Efficacy of vitamin D supplementation on the incidence of recurrent pneumonia in children: A systematic review and meta-analysis study

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Abstract---Recurrent pneumonia may develop into severe pneumonia. Many evidences showing that vitamin D supplementation can reduce the risk of pneumonia, but the results are not yet definitive. We aim to investigate and determine the effect of vitamin D supplementation on the incidence of recurrent pneumonia in children. Data sources published were searched from PubMed, Web of Science, Science Direct, Scopus, and clinicaltrial.gov up to December 2021. This review included the Randomized controlled trials (RCT) study which compare vitamin D supplementation with placebo and/or non-intervention in children with pneumonia under 18-years-old. We used Risk of Bias (RoB) 2 tools to assessed the risk of bias. The results are combined with a random effect or fixed-effect model, and sensitivity analysis was conducted to explore potential factors. Seven RCT studies with a total of 1852 participants met the eligibility criteria. There was a positive correlation between vitamin D supplementation and the incidence of recurrent pneumonia (RR 0.59; 95% Confidence Interval 0.40 – 0.89), with a combined effect of 2.52. The heterogeneity test was 77%. The results were statistically significant with a p-value of 0.01. Vitamin D supplementation may reduce the incidence of recurrent pneumonia in children and be considered an additional therapy.

Keywords---vitamin D supplementation, recurrent pneumonia, pneumonia, children.

Introduction

Recurrent pneumonia is a common symptom that occurs in general pediatric practice and is often referred to a pediatric respiratory specialist (Chen et al., 2021; Hoang et al., 2021; Montella et al., 2017). Inappropriate or incomplete treatment is considered to be the main cause of recurrent pneumonia (Yousif & Elnazir, 2015). Pneumonia causes mortality of 1.1-1.4 million children every year and for about 119% of all deaths in children under 5 years of age, mostly in developing countries (Bhutta et al., 2013). Despite improvements in living conditions, nutrition, and vaccinations, more than 700,000 children under 5 years of age have died from pneumonia globally (Marangu & Zar, 2019). The incidence of recurrent pneumonia in children is still unclear (Yousif & Elnazir, 2015). Children with pneumonia will develop recurrent pneumonia about 7.7% to 9%, even in developed countries. More than 90% of children who develop recurrent pneumonia have an underlying disease. One-third of children with recurrent pneumonia will have severe attacks and about 75% will require intensive care due to shock, respiratory failure, and multiple organ failure (Hoang et al., 2021; Montella et al., 2017).

Recent epidemiology shows that vitamin D has an important role in adaptive and innate immunity. Local innate defenses that quickly recognize pathogenic microbes play an important role in preventing microbial colonization that can lead to repeated infections (Bartley, 2010). Vitamin D's ability to boost innate immunity through its role in stimulating the production of several antibacterial proteins, similarly to cathelicidin and β-defensins has been well studied in association with pneumonia (Pettifor, 2016). A study has identified an association between inadequate vitamin D levels and respiratory infections in children (Esposito & Lelii, 2015). There is currently ample evidence showing that replacing vitamin D with supplementation can reduce the risk of acute respiratory infections in patients with deficiency or insufficiency conditions (Bradley et al., 2020), as stated by Chowdhury et al. who revealed that vitamin D reduced the risk of recurrent episodes of pneumonia by 0.53 times compared to no vitamin D or standard therapy alone (Chowdhury et al., 2021).

More economical alternatives are urgently needed to increase children's resistance to respiratory infections and to reduce disease severity (Pettifor, 2016). New strategies in prevention and management are needed for this problem. Giving vitamin D supplementation has been shown to improve the outcome of children with pneumonia, including reducing recurrent attacks of pneumonia (Jadhav et al., 2021). From some previous evidence, vitamin D supplementation in children with pneumonia is expected to be given in a comprehensive management in dealing with recurrent pneumonia to prevent mortality and morbidity (Hoang et al., 2021). The existence of evidence regarding the effect of vitamin D on respiratory tract infections has prompted many intervention and observational studies to investigate the effect of vitamin D supplementation on outcomes in children with pneumonia, one of which is the incidence of recurrent pneumonia. We aim to investigate the results of others studies and determine the effect of vitamin D supplementation on the incidence of recurrent pneumonia in children.

