Scientific Advisory Committee on Nutrition

Update of rapid review:

Vitamin D and acute respiratory tract infections

December 2020

Contents

Introduction

1. Current government advice on vitamin D relates to protection of musculoskeletal health and is based on the recommendations of the Scientific Advisory Committee on Nutrition (SACN) following publication of its report on Vitamin D and Health (SACN, 2016).

2. In June 2020, SACN conducted a rapid review (SACN, 2020) of the evidence on vitamin D and acute respiratory tract infections (ARTI) that had been published since the SACN report on Vitamin D and Health (SACN, 2016). SACN concluded that "overall, the evidence at this time does not support recommending vitamin D supplementation to prevent ARTIs in the general UK population". The review reiterated the importance of vitamin D for bone and muscle health.

3. The rapid review was conducted in the context of suggestions that vitamin D supplementation could reduce the risk of COVID-19, an infectious disease caused by a coronavirus known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). These suggestions were based largely on a systematic review and meta-analysis of individual participant data (IPD) reporting that vitamin D supplementation reduces the risk of ARTI (Martineau et al, 2017). The IPD analysis by Martineau et al (2017) was published after the SACN report on Vitamin D and Health (SACN, 2016).

4. In parallel with SACN's rapid review of vitamin D and ARTI risk (SACN, 2020), the National Institute for Health and Care Excellence (NICE), supported by Public Health England (PHE), reviewed emerging evidence on vitamin D for the prevention and treatment of COVID-19. NICE's evidence review concluded that "there is no evidence to support taking vitamin D supplements to specifically prevent or treat COVID-19".

5. Since publication of these rapid reviews, the Secretary of State for Health and Social Care requested NICE and PHE to re-review the evidence on vitamin D and COVID-19. As part of this work, SACN has updated its rapid review on vitamin D and ARTI (SACN, 2020) and has supported NICE in its review of the evidence on vitamin D and COVID-19.

6. The term ARTI refers to any infection of the sinuses, throat, airways or lungs. Upper RTIs (URTI) include tonsillitis, laryngitis and the common cold. Lower RTIs (LRTIs) include bronchitis and pneumonia. Influenza affects both upper and lower respiratory tracts.

Objective

7. The purpose of this update to the rapid review was to:
   - assess evidence from systematic reviews and meta-analyses of randomised controlled trials (RCTs) and individual RCTs on vitamin D and risk of ARTIs published since the SACN rapid review (SACN, 2020)
   - consider if the evidence on vitamin D and ARTIs published since the SACN rapid review (SACN, 2020) changes its previous conclusions.

8. This update to the rapid review does not assess evidence on vitamin D and COVID-19 (see paragraph 5 above).

Background

SACN's remit

9. SACN's remit is to provide scientific advice on, and risk assessment of, nutrition and related health issues by evaluating published scientific evidence and, based on its assessment, make dietary recommendations for the UK general healthy population including any vulnerable (at-risk) groups which have been identified (see SACN Code of Practice).

SACN advice on vitamin D

10. In its report on Vitamin D and Health (SACN, 2016), SACN carried out a comprehensive assessment of the evidence on vitamin D and a wide range of musculoskeletal and non-musculoskeletal health outcomes. Recommendations for vitamin D were based on protection of musculoskeletal health as evidence on non-musculoskeletal outcomes was considered insufficient to inform the setting of recommendations for vitamin D.

11. SACN concluded that the evidence suggested overall that the risk of poor musculoskeletal health is increased at serum 25-hydroxyvitamin D (25(OH)D) concentrations below 25 nmol/L. Serum 25(OH)D concentration is an indicator of exposure to vitamin D from skin synthesis and dietary intake. The reference nutrient intake (RNI) for vitamin D was set to maintain serum 25(OH)D concentration ≥25 nmol/L.

12. A RNI of 10 µg/d (400 IU/d) of vitamin D was set for the UK population (aged 4 years and above). This is the average daily amount of vitamin D needed by the majority (97.5%) of the population to maintain a serum 25(OH)D concentration ≥ 25 nmol/L

when UVB sunlight exposure is minimal (from October to March and for people who have limited sun exposure).

13. Data were insufficient to set RNIs for infants and children aged under 4 years. As a precaution, a 'safe intake' of vitamin D was recommended for these ages: 8.5 to 10 µg/d (340 to 400 IU/d) for ages 0 up to 1 year (including exclusively breastfed and partially breastfed infants, from birth); and 10 µg/d (400 IU/d) for ages 1 up to 4 years.

SACN's previous assessments of vitamin D and ARTI risk

SACN report on Vitamin D and Health (2016)

14. In its report on Vitamin D and Health (SACN, 2016), SACN assessed the evidence on vitamin D and infection risk (ARTI and tuberculosis). The following studies on vitamin D supplementation and ARTI risk were considered: 3 systematic reviews and meta-analyses (Bergman et al, 2013; Charan et al, 2012; Mao and Huang, 2013); 1 systematic review (Joliffe et al, 2013); and 7 RCTs published after the systematic reviews and meta-analyses.

