract infection.** *Abbreviation:* M-H, Mantel-Haenszel.

occurrence of the first laboratory-confirmed URTI between the study groups and observed no significant difference. The median time to the first URTI in the standard-dose group was 3.29 months (95%CI, 2.66–4.14) compared with 3.95 months (95%CI, 3.02–5.95) in the high-dose group.

Manaseki-Holland et al[98] and Zhou et al[102] reported the incidence of first or only episodes of pneumonia. However, Manaseki-Holland et al[98] further reported the incidence of repeat episodes of pneumonia confirmed or unconfirmed by chest radiograph. Since Zhou et al[102] did not report repeat episodes, only data from first or only episodes of pneumonia were meta-analyzed. The pooled analysis of the two trials showed no effect of high-dose treatment compared with standard treatment or placebo on the incidence of the first pneumonia episode (OR = 0.63; 95%CI, 0.16–2.44; $P = 0.5$) (Figure 4[98,102]).

The certainty of this evidence was graded as very low because one of the studies had a high risk of bias,[102] the dose of vitamin D supplemented varied widely between the two studies (ie, 1200 IU/d vs 100 000 IU/quarter), and the duration of the intervention differed (ie, 4 months vs 18 months). Both studies were highly heterogenous ($I^2 = 78\%$, $P = 0.03$), hence a subanalysis was performed. Zhou et al,[102] when comparing the effect of daily/weekly vs bolus supplementation on the incidence of pneumonia after daily supplementation with 1200 IU/d vs standard dose for 4 months, observed a reduced incidence of pneumonia in the higher-dose group (OR = 0.27; 95%CI, 0.07–0.97; $P = 0.05$). In contrast, Manaseki-Holland et al[98] observed no effect of 100 000 IU of vitamin D per quarter on pneumonia incidence (OR = 1.10; 95%CI, 0.91–1.33; $P = 0.34$) but an increased incidence of repeat episodes of radiographically confirmed pneumonia (OR = 1.75; 95%CI, 1.32–2.33; $P < 0.001$). The only study that compared the effect of high-dose (ie, 1200 IU/d) vs standard-dose (400 IU/d) treatment on pneumonia incidence found a significantly reduced incidence of pneumonia (by 73%) in the high-dose group (OR = 0.27; 95%CI, 0.07–0.97; $P = 0.05$).[102] The effect of vitamin D supplementation on the incidence of pneumonia was also investigated by considering the baseline vitamin D concentrations of participants in the studies by Manaseki-Holland et al[98] and Zhou

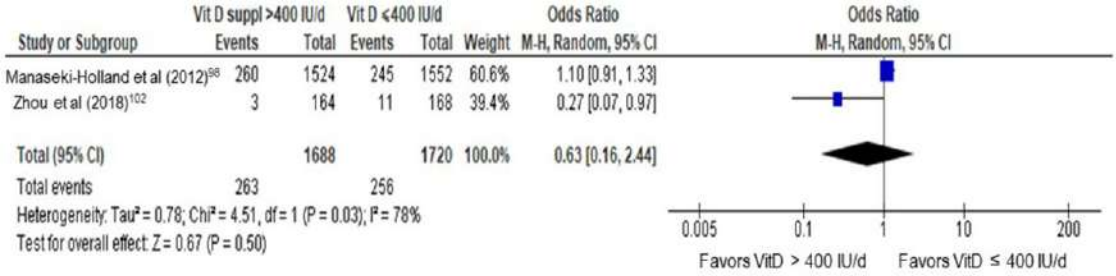

Figure 4 **Forest plot of the meta-analysis of the effect of vitamin D supplementation on the incidence of pneumonia.** *Abbreviation:* M-H, Mantel-Haenszel.

et al.[102] Manaseki-Holland et al[98] reported no baseline vitamin D concentrations of participants, whereas Zhou et al[102] reported that their participants, in whom pneumonia incidence was significantly reduced (see above), presented with a baseline concentration of 17.04 ng/mL.

Secondary outcomes

This review reports the incidence of other infections, including bronchiolitis, bronchitis, influenza/cold, croup, otitis media, and diarrhea/gastroenteritis (as described by trial authors), along with the incidence of clinical signs and symptoms of infections such as fever, diarrhea, and cough. Other outcomes reported include antibiotic use and the number of hospital visits due to infections.

