North Central London
Medicines Optimisation Committee

Vitamin D: A rapid review of the evidence for treatment or prevention of COVID-19 in adults (excluding pregnant & breastfeeding women)

Document control

Date	Version	Amendments
07 May 2020	1.0	New document
19 May 2020	1.1	Clarified scope limited to adults (excluding pregnant & breastfeeding women). Corrected NHS England exclusion criteria.

Document management

Groups / Individuals who have overseen the development of this guidance:	Mr Andrew Barron (NCL Joint Formulary Committee); Ms Nisha Patel (NCL CCG – Barnet borough)
Groups which were consulted and have given approval:	COVID-19 NCL Pharmacy Cell
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Contents

Document scope

This document summarises available information relating to the use of Vitamin D monotherapy (VitD) for treatment or prevention of COVID-19.

Scope is limited to adults only, including those admitted for mental health indications or otherwise institutionalised, and those of black and ethnic minority groups with dark skin.

Pregnant and breastfeeding women are excluded.

Summary

1.1. There is no evidence that VitD is preventative/protective for COVID-19 (link).[1] Clinical trials are ongoing.

1.2. The NHS website[2] (link) and Public Health England[3] (link) advise that those at risk of VitD deficiency should take a daily VitD supplement of 10 mcg (400 iU) to protect bone and muscle health.

1.3. People at risk of deficiency[2,3]:

- Autumn and winter months:
  - All people
- All year round:
  - All people during COVID-19 lockdown due to being indoors for most of the day **(new 2020)**
  - Those in institutions such as care homes
  - Those who always cover their skin when outside
  - Ethnic minority groups with dark skin, from African, Afro-Caribbean and South Asian backgrounds

1.4. NICE CKS recommend patients are not routinely tested for VitD deficiency[4].

1.5. There is some evidence that daily vitamin D3 supplementation over weeks to months may prevent other acute respiratory infections, particularly in people with low or very low vitamin D status.[5] This evidence has limitations, including heterogeneity in study populations, interventions, and definitions of respiratory infections that include upper and lower respiratory tract involvement.[1] Readers should note that NICE/PHE recommend VitD supplementation for those at risk of deficiency to protect bone and muscle health, and not to lower the risk of acute respiratory tract infection.

1.6. The above summary applies to adults (excluding pregnant & breastfeeding women) only.

Action for Provider Trusts and CCG boroughs during COVID-19

2.1. Check local VitD guidance to ensure it reflects latest NICE CKS and PHE guidance

2.2. Consider extending usual advice on VitD supplementation to all individuals during the COVID-19 lockdown. The recommended dose for adults is VitD 10 mcg (400 iU) per day. Suitable products for supplementation can be bought OTC and should not be routinely prescribed; see NHSE guidance on OTC medicines.

- To note: it is appropriate to prescribe VitD for medically diagnosed deficiency including for those patients who may have a lifelong or chronic condition or have undergone surgery that results in malabsorption [p. 16 of NHSE guidance].

2.3. No change to advice on VitD supplementation is required for (i) patients residing in institutions, (ii) those who cover their skin and (iii) ethnic minority groups. These individuals should be considered for year-round VitD supplementation as part of PHE guidance from 2016 to protect bone and muscle health.

2.4. NICE CKS advise it is inappropriate to routinely test of VitD deficiency. Testing should be reserved for patients who have symptoms of osteomalacia or where there is a clinical reason to do so e.g. fall, symptom of hypocalcaemia, bone disease or where correcting VitD is appropriate for a specific treatment[a]; see link.

2.5. Guidelines for the treatment of confirmed VitD deficiency or insufficiency are available from NICE CKS and the Royal Osteoporosis Society (formally NOG)

References

1. Oxford COVID-19 Evidence Service Team. Vitamin D: A rapid review of the evidence for treatment or prevention in COVID-19. https://www.cebm.net/covid-19/vitamin-d-a-rapid-review-of-the-evidence-for-treatment-or-prevention-in-covid-19/ (2020).