15. SACN concluded that the evidence on vitamin D supplementation and infection risk (ARTIs and tuberculosis) was inconsistent and generally did not show a beneficial effect of vitamin D supplementation on infectious disease risk. For further details see SACN's Vitamin D and Health Report.

SACN rapid review on vitamin D and ARTI (SACN 2020)

16. SACN's rapid review (SACN, 2020) assessed the evidence on vitamin D and ARTI risk published since the SACN report on Vitamin D and Health (SACN, 2016).

17. A comprehensive search of online databases was conducted to identify systematic reviews, meta-analyses and pooled analyses of randomised trials, RCTs and controlled trials on vitamin D supplementation and incidence of ARTIs in children and adults. Searches were conducted for papers published between 1 January 2016 and 22 April 2020 to identify studies published after the systematic review search dates covered by Martineau et al (2017) (which included RCTs published up to December 2015).

18. Studies eligible for consideration were those that examined whether vitamin D reduced ARTI risk in general healthy populations rather than its effect as a therapeutic agent in populations with pre-existing disease.

19. The following evidence was considered in the rapid review (SACN, 2020):

    - systematic review and IPD meta-analysis by Martineau et al (2017)
    - systematic review and meta-analysis by Vuichard Gysin et al (2016); although published before the systematic review and meta-analysis by Martineau et al (2017), it was considered because it included only RCTs with healthy populations
    - 5 RCTs: Aloia et al (2019); Camargo et al (2018); Jung et al (2018); Loeb et al (2019); and Shimzu et al (2018).

20. The systematic review and meta-analysis by Martineau et al (2017) included 25 RCTs (11,321 participants from 14 countries, aged 0 to 95 years). Ten of the included trials were in populations with pre-existing respiratory disease. IPD analysis reported that daily or weekly vitamin D supplementation reduced the risk of ARTIs (Odds ratio [OR], 0.88; 95% confidence interval [CI], 0.81 to 0.96; p=0.003; 25 RCTs, 10,933 participants), particularly among individuals with serum 25(OH)D concentrations below 25 nmol/L (OR 0.58, 95% CI, 0.40 to 0.82, p=0.002; 14 RCTs; 538 participants). The authors noted, however, that there was: considerable variation between studies in baseline 25(OH)D concentration and in vitamin D supplemental doses and use of vitamin D bolus doses; evidence of publication bias; lack of data relating to adherence; and diverse definitions of ARTI (which were not medically confirmed in most studies). An additional limitation to those identified by the authors, was that different methods were used to measure serum 25(OH)D concentration, which can vary considerably depending on the type of assay used (SACN, 2016).

21. The systematic review by Vuichard Gysin et (2016) (15 RCTs, 7053 participants from 10 countries; aged 0 to 84 years) reported that vitamin D supplementation did not reduce the risk of ARTIs in healthy populations (risk ratio [RR], 0.94; 95% CI, 0.88 to 1.00; p=0.06; 14 RCTs, 6985 participants). The authors noted, however, that there were major differences across studies with respect to populations, settings, vitamin D dosing regimens and outcome measurements.

22. Out of the 5 RCTs published after the Martineau et al (2017) review: 3 reported no evidence of difference in ARTI risk between the vitamin D and placebo groups (Aloia et al, 2019; Camargo et al, 2019; Shimzu et al, 2018) 1 reported URTI symptoms were significantly lower in the vitamin D group (Jung et al, 2018); 1 reported no difference between groups for influenza infections but a significantly greater reduction in the vitamin D group for non-influenza virus infections (Loeb et al, 2019).

23. Out of the 2 RCTs that reported significant reductions in ARTI risk with vitamin D supplementation: 1 (Jung et al, 2018), was small in size and in a very particular population (25 male athletes undergoing intense training); in the other (Loeb et al, 2019), mechanisms for the differential effect by type of viral infection (vitamin D reduced non-influenza virus infections but not influenza) was unclear.

24. SACN noted that interpretation of the evidence on vitamin D supplementation and ARTI risk was complicated by differences in vitamin D supplementation doses and regimens, study settings, participants, study duration and definition and verification of outcomes (including type of respiratory infection).

25. SACN concluded that, overall, evidence at that time did not support recommending vitamin D supplementation to prevent ARTIs in the general UK population.

26. For further details of SACN's considerations see SACN rapid review: vitamin D and acute respiratory tract infections.

Review of evidence on vitamin D and ARTI published since SACN's rapid review (SACN 2020)

Methods

Literature search

27. Searches were conducted for papers published between 22 April 2020 (final date of previous literature search) and 26 October 2020. The search strategy, search terms and inclusion and exclusion criteria were similar to the previous search except that preprints were included, and web of science was not searched (no longer available to PHE). Reference lists of relevant papers were also searched.

28. For further details of the protocol and search results see Annex A.

Selection of studies included in update

29. The updated search identified 207 records. After removal of duplicates, 177 records were screened by title and abstract. Of these, 23 full-text articles were assessed for eligibility. Screening was undertaken independently by 2 reviewers and differences were resolved by discussion.

30. Three studies were included for assessment in this update:

    - 2 systematic reviews with meta-analyses (Jolliffe et al, 2020; Wang et al, 2020)
    - 1 RCT (Ganmaa et al, 2020).