Bronchiolitis, bronchitis, and croup. Grant et al[97] reported the number of children with bronchiolitis diagnosed at primary healthcare visits. There was no effect of daily administration of 800 IU of vitamin D compared with 400 IU/d or placebo for 6 months (OR = 0.82; 95%CI, 0.49–1.36; $P = 0.44$) (see Figure S1 in the Supporting Information online). The certainty of the evidence was graded as moderate because analysis of this outcome included data from only one trial, which was judged as having a low risk of bias. Furthermore, Grant et al[97] reported the incidence of bronchitis and croup and observed no significant difference between the high-dose treatment and the standard treatment or placebo for incidence of bronchitis (OR = 1.06; 95%CI, 0.43–2.61; $P = 0.91$) (see Figure S2 in the Supporting Information online) or croup (OR = 0.83; 95%CI, 0.51–1.37; $P = 0.47$) (see Figure S3 in the Supporting Information online). The certainty of the evidence for the incidence of bronchitis and croup was graded as moderate because data for these outcomes were synthesized from only one study.

Cold and influenza. Four studies assessed the effect of vitamin D supplementation on the incidence of cold and/or influenza.[96,97,101,102] Two of these studies reported the incidence of influenza virus infection,[96,102] while the other two reported the diagnosis of influenza/cold by a physician during a primary care visit.[97,101] According to the pooled analysis of data from these 4 trials, daily supplementation with 2000 IU, 800 IU, or 1200 IU of vitamin D over a 1- to 8-month period compared with standard treatment or placebo did not significantly reduce the incidence of cold and/or influenza (OR = 0.64; 95%CI, 0.38–1.06; $P = 0.08$) (see Figure S4 in the Supporting Information online). Of the 4 trials analyzed for this outcome, one was judged as having a high risk of bias[102] and another to have some concerns.[101] The doses and comparator varied between the studies, hence the low certainty of the evidence for this outcome. Additionally, there was considerable heterogeneity between the studies, as shown by an I^2 of 64% and a significant χ^2 test P value of 0.03. A subgroup analysis was performed to compare the effect of a vitamin D supplementation dose of less than 1000 IU with a dose of more than 1000 IU on the incidence of cold/influenza. Both Aglipay et al[96] and Huang et al[101] supplemented 2000 IU/d, while Zhou et al[102] supplemented 1200 IU/d and Grant et al[97] administered 800 IU/d. Meta-analysis of data from Aglipay et al,[96] Huang et al,[101] and Zhou et al[102] demonstrated a significantly reduced incidence of cold/influenza with a vitamin D dosage of more than 1000 IU/d (OR = 0.43; 95%CI, 0.30–0.61; $P < 0.001$; $I^2 = 0\%$; χ^2 test $P = 0.64$) (Figure 5[96,101,102]) when compared with the daily standard dose or placebo. The certainty of the evidence for this subgroup analysis was considered moderate because one of the studies is at high risk of bias. In contrast, Grant et al[97] found no significant effect of 800 IU of vitamin D per day on the incidence of cold/influenza compared with either the standard dose or placebo (OR = 1.09; 95%CI, 0.70–1.71; $P = 0.7$; $I^2 = 0\%$; χ^2 test $P = 0.82$).

Otitis media. Two trials reported the incidence of otitis media.[97,99] Marchisio et al[99] reported the occurrence of new episodes of otitis media in otitis media–prone children (as defined by study authors). Grant et al[97] reported the number of children diagnosed with otitis

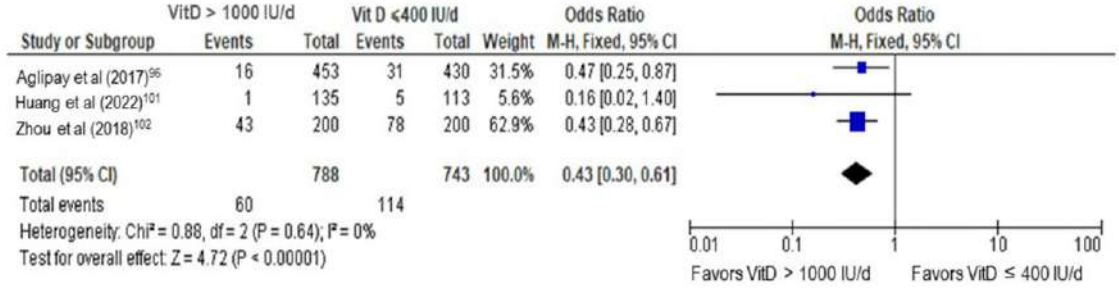

Figure 5 **Subgroup analysis of the effect of supplementation with > 1000 IU of vitamin D per day on the incidence of cold/influenza.** *Abbreviation:* M-H, Mantel-Haenszel.

