



# Use of High Dose Vitamin D and its Association with COVID 19

## INTRODUCTION

Vitamin D is an essential fat-soluble vitamin obtained from the diet or can be produced in the skin. Dietary vitamin D can be obtained through naturally occurring vitamin D<sub>2</sub> (ergocalciferol) or D<sub>3</sub> (cholecalciferol) in food, dietary supplementation, or food fortification. Vitamin D enters the circulation and is bound to the vitamin D binding protein. It is transported to the liver or other tissues in which it is hydroxylated by one or more 25-hydroxylases into 25 hydroxyvitamin D (25(OH)D).<sup>1</sup>

Some research suggested that vitamin D has a potential role in the prevention of acute respiratory infections by increasing immunity. In some observational studies, it was observed that low vitamin D level in blood is associated with the increased incidence of respiratory tract infections.<sup>2</sup> Vitamin D supplement is not listed in the Ministry of Health Medicines Formulary, but available in the market. This rapid evidence review is conducted to provide brief information on Vitamin D or its deficiency on the determinants of severity of COVID-19 infections, and the safety and effectiveness of the treatment related to vitamin D. This review is requested by the Director General of Health Malaysia.

## EVIDENCE on EFFECTIVENESS and SAFETY

There was no article retrieved from the scientific databases such as Medline, EBM Reviews, EMBASE via OVID, PubMed and from the general search engines [Google Scholar and US Food and Drug Administration (USFDA)] on the association of Vitamin D supplementation or deficiency on the treatment and/or determinants of severity of COVID-19 infections. 131 articles were retrieved from PubMed on acute respiratory tract infection and Vitamin D and two relevant articles were included in this report. Other studies have been included in the WHO commentary overview.

The World Health Organization (WHO) published a commentary overview of four systematic reviews and meta-analyses on Vitamin D for prevention of respiratory tract infections.<sup>4</sup> The reviews highlighted the overall findings based on three components, as summarized below in Table 1.

Table 1: Summary from WHO evidence review on Vitamin D for prevention of respiratory tract infections.

Components	Discussion
<b>Applicability of results from reviewed evidences</b>	<ol style="list-style-type: none"> <li>1. Three of the reviews showed a benefit of vitamin D supplementation for preventing respiratory tract infection mainly in children younger than 16 year.</li> <li>2. Protective effect is observed only when single daily doses are used but not bolus doses.</li> <li>3. Evidence on the dose-effect of vitamin D in protection of respiratory tract infection is not conclusive.</li> <li>4. Most reviews reported significant heterogeneity, hence, the generalizability of the results are difficult.</li> <li>5. Large boluses may increase the risk of adverse outcomes, such as increased risk of pneumonia, suppressed proliferative responses of peripheral blood monocytes, suppressed inflammation, and greater positive sputum cultures.</li> </ol>
<b>Implementation in settings with limited resources</b>	<ol style="list-style-type: none"> <li>1. Vitamin D supplementation for preventing respiratory tract infection is not routinely done.</li> <li>2. For this intervention to be effective, it should be done continuously, before the respiratory tract infection starts.</li> <li>3. Major challenges of implementation: planning for procurement of the preparation, storage, distribution, quality-control, and compliance assurance of vitamin D supplements.</li> <li>4. Failures in implementation of this intervention have been attributed in many instances to inadequate infrastructure and poor compliance, particularly in developing countries.</li> </ol>
<b>Suggestion for further research</b>	<ol style="list-style-type: none"> <li>1. Additional trials testing different dosing regimen (level of dose and intervals) are needed before implementing this intervention at a population level.</li> </ol>

Pham H et al. included 14 studies (N = 78,127) in a systematic review and meta-analysis of observational studies of adolescents aged  $\geq 12$  years or adults to assess the association between 25(OH)D concentration and risk of Acute Respiratory Tract Infection (ARTI). The risk of ARTI was either self-reported via surveys or symptom diaries, or clinically confirmed with or without evidence from X-rays or laboratory tests. There was a significantly higher risk of ARTI in the lowest ( $< 25$  nmol/L) compared with the highest ( $\geq 25$  nmol/L) 25(OH)D concentration (pooled OR 1.83; 95% CI: 1.42, 2.37; I<sup>2</sup> = 78.8%; p < 0.001). Further analysis of 10 studies (N = 69,048) reported the pooled OR of ARTI risk per 10 nmol/L decrease in 25(OH)D was 1.02 (95% CI: 0.97, 1.07; I<sup>2</sup> = 72.7%; p < 0.001). However, the association between 25(OH)D concentration and risk of ARTI was a non-linear association (p for non-linearity = 0.029). Five of the studies (N=1495) were also analysed to assess the association of severe ARTI or mortality combined comparing the highest and the lowest 25(OH)D. The pooled ORs for severity/mortality combined and mortality separately were 2.46 (95% CI: 1.65, 3.66; I<sup>2</sup> = 49.8%; p = 0.093) and 3.00 (95% CI: 1.89, 4.78; I<sup>2</sup> = 66.7%; p = 0.029). Among the studies, four reported that longer duration of ARTI was significantly associated with low 25(OH)D concentration (p $\leq$ 0.05). However, generalisability of the results from this review is difficult due to the heterogeneity of each studies included (I<sup>2</sup> >70%).<sup>5</sup>

Dimitra Z et al. in a narrative review summarised the potential associations of 25-hydroxyvitamin D [25(OH)D] with infectious respiratory tract diseases of childhood and the possible health benefits from vitamin D supplementation in children and adolescents (<18 years). Successful outcomes have been reported in children with tuberculosis and those with a history of recurrent acute otitis media and bronchiolitis, whereas no benefit was found in children with pneumonia. Conflicting results were found as regards to influenza, while there was no sufficient evidence on pharyngotonsillitis and rhinosinusitis. Another perspective could be maternal vitamin D supplementation during pregnancy and breastfeeding in order to reduce future RTIs in offspring, though the ideal dose of supplementation is still difficult to define. Studies with vitamin D supplementation revealed conflicting results as to whether supplementation may be of benefit, and at what doses.<sup>6</sup>

## CONCLUSION

There was no evidence retrieved to suggest the role of Vitamin D as determinants of risk and severity of COVID-19 infections. However, available evidence suggests significant associations between 25(OH)D concentration and both risk and severity of respiratory tract infection in adults and adolescents aged  $\geq 12$  years with low 25(OH)D concentration, but with significant heterogeneity. Evidence on the dose-effect of vitamin D and optimal 25(OH)D concentration in protection of respiratory tract infection is not conclusive. For children and adolescents <18 years, one narrative review suggested links between inadequate 25(OH)D concentrations and the development of upper or lower respiratory tract infections. However, studies with vitamin D supplementation revealed conflicting results as to whether supplementation may be of benefit, and at what doses.

## REFERENCE

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Based on available evidence up to 7 April 2020

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**Disclaimer:** This rapid assessment was prepared to provide urgent evidence-based input during COVID-19 pandemic. The report is prepared based on information available at the time of research and a limited literature. It is not a definitive statement on the safety, effectiveness or cost effectiveness of the health technology covered. Additionally, other relevant scientific findings may have been reported since completion of this report.

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