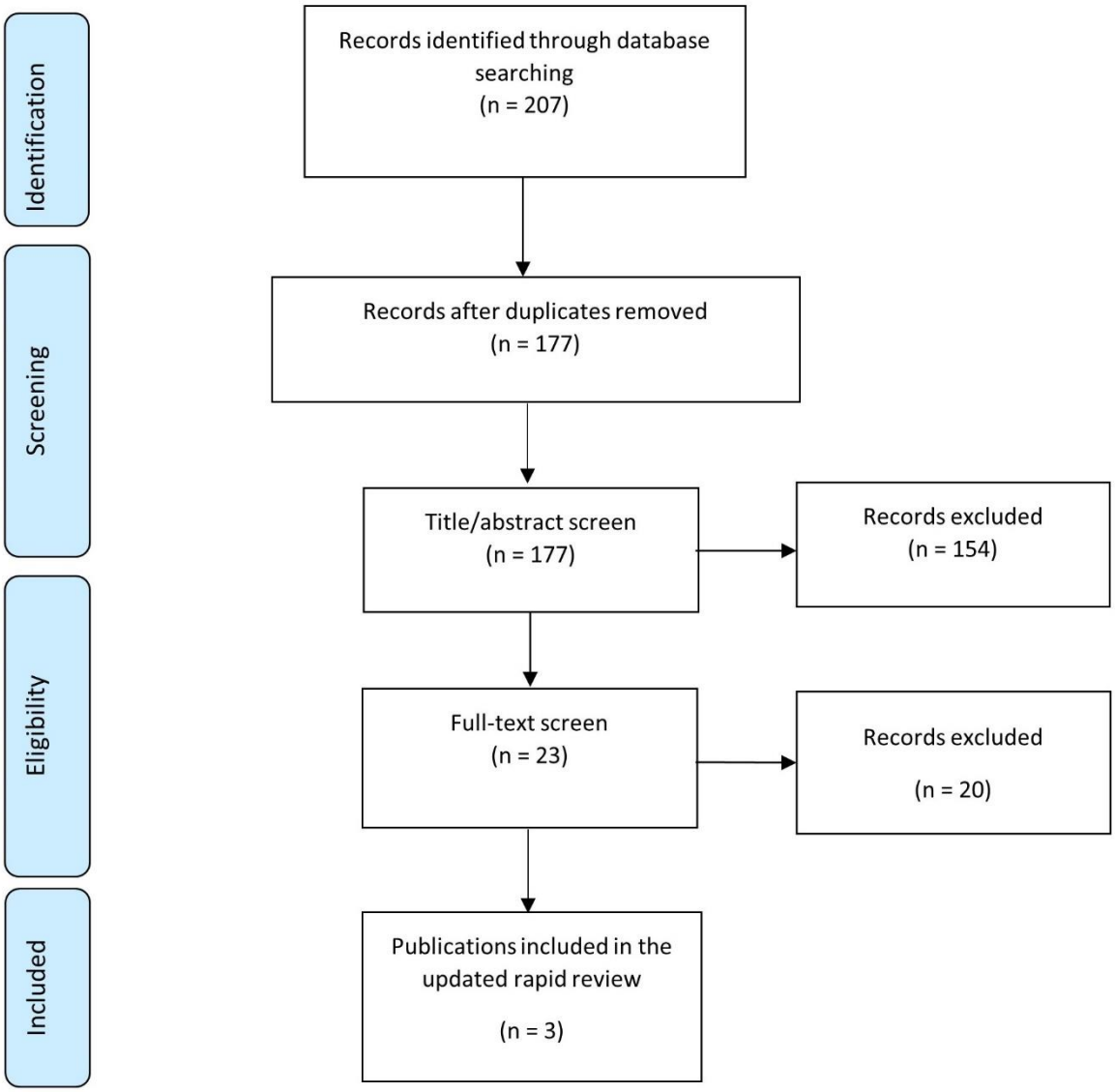
31. One of the systematic reviews identified (Jolliffe et al, 2020) is an update of the review by Martineau et al (2017). The systematic review and meta-analysis by Jolliffe et al (2020) was available as a preprint when the literature search was conducted,

and a peer-reviewed version of this paper was subsequently considered (available on MedRxiv as v3: https://www.medrxiv.org/content/10.1101/2020.07.14.20152728v3).

32. A flow diagram of the study selection process for the update is shown in Figure 1. Further details of the studies included in this update are provided in Annex B.

33. This update of the rapid review (SACN, 2020) was undertaken in line with SACN's Framework for the Evaluation of Evidence. However, due to the rapid nature of this update, it was not possible, within the required timeframe, to grade the quality of the available evidence.

Figure 1 – Flow diagram showing number of publications assessed for eligibility and included in the update



Assessment of evidence published since SACN's rapid review (SACN 2020)

Systematic reviews and meta-analyses

Jolliffe et al (2020)

34. The systematic review and meta-analysis by Jolliffe et al (2020) assessed the effect of vitamin D supplementation on incidence of ARTI. Forty five eligible studies were identified and data were obtained from 42 trials (46,331 participants from 18 countries, aged 0 to 95 years), including from an additional 17 studies (35,398 participants), published between December 2015 (date of final literature search in the previous meta-analysis by Martineau et al, 2017) and 1 May 2020. In contrast to the previous meta-analysis of IPD data (Martineau et al, 2017), the updated meta-analysis used a trial-level approach. A comparison of the updated meta-analysis (Jolliffe et al, 2020) and the previous IPD analysis (Martineau et al, 2017) is provided in paragraphs 51 to 54 and in Annex C.