2. NHS. Vitamins and minerals - Vitamin D. https://www.nhs.uk/conditions/vitamins-and-minerals/vitamin-d/ (2017).

3. PHE publishes new advice on vitamin D. GOV.UK https://www.gov.uk/government/news/phe-publishes-new-advice-on-vitamin-d.

4. NICE CKS. Vitamin D deficiency in adults - treatment and prevention. https://cks.nice.org.uk/vitamin-d-deficiency-in-adults-treatment-and-prevention#!diagnosisSub.

5. Martineau, A. R. et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ i6583 (2017) doi:10.1136/bmj.i6583.

6. Greater Manchester Medicines Managment Group - Regional Drugs & Therapeutics Centre. COVID-19 Questions, Answers and Actions - Vitamin D and infection risk v1.0. (2020).

7. Royal Osteoporosis Society. Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management. https://strwebprdmedia.blob.core.windows.net/media/ef2ideu2/ros-vitamin-d-and-bone-health-in-adults-february-2020.pdf (2020).

[a] For example antiresorptive treatments such as IV bisphosphonates[6]

Appendix 1: Does VitD reduce the risk of COVID-19?

3.1. A literature search did not identify any publications reporting on the efficacy of VitD in this context. Multiple clinical trials are underway[b]. It is therefore unknown whether VitD is beneficial in this context.

3.2. Oxford COVID-19 Evidence Service Team have published a rapid review of the evidence for treatment or prevention in COVID-19 and came to the same view (link)

Appendix 2: What are the national guidelines relating to VitD supplementation during COVID-19 pandemic?

4.1. Public Health England

- Nothing identified on PHE website
- Multiple news channels report that "PHE is recommending people consider taking daily vitamin D supplements throughout the spring and summer as the coronavirus lockdown continues" (link)

4.2. NHS Choices website (link)

- *Consider taking 10 micrograms of vitamin D a day to keep your bones and muscles healthy.*
- *This is because you may not be getting enough vitamin D from sunlight if you're indoors most of the day.*
- *There have been some news reports about vitamin D reducing the risk of coronavirus. However, there is no evidence that this is the case.*

4.3. NICE:

- Nothing identified

4.4. NHS England:

- Nothing identified

[b] CoVitTrial/NCT04344041, NCT04334005, ZnD3-CoVici/NCT04351490, LEAD-COVID-19/NCT04363840

Appendix 3: What are the national guidelines relating to VitD supplementation outside the context of COVID-19 (excluding treatment of vitamin D deficiency)?

5.1. Public Health England from 2017 (link)

- People should consider taking 10 mcg VitD daily in autumn and winter.
- People who have little or no exposure to the sun risk VitD deficiency need to take a supplement throughout the year:
  - Those in institutions such as care homes
  - Who always cover their skin when outside
- People from ethnic minority groups with dark skin, from African, Afro-Caribbean and South Asian backgrounds may not get enough VitD from sunlight in the summer and therefore should consider taking a supplement all year round

5.2. NICE

- Nothing relevant (see PH56 only)

5.3. NICE CKS (link)

- People at risk of VitD deficiency (defined here) should take a daily supplement containing 10 mcg of VitD throughout the year
- Excluding pregnant and breastfeeding women eligible for the NHS Healthy Start scheme, all other people can purchase multivitamin preparations containing 10 mcg VitD
- Do not routinely monitor serum VitD levels
- Give lifestyle advice (provided here)

5.4. NHS England (link)

- VitD maintenance therapy should not be routinely prescribed in primary care [pg. 10 + pg. pg. 16]
  - However multiple scenarios are given whereby treatments can be prescribed [pg. 12] in addition to medically diagnosed deficiency including for those patients who may have a lifelong or chronic condition or have undergone surgery that results in malabsorption [p. 16]
- Inferred is that preparations for maintenance therapy (aka preventative treatment) are ≤25mcg (≤1000 iU) per dose. NHSE guidance does not apply to high-dose preparations (i.e. ≥ 10,000 iU capsules)

Appendix 4: Is VitD supplementation safe?

