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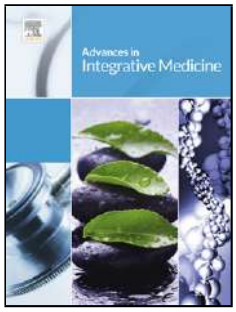

The effects of Vitamin D on acute viral respiratory infections: a rapid review

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The effects of Vitamin D on acute viral respiratory infections: a rapid review

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Brief Overview:

Current evidence suggests vitamin D replacement may reduce risk for acute respiratory tract infections (ARTI) in people with deficiency or insufficiency, although the effects of supplementation on incidence and severity of ARTI in the general population remain unknown. Oral vitamin D supplementation taken at routine doses appears to be generally safe and well tolerated.

Verdict:

Current experimental evidence remains inconclusive regarding the effects of vitamin D supplementation in the general population for the prevention and treatment of acute respiratory tract infections (ARTI). There is also insufficient evidence to draw conclusions regarding the impact of vitamin D supplementation on the severity or duration of ARTI, nor on outcomes related to lung injury or hospitalization from ARTI. Based on this rapid review, sources of significant heterogeneity in published clinical trials include: differences study populations, inconsistent assessment of serum status at baseline, dosing variability, varying routes of administration, and/or inconsistent definitions of outcome measures. Experimental evidence and observations in large cohorts are generally consistent that deficiency and insufficiency of vitamin D is associated with increased risk of ARTI, and supplementation for those with deficiency/insufficiency may lead to clinically meaningful reductions in the incidence of ARTI. In this rapid review, vitamin D was primarily administered as oral supplementation, and findings suggested significant differences in daily oral dosing compared to periodic bolus dosing. Based on the available experimental evidence, vitamin D supplementation appears to have a high margin of safety with very few adverse events reported in children or adults

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from a variety of dosing strategies. Future clinical trials on vitamin D should consider the sources of heterogeneity in the existing experimental research and design trials that account for baseline status, evaluate the potential for prevention and treatment in at risk populations, standardize dosing strategies, assess product quality, assess outcomes according to gold standard definitions/diagnostic methods, and delineate viral ARTI from other causes when possible. The available mechanistic evidence related to immunological requirements for adequate vitamin D, the availability of observational and experimental evidence suggestive of clinically meaningful benefits (especially in deficient/insufficient participants), and the high margin of safety, should make vitamin D a high priority for additional clinical research during the current COVID-19 pandemic.

Background:

Vitamin D, is a fat-soluble, secosteroidal hormone available to humans in the diet, nutritional supplements, and via direct production in the skin upon exposure to adequate ultraviolet light. Vitamin D has numerous fundamental functions in the innate and acquired immune response. Activation of both T- and B- cells leads to upregulation of the vitamin D receptor (VDR), allowing for changes in expression of over 500 vitamin D related genes.[1-3] Select mechanistic effects of Vitamin D on immune function include: enhancement of chemotaxis and phagocytosis[4], regulation of antibody production in B cells[5], inhibition of interleukin (IL)-2, interferon (IFN)-gamma, tumor necrosis factor (TNF)-alpha IL-9, and IL-22[6-10], and increased IL-3, IL-4, IL-5, and IL-10.[11] Observational research in the British Birth cohort has demonstrated significant linear relationships between serum vitamin D concentration (i.e., 25-hydroxycholecalciferol or 25-OHD) and lower risk of acute respiratory tract infection (ARTI), with each 10 nmol/L increase associated with a 7% lower risk.[12] Further observational research in the United States (US)-based National Health and Nutrition Examination Survey (NHANES) 2001-20016 suggested those with insufficient serum status (25-OHD<30 nmol/L [<20 ng/ml]) had 58% higher odds of ARTI.[13] Based on the numerous roles of vitamin D in the regulation of immune function, and notable observational research suggesting potential effects on ARTI, numerous randomized controlled trials in adults and children have aimed to learn the direct effects of vitamin D on risk of ARTI and their potential complications. The purpose of this rapid review is to summarize available systematic reviews of randomized, controlled clinical trials of vitamin D on ARTI and related outcomes.

Search Strategy

Research question

What are the effects of Vitamin D on acute respiratory tract infections (ARTI) and associated complications?

Inclusion/exclusion criteria

Reviews were included if they were described as "systematic" and exhibited methods consistent with systematic reviews (i.e., defined clinical question, detailed search protocol, etc.) and reported on human prospective intervention trials sampling adults and/or children with reported ARTI. Reviews were excluded if they were designed as narrative

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reviews, non-review manuscripts, included only observational studies, and/or the study sample was not reported as diagnosed with ARTI.