35. Study duration ranged from 8 weeks to 5 years. Mean baseline serum 25(OH)D concentrations (reported in 34 out of 42 trials) ranged from 19 to 91 nmol/L (assessed using different methodologies). Forty-one trials administered oral vitamin D3 to participants in the intervention arm, while 1 administered oral 25(OH)D. Vitamin D was given as: monthly to 3-monthly bolus doses (13 studies); weekly doses (6 studies); daily doses (21 studies); and as a combination of bolus and daily doses (2 studies).

36. The primary outcome was the proportion of participants experiencing 1 or more ARTIs. Incidence of ARTI was the primary or co-primary outcome for 22 studies and a secondary outcome for 20 studies.

37. The primary comparison was of participants randomised to vitamin D vs placebo and the secondary comparison was of participants randomised to higher- vs lower-dose vitamin D.

38. Meta-analyses were performed using a random effects model to obtain a pooled OR with a 95% CI.

39. The following additional analyses were performed:

    - Subgroup analyses (predefined): baseline serum 25(OH)D concentration, age at baseline, vitamin D dosing regimen, dose size, trial duration and presence of airway disease. An exploratory analysis restricted to studies with optimal dosing frequency, dose size and duration was also performed.

- Multivariable meta-regression analysis: on dose frequency, dose size and trial duration to produce an adjusted OR, a 95% CI and a p-value for interaction for each factor
- Sensitivity analyses: 2 sensitivity analyses for the primary comparison: 1 excluded RCTs where risk of bias was assessed as being unclear; the other excluded RCTs in which incidence of ARTI was not the primary outcome.

Results

40. Vitamin D supplementation compared to placebo control resulted in a significant reduction in the proportion of participants experiencing at least one ARTI (OR 0.91, 95% CI 0.84 to 0.99; I^2 37.2%, p for heterogeneity 0.01; 36 studies, 44,009 participants).

41. Higher- vs lower-dose vitamin D: no significant difference in the proportion of participants with at least one ARTI (OR 0.87, 95% CI 0.73 to 1.04; I^2 0.0%, p for heterogeneity 0.50; 11 studies, 3047 participants).

Subgroup analyses:

42. Compared to placebo, no significant effect of vitamin D was reported for participants with baseline 25(OH)D concentration: <25 nmol/L (OR 0.78, 95% CI 0.53 to 1.16; 19 studies, 3617 participants); 25-49.9 nmol/L (OR 1.03, 95% CI 0.92 to 1.15; 28 studies, 9167 participants); 50-74.9 nmol (OR 0.90, 95% CI 0.76 to 1.06; 29 studies, 5,417 participants), or ≥75 nmol/L (OR 0.97, 95% CI 0.81 to 1.16; 25 studies, 3014 participants).

43. Compared to placebo, protective effects of vitamin D supplementation were reported:
    - for participants aged 1 to <16 years (OR 0.71, 95% CI 0.57 to 0.90; 15 studies, 11,871 participants) but not in those aged < 1 year (OR 0.95, 95% CI 0.82 to 1.10; 5 studies, 5697 participants), 16 to <65 years (OR 0.97, 95% CI 0.93 to 1.09; 21 studies, 9603 participants), or ≥ 65 years (OR 0.96, 95% CI 0.90 to 1.02; 16 studies, 16,983 participants).
    - in trials where vitamin D was administered daily (OR 0.75, 95% CI 0.61 to 0.93; 18 studies, 4005 participants) but not weekly (OR 0.97, 95% CI 0.88 to 1.06; 6 studies, 12,756 participants) or monthly to 3-monthly (OR 0.98, 95% CI 0.93 to 1.03; 12 studies, 27,248 participants).
    - in trials where vitamin D was administered at daily doses of 10-25 µg (400-1000 IU) (OR 0.70, 95% CI 0.55 to 0.89; 10 studies, 2305 participants) but not <10 µg (400 IU) (OR 0.65, 95% CI 0.31 to 1.37; 2 studies, 2308 participants), >25-50 µg (1000-2000 IU) (OR 0.97, 95% CI 0.92 to 1.03; 15 studies, 31,702 participants), or >50 µg (2000 IU) (OR 1.05, 95% CI 0.84 to 1.31; 7 studies, 6906 participants).

- in trials with a duration of ≤12 months (OR 0.82, 95% CI 0.72 to 0.93; 29 studies, 9255 participants) but not in those >12 months (OR 0.99, 95% CI 0.95 to 1.04; 7 studies, 34,754 participants).
- in trials without participants who had a respiratory comorbidity (OR 0.91, 95% CI 0.84 to 0.99; 30 studies, 42,799 participants in 30 studies), but not in those that exclusively enrolled participants with asthma (OR 0.73, 95% CI 0.36 to 1.49; 4 studies, 795 participants) or with chronic obstructive pulmonary disease (OR 1.01, 95% 0.68 to 1.51; 2 studies, 415 participants).