media during primary care visits. Marchisio et al[99] observed a significant reduction in the incidence of otitis media in the higher daily dose group compared with the placebo group (OR = 0.43; 95%CI, 0.1–0.90; $P = 0.03$). Nonetheless, the pooled ORs from both trials showed that daily supplementation with 800 IU or 1000 IU of vitamin D was not effective in reducing the incidence of otitis media (OR = 0.79; 95%CI, 0.53–1.18; $P = 0.25$) (see Figure S5 in the Supporting Information online).[97,99] The certainty of the evidence was graded as low because one of the studies[99] was judged to have a high risk of bias and the dose supplemented differed between the two studies. According to the statistical evaluation of the heterogeneity, both studies were fairly homogenous ($I^2 = 49\%$; $P = 0.14$).

Other infections. Rosendahl et al[100] reported the number of events, the incidence rate, and the incidence rate ratio (IRR) of unspecified respiratory infections, infection episodes, and other infections aside from respiratory infections and gastroenteritis. When high-dose and standard-dose groups were compared, daily supplementation with 1200 IU of vitamin D conferred no reduction in the incidence of respiratory infections (IRR = 1.00; 95%CI, 0.93–1.07), infection episodes (IRR = 1.00; 95%CI, 0.93–1.06), or other infections (IRR = 1.04; 95%CI, 0.91–1.19), respectively. The incidence of enterovirus infection was reported by Huang et al,[101] but daily supplementation with 2000 IU compared with placebo had no effect (OR = 1.02; 95%CI, 0.48–2.17; $P = 0.96$).

Clinical signs and symptoms of infection

Diarrhea. Manaseki-Holland et al[98] reported the first incidence and repeat episodes of diarrhea. Quarterly supplementation with 100 000 IU of vitamin D compared with placebo did not confer a reduction in the risk of incidence of the first diarrheal episode between the study groups (hazard ratio = 1.02; 95%CI, 0.95–1.11; $P = 0.56$). Similarly, the risk of repeat episodes of diarrhea did not significantly differ between the intervention and placebo groups (hazard ratio = 1.05; 95%CI, 0.98–1.17; $P = 0.15$). Furthermore, Rosendahl et al[100] reported the number of events, the incidence rate, and the IRR of gastroenteritis, observing no significant effect of supplementation with 1200 IU/d compared with the standard dose (incidence ratio = 0.92; 95%CI, 0.79–1.08). Altogether, evidence from Manaseki-Holland et al[98] and Rosendahl et al[100] showed no effect of high-dose vitamin D supplementation in preventing the incidence of diarrhea or gastroenteritis.

Cough and fever. Only one trial gave an account of the number of children who developed cough and fever.[102] Daily supplementation with 1200 IU of vitamin D was reported to be protective against the incidence of cough (OR = 0.44; 95%CI, 0.27–0.70; $P < 0.001$) (Figure 6)[102] and fever (OR = 0.41; 95%CI, 0.26–0.65; $P < 0.001$) (Figure 7)[102] compared with the standard dose.[102] However, the certainty of this evidence was downgraded to low because the study had a high risk of bias and was the only study that reported these outcomes (cough and fever).

Wheezing. Grant et al[97] and Zhou et al[102] reported the incidence of wheezing after daily administration of 800 IU and 1200 IU of vitamin D compared with standard dose and placebo. Meta-analysis of data from both trials show that daily high-dose vitamin D supplementation did not confer significant protection against wheezing (OR = 0.81; 95%CI, 0.36–1.84; $P = 0.62$) (see Figure S6 in the Supporting Information online). The certainty of this evidence was low because of the high risk of bias of one study and the difference in the dose of vitamin D administered between the two studies. Since heterogeneity between the studies was high ($I^2 = 79\%$; $P < 0.001$), further analysis of the effect of the different dosages was examined. Supplementation with a vitamin D dose of more than 1000 IU/d by Zhou et al[102] demonstrated a significant reduction in the incidence of wheezing by 60% (OR = 0.40; 95%CI, 0.24–0.66; $P < 0.001$), even though the certainty of the evidence is graded as low because of the high risk of bias