Databases
Medline (OVID), Embase (OVID), AMED (OVID), and CINAHL

Search terms (example)
Five search strategies were pursued and compiled as follows:

#1: exp Coronavirus Infections/ or exp Coronavirus/ or exp Coronaviridae/ or Influenza, Human/ or Influenza A Virus, H1N1 Subtype/ or Influenza A virus/ or Influenza A Virus, H3N2 Subtype/ or Middle East Respiratory Syndrome Coronavirus/ or respiratory tract infections/ or bronchitis/ or common cold/ or Pneumonia, Viral/ or (Coronavir* or nCov or Influenza or H1N1 or MERS-COV or flu or Bronchit* or cough or rhinosinusit* or rhinit* or common cold or (respiratory adj2 (infect* or illness or symptom* or acute or virus* or disease))).ti,ab,kw.

#2: exp Vitamin D/ or exp Calcitriol/ or exp Cholecalciferol/ or exp Ergocalciferol/ or exp 25-hydroxyvitamin d 2/ or ("Vitamin d$" or "Vit d" or Calcitriol$ or Cholecalciferol or Ergocalciferol or "25-Hydroxyvitamin D 2").ti,ab,kw

#3: Systematic Review/ or Meta-analysis/ or Systematic Review as Topic/ or Meta-Analysis as Topic/ or Review Literature as Topic/ or (Systematic review or meta analy$ or metaanaly$).ti,ab,kw

#4: comment/ or letter/ or editorial/

#5: (#1 AND #2 AND #3) NOT #4

Screening
Titles and abstract screening and full text screening were completed by one reviewer and checked for accuracy by a second reviewer. Similarly, data extraction was completed by a single reviewer and checked for accuracy by a second reviewer. Any discrepancies were resolved by consensus.

Critical appraisal
The critical appraisal tool for this rapid review was performed using the BMJ Best practice criteria for appraising systematic reviews (https://bestpractice.bmj.com/info/toolkit/learn-ebm/appraising-systematic-reviews/).

Results
The initial search resulted in 270 citations [Medline (n=57), Embase (n=154), AMED (n=1), and CINAHL (n=58)], after duplicates (n=68) were removed, 202 remained for title and abstract screening. Based on title and abstract review, an additional 138 manuscripts were excluded as irrelevant due methodology (i.e., editorials, commentaries, and/or non-systematic reviews), or broad outcome measures (i.e., not focused on ARTI outcomes). Following abstract review, 36 manuscripts were excluded by full text screening due to methodological limitations not apparent in the abstracts (i.e., narrative reviews), leaving 28 manuscripts for detailed extraction. During detailed data extraction, 5 additional manuscripts were excluded due to inclusion of only observational studies, plus 3 additional exclusions included: an editorial (n=1), a poster citation (n=1), and a duplicate republished as a report (n-=1), leaving 20 for the final detailed

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extraction; see Figure 1. All citations were imported into Covidence software (Melbourne, Australia) for title and abstract reviews. Full texts were also imported into Covidence for review and data extraction upon finalization of the manuscripts meeting inclusion criteria.

Critical Appraisal

From the appraisal, seven of the 20 reviews met all the requirements. The majority of the studies met most of the criteria in the appraisal tool, however, three reviews were determined to be very poor quality because they met four or fewer of the requirements. The quality of data from these reviews [14-16] in our conclusions and summaries.

Description of included studies

See Table 1 for a summary of all included studies in the final, detailed review. Of the 20 studies, 13 were systematic reviews and/or of meta-analysis [16-27], 3 were systematic reviews of randomised controlled trials (RCTs)[28-30], 2 were systematic reviews of various studies [14, 31] and 1 was a detailed narrative review of RCTs (and therefore was included), despite low formal quality of design [15]. The 2 systematic reviews with various studies included RCTs, cohort studies, case-control series, retrospective case studies and cross-sectional studies [14, 31]. The majority of reviews searched 3 or more databases with Pubmed, Embase, Cochrane, Cinahl and Medline being the main ones [15, 17-23, 25-32]. Two studies only used one database, Pubmed [14, 33] and 1 didn't specify the databases searched [16].

The study population and size, type of respiratory condition, form and dose, and administration route or screening of vitamin D varied across the studies reviewed. Fourteen studies included all populations including children, adults and elderly [14-18, 20, 22, 23, 26-30, 32] and 5 reviews were conducted on children only [19, 21, 24, 31], 1 was for pregnant women and children [25] and 1 for children and young men [33]. The number of studies included for the reviews on children included 26 in total, encompassing 12 RCTs, 3 cohort, 2 cross-sectional and 9 case-control studies [19, 21, 24, 31]. The pregnancy and children review contained 22 studies including 4 RCTs and 18 observational [25] while the children and young men review contained 10 RCTs [33]. For the studies that included all populations, 222 studies were identified in the reviews. These included 171 RCTs, 24 cohort studies, 8 case-control studies and 4 cross-sectional [14-18, 20, 22, 23, 26-30, 32] .