44. Exploratory analysis restricted to 8 placebo-controlled trials investigating effects of daily dosing at doses of 10-25 µg (400-1000 IU) with duration ≤12 months: protective effects of vitamin D on the proportion of participants experiencing at least one ARTI (OR 0.58, 95% CI 0.45 to 0.75; I^2 0.0%, p for heterogeneity 0.67, 8 studies, 1232 participants).

45. Meta-regression analysis: no interaction between allocation to vitamin D vs placebo and dose frequency, size or trial duration identified.

46. Sensitivity analyses: after exclusion of 4 studies assessed as being at unclear risk of bias, protective effects of vitamin D were reported, consistent with the main analysis, on the proportion of participants experiencing at least one ARTI (OR 0.93, 95% CI 0.86 to 1.00; 33 studies, 43,626 participants). Another sensitivity analysis, excluding 18 trials where ARTI was a secondary outcome, did not report a significant protective effect of vitamin D (OR 0.89, 95% CI 0.77 to 1.03; 18 studies, 7537 participants).

Study limitations

47. The updated systematic review and meta-analysis by Jolliffe et al (2020) was well conducted with robust methods. The authors noted the following limitations: evidence of publication bias suggesting overall effect size may have been overestimated (and therefore downgraded the quality of the evidence to 'moderate'); meta-analyses were of aggregate (trial-level) data rather than IPD; unable to investigate race/ethnicity and obesity as potential effect-modifiers due to lack of IPD; unable to account for other factors that might modify vitamin D efficacy for ARTI such as taking the supplement with or without food, or secular trends that could influence trials such as increased population intake of vitamin D supplements.

48. In addition to those highlighted by the authors, limitations previously identified in the systematic review and meta-analysis by Martineau et al (2017) also apply here, including: trials on vitamin D and ARTI were conducted in diverse populations from a number of countries (low, middle and higher income) and included healthy population groups as well as those with pre-existing disease; different methods were used across trials to measure serum 25(OH)D concentration, which can vary considerably depending on the type of assay used (SACN, 2016), and is relevant to

the assessment of the effect of baseline 25(OH)D concentration on the response to vitamin D supplementation.

Comparison with evidence included in SACN's rapid review (SACN 2020)

49. The systematic review and meta-analysis by Jolliffe et al (2020) included 4 (**Aloia** et al, 2019; Camargo et al, 2019; Loeb et al, 2019; Shimzu et al, 2018) out of the 5 individual RCTS that were considered by SACN in its rapid review (SACN, 2020). One RCT (Jung et al, 2018) that was included in the SACN rapid review (SACN, 2020) was excluded from Jolliffe et al (2020) because ARTI outcome was not prespecified.

50. Two studies (Aglipay et al, 2017; Rosendahl et al, 2018) that were included in Jolliffe et al (2020) were excluded from SACN's rapid review (SACN, 2020) because they did not include a placebo group (comparison was lower vitamin D dose).

Comparison with previous systematic review and meta-analysis by Martineau et al (2017)

51. A detailed comparison of the 2 systematic reviews and meta-analyses in terms of study characteristics, methodologies and results is provided in Annex C. The main points are summarised below.

52. Martineau et al (2017) was an IPD analysis while meta-analyses in Jolliffe et al (2020) were conducted at trial level.

53. Out of the 25 RCTs in Martineau et al (2017) 10 were in populations with pre-existing disease; 1 was in low birthweight infants; and 1 was in older care home residents (with a range of comorbidities). Out of the 42 RCTs included in Jolliffe et al (2020), 13 were in populations with pre-existing disease, 1 was in low birthweight infants, 2 were in preterm infants and 1 was in older care home residents with a range of comorbidities.

54. Both Martineau et al (2017) and Jolliffe et al (2020) reported that compared to placebo, vitamin D supplementation reduced the risk of ARTI overall. However, in contrast to findings of Martineau et al (2017), Jolliffe et al (2020) did not report a protective effect of vitamin D supplementation in participants with the lowest baseline serum 25(OH)D concentrations (<25 nmol/L).

Wang et al (2020)

55. Wang et al (2020) assessed the effects of a range of micronutrients (including vitamin D) compared to placebo (or no intervention) on self-reported cold incidence and included only RCTs of healthy individuals. The primary outcomes were: incidence, duration, or severity of common cold. The results of the vitamin D interventions are reported here.

56. For cold incidence, meta-analysis was performed using a fixed effects model to obtain a RR with 95% CI. For cold duration, mean differences between intervention and placebo groups were pooled using a random effects model and the result was reported as weighted mean difference (MD) and 95% CI.

57. Eight RCTs were identified (2312 participants from 7 countries; mean age, 19 to 61 years). Study duration ranged from 2 to 18 months. Mean baseline serum 25(OH)D concentrations of participants were not provided. All studies administered oral vitamin D3; dose/frequency ranged from between 10-50 µg (400-2000 IU) daily (6 studies), 250 µg (10,000 IU) weekly (1 study) to 5000 µg (200,000 IU) per month for initial 2 months and then 2500 µg (100,000 IU) for each remaining month (1 study). Further details of this systematic review are provided in Annex B (Table B1).