Method

Protocol and registration
The systematic review evaluation was written using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Page et al., 2021). The protocol in this study will be registered on the registration site for a systematic review of either Cochrane or PROSPERO. This study also uses a Systematic Literature Review (SLR) to review several literatures that identify, assess and interpret all findings regarding the effect of vitamin D supplementation on the incidence of recurrent pneumonia in children.

Search strategy and information resources
The literature search was carried out through a free search or through an electronic database and was conducted by two people independently. The electronic database in this research literature search used PubMed, Science Direct, Web of Science, Scopus, and clinicaltrial.gov to identify relevant research. Concepts and keywords that are expressed as synonymous keywords and index terms, such as Medical Subject Headings (MeSH), must be combined using the Boolean operators AND and OR. The search terms used were "vitamin D supplementation" and "pneumonia" or "respiratory tract infection" and "recurrent" or "frequency attack" or "repeat episode" and "children" or "childhood".

Data management and study selection
A search was conducted on published articles ranging from 2010 to December 31st, 2021. Eligibility articles in this review were the following: 1) English literature; 2) Participants were pediatric patients with pneumonia under 18-year-old; 3) Studies with intervention; 4) A Journal containing the full text; 5) Derived from the Science Direct database, Web of Science, Scopus, PubMed, and clinicaltrial.gov. We exclude articles based on non-research studies, for example, conference papers, book chapters, case report/case series, and/or review articles as well as incomplete research journals which only consist of abstracts and duplication journals. In addition, in this systematic review, the preparation of research questions uses population, intervention/issue, comparison/context, and outcome (PICO). The population is children with pneumonia under 18-year-old. The intervention/issue in this systematic review is vitamin D supplementation, while the comparison/content is placebo and/or without vitamin D supplementation. And lastly, the outcome is the incidence of recurrent pneumonia in children.

Literature Quality Assessment
Data is collected and then managed according to PRISMA. All articles collected were identified, screened, and included to determine the articles to be analyzed. Risk of Bias 2 (RoB 2) is a tool that provides a framework for considering the risk of bias in the findings of any type of randomized control trial (RCT). ROB2 refers to interventions including experimental interventions and comparison interventions, although the results may sometimes refer to a comparison of two active interventions. The five domains for a RCT include: 1) bias due to randomized process, 2) bias due to deviations from the intended intervention, 3) bias due to lack of outcome data, 4) bias for outcome measurement, and 5) bias

in selective report-ing results. The RoB 2 tool includes several questions to ensure clarity on which interventions are referred to as experimental and which are referred to as comparisons in the assessment (Sterne et al., 2019).

Data extraction
In the data extract process, we transfer the important information from the selected literature into a specific table to identify the literature. We used a modified data collection form (DCF) by Cochrane (The Cochrane Library). This DCF consisted of the identity, methods, characteristics, and results of the study, specifically to facilitate the analysis the literature reviewed and then presented in tabular form to make it easier for researchers to analyze the characteristics of study reviewed. Recorded data were the following: main author, year of study, place of study, participants (including sample size, age, and sex), baseline characteristics, intervention given (dose, route, and time of administration of vitamin D), time of follow-up further, and study results.

Data analysis
The process of calculating data analysis and the outcome was performed using the software Review Manager 5.4. The meta-analysis process includes calculating the treatment effect incidence and 95% confidence interval (CI) in each study. Overall effect size is also calculated as a summary of the results of the analysis. Heterogeneity was calculated using the Chi-Square test with a limit of 50%, then calculated the use of fixed-effects models or random-effects models. Sensitivity analysis is done by eliminating several factors or low evidence, then looking at the sensitivity results. The publication bias test was also identified using a funnel plot. The funnel plot is used to see the distribution of articles that are combined in the meta-analysis. If the distribution of articles is not symmetrical, then there is a publication bias in the relationship between the variables being studied.