The 7 reviews which mainly focused on children comprised a total sample of 33,503 participants; of those reviews that reported allocation, there were 6,474 participants in intervention arms and 6,464 participants in placebo arms [19, 21, 24, 25, 31, 33]. The fourteen studies that included all population groups comprised a total sample of 314,979 participants. Of the reviews reporting group allocation, there were 41,738 participants in intervention arms and 39,655 participants in placebo arms. [14-18, 20, 22, 23, 26-30, 32].

Sixteen reviews addressed oral administration of vitamin D [15-17, 19-27, 30, 31, 33], 2 reviews addressed intravenous and oral administration of vitamin D [29, 32] and 3 reviews did not state the route of administration (and focused solely on serum concentrations of vitamin D) [14, 18, 28].

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The reviews exclusive to children all used oral administration of vitamin D with 4 reviews reporting on administration of a dose ranging from 300 IU -2000 IU per day [19, 21, 24, 31]. In the 2 reviews exclusive to pregnant women plus children and young men plus children, the dose ranged from 800 IU-2000 IU daily [25, 33]. The oral doses for vitamin D in the reviews of all ages varied dramatically from 100 IU to 100,000 IU. See Table 2 for dosage range included in each review.

Summary of Findings:

The measurement outcomes from the reviews varied; however, the primary outcome measure evaluated for this review was the incidence of ARTIs (n=13) [14, 15, 17, 18, 20-23, 25, 27-29, 31]. The other main outcome measures included were: the association between vitamin D levels and ARTI risk (5 reviews) [16, 26, 32, 33], pneumonia incidence (3 reviews) [14, 19, 24], and frequency of hospitalization rates (2 reviews) [14, 24]. Several individual reviews reported additional, less specific, outcomes including: frequency of doctor visits, [25], asthma exacerbations [25], incidence of influenza [14], tuberculosis [15] and extra-skeletal disease [30].

Of the 21 reviews, 15 concluded vitamin D was safe and has the potential reduce the risk of ARTI [15-18, 22, 23, 25, 27, 29-33]. The other 6 reviews each concluded that there was insufficient evidence to support the protective effect of vitamin D for ARTIs[14, 19-21, 24, 28] .

Reviews Supporting a Protective Effect of Vitamin D and ARTI.

Autier P., et al. (2017) concluded vitamin D may help to prevent the common upper respiratory tract infections and asthma exacerbation. A 6% risk reduction with vitamin D3 supplementation was identified for clinical RTIs but was of borderline statistical significant; relative risk (RR)= 0.94 [95% CI: 0.88, 1.00] [32]. They hypothesized vitamin D supplementation may exert immunomodulating effects leading to reduced risk of ARTI.

Bergman P., et al. (2013) concluded vitamin D has a protective effect against RTI; odds ratio (OR)= 0.64 [95% CI: 0.49, 0.84]. They also identified that the protective effect was larger in studies that used once-daily dosing compared to bolus doses , OR= 0.51 vs. OR= 0.86 respectively (p=0.01 for difference) [27].

Charan J., et al. (2012) concluded the overall events of ARI in vitamin D group were 21.7% (205/943) whereas in placebo group it was 30.1% (279/925), or an -8.4% absolute risk reduction in favour of vitamin D. According to their random effects model in children and adults combined, there was significant reduction in the incidence of respiratory tract infection in vitamin D group as compared to placebo group; OR = 0.58 [95% CI: 0.42, 0.81], p= 0.001. In their random effects model for children only (2 studies), vitamin D supplementation reduced the risk of respiratory tract infections significantly (OR=0.58 [95% CI: 0.42, 0.815], p=0.001), with identical risk reduction in their fixed effects model (OR=0.58 [95% CI: 0.42, 0.81], p=0.001). Limiting analyses to trials in adults only (3 studies), the point estimate for risk favoured vitamin D supplementation but was not statistically significant [22].

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Christensen N., et al. (2017) concluded RCTs results and effects from supplementation differed depending on the baseline 25OHD concentration. However, overall the level I-II moderate to high quality evidence suggested vitamin D has a protective effect for RTI's. (dose >800 IU/day) [25].

Jat K.R., et al. (2017) found that children with lower RTI were found to have significantly lower mean vitamin D levels as compared to controls. There was likewise a correlation between vitamin D levels and incidence and severity of RTI's .

Jayawardena R., et al. (2020) concluded serum status is likely to be a predictor of immune responses to vitamin D supplementation, and ARTI may be significant lower in vitamin D groups among elderly participants in long term care facilities, but concluded most trials demonstrated no overall differences in the incidence of upper respiratory tract infections between vitamin D and controls, likely due to participant and dosing heterogenicity [29].

Larkin A., et al. (2013) results showed that a vitamin D deficiency was notably prevalent among both mothers and infants and deficiency was associated with an increased risk of ARTIs [31].

Maretzke F., et al. (2020) concluded observational data supported primary prevention, with a significant inverse association between vitamin D status and risk of ARTIs, with RCTs supporting similar conclusions [30].