Results

58. Risk of cold incidence: no difference between vitamin D and placebo group (RR 0.95; 95% CI 0.90 to 1.01; I^2=13%, p for heterogeneity 0.33; 8 studies, 2204 participants).

59. Cold duration: no difference between vitamin D and placebo group (MD 0.14 days; 95% CI −0.48 to 0.20; I^2=0%, p for heterogeneity 0.65; 5 studies, 1022 participants).

60. Cold severity: no difference between vitamin D and placebo group in severity scores (5 studies; meta-analysis not conducted). Subjective symptom severity was assessed using different scales.

Limitations

61. There were differences across studies with respect to: populations; intervention durations and doses; and assessment of outcomes which were self-reported in most studies.

Comparison with evidence included in SACN's rapid review (SACN 2020)

62. All except 1 (Shimzu et al, 2018) of the RCTs included in Wang et al (2020) were in the systematic review by Vuichard Gysin et al (2016) which was previously considered in SACN's rapid review (SACN, 2020).

63. All except 1 (de Gruijl et al, 2012) of the RCTs in Wang et al (2020) were included in Jolliffe et al (2020). The RCT by de Gruijl et al (2012) was excluded from Jolliffe et al (2020) because it did not include a placebo group (comparison was lower dose of vitamin D).

Randomised controlled trials published since SACN's rapid review (SACN 2020)

Ganmaa et al, 2020 (Mongolia) (3 years)

64. Participants (8851 children, mean age 9 years) received 350 µg (14,000 IU) of vitamin D3 weekly or a placebo. ARTI incidence was recorded at weekly face-to-face visits when vitamin D or placebo was administrated.

65. There was no significant difference in the proportion of children: hospitalised for ≥ 1 episode of ARTI (adjusted RR 0.86; 95% CI 0.52 to 1.40); who had ≥ 1 episode of ARTI (adjusted RR 1.00; 95% CI 0.98 to 1.02); who received ≥ 1 course of antibiotics for treatment of ARTI (adjusted RR 0.99; 95% CI 0.93 to 1.05).

66. This RCT was included in the systematic review and meta-analysis by Jolliffe et al (2020).

Overall summary and conclusions

Summary

67. The systematic review and meta-analysis by Jolliffe et al (2020) updates the analysis by Martineau et al (2017) which was previously considered by SACN in its rapid review of vitamin D and ARTI (SACN, 2020). Jolliffe et al (2020) used a trial-level approach and included data from 42 trials (46,331 participants) while the Martineau et al (2017) review used IPD. The trials on vitamin D and ARTI were conducted in diverse populations from a number of countries (low, middle and higher income) and included healthy population groups as well as those with pre-existing disease. Studies also differed in terms of settings; vitamin D supplemental doses and in reporting and assessment of ARTIs and trial results.

68. In agreement with Martineau et al (2017), Jolliffe et al (2020) reported an overall protective effect of vitamin D supplementation on ARTI risk (OR 0.91, 95% CI 0.84 to 0.99), with heterogeneity across trials (I^2 37.2%; p=0.014). In subgroup analyses, significant beneficial effects of vitamin D supplementation were reported when vitamin D was given: daily (but not weekly or monthly); at doses of 10 to 25 µg/day (400 to 1000 IU) but not at doses below 10 µg/day (400 IU) or above 25 µg/day (1000 IU); for a duration of up to 12 months; and in participants aged 1-15.9 years but not in those aged under 1 year or 16 years and over. In contrast to Martineau et al (2017), Jolliffe et al (2020) did not find a protective effect of vitamin D supplementation compared to placebo in subgroups based on baseline serum 25(OH)D concentrations. The authors identified evidence of publication bias and downgraded the quality of the evidence to 'moderate'.

69. The systematic review and meta-analysis by Wang et al (2020) included only healthy populations and reported that vitamin D supplementation did not reduce incidence of colds. However, the included RCTs differed with respect to populations, vitamin D dosing regimens and assessment of outcomes. All the RCTs in Wang et al (2020) were included in a systematic review and meta-analysis (Vuichard Gysin et al, 2016) previously considered in SACN's rapid review (SACN, 2020) or were included in the systematic review and meta-analysis by Jolliffe et al (2020).

70. The RCT by Ganmaa et al (2020) reported no effect of weekly vitamin D supplementation (350 µg/14,000 IU) on ARTI risk in children (mean age, 9 years). This RCT was included in the systematic review and meta-analysis by Jolliffe et al (2020).

71. As previously highlighted in SACN's rapid review of vitamin D and ARTI risk (SACN, 2020) differences in vitamin D supplementation doses and regimens, study settings, population groups, study duration, definition and confirmation of outcomes (including type of respiratory infection) complicate interpretation of the evidence on vitamin D and ARTI risk.

72. This update of the rapid review (SACN, 2020) was undertaken in line with SACN's Framework for the Evaluation of Evidence. However, due to the rapid nature of this review, it was not possible, within the required timeframe, to grade the quality of the available evidence.