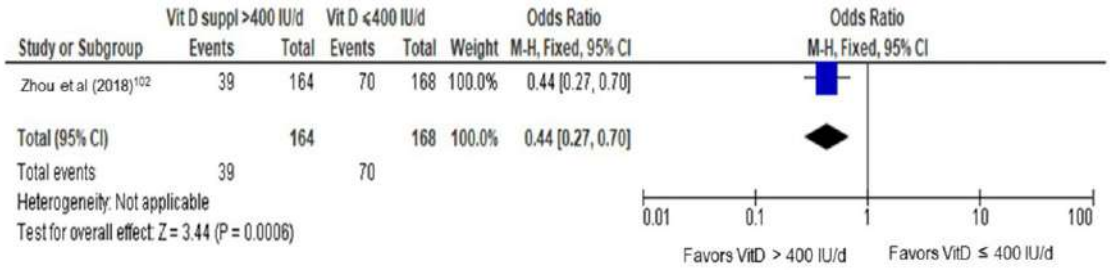

Figure 6 **Forest plot of the effect of vitamin D supplementation on the incidence of cough.** *Abbreviation:* M-H, Mantel-Haenszel.

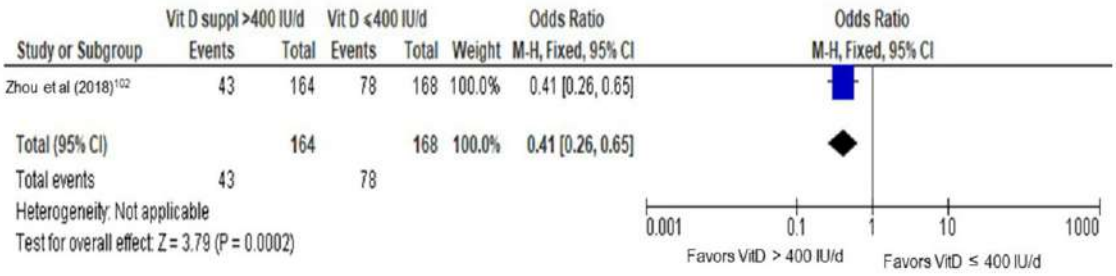

Figure 7 **Forest plot of the effect of vitamin D supplementation on the incidence of fever.** *Abbreviation:* M-H, Mantel-Haenszel.

of Zhou et al[102] and the outcome data being extracted from a single study. Supplementation with a vitamin D dose of less than 1000 IU/d by Grant et al[97] did not affect the incidence of wheezing (OR = 1.23; 95%CI, 0.73–2.06; $P = 0.43$).

Primary care visits

Three studies reported the effect of high-dose vitamin D supplementation on primary care visits.[96,97,100] Grant et al[97] reported the total and median number of children who had primary care doctor visits, visits for acute respiratory infections, and visits for any other infections determined by parental report and primary care audit. Nonetheless, only data from the primary care audit is presented in this review. According to Grant et al,[97] daily supplementation with 800 IU of vitamin D did not make a difference in the number of primary care visits compared with the standard dose or placebo (OR = 0.21; 95%CI, 0.04–1.27; $P = 0.09$). Similarly, Rosendahl et al[100] reported the number, the incidence rate, and the IRR of physician visits for infections between the high-dose and standard-dose groups and observed no significant difference (IRR = 1.07; 95%CI, 0.94–1.21). Data on primary care visits from Grant et al[97] and Rosendahl et al[100] were not meta-analyzed because Grant et al[97] reported the number of children with primary care visits while Rosendahl et al[100] reported the number of physician visits and the incidence rate.