Martineau A., et al. (2016) found that vitamin D supplementation reduced risk of ARTIs among all participants (adjusted OR= 0.88 [95% CI: 0.81, 0.96]; p for heterogeneity <0.001). Protective effects seen in those receiving daily or weekly vitamin D without additional bolus doses. Among those receiving daily or weekly vitamin D, protective effects were stronger in those with baseline 25-hydroxyvitamin D levels <25 nmol/L (adjusted OR=0.30 [95% CI: 0.17, 0.53) compared to those with baseline 25-hydroxyvitamin D levels ≥25 nmol/L (adjusted OR=0.75 [95% CI: 0.60, 0.95], p for interaction=0.006). Vitamin D did not influence the proportion of participants experiencing at least one serious adverse event (adjusted OR=0.98 [95% CI: 0.80, 1.20], p=0.83) [23].

Martineau A., et al. (2017) concluded vitamin D supplementation resulted in statistically significant reduction in the proportion of participants experiencing at least one ARTI. Vitamin D supplementation was a strong protective factor among people with a baseline circulating 25-OHD <25 nmol/L; however, no significant effects among those with levels of ≥25 nmol/L. Baseline vitamin D status and dosing frequency independently modified the effect of Vitamin D supplementation on risk of ARTI. Daily or weekly vitamin D treatment was associated with a greater degree of protection against ARTI among participants with low baseline levels of 25-OHD. Bolus dose of Vitamin D did not appear to offer protection against ARTI. Vitamin D did not influence the risk of serious adverse events or mortality due to any cause [17].

Moroti R., et al. (2012) concluded 25-OHD at least 10 nmol/L higher than the mean concentration offered protection against ARTI, and vitamin D may be an effective adjuvant in the anti-infective therapy [33].

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Reinehr T., et al. (2018) concluded vitamin D may potentially reduce the risk of influenza, improve asthma and reduce exacerbation of bronchiole spasms, but had no impact on severity of bronchiole spasms [16].

Rejnmark L., et al. (2017) concluded 3 out of 7 meta-analysis reported beneficial effects of Vitamin D supplementation on RTI while the rest reported null effects. In 2 RCTs, vitamin D supplementation significantly reduced the risk of RTI by 40% in paediatric population. The risk of ARTI was significantly reduced in 25 RCTs in the general population (OR= 0.88 [95% CI: 0.81, 0.96]. Response to a daily or weekly vitamin D dose showed as a protective effects, but null effect in response to one or more bolus doses [18].

Zittermann A., et al. (2015) concluded vitamin D deficiency increased the risk of ARTI but there was no evidence vitamin D lowered risk of other common infections. They also recommended supplementation with vitamin D (dose 600-2,000 IU/day) for prophylaxis, particularly in winter, due to the high vitamin D deficiency found in the European population [15].

Reviews Supporting Null Effects of Vitamin D and ARTI

Jolliffe D., et al. (2013) concluded observational studies found a statistical significance between vitamin D deficiency and increased risk of ARTIs. However, they also identified conflicting RCTs, and therefore concluded vitamin D supplementation did not conclusively demonstrate protection against ARTIs [14].

Mao et al. (2013) reported a pooled RR=0.98 [95% CI: 0.93-1.03], p=0.45 of ARTI from vitamin D supplementation of and therefore concluded the routine use of vitamin D supplementation cannot be recommended for ARTI prevention in healthy populations [26].

Xiao L., et al. (2015) reported no significant decreases in the incidence of ARTI (RR=0.79 [95% CI: 0.55-1.13]), all-cause mortality (RR=1.18 [95% CI: 0.71-1.94]), or the rate of hospitalization due to RTI's in healthy children (RR= 0.95 [95% CI: 0.72-1.26]) from vitamin D supplementation [21].

Yakoob M., et al. (2016) concluded, based on moderate quality evidence, there was no effect of vitamin D supplementation on the occurrence of pneumonia; nor any effect in children with pneumonia. No conclusions could be made regarding whether vitamin D influenced hospital admissions as there was only one small study assessing this outcome, which had very low quality [24]. The types or causes of pneumonia were not specifically evaluated.

Vuichard Gysin D., et al (2016) reported a pooled risk of ARTI 6% lower in the vitamin D group compared to non-treatment group, a 10% lower risk of lab-confirmed ARTI among vitamin D group, a marginal mean reduction in symptom duration, and lower symptom severity in vitamin D groups; however the point estimates for these risk reductions did not reach statistically significance [20].

Yamshchikov A., et al. (2009) reported no difference in frequency, severity, or duration of upper respiratory tract infections (URTIs), but statistical trends favoured vitamin D in all outcomes, including a lower frequency of wintertime URTI symptoms in intervention group, and a lower frequency of reported URTI symptoms while receiving 2,000 IU

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vitamin D3/day compared to 800 IU vitamin D3/day. However, the difference in infection rates between groups was no longer significant after 6 months of intervention. There was also no difference in the change in CD4 count or viral load between groups [28].