Discussion

Our search on December 31th, 2021 produced 27,782 articles regarding vitamin D supplementation on the incidence of recurrent pneumonia in children identified in the five literature search sources (Figure 1). This systematic review and meta-analysis study included seven RCT studies to determine the effect of vitamin D supplementation on the incidence of recurrent pneumonia in children. A total of 1852 children with pneumonia participated in the study. The seven studies differed in terms of inclusion criteria, dose and method of administering vitamin D supplementation, and duration of observation. Almost all studies reported a reduction in the incidence of pneumonia in the intervention group although some results were not significant, except for the study by Somnath et al. (Chowdhury et al., 2021; Dhungel & Alam, 2015; Gupta et al., 2016; Jadhav et al., 2021; Manaseki-Holland et al., 2010; Singh et al., 2019; Somnath et al., 2017).

All studies were assessed for quality using the RoB 2 tool due to the randomized control trial design. Five domains are assessed in each study. The assessment of all research quality and the assessment of each domain of each study are summarized in Figure 2A. There are five studies with a low risk of bias and 2 other studies with an unclear risk of bias (same concerns) Figure 2B. We collected data from the articles included: the main author, year of study, place of study,

study sample (including sample size, age, and sex), baseline characteristics (vitamin D deficiency, malnutrition, and incomplete immunization), the intervention provided (dose, route, and timing of vitamin D administration), follow-up time, and study results Table 1.
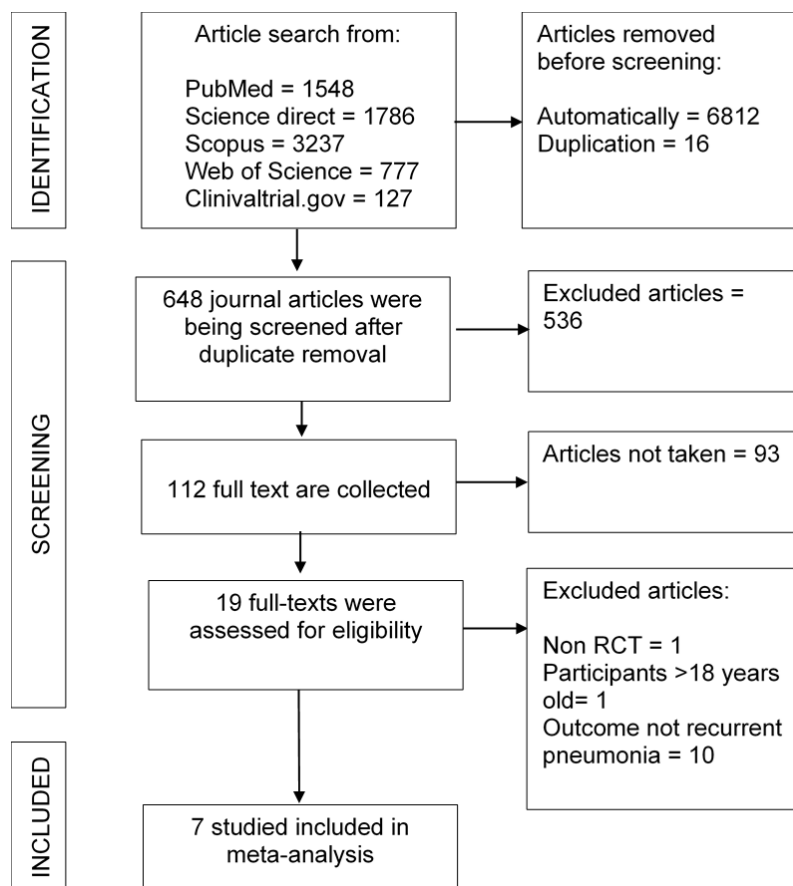