Aglipay et al[96] reported the effect of 2000 IU of vitamin D per day on outpatient physician and emergency department visits due to URTI. Similarly, Grant et al[97] reported the number of primary care visits for acute respiratory infections. Grant et al[97] observed a significantly reduced number of primary care visits for acute respiratory infection in the higher-dose group compared with the placebo group (87% vs 99%; $P = 0.004$). However, Aglipay et al[96] showed a protective effect of standard-dose over high-dose vitamin D supplementation against outpatient and emergency department visits for URTI combined (OR = 1.43; 95%CI, 1.06–1.93; $P = 0.02$). A pooled analysis of both studies demonstrated that supplementation with 800 IU/d and 2000 IU/d compared with standard treatment and placebo did not reduce the number of primary care visits for respiratory infections (OR = 0.45; 95%CI, 0.09–2.12; $P = 0.31$) (see Figure S7 in the Supporting Information online).[96,97] Both studies that reported this outcome were at low risk of bias, but the dose administered differed between the studies, and hence the certainty of the evidence was graded as moderate. Nonetheless, between-study heterogeneity was high ($I^2 = 83\%$; $P = 0.003$).

Hospitalizations

Three trials reported the number of hospital admissions as an outcome.[97,98,100] However, Manaseki-Holland et al[98] and Rosendahl et al[100] were not meta-analyzed because Rosendahl et al[100] reported the incidence rate and IRR while Manaseki-Holland et al[98] reported no numerical data on hospitalizations. Grant et al[97] found

that daily administration of 800 IU had no significant effect on the number of hospital admissions (OR = 0.94; 95%CI, 0.61–1.44; $P = 0.78$; moderate certainty of evidence) (see Figure S8 in the Supporting Information online). Rosendahl et al[100] reported a similar finding. They compared the effect of daily supplementation with 1200 IU of vitamin D vs standard dose on the number of hospitalizations due to infections and found no significant effect of daily high-dose vitamin D supplementation (IRR = 1.16; 95%CI, 0.71–1.89). In agreement, Manaseki-Holland et al[98] reported no effect of vitamin D supplementation on hospital admissions.

Antibiotic use

Two trials reported the effect of high-dose vitamin D supplementation on frequency of antibiotic treatment.[96,100] In both trials, no significant difference was observed between the high-dose and the standard treatment groups. Aglipay et al[96] reported an IRR of 1.02 (95%CI, 0.61–1.72; $P = 0.94$), while Rosendahl et al[100] reported an IRR of 1.17 (95%CI, 1.00–1.36).

Mortality

Only one trial reported the effect of high-dose vitamin D supplementation on all-cause and case-specific mortality.[98] Supplementation with 100 000 IU of vitamin D did not affect all-cause mortality (OR = 1.43; 95%CI, 0.54–3.77; $P = 0.47$; moderate certainty of evidence) (see Figure S9 in the Supporting Information online). Furthermore, there was no difference in the number of deaths from septicemia or pneumonia between the high-dose vitamin D and the placebo groups[98] (OR = 1.50; 95%CI, 0.42–5.33; $P = 0.53$; moderate certainty of evidence) (see Figure S10 in the Supporting Information online).

Serum vitamin D concentrations

Serum calcidiol concentrations prior to supplementation were reported in 4 trials,[59,96,99,100] with no significant difference observed between the high-dose groups and the control groups (mean difference [MD] = −0.35, calcidiol concentrations between the high-dose and the placebo groups [25.8 ng/mL in the placebo group and 26.5 ng/mL in the intervention group]). On the contrary, in the Grant et al[97] trial, supplementation with vitamin D during pregnancy resulted in a significantly higher baseline calcidiol concentration in the cord blood of infants in the higher-dose vitamin D group relative to the placebo and standard-dose groups (26.25 ng/mL vs 13.25 ng/mL and 24.0 ng/mL, respectively; $P < 0.001$). Manaseki-Holland et al,[98] however, did not report presupplementation serum calcidiol concentrations. Post supplementation, 6 trials reported the effect of high-dose vitamin D on serum calcidiol concentrations. The high-dose intervention groups had a higher serum calcidiol concentration post supplementation compared with the control groups (MD = 8.91; 95%CI, 5.90–11.92; $P < 0.001$) (see Figure S11 in the Supporting Information online). Huang et al[101] reported that 9 (100%) participants in the supplementation group had a serum calcidiol concentration above 30 ng/mL compared with 2 (16.5%) in the placebo group, although the mean calcidiol concentration was not reported.

Adverse effects

Aglipay et al,[96] Manaseki-Holland et al,[98] Marchisio et al,[99] Rosendahl et al,[100] and Zhou et al[102] reported no adverse outcomes attributable to supplementation or vitamin D toxicity. However, Grant et al[97] reported elevated calcidiol levels (≥ 100 ng/mL) in 5 infants, but no hypercalcemia.