Clinical significance:

Despite several positive systematic reviews and meta-analyses, the available experimental evidence related to the effects of vitamin D on acute respiratory tract infection (ARTI) is plagued with heterogeneity and mixed quality, and therefore is insufficient to recommend vitamin D supplementation to the general population as a protective agent against ARTI. However, based on the evidence identified in this rapid review (including a high margin of clinical safety), combined with strong mechanistic rationale, the following recommendations can be made for those at risk of ARTI: 1. vitamin D status should be tested for those at risk of ARTI; 2. patients identified with deficiency or insufficiency should be supplemented with vitamin D until their status is normalized; and 3. daily dosing of vitamin D3 is preferred to achieve serum concentrations > 30 nmol/L in a timely manner. Clinical trials support vitamin D doses of 800 IU/day up to 10,000 IU/day[34], with 1,000-2,000 IU/day being a common dosing strategy in clinical trials, and potentially more effective then lower daily or bolus dosing strategies.

Disclaimer: This article has not been peer-reviewed; it should not replace individual clinical judgement. The views expressed in this rapid review are the views of the authors and not necessarily from the host institutions. The views are not a substitute for professional medical advice.

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Figure 1: Search and review flowchart

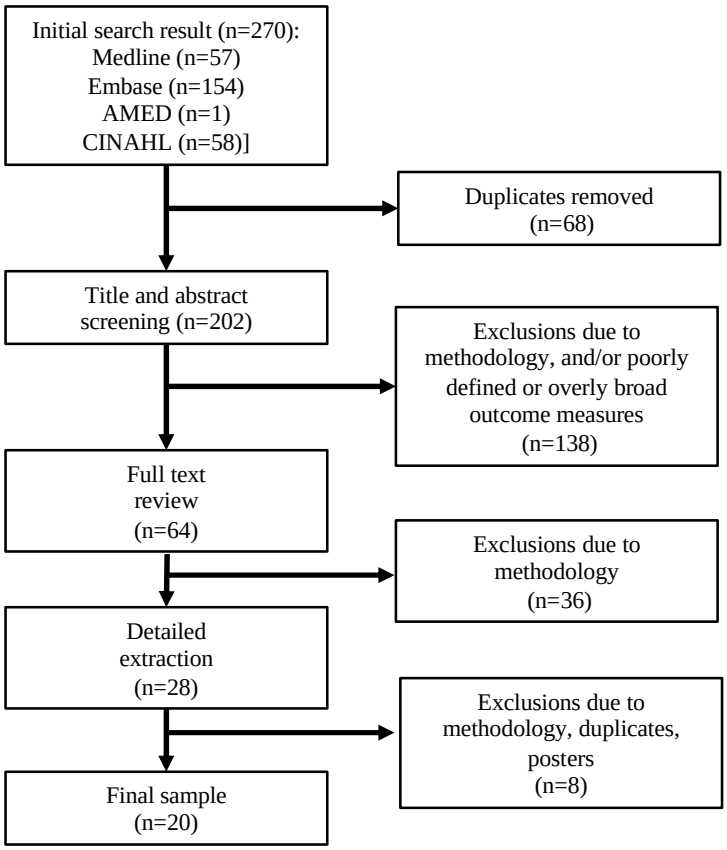

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Table 1: Summary of Included Studies

Author	Year	Design	Types of Studies included	Databases Used	Intervention	Participants	Number of Studies	#RCT	Route of Administration (PO, IV)	Total n	Dose	Placebo or other control	N in intervention and placebo/ control	Measure of Outcome	Outcome
Jolliffe, D	2012	SR	RCTs, cohort studies, case-control, cross-sectional	PubMed	Vitamin D3	Healthy adults, post-menopausal African American women, recent hip fracture, school children, military conscripts, children with pneumonia, low birth weight infants, children w/ treated asthma, children w/ COPD, healthy children.	39	14	Not stated	47,360	200 IU, 300 IU, 400 IU, 500 IU, 800 IU, 1200 IU, 2000 IU, 3000 IU, and 1111-6800 IU per day	Placebo	Total in RCT = 11,431; Intervention = 5,754, Placebo = 5,677	ARTI	Inconsistent effects on incident ARTI
Martineau, A	2017	SR and MA	RCT	Medline, Embase, Cochrane Central Register of Controlled trials, Web of Science, ClinicalTrials.gov, and Int RCT's	D3 and D2	Healthy adults, healthy preschool children, pre-school children with pneumonia, military conscripts, children with asthma, low birth weight infants, adults w/ COPD, infants, school children (3rd/4th graders), adults with increased susceptibility to ARTI, children with recurrent acute otitis media, adults with previous colorectal adenoma, healthy older adults, healthy college	25	25	PO	11,321	Daily dose: 2.5 µg -100 µg Monthly bolus: 0.75-5 mg	Placebo	Intervention = 4,844; control = 4,548	Incident ARTI: combined URTI and LRTI	Statistically significant reduction in the proportion of all participants experiencing at least one ARTI; strong protective factor among people with a baseline circulating 25-OHD levels less than 25 nmol/L; however, no significant with levels of 25 or more. Baseline 25-OHD modified the effect on risk of ARTI. Daily or weekly treatment associated with greater degree of protection