Figure 1. PRISMA study selection diagram

From all studies included in this meta-analysis, it was found that vitamin D supplementation could reduce the incidence of recurrent pneumonia by 59%. Overall, the results of this study revealed that vitamin D supplementation can reduce the incidence of recurrent pneumonia in children. Most of the studies were conducted in low-income countries, four studies were conducted in India (Gupta et al., 2016; Jadhav et al., 2021; Singh et al., 2019; Somnath et al., 2017), one in Pakistan (Dhungel & Alam, 2015), one in Bangladesh (Chowdhury et al., 2021), and the rest in Afghanistan (Manaseki-Holland et al., 2010). From 2000 to 2015, India had the highest number of clinical pneumonia episodes (32% of all episodes in developing countries) and a decrease of only 3% in the number of pneumonia episodes over a 15-year period. (McAllister et al., 2019) Despite the dissemination of preventive strategies and effective management, pneumonia remains a problem in many low- and middle-income countries (Alamneh & Adane, 2020).
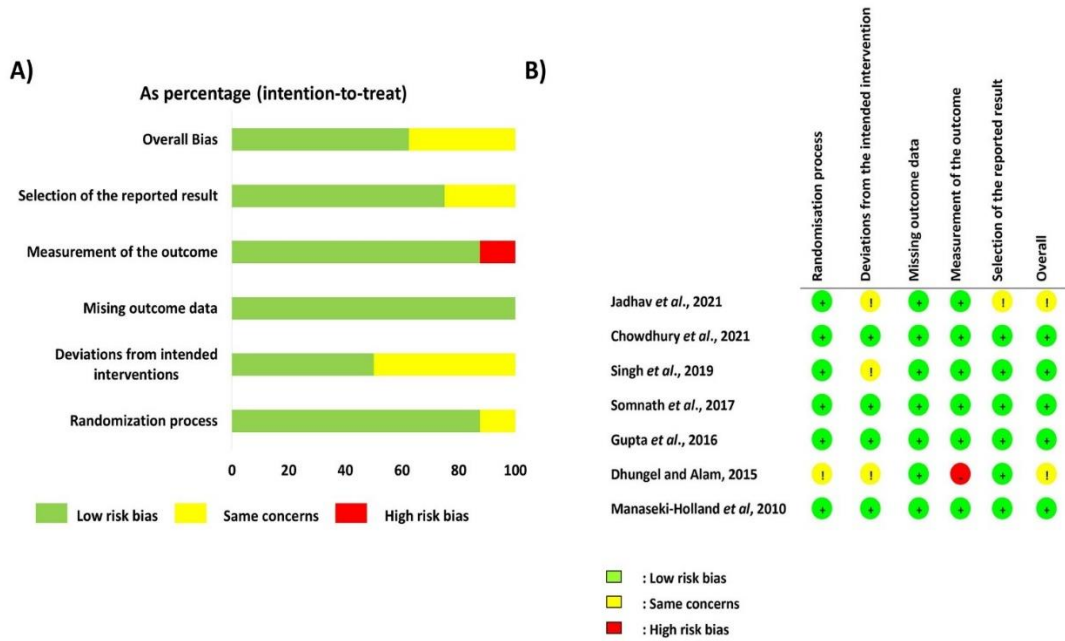
Figure 2. A) Assessment of literature quality based on the RoB 2 framework; B) The assessment of each domain is based on each research article.
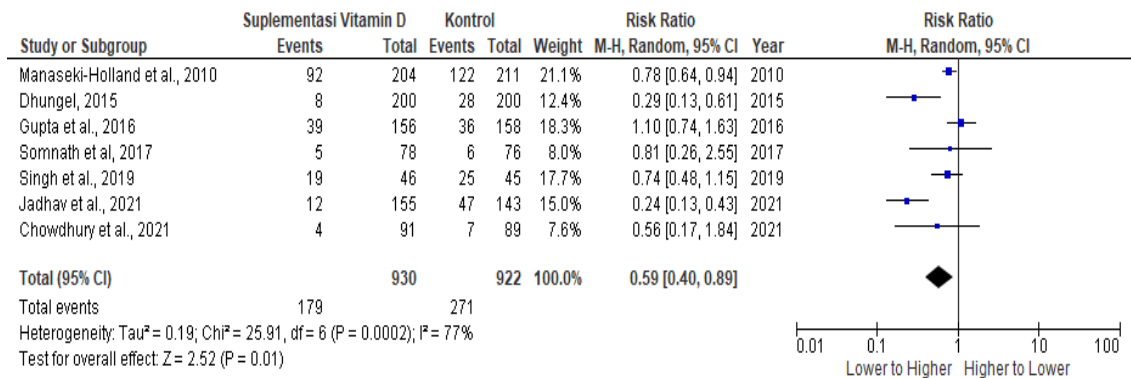