6.1. An NIHR funded meta-analysis found that VitD supplementation (used at a large variety of doses) was safe[5].

6.2. VitD <10,000 iU per day is not usually associated with toxicity, whereas doses ≥50,000 iU per day for several weeks or months are frequently associated with toxicity[7]

Appendix 5: Does VitD reduce the risk of acute respiratory tract infection?

7.1. A basic literature search identified multiple meta-analyses, the highest quality of which was an NIHR funded meta-analysis published in the BMJ in 2017[5].

7.2. This study found VitD supplementation was likely to lower the risk of (non-COVID-19) aRTI by 10%. Participants recruited into individual studies were extremely diverse which raises questions over how generalisable this finding is to individual patient groups in NCL. VitD may have a greater treatment effect when used regularly (daily or weekly) and for individuals with serum VitD level <25 nmol/L. Adult doses used in these studies were generally higher than 10 mcg per day equivalent.

7.3. VitD has not been shown to reduce AE admissions or hospitalisations, nor has it been shown to reduce mortality in this mixed aged cohort.

7.4. A detailed summary of this study is provided in Appendix 1.

Appendix 6: Detailed summary of results from NIHR/BMJ meta-analysis

A literature search for VitD and 'respiratory tract infection' was not performed owing to the large number of hits. As an alternative, a basic search was run on evidence.nhs.uk (limited to the first 100 hits).

Multiple systematic literature reviews and meta-analyses published between 2013 and 2019 were identified. One study was assessed as being the most rigorous (NIHR funded and published in BMJ) are is summarised below[5]:

- **Study design**:
  - Individual patient level data (IPD) meta-analysis[c]
- **Included studies**:
  - Randomised controlled trials of VitD in which data relating to incidence of aRTI
- **Intervention**:
  - VitD supplementation administered at any dose with any frequency via any route for any duration
  - *Included study characteristics: VitD given orally at variable doses from daily +/- bolus doses to every 3 month boluses only; study duration was 7 weeks to 1.5 years*
- **Comparator**:
  - Placebo or different dose of VitD
- **Cohort:**
  - Any age, any ethnic origin, any baseline VitD serum level
  - *Included study characteristics: Age ranged from birth to 95 years both with an without important comorbidities (i.e. low birth weight, COPD, asthma, care home) ; trials included 14 countries on 4 continents; mean baseline VitD level ranged from 19 to 90 nmol/L.*
- **Outcome:**
  - *Primary:* Incidence of aRTI (URTI, LRTI, unspecified RTI)
  - *Secondary:* URTI; LRTI; ED attendance or hospital admission; serious adverse effects
- **Statistical methods:**
  - One step[d] and two step[e] analyses
- **Results:**
  - Full details in Appendix 6
  - When viewing all the results together, the use of VitD was associated with
    - Lower <u>proportion of patients</u> with at least one aRTI
    - Lower <u>event rate</u> of aRTI

[c] IPD meta-analysis contrasts with aggregate meta-analysis. Aggregate data are often not available, poorly reported, derived and presented differently across studies (for example, odds ratio versus relative risk), and more likely to be reported (and in greater detail) when statistically or clinically significant, amplifying the threat of publication bias and within study selective reporting. On the contrary, having individual participant data facilitates standardisation of analyses across studies and direct derivation of the information desired, independent of significance or how it was reported. Individual participant data may also have a longer follow-up time, more participants, and more outcomes than were considered in the original study publication. This means that individual participant data meta-analyses are potentially more reliable than aggregate data meta-analyses, and the two approaches may lead to different conclusions. In contrast, IPD meta-analysis are more costly to undertake, require a higher level of statistical skill and rely on IPD being attainable (which may not be the case) – this can introduce bias.