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						students, high school students, pregnant women and offspring, adults with asthma								Mortality of all-causes and ARTI	against ARTI among participants with low and high baseline levels of 25-hydroxyvitamin D. Bolus dose of did not offer any protection against ARTI. No effect on risk of serious adverse events or mortality.
Yamshchikov, A	2009	SR	RCT	PubMed and Ovid MEDLINE	D2 or D3	Healthy volunteers receiving flu vaccine; outpatient healthy adults; HIV infected children and teenagers; elderly; healthy menopausal women; children with recent respiratory illness; hemodialysis patients with low PTH levels not otherwise on VitD therapy.	13 RCT; 7 on viral infections	13	Not stated	4,724	Wide range: 40 IU daily for 20 years to 100,000 IU of vitamin D3 given bimonthly for 12 months	Placebo	Intervention = 2,060; Placebo= 2,664	RTI	No difference in frequency, severity, duration of RTIs, but statistical trend noted to favor VitD in all outcomes. Lower rate of reported URI symptoms while receiving 2000 UI D3 per day vs 800 UI D3 per day. Difference in the infection rates between groups no longer significant after 6 months of intervention.
Rejnmark, L	2017	SR of MA	RCT	PubMed, Embase, and Cochrane Library	D3	Studies included newborns, infants, adults, and older adults. 23 of the RCTs studies had respiratory infections as the primary outcomes, while 7 had it as a secondary outcome. Some RCTs	46 studies | 7 in MA on RTI	46	Not stated	28 studies <1000; 2 of the studies had >1000	VitD3 dose was administered daily, no range stated	Not stated	Not stated	RTI	3 out of 7 MA reported beneficial effects on RTI while the rest reported null effects. In 2 RCTs, risk reduced by 40% in pediatric population.

						investigated the risk of pneumonia, upper or lower RTI, or exacerbations in patients with asthma or COPD.									The risk significantly reduced in 25 RCTs (OR 0.88, 95% CI (0.81 - 0.96). Response to a daily or weekly VitD dose showed as a protective effect, but null effect in response to one or more bolus doses.
Jayawardena, R.	2020	SR	RCTs	PubMed, Web of Science, and SciVerse Scopus	Vitamin D, any form	Healthy adults and children, HCV and HBV patients, elderly, children with HBV, male smokers (immunity to influenza-like viral infections)	43	6 re: VitD	PO, IV	26803	Vitamin D (2000 IU) days 0 & 28, Vitamin D3 (2000 IU/day), Vitamin D3 (100,000 IU/month), Vitamin D (6 doses 100,000 IU, 1 vial/15 days)	Control and placebo	Intervention =13947 Placebo/ control =12856	Incident wintertime URTI	Significantly lesser URTI in elderly participants No difference in URTI overall
Jat, K.R et al.	2016	SR and MA	RCTs	PubMed, Embase, and Cochrane	Vitamin D, any form	Infants aged 1-11 mo, Children between 2 mo-5yrs with a diagnosis of severe pneumonia, School-aged children from 3rd-4th grade classrooms, and Children with pneumonia and severe pneumonia (LRTI in children)	4	4	PO	3,946	100,000 U D3 every 3 mo for 18 mo, 1000 U (to <1 y) and 2000 U (for 1-5y) daily x 5 d, 300 U of vitamin D3 daily in milk for 7 wk, 100,000 IU of vitamin D3 single dose	Placebo (2) Control (2): Olive oil; unfortified regular milk	Intervention =1991 Placebo/ control = 1955	First/only episode of radiologically confirmed pneumonia Parent-reported number of ARIs that occurred over 3 months Adverse effects	MA found no difference in incidence of the first/only episode of pneumonia. Lower incidence of pneumonia in the following 3 months. No difference in LRTI. Adverse events in 2 children (single episode of vomiting and another had diarrhea for 2 days).
Vuicharddgysin, D.	2016	SR and MA	RCTs	Medline, EMBASE, CENTRAL,	Vitamin D, any form	Healthy individuals: infants,	15	15	PO	7,053	7.5 mcg-2500 mcg/daily.	Placebo	Intervention =3844	Incidence RTI	-6% risk lower in the vitamin D group (not