Figure 3. A forest plot estimated the effect of vitamin D supplementation on the incidence of recurrent pneumonia in children

Table 1.
Literature characteristics of vitamin D supplementation on the incidence of recurrent pneumonia in children

Study	Year of published article	Country	Age	M : F (%)	Participants (n)		Vitamin D Deficiency (%)*		Malnutrition (%)		Incomplete Immunization (n)		Dosage and Duration of administration of vitamin D	Timely administration of vitamin D	Rute	Control	Follow-up time	Outcome
					I	C	I	C	I	C	I	C						
(Jadhav et al., 2021)	2021	India	1-5 year	63.7 : 36.3	155	155	NA	NA	NA	NA	NA	NA	120.000 IU Single dose	First day of treatment	or al	Placebo	6 months	The proportion of recurrent acute respiratory infection was significantly lower in the intervention group 12 (7.7%) than in the control group 47 (32.4%).
(Chowdhury et al., 2021)	2021	Bangladesh	> 2-59 months	49 : 51	97	100	52	49	24.7	34	NA	NA	Based on age: <6 months: 20.000 IU; 6-12 months: 50.000 IU; 13-59 months: 100.000 IU Maintenance dose: 10.000 IU	The first day of treatment and maintenance dose for 4 days later or until the patient is discharged from the hospital	oral	Placebo	6 months	During follow-up, the incidence of RP in the intervention group 4 (4.4%) and control group 7 (7.9%) with an RR value of 0.53 (95% CI

RP = recurrent pneumonia; M = Male; F = Female; I = Intervention; C = Control; NA = Not applicable; im = intramuscular;
* Measurement of vitamin D levels was carried out before the intervention; ** All children are fully immunized; *** Serum vitamin D levels are normal in all childrenThe administration of vaccines, especially the pneumococcal conjugate vaccine can significantly reduce the number of treatments due to pneumonia in children compared to children who do not get the vaccine (Zhu & Li, 2021). There are only 3 studies that include the immunization status of research subjects

(Gupta et al., 2016; Singh et al., 2019; Somnath et al., 2017). Almost all participants in Somnath et al. study was not fully immunized in both study groups (>90%) (Somnath et al., 2017), in contrast, Singh et al., had all participants fully immunized (Singh et al., 2019). In research by Gupta et al. only about 6-9% are not fully immunized. Oliwa and Marais stated that 5 simple interventions have been recommended to reduce the incidence of pneumonia in children, including 1) exclusive breastfeeding for six months and continuing breastfeeding supplemented with nutritious solid foods until the age of two years; 2) routine vaccination against pertussis, measles, *Haemophilus influenza type b* (HiB) and pneumococcal; 3) drinking water, sanitation and handwashing facilities; 4) improvement of cooking stoves to reduce indoor air pollution; and 5) effective treatment including antibiotics and oxygenation (Oliwa & Marais, 2017). WHO declare approximately 40 vaccine-preventable or potentially preventable diseases. Routine vaccination for common childhood diseases is one of the most cost-effective strategies to prevent death from pneumonia, the leading cause of mortality in young children (Oliwa & Marais, 2017; Organization, 2018, 2021).

This meta-analysis was conducting by summarizing and comparing data on the number and percentage of incidences of recurrent pneumonia in children who were given vitamin D supplementation. Seven journals reported the results regarding the effect of vitamin D supplementation on the incidence of recurrent pneumonia in children with a combined effect magnitude of 2.52 and a Relative Risk (RR) value of 0.59 (95% CI 0.40 – 0.89), whereas vitamin D supplementation reduced the risk of recurrent pneumonia in children by 0.59 times (Figure 3). Analysis of the results showed with a p-value of 0.01 which means that in this study there is a significant relationship. The results of the heterogeneity analysis showed a value of 77% where this study was heterogeneous, thus using a random-effects model to combine the results. All studies in this meta-analysis formed a symmetrical picture, so there was no publication bias in this study (Figure 4).