[d] Modelled all IDP simultaneously whilst accounting for the clustering of participant within studies

[e] IPD analysed in each study independently to create aggregate data for each study (e.g. mean treatment effect estimate and its standard error), before combining using standard approaches i.e. weighting studies by the inverse of variance while assuming either fixed or random effects

        - No benefit in time to first event of aRTI
        - No benefit in any secondary outcomes (inc. UTRI, LRTI, ED or hospitalisation, mortality)
        - No increased risk of adverse effects
    - When looking at subgroups
        - The authors conclude that VitD is more effective in patients who were VitD deficient at baseline. This is true for their <> 25nmol/L analysis (OR, RR but not HR) but when VitD levels were categorised into four groups, there was no apparent correlation between treatment effect and serum level, which reduces confidence in this conclusion.
        - The authors state strongly that VitD is more effective when used in regimens that did not include loading doses. This is true for their OR analysis but does not hold for the RR or HR analyses although data trends in the correct direction. The authors do not state what daily/weekly dose should be used.

This meta-analysis included a very diverse group of studies, which leads to concerns over generalisability when applied to specific patients in NCL e.g. inpatients mental health. Reassurance is taken from knowledge that the studies reporting the largest treatment effects include a range of ages and morbidities:

- Preschool with pneumonia from Afghanistan (n=453)
- Military conscripts from Finland (n=164)
- Children with asthma from Poland (n=48)
- 3/4th grade school children from Mongolia (n=247)
- Adults with increased susceptibility to ARTI from Sweden (n=140)
- Children with recurrent acute otitis media from Italy (n=116)
- Healthy university students from Canada (n=600)
- Adults with asthma from UK (n=250)
- Children with asthma from Japan (n=89)
- Older care home residents from USA (n=107)

Results are presented in Table 1.

Table 1: Results summary from NIHR/BMJ meta-analysis

	One-step analysis	Two-step analysis
Primary outcome		
Incidence of aRTI - Participants with ≥1 event (%) - Rate - Time to first event	 OR = 0.88 (0.81-0.96)* RR = 0.96 (0.92-0.997)* HR = 0.95 (0.89-1.01)	 OR = 0.80 (0.69-0.93)* RR = 0.91 (0.84-0.98)* HR = 0.92 (0.85-1.00)
Secondary outcomes (Participants with ≥1 event (%))		
URTI	OR = 0.93 (0.83-1.03)	NR
LRTI	OR = 0.96 (0.83-1.10)	NR
ED attendance or hospital admission	OR = 0.83 (0.54 to 1.27)	NR
Serious adverse effects	OR = 0.98 (0.80 to 1.20)	NR
Death due to any cause	OR = 1.39 (0.84 to 2.27)	NR
Subgroup analyses for primary outcome (Participants with ≥1 event %)		
Baseline VitD level† - < 25 nmol/L - ≥ 25 nmol/L	 OR = 0.58 (0.40-0.82)* OR = 0.89 (0.77-1.04)	NR
Baseline VitD level‡ - < 25 nmol/L - 25 to 49.9 nmol/L - 50 to 74.9 nmol/L - ≥ 75 nmol/L	 OR = 0.58 (0.40-0.82)* OR = 0.98 (0.79-1.23) OR = 0.91 (0.71-1.16 OR = 0.68 (0.46-0.99)*	NR
Dosing regimen† - Daily/weekly dosing only - Boluses ± daily/weekly dosing	 OR = 0.81 (0.72 to 0.91)* OR = 0.97 (0.86 to 1.10)	NR
Subgroup analyses for primary outcome (Rate)		
Baseline VitD level† - < 25 nmol/L - ≥ 25 nmol/L	 RR = 0.78 (0.66-0.93)* RR = 0.95 (0.90-1.00)*	NR
Dosing regimen - Daily/weekly dosing only - Boluses ± daily/weekly dosing	 RR = 0.93 (0.88 to 0.98)* RR = 0.99 (0.94 to 1.05)	NR
Subgroup analyses for primary outcome (Time to first event)		
Baseline VitD level - < 25 nmol/L - ≥ 25 nmol/L	 HR = 0.92 (0.66-1.28) HR = 0.97 (0.97-1.06)	NR
Dosing regimen - Daily/weekly dosing only - Boluses ± daily/weekly dosing	 HR = 0.91 (0.94 to 0.99)* HR = 0.98 (0.89 to 1.08)	NR

* $p < 0.05$; † Statistically significant interaction between subgroup ($p<0.05$); ‡ No significant interaction between subgroup ($p>0.05$).