				and CINAHL		children, adults, and elderly					Average daily dose 1500 IU (300-3700 IU)		Placebo/ control =3209	Duration of RTI Severity of RTIs	statistically significant) 10% lower risk of lab-confirmed RTI (not statistically significant) Marginal reduction in duration (not statistically significant) Less severe (not statistically significant).
Xiao L et al	2015	SR with MA	RCT	Medline, EMBASE, Cochrane Central Register of Controlled Trials	Vitamin D, any form	Younger than 18 years old	4 RCT for ARTI	4	PO	3,771	Daily: 300 - 1200 IU	Placebo	Not reported	Incidence of ARI	No significant decrease: RR= 0.79 [95% CI: 0.55-1.13]
Charan J et al.	2012	SR with MA	RCT	Pubmed, Cochrane clinical trial register, google scholar	Vitamin D, any form	children and adults	5 RCT	5	PO	Not stated	400-2000 IU/day	Placebo	Unclear	Frequency of acute respiratory infection	-8.4% risk reduction in overall ARI in adults and children combined, and in subgroup of children only, but not subgroup of adults only
Marzetke, F.	2020	SR	RCTs	PubMed, Cochrane Reviews Library	Vitamin D, any form	14 just on children, 3 both children and adults	18	8	PO	N/A - Mendelian RCT alone = 146,761	Ranged between 10 µg - 10,000 µg (bolus dose)	Control	N/A	ARTI	Beneficial effect in primary prevention No significant treatment effect measured
Larkin, A.	2013	SR	CS: 6, CCS: 2, RCS:1, CSS:1, RCT: 2	Medline, CI-NAHL, Cochrane Library	Vitamin D, any form	Children age 0 to 5 with and without ALRTI	2	2	PO	3499 (from the 2 RCTs in review)	2.5 mg	Control	Intervention = 1748 Placebo = 1751	ALRTI	Increased incidence or severity if deficient in Vitamin D
Martineau, A.R.	2016	SR with MA	RCT	Medline, Embase, Cochrane Central Registered of Control	Vitamin D, any form	All ages	25	2	PO	11,321	10 µg - 100 µg	Control	Intervention = 5,904; Placebo= 5,417	Incident ARTI	Reduced risk: Adjusted OR= 0.88 [95% CI:0.81 to 0.96]

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				Trials (CENTRAL), Web of Science, ClinicalTrials.gov, and International Standard RCT Number (ISRCTN)											Protective effects seen in those receiving daily or weekly doses. Protective effects were stronger in those with baseline 25-OH D levels <25 nmol/L (adjusted odds ratio=0.30 [95% CI: 0.17 to 0.53] Did not influence risk of serious adverse event (adjusted odds ratio 0.98, 0.80 to 1.20, P=0.83).
Zittermann, A.	2015	Narrative Review	RCT	PubMed and Google Scholar	Vitamin D, any form	6 studies for treatment of TB (tuberculosis), while 16 studies examined prevention of respiratory tract infection in healthy recruits and/or amongst patients	22	16 on ARTI	PO	8,705	Daily: 10 µg - 20 µg Bolus: 250 µg -2,500 µg	Control	N/A	Incident ARTI	Significant risk reduction by vitamin D supplements [OR = 0.65 [95 % CI: 0.50–0.85] Daily administration more effective than high-dose bolus administration (OR = 0.48 [95 % CI: 0.30–0.77] vs. OR = 0.87 [95 % CI: 0.67–1.14] and more effective in deficiency.
Yakoob, M.Y.	2016	SR	RCT and MA	Cochrane Infectious Diseases Group (CIDG) Specialized Register; the Cochrane Central Register for Controlled	Vitamin D, any form	3198 children under 5 years of age (conducted in Afghanistan, Spain, and the USA)	4	4	PO	3198	10 µg - 2.50 mg	Control	Intervention = 1,596; Placebo= 1602	Pneumonia incidence (n=2)	No effect on the occurrence of the first or only episode of pneumonia; or on children with pneumonia, irrespective of whether this had been confirmed by hospital tests (moderate

				Trials (CENTRAL), MEDLINE (PubMed); EMBASE, LILACS, WHO International Clinical Trials Registry, ClinicalTrials.gov, ISRCTN Registry										Mortality (n=2)	quality evidence). No effect on death (low quality evidence);
Christensen, N.	2017	SR	RCTs , MA and observational studies	Pubmed, Embase and, the Cochrane	Vitamin D, any form	Pregnant women and children with 5 years old or younger	22	4	PO	RTCs = 1944 Observational Studies = 11517	Daily 2,000 IU, 800 IU	Placebo	Not specified	Wheeze RTI	Protective effect on infant wheeze Inconclusive on RTI Favorable doses higher than 800 IU/d.
Mao, S.	2013	MA	MA of RCTs	Pubmed, Embase and, the Cochrane	Vitamin D, any form	"Healthy patients"	7	7	PO	4827	300 to 6,800 IU/day	Placebo	Intervention: 2,440 Placebo: 2,387	Incident ARTI	Supplementation of VitD in healthy population does not prevent RTI.
Moroti, R.	2012	SR	RCTs	Pubmed	Vitamin D, any form	Children and young men	10	10	PO	3349	800-2000 IU	Placebo	625/715	Serum VitD levels	A serum level of with at least 10 nmol/L higher than the mean basic serum level concentration appears to be protective. Vitamin D may be an effective adjuvant in the anti-infective therapy.
Reinehr, T.	2018	MA	MA of RCT	Not reported	Vitamin D, any form	Children, adolescents and adults	Unspecified	MA and RCTs	PO	Unspecified	400-1000 IU	Placebo	Not stated	ARTI, influenza Asthma symptoms	Potentially reduces the risk of influenza in school aged children, and higher dose in children aged 1-5 did not make a difference. Both had lower number of ARI. Improves