Vitamin D has a regulatory role in various immune processes, including host defense, immunity, inflammation, and epithelial repair. Patients with respiratory disease more likely to experience vitamin D deficiency, implying that supplementation may provide significant benefits to the patient. Respiratory monocytes or macrophages and epithelial cells constitutively express the vitamin D receptor. Vitamin D, acting through this receptor, plays an important role in protection against respiratory infections. There are in vitro data on the role of vitamin D in innate immunity, data on the extent of vitamin D deficiency in lung disease, and the role of in vivo supplementation as protection against respiratory tract infections in healthy individuals and patients with chronic respiratory disease. Vitamin D as adjuvant therapy is suggested to increase its effectiveness in the prevention and treatment of acute respiratory infections (Zdrenghea et al., 2017).
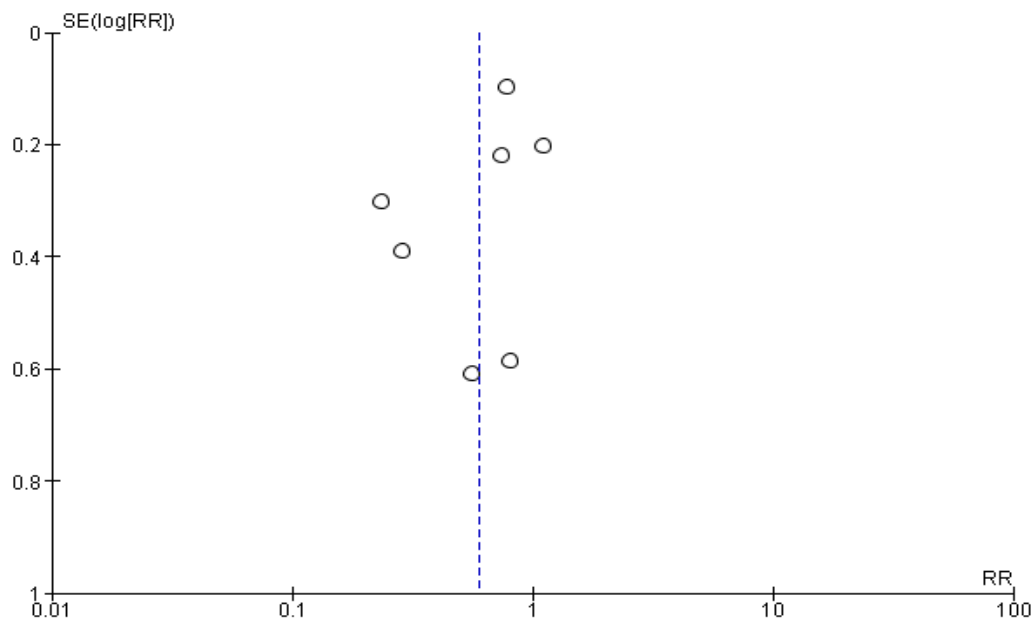
Figure 4. A meta-analysis of funnel plots

Loeb et al. conducted a study on whether vitamin D supplementation can reduce the influenza virus and upper respiratory tract infections caused by other viruses. A healthy children and adolescents aged 3 to 17 years were randomized to receive either vitamin D supplementation at a dose of 14,000 IU/week or a placebo for 8 months in Vietnam. It can be concluded that vitamin D supplementation did not reduce the incidence of influenza but did moderately reduce non-influenza respiratory viral infections (Loeb et al., 2019). All studies in this meta-analysis did not include comorbid or underlying diseases that could be a risk of recurrent pneumonia incidence (Dhungel & Alam, 2015; Gupta et al., 2016; Jadhav et al., 2021; Manaseki-Holland et al., 2010; Singh et al., 2019; Somnath et al., 2017). Dhungel and Alam excluded patients with heart disease and chronic respiratory diseases, such as asthma and TB. Manaseki-Holland et al. included heart or kidney disease, meningitis, measles, malnutrition, and TB as exclusion criteria. Children diagnosed with recurrent pneumonia mostly have an underlying disease. The underlying disease can be confirmed in each case according to the clinical characteristics and diagnostic tests (Barakat et al., 2021). A case-control study describes the clinical characteristics, risk factors, and causes of recurrent pneumonia in children. As many as 11.4% of them experienced recurrent pneumonia due to a history of prematurity, low birth weight, and respiratory distress at birth, which was significantly different between cases and controls. Aspiration syndrome, gastroesophageal reflux, congenital heart disease, wheezing, oro-motor incoordination, and asthma are the risk factors for recurrent pneumonia (Baseer et al., 2020). Children with a history of underlying disease are more susceptible to recurrent pneumonia and are more susceptible to resistant microorganisms, have more severe disease, and poorer clinical outcomes (Chen et al., 2021).