The prespecified subanalysis to investigate the effect of the supplementation period, ie, 3 months or less vs more than 3 months, in the meta-analysis could not be performed because the duration of supplementation in all the included trials was longer than 3 months.

DISCUSSION

The primary objective of this review was to appraise existing evidence from RCTs of high-dose oral vitamin D supplementation in preventing the incidence of URTI and pneumonia in children below 5 years of age. This review compared high-dose vitamin D supplementation with placebo, no intervention, or the standard dose of 400 IU. Additionally, evidence of the effect of high-dose vitamin D supplementation on the prevention of other infections was evaluated.

Main findings

The incidence of URTI was not different in the high-dose vitamin D group compared with the placebo and standard-dose groups.[96,97] Similarly, the incidence of first and repeat episodes of radiologically confirmed pneumonia did not seem to be affected by high-dose vitamin D supplementation in comparison with placebo or the standard dose in the pooled analysis.[98,102] However, subgroup analysis showed that daily supplementation could be protective over bolus dose administration against pneumonia incidence, despite limited evidence. When secondary outcomes were examined, subgroup analysis demonstrated a reduced incidence of

cold and/or influenza and wheezing with vitamin D supplementation of more than 1000 IU/d compared with less than 1000 IU/d. Similarly, the incidence of cough and fever as a sign of infection was reported by one trial,[102] which found a reduced incidence in the high-dose supplementation group. There was no effect of high-dose vitamin D supplementation on the incidence of bronchiolitis, croup, bronchitis, otitis media, or diarrhea/gastroenteritis; the number of hospitalizations and primary care visits; the frequency of antibiotic treatment; or all-cause and specific-cause mortality. Additionally, the serum calcidiol concentration was significantly increased post supplementation in the high-dose group compared with the placebo and standard-treatment groups.

Completeness and applicability of evidence

For the primary outcome of interest, high-dose oral vitamin D supplementation was not beneficial in preventing the incidence of URTI or pneumonia. However, there were some limitations. First, only two trials reported the incidence of URTI.[96,97] Second, both trials supplemented participants who were not vitamin D deficient (serum calcidiol < 20 ng/mL) at baseline, and this may be why supplementation showed no effect compared with the standard dose and placebo, as vitamin D supplementation in replete individuals may not induce significant effects.[106] Similarly, the incidence of the first episode of pneumonia was reported by only two trials.[98,102] Even though the trial by Manaseki-Holland et al[98] was large and sufficiently powered, the authors did not report the mean serum calcidiol concentration prior to supplementation. Hence, it was challenging to evaluate the confounding effect of baseline calcidiol concentrations on both the response to high-dose vitamin D supplementation and the effect on the expected outcome. For this reason, the generalizability of this outcome is limited. On the contrary, Zhou et al[102] conducted a relatively small trial in participants who were vitamin D deficient at baseline and observed a reduction in the incidence of pneumonia with daily supplementation of 1200 IU. The strength of this evidence is limited, however, by the high risk of bias of the study, which restricts the generalizability of the findings. The evidence from RCTs on the effect of vitamin D supplementation on URTI and pneumonia incidence synthesized in the present review highlights the need for further research in which the baseline serum calcidiol concentration of participants is considered and bolus administration is compared with daily supplementation.

Evidence from 4 trials that were highly heterogenous showed a trend toward a positive effect of vitamin D supplementation on reducing the incidence of cold/influenza.[96,97,101,102] However, subgroup analysis of 3 of the trials to assess possible sources of heterogeneity demonstrated that supplementation with vitamin D at more than 1000 IU/d significantly reduced the incidence of cold/influenza.[96,101,102] One of the trials analyzed had some limitations.[102] It was not blinded to participants and trial assessors, leading to downgrading of the evidence. Nonetheless, considering the diverse settings and doses of vitamin D supplemented across the 3 trials, the evidence, which was graded as moderate, seems to be generalizable. Likewise, supplementation with high-dose vitamin D reduced the incidence of cough and fever as symptoms of infection compared with the standard dose. A major limitation of this evidence is that the data were synthesized from only one trial, making the findings less generalizable, although they may be applicable in similar settings. Furthermore, the incidence of bronchiolitis, croup, and bronchitis was not influenced by high-dose vitamin D supplementation. These outcomes were reported in a single trial that compared high-dose supplemental vitamin D during pregnancy to infancy with standard-dose vitamin D and placebo.[97] The quality of evidence of these outcomes was downgraded because the data were from a single trial, which limits the generalizability of the evidence and highlights the need for further research.