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															asthma and hospital admission.

SR=systematic review, MA=meta-analysis, RCT=randomized clinical trial, ARTI=acute respiratory tract infection, URTI= upper respiratory tract infection, LRTI=lower respiratory tract infection, CS=Cohort Studies, CCS=Case Control Studies, RCS=Retrospective Case Studies, CSS=Cross-Sectional Studies

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Table 2: Dosing Ranges in Reviewed Manuscripts

	Dose (IU)													
Author/Year	U/S	40	200	300	400	500	800	1,000	1,500	2,000	3,000	4,000+	10,000+	100,000+
Yamshchikov/2009		X												X/B
Charan/2012					X	X	X	X	X	X				
Jolliffe/2012			X	X	X	X	X	X		X	X	X		
Moroti/2012							X	X	X	X				
Bergman/2013			X	X	X	X	X	X	X	X	X	X		
Larkin/2013														X/B
Mao/2013				X	X	X	X	X	X	X	X	X		
Xiao/2015				X	X	X	X	X	X					
Zittermann/2015											X/B	X/B	X/B	X/B
Jat/2016				X				X		X			X/B	
Martineau/2016											X/B	X/B	X/B	X/B
Vuichard Gysin/2016				X					X		X/B	X/B	X/B	X/B
Yakoob/2016											X/B	X/B	X/B	X/B
Autier/2017											X/B	X/B	X/B	X/B
Christensen/2017							X			X				
Martineau/ 2017												X/B	X/B	X/B
Rejnmark/2017	X/B/IV													
Reinehr/2018					X	X	X	X						
Jayawardena/2020										X			X/B/IV	
Marzetke/2020											X/B	X/B	X/B	X/B

U/S=unspecified; B=bolus dosing; IV=intravenous administration; X indicates the review identifies the use of this dose in the studies they reviewed.

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Table 3: Risk of Bias evaluation for Vitamin D Review

Author	1: Comprehensive and reproducible search?	2. Clearly focussed question?	3. Inclusion/exclusion criteria clearly stated?	4. Are primary RCT data reported	5. Methodological quality assessment?	6. Meta: Are primary studies combined appropriately?	7. Meta: Combined statistics reported?	8. Meta: Report absolute numbers and summary stats?	9. Is heterogeneity discussed?	10. Is relevance/ significance discussed?	Total out of 10
Jolliffe, D	?	+	+	+	?	?	?	?	?	+	4
Martineau, A	+	+	+	+	+	?	+	+	+	+	9
Yamshchikov, A	+	?	+	+	+	?	?	?	+	+	6
Rejnmark, L	?	+	+	?	?	+	?	+	-	+	5
Jayawardena, R.	+	+	+	+	+	?	?	?	+	+	7
Jat, K.R et al.	+	+	+	+	+	+	+	+	+	+	10
VuichardGysin, D.	+	+	+	+	+	+	+	+	+	+	10
Xiao L et al	+	+	+	-	+	+	+	+	+	+.	9
Charan J et al.	+	+	+	+	+	-	+	+	+	+	9
Marzetke, F.	+	+	+	-	+	?	?	?	+	+	6
Larkin, A.	+	+	+	+	+	?	?	?	-	+	6
Martineau, A.R.	+	+	+	+	+	+	+	+	+	+	10
Zittermann, A.	+	-	-	+	?	?	?	?	+	+	4
Yakoob, M.Y.	+	+	+	+	+	+	+	+	+	+	10
Christensen, N.	+	+	+	+	+	+	+	+	+	+	10
Jat KR	+	+	+	-	+	+	+	+	+	+	9
Mao, S.	+	+	+	+	+	+	+	+	+	+	10
Moroti, R.	-	-	-	+	-	+	+	+	-	-	4
Reinehr, T.	-	-	-	-	-	-	-	-	-	+	1
Autier 2017	+	+	+	-	+	+	-	+	-	+	7
Bergman 2013	+	+	+	+	+	+	+	+	+	+	10

Legend: Yes (+); No (-); Can't Tell (?)

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