Vitamin D supplementation is beneficial in the treatment and prevention of pneumonia. Children with low serum vitamin D levels are at risk for pneumonia compared to children with high vitamin D concentrations (Li et al., 2018). Four studies measure serum vitamin D levels in patients before intervention (Chowdhury et al., 2021; Gupta et al., 2016; Singh et al., 2019; Somnath et al., 2017). Two other studies by Jadhav et al., and Dhungel and Alam excluded children with normal serum vitamin D levels, meaning that the participants were in a state of vitamin D deficiency, while Manaseki-Holland et al.(Manaseki-Holland et al., 2010) did not include participants' vitamin D status but excluded children who received high doses of vitamin D 3 months before the study as in the case of the study. The acute inflammatory response may decrease serum vitamin D concentrations through the use of 25 Hydroxyvitamin D (25(OH)D). This can inhibit the immune response in children even though they take vitamin D supplementation due to vitamin D deficiency that occurs. Beneficial effects of vitamin D supplementation in children with adequate vitamin D levels suggest a possible pharmacological effect independent of vitamin D adequacy (Chowdhury et al., 2021). Patients with vitamin D deficient pneumonia with serum 25(OH)D levels < 20 ng/mL) had a significantly increased risk of pneumonia (OR 2.64; 95% CI 1.00 – 2.67) and decreased serum vitamin D levels of 5.63 ng/mL (95% CI 9.11 - 2.14) was demonstrated in pneumonia patients. The findings of this meta-analysis reported a correlation between vitamin D deficiency and an increased risk of children with pneumonia (Zhou et al., 2019).

Recent recommendations in Europe continue to emphasize the need for vitamin D supplementation for infants and adding recommendations for pregnant women, but are reducing recommendations for adolescents and older children due to the dubious results of RCTs on vitamin D supplementation and because of difficulties in interpreting vitamin D status. The higher risk of vitamin D deficiency is a consideration for recommending supplementation of 10 g/day (Taylor, 2020). Elevated serum 25(OH)D levels have been compared either after oral or intramuscular administration. In the general population or when vitamin D is required, the oral route is preferred for maintenance. The two routes of administration appear to be equivalent. The parenteral route of vitamin D administration is effective and safe in patients with vitamin D deficiency caused by severe intestinal malabsorption (Bilezikian et al., 2021). Vitamin D supplementation is safe and may protect against overall acute respiratory infections. Vitamin D supplementation did not affect the proportion of participants who experienced at least one side effect (Bergman et al., 2013; Jolliffe et al., 2021; Manaseki-Holland et al., 2010; Martineau et al., 2017).

When determining the appropriate dose of vitamin D supplementation, the potential for toxicity must be considered. Damage is possible at concentrations of 25(OH)D above the therapeutic dose range, but toxicity due to misuse or accidental ingestion has been reported at doses of 6,000-112,500 g and results in severe hypercalcemia. Overdose is a rare but potential risk. Education of parents about proper giving is highly recommended (Taylor, 2020). Almost all studies included high-dose of vitamin D (>100,000 IU) but no adverse events were reported in any of these meta-analyses. Most studies that excluded comorbid or underlying diseases from study participants were not included in the study, which is a limitation in this systematic review and meta-analysis study. As

previously explained, comorbidity is a risk factor for recurrent pneumonia and thus can be a confounding factor.

Conclusion

Vitamin D supplementation can be given as adjunctive therapy to reduce possibility of recurrent pneumonia in children. Vitamin D supplementation also needs to be considered a supportive therapy. Health personnel should provide precise and clear advice to parents regarding the right amount of daily dose and when to give it to children. For this reason, further RCT studies on the provision of vitamin D supplementation need to be carried out, especially in developing countries with the most cases.

Acknowledgments

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