Quality of the evidence

Seven RCTs were included in this review, all of which presented data on the primary and secondary outcomes. Each of the primary outcomes was assessed by two trials, and the secondary outcomes were examined across all the included trials. Four of the included trials were judged as being at low risk of bias for randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results.[96–98,100] Two of the trials were judged to have a high risk of bias,[99,102] while one was judged to have some concerns.[101] Details of the risk-of-bias assessment are presented in Appendix S3 in the Supporting Information online, while the GRADE summary of findings is available in Appendix S4 in the Supporting Information online.

Potential biases in the review process

There were minimal potential biases in this systematic review process. At each stage of the review process, which included literature searches, screening of titles and abstracts, screening of full-text reports, extraction of data, risk-of-bias assessments, and GRADE assessments, a systematic evaluation was performed independently by two authors. Disparities that arose during the process were discussed with the entire review team

for resolution. The primary and secondary outcomes prespecified in the protocol were not modified. However, the duration of infection as well as some symptoms of infections, such as nausea, vomiting, sore throat, and headache, could not be reported as prespecified because none of the included studies reported these outcomes. The average time to the incidence of URTI was also reported even though it was not prespecified. Finally, although only case-specific mortality was prespecified in the secondary objectives, all-cause mortality was included since this was reported by one of the included studies.

Comparison with other studies or reviews

A previous Cochrane review studied the effect of oral vitamin D supplementation on the prevention of infection in children younger than 5 years. The authors found no benefit of vitamin D supplementation on all-cause or case-specific mortality, hospitalization, incidence of pneumonia, or incidence of diarrhea among studies with moderate to low certainty of evidence.[107] The review included Manaseki-Holland et al[98] and Alonso et al,[108] the former included in the present review and the latter excluded because it compared supplemental vitamin D (402 IU) with no treatment. Very-low certainty evidence from the present review showed that bolus dose vitamin D supplementation may not prevent the incidence of pneumonia, which is in congruence with the findings of Yakoob et al.[107] Nonetheless, the observed protective effect of daily vitamin D supplementation over bolus against pneumonia incidence is in agreement with the findings of Martineau et al,[62] who reported a beneficial effect of administering daily/weekly vitamin D over bolus dose against acute respiratory tract infections. Additionally, moderate-certainty evidence from the present review indicates that the incidence of URTI is not reduced by supplementation with high-dose vitamin D. This finding is consistent with two randomized trials that assessed the effect of vitamin D supplementation in preventing URTI in adults.[63,64] Daily supplementation with 2000 IU of vitamin D for 12 weeks did not make a difference in the incidence of URTI.[64] Similarly, Murdoch et al[63] observed that monthly supplementation with 100 000 IU of vitamin D had no effect on the incidence of URTI.

In a systematic review, Martineau et al[62] assessed the role of vitamin D supplementation in the prevention of acute respiratory tract infections in children and adults. They found vitamin D to be protective against acute respiratory tract infections, with participants who were vitamin D deficient at baseline benefiting more. In the present review, vitamin D supplementation above 1000 IU/d was beneficial in preventing cold/influenza. This effect was more profound in participants with vitamin D deficiency, despite the low certainty of the evidence. This finding is similar to the outcome of a previous RCT in which the incidence of influenza A was reduced among schoolchildren who received daily supplementation with 1200 IU of vitamin D during winter.[60]

Another meta-analysis that assessed the effect of vitamin D supplementation on the risk of respiratory tract infection observed no difference between the supplementation and control groups.[109] The meta-analysis, however, was not restricted to studies involving children only. Similar to the findings of Mao and Huang,[109] evidence from one trial in the present review showed no effect of vitamin D in preventing the incidence of respiratory tract infection. Furthermore, the present review found no influence of vitamin D supplementation on the incidence of bronchiolitis, bronchitis, otitis media, or croup. These findings are in agreement with those of Moreno Galdo et al,[110] who observed no benefit of daily supplementation with 1000 IU of vitamin D in preventing acute bronchitis, recurrent bronchitis, URTI, or bronchiolitis in healthy infants.

Low-certainty evidence in the present review also shows that vitamin D supplementation is beneficial for reducing the incidence of cough and fever in children who are vitamin D deficient. This finding is consistent with the results of another trial in which daily supplementation with 1000 IU of vitamin D as adjunct treatment of tuberculosis in children was significantly beneficial in improving the resolution of fever and cough,[111] demonstrating that vitamin D supplementation may have some prophylactic benefits against fever and cough. Furthermore, the finding of no effect of vitamin D supplementation on the reduction of all-cause or specific-cause mortality, diarrhea and gastroenteritis incidence, and hospitalization is similar to the findings of a previous systematic review by Yakoob et al.[107]

This study has some limitations. First, the primary and secondary outcome measures were reported by few trials, thus limiting subgroup analysis. Second, owing to the small number of studies, publication bias could not be estimated by funnel plots.

CONCLUSION

Evidence from this systematic review suggests that high-dose oral supplementation with vitamin D may not be protective against the incidence of URTI, bronchiolitis, croup, otitis media, bronchitis, or diarrhea/gastroenteritis in children. However, vitamin D supplementation with >1000 IU/d may be beneficial for preventing cold and/or influenza, wheezing, cough, and fever in healthy children. Limited evidence suggests that daily supplementation may be more beneficial than

bolus administration in preventing the incidence of pneumonia, although further research is needed. Considering the limited number of trials upon which the evidence of this review is based, the results must be interpreted with caution.

This review highlights the need for more RCTs to evaluate the effects of high-dose oral vitamin D supplementation on the incidence of pneumonia, respiratory infections, and infections in general, given that only 7 trials were available for inclusion. Future RCTs should also investigate the effect of baseline vitamin D concentrations on outcome measures, given that the participants in Zhou et al[102] were vitamin D deficient and benefited profoundly from vitamin D supplementation. Additionally, this review does not provide enough evidence to determine whether daily/weekly supplementation is more efficient than bolus therapy in preventing infections in children. In conclusion, high-dose vitamin D oral supplementation is beneficial in preventing cold/influenza, wheezing, cough, and fever but may not prevent URTI, bronchiolitis, bronchitis, otitis media, or diarrhea/gastroenteritis in healthy children. Daily supplementation may be beneficial to prevent the incidence of pneumonia.

Acknowledgment

We would like to thank our librarian, Gerda Beukman, for assisting with our preliminary literature search.

Author contributions. J.A.C., L.M., R.C.D-M., and M.J.L. contributed to the conceptualization of the review. J.A.C. and M.J.L. performed data extraction and analysis. J.A.C. wrote the first draft of the manuscript. J.A.C., L.M., R.C.D-M., and M.J.L. edited and revised the manuscript. All authors read and approved the final version of the manuscript.

Funding. No external funds supported this work.

Declaration of interest. The authors have no relevant interests to declare.

Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Appendix S1 **PRISMA 2020 checklist.**

Appendix S2 **Search strategy: key search terms for identifying studies.**

Appendix S3 **Risk-of-bias assessment.**

Appendix S4 **GRADE summary of findings table and certainty of evidence.**

Figure S1 **Forest plot of meta-analysis of the effect of vitamin D supplementation on the incidence of bronchiolitis.**

Figure S2 **Forest plot of meta-analysis of the effect of vitamin D supplementation on the incidence of bronchitis.**

Figure S3 **Forest plot of meta-analysis of the effect of vitamin D supplementation on the incidence of croup.**

Figure S4 **Forest plot of meta-analysis of the effect of vitamin D supplementation on the incidence of cold/influenza.**

Figure S5 **Forest plot of meta-analysis of the effect of vitamin D supplementation on the incidence of otitis media.**

Figure S6 **Forest plot of meta-analysis of the effect of vitamin D supplementation on the incidence of wheezing.**

Figure S7 **Forest plot of meta-analysis of the effect of vitamin D supplementation on the number of primary care visits for respiratory infections.**

Figure S8 **Forest plot of meta-analysis of the effect of vitamin D supplementation on the number of hospitalizations.**

Figure S9 **Forest plot of the effect of vitamin D supplementation on all-cause mortality.**

Figure S10 **Forest plot of the effect of vitamin D supplementation on case-specific mortality.**

Figure S11 **Forest plot of meta-analysis of the effect of vitamin D supplementation on serum concentrations of vitamin D.**

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