73. Effects of vitamin D on ARTI risk in populations from black, Asian and minority ethnic groups and people living with overweight and obesity were not considered in the evidence that was assessed due to a lack of available data.

74. This update of SACN's rapid review (SACN, 2020) did not assess evidence on vitamin D and COVID-19. Evidence on vitamin D and ARTI risk does not necessarily extrapolate to infection with SARS-COV-2. SACN has supported NICE in the development of a rapid guideline on vitamin D and COVID-19.

Conclusions

75. Evidence considered in this update suggests, overall, that there may be some benefit from daily, low-dose vitamin D supplementation (between 10 and 25 µg/day; 400 to 1000 IU/day) in reducing risk of acute respiratory tract infections (ARTI). The size of any potential benefit of vitamin D in reducing ARTI risk may be small.

76. In subgroup analysis by age, the beneficial effect of vitamin D supplementation in reducing ARTI risk was only observed in children and young people (ages 1 up to 16 years). No effect of vitamin D supplementation was observed in other age groups (under 1 year or 16 years and above).

77. In subgroup analysis, the beneficial effects of vitamin D supplementation on ARTI prevention were not observed with higher doses (>25 µg/1000 IU per day or more) or when vitamin D supplementation was weekly or monthly.

78. It is not known if reported effects apply equally to populations from black, Asian and minority ethnic groups or people living with overweight or obesity since data were not available for these populations.

Recommendations

79. It is recommended that the reference nutrient intake for vitamin D remains unchanged.

80. In order to protect musculoskeletal health, serum 25(OH)D concentrations of all individuals in the UK should not fall below 25 nmol/L at any time of the year.

81. A vitamin D intake of 10 µg/d (400 IU/d) is recommended for the UK population aged 1 year and above. This is the average amount needed by 97.5% of the population to maintain a serum 25(OH)D concentration ≥ 25 nmol/L when UVB sunlight exposure is minimal.

82. A vitamin D intake of 10 µg (400 IU) per day, as currently recommended, may provide some additional benefit in reducing the risk of acute respiratory tract infections.

83. This topic should be kept under urgent review. These recommendations may be updated if findings from robust, high quality RCTs provide clarification on vitamin D and acute respiratory tract infections.

Research recommendation

84. Research is urgently required on vitamin D and risk of acute respiratory tract infections in black, Asian and minority ethnic groups and people living with overweight or obesity.

UK government advice on vitamin D

85. In spring and summer, most people get enough vitamin D through UVB sunlight exposure on the skin and a healthy, balanced diet. During autumn and winter everyone needs to rely on dietary sources of vitamin D. Since it is difficult for people to meet the 10 µg/day (400 IU/d) recommendation from consuming foods naturally

containing or fortified with vitamin D, everyone should consider taking a daily supplement (10 µg; 400 IU) of vitamin D between October and early March.

86. People whose skin has little or no sunlight exposure (those who are not often outdoors, for example, if they are frail, housebound or living in a care home or those who always cover their skin when outdoors) and people with dark skin (for example, if they are of African, African-Caribbean or south Asian family origin) should take a vitamin D supplement (10 µg/day; 400 IU/d) throughout the year.

87. Throughout the year, children aged 1-4 years should have a daily vitamin D supplement of 10 µg (400 IU) and all babies aged under 1 year should have a daily vitamin D supplement of 8.5-10 µg. Children who have more than 500ml of infant formula a day do not need any additional vitamin D as formula is already fortified.

88. This advice is based on SACN recommendations following its review of the evidence on Vitamin D and Health (SACN, 2016).

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Annex A. Vitamin D supplementation and acute respiratory tract infections [update]: protocol and results

This is an update of the SACN review published in June 2020 (search up to 22 April 2020) (SACN, 2020)

The search strategy, search terms and inclusion and exclusion criteria were similar to the previous search except that preprints were included, and web of science was not searched (no longer available to PHE).

Review question

Does vitamin D supplementation reduce the risk of acute respiratory tract infections in healthy children and adults?

Table A.1. Eligibility criteria

	Included	Excluded
Population	Children and adults (including overweight and obese) in the UK and other countries	Children and adults with chronic respiratory conditions
Intervention	Vitamin D supplementation Studies that included a co-intervention were included, provided that the co-intervention was also applied identically in the control arm	
Comparator	Placebo (or no vitamin D)	
Outcomes	Incidence of acute respiratory tract infection	COVID-19
Language	English	
Date of publication	22 April 2020 to 26 October 2020	
Study design	• Systematic reviews, meta-analyses, pooled analyses of randomised trials • Randomised controlled trials and controlled trials	• Cohort studies, case control studies, cross-sectional studies, case reports
Publication type	• Peer-reviewed journals • Preprints	Grey literature

Sources of evidence

Medline, Embase, Cochrane, medRxiv preprints, ClinicalTrials.gov and the International Standard Randomized Controlled Trials Number (ISRCTN) Registry

Search strategy

Searches were conducted for papers published between 22 April 2020 and 26 October 2020. Search terms covered key aspects of the research question, including terms related to the intervention (same search terms as in the April version).

