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# Optimisation of Vitamin D Status for Enhanced Immuno-protection Against Covid-19

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**Abstract**

***Background***
Vitamin D deficiency (serum 25(OH)D<50nmol/l) is common in Ireland, particularly amongst older adults, hospital inpatients and nursing home residents. Vitamin D deficiency is associated with increased risk of acute viral respiratory infection and community acquired pneumonia, with several molecular mechanisms proposed to explain this association. Vitamin D supplementation has also been shown to reduce the risk of respiratory infection.

***Vitamin D and Covid-19***
Correction of vitamin D deficiency is thought to suppress CD26, a putative adhesion molecule for Covid-19 host cell invasion. Vitamin D may also attenuate interferon gamma (IFNγ) and interleukin-6 (IL-6) inflammatory responses, both potent predictors of poorer outcome in critically-ill ventilated patients including those with Covid-19.

**Vitamin D Requirements**
Irish adults require 25-30µg/d of vitamin D3, an intake not achievable by diet alone, to reliably maintain serum 25(OH)D levels >50nmol/l. Supplementation with doses up to 100µg/d has been shown to be safe for adults, and many agencies and expert groups now advocate supplementation in older adults, albeit at lower levels than this.

***Conclusions and Recommendations***
Vitamin D deficiency is common and may contribute to increased risk of respiratory infection including Covid-19. We recommend that all older adults, hospital inpatients, nursing home residents and other vulnerable groups (e.g. those with diabetes mellitus or compromised immune function, those with darker skin, vegetarians and vegans, those who are overweight or obese, smokers and healthcare workers) be urgently supplemented with 20-50µg/d of vitamin D to enhance their resistance to Covid-19, and that this advice be quickly extended to the general adult population.

## Background

Vitamin D is a steroid hormone which may be synthesised endogenously from the effect of UVB irradiation on skin, or consumed from exogenous dietary sources or supplements. Recent studies have shown an inverse relationship between serum vitamin D levels and risk of acute respiratory tract infection[1]. Notably, a September 2019 meta-analysis by Zhou and colleagues incorporating data from 21,000 subjects across eight observational studies showed that those with a serum vitamin D level <20ng/ml (i.e. <50nmol/l) had a 64% increased risk of community-acquired pneumonia[2].

While the latter data are associative, and do not in and of themselves indicate a causal role for low vitamin D levels in community-acquired pneumonia, there is existing experimental evidence which suggests several mechanisms by which optimisation of vitamin D status contributes to enhanced resistance to viral respiratory tract infection[3,4,5]. Moreover, notwithstanding the heterogeneity of infection types included and population groups captured, a recent systematic review which evaluated the findings of 7 meta-analyses incorporating data from 30 randomised controlled trials concluded that vitamin D supplementation, particularly in those with low serum levels at baseline, is likely to reduce the risk of respiratory tract infection[6], a finding corroborated by two further systematic reviews the same year[1,7].

**Relevance of Vitamin D to Covid-19**

With regard to Covid-19, it is salient that while the virulence mechanisms of this virus have not been fully characterised, a number of molecular virulence mechanisms including dipeptidyl peptidase-4 receptor (DPP-4/CD26) binding, Papain-like protease (PLpro)-mediated replication, MDA5 and RIG-I host-recognition evasion, and disruption of M-protein mediated type-1 IFN induction have been identified in the closely-related Covid-MERS virus[8]. Of these, human DPP-4/CD26 has recently been shown to interact with the S1 domain of the COVID-19 spike glycoprotein, indicating that it may also be an important virulence factor in Covid-19 infection[9]. Critically in this regard, DPP-4/CD26 receptor expression has been shown to be significantly reduced *in vivo* upon correction of vitamin D deficiency[10]. There is also evidence that optimisation of vitamin D may attenuate some of the critical downstream immunological sequelae thought to elicit poorer clinical outcome in Covid-19 infection, such as prolonged interferon-gamma response[4], and persistent interleukin 6 elevation, a negative prognostic indicator in acutely-ill pneumonia patients[11], including those with Covid-19.

**Prevalence of Deficiency**

In Ireland, as a consequence of poor dietary intake, low supplementation rates and sub-optimal sun exposure, the prevalence of vitamin D deficiency is high, particularly amongst older adults, the most vulnerable constituency to Covid-19 mortality. In the last nationally representative sample, 35.7% of adults aged 50-64 years, and 44.0% of adults aged 65-84 years had serum vitamin D levels less than 50nmol/l on a year-round basis, while these figures rose to 55.4% and 48.1% respectively in winter[12]. These data are critical, as they suggest that one half of our older adults currently have serum vitamin D levels below the threshold at which viral respiratory infection risk is known to increase. It is also noteworthy that vitamin D levels are even poorer amongst nursing home and hospital inpatients in Ireland, with 37-42% of these individuals having serum levels less than 25nmol/l[13].

**Intake Requirements and Supplementation Guidelines**

Existing guidance from the Food Safety Authority of Ireland (FSAI) recommends that older adults should supplement with 10 micrograms of vitamin D per day[14]. However, most countries in Europe now recommend intakes of 15-20 micrograms per day for these older age groups, with the Institute of Medicine (IoM) and the Endocrine Society in the US recommending intakes of 20 micrograms per day and 37.5-50 micrograms per day respectively for older adults since 2011[15]. Two well-designed modelling studies have been conducted to estimate the oral dose of vitamin D required to achieve and maintain adequate serum levels in Irish adults on a year round basis. The first of these proposed a daily dose of 28.0 micrograms to maintain serum vitamin D levels above the critical 50nmol/l threshold in 97.5% of healthy Irish adults throughout the year[16], while the second suggested a daily requirement of 24.7 micrograms for Irish adults aged 64 years and over to achieve and maintain these serum levels[17].

**Safety of Vitamin D Supplementation**

While documented cases of vitamin D toxicity do appear in the literature, these are rare, and invariably relate to extremely high doses taken over an extended period of time[18]. There is no evidence however, that vitamin D supplementation at 20-50 micrograms per day has any adverse effects on health. Indeed several studies have explicitly cited the safety of vitamin D3 supplementation at doses of up to 100 micrograms per day[19,20], with a further review proposing a tolerable upper limit (TUL) of 250 micrograms per day[21]. These findings are perhaps unsurprising, given that cutaneous synthesis yields a typical 'dermal dose' of ~70 micrograms per day from regular

sunlight exposure during the Summer months, and that one single whole-body minimum erythemal dose can produce a rise in serum vitamin D levels which is equivalent to an oral dose of ~250-625 micrograms[22]. For context, a minimum erythemal dose can be produced by as little as 10–15min of whole-body sun exposure at mid-day in mid-summer in a pale-skinned individual, and is therefore not an uncommon occurrence. Further research and clinical data demonstrating the safety of vitamin D supplementation at doses of 20-50 micrograms per day abound in the literature[23,24], highlighting its viability as a means of addressing this common but important nutritional deficit.

**Conclusions and Recommendations**

Vitamin D intakes and status are low in Ireland, particularly amongst older adults, hospital inpatients and nursing home residents. Low serum vitamin D has been associated with increased risk and severity of viral respiratory infections including community acquired pneumonia, whilst there is also evidence that vitamin D supplementation which raises serum vitamin D levels above 50nmol/l may ameliorate this risk. Among the proposed protective effects of vitamin D are several which may reduce the risk of Covid-19 infection, or which may attenuate the immunological sequelae responsible for its fulminant respiratory effects. There is existing guidance from health authorities in Ireland and globally that older adults should supplement with vitamin D, and there now exists a wealth of evidence which demonstrates the safety of vitamin D3 supplementation at doses of 20-50 micrograms per day.

In the face of the impending Covid-19 epidemic, and in the absence of a vaccine or any effective anti-viral drug therapy to treat those infected, these findings call for the prioritised supplementation of all hospital inpatients, nursing home residents and community-dwelling older adults with vitamin D at a *minimum* daily dose of 20 micrograms per day. It is further recommended that supplementation be targeted at other vulnerable constituencies (e.g. those with diabetes mellitus or compromised immune function, those with darker skin, vegetarians and vegans, those who are overweight or obese, smokers and healthcare workers), and ultimately extended to the rest of the population in order to mitigate the grave public health risks associated with Covid-19 infection.

**Declaration of Conflicts of Interest:**
The authors declare that they have no conflict of interest.

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