Reference lists of relevant papers were also searched.

Screening

Screening was undertaken in duplicate by 2 reviewers. Disagreement was resolved by discussion.

The list of studies excluded on full text is presented in Table A.2. The list of ongoing studies identified is presented in Table A.3.

Table A.2. List of studies excluded on full text

Papers excluded on full text	Reason for exclusion
Ali (2020) Role of vitamin D in preventing of COVID-19 infection, progression and severity. Journal of infection and public health.13(10):1373-1380.	Narrative review (not systematic)
Bradley et al (2020) The effects of vitamin D on acute viral respiratory infections: A rapid review. Advances in Integrative Medicine. 7(4):192-202.	Systematic review of reviews
Brenner et al (2020) Vitamin D Insufficiency and Deficiency and Mortality from Respiratory Diseases in a Cohort of Older Adults: Potential for Limiting the Death Toll during and beyond the COVID-19 Pandemic?. Nutrients. 12(8):2488.	Cohort study
Charoenngam et al (2020) Immunologic Effects of Vitamin D on Human Health and Disease. Nutrients. 12(7):2097.	Narrative review (not systematic)
Ganmaa et al (2020) Vitamin d supplementation and respiratory health outcomes: A phase 3 randomized trial of Vitamin D supplementation in 8,851 mongolian schoolchildren. American Journal of Respiratory and Critical Care Medicine. 201(1): A1053	Conference abstract
Jovic et al (2020) Could Vitamins Help in the Fight Against COVID-19?. Nutrients. 12(9):2550.	Narrative review (not systematic)
Kuwabara et al (2020) Vitamin D deficiency as the risk of respiratory tract infections in the institutionalized elderly: A prospective 1-year cohort study. Clinical Nutrition ESPEN.	Prospective observational study
Mustapa et al (2020) Risk of eczema, wheezing and respiratory tract infections in the first year of life: A systematic review of vitamin D concentrations during pregnancy and at birth. PloS one. 15(6): e0233890.	Systematic review of observational studies
NCT04368520. Clinical Trial to Optimise Levels of Vitamin D for Rhinovirus Protection https://clinicaltrials.gov/show/NCT04368520	Trial registry only
NCT04408443. Evaluation of Lactobacillus Reuteri DSM 17938 + Vitamin D3 in the Prevention of RRI in Paediatric Patients. https://clinicaltrials.gov/ct2/show/NCT04408443	Trial registry only (Intervention: probiotic + vitamin D3)
NCT04579640. Trial of Vitamin D to Reduce Risk and Severity of COVID-19 and Other Acute Respiratory Infections (CORONAVIT). https://ClinicalTrials.gov/show/NCT04579640	Trial registry only
NCT04596657. Vitamin D3 Supplementation to Prevent Respiratory Tract Infections. https://ClinicalTrials.gov/show/NCT04596657	Trial registry only
Panfili et al (2020) Possible role of vitamin D in Covid-19 infection in pediatric population. Journal of Endocrinological Investigation.	Narrative review (not systematic)

Ribeiro et al (2020) Does Vitamin D play a role in the management of Covid-19 in Brazil?. Revista de saude publica. 54:53	Narrative review (not systematic)
Santos et al (2020) Reasons to avoid vitamin D deficiency during COVID-19 pandemic. Archives of endocrinology and metabolism.	Narrative review (not systematic)
Scheffer-Rath et al (2020) The Many Facets of Vitamin D in the Pediatric Population. Pediatric endocrinology reviews : PER. 17(4): 293-301.	Narrative review (not systematic)
Siddiqui et al (2020) Immune Modulatory Effects of Vitamin D on Viral Infections. Nutrients. 12(9)	Narrative review (not systematic)
Slow et al (2020) Effect of genetic factors on the response to vitamin D3 supplementation in the VIDARIS randomized controlled trial. Nutrition. 75.	Trial focuses on genetic variation in response to vitamin D supplementation
Su et al (2020) Early life primary prevention against infant bronchial asthma: a 3-year follow-up. International journal of clinical and experimental medicine. 13(3):2009-2015.	Multiple interventions given to intervention group
Wang et al (2020) Il-10 changes in children with recurrent upper respiratory tract infections after vitamin d supplementation. Acta Medica Mediterranea. 36(5): 3149-3154.	Not healthy population (participants had recurrent upper respiratory tract infections).

Table A.3. List of ongoing trials

Trial	Contact	Comment
Clinical Trial to Optimise Levels of Vitamin D for Rhinovirus Protection https://clinicaltrials.gov/show/NCT04368520	Martineau and Jolliffe Queen Mary University of London	First posted: 29 April 2020 Last update: 29 April 2020 Recruitment status: not yet recruiting
Trial of Vitamin D to Reduce Risk and Severity of COVID-19 and Other Acute Respiratory Infections (CORONAVIT) https://clinicaltrials.gov/ct2/show/NCT04579640	Martineau and Jolliffe Queen Mary University of London	First posted: 8 October 2020 Last update: 29 October 2020 Recruitment status: recruiting
Vitamin D3 Supplementation to Prevent Respiratory Tract Infections https://clinicaltrials.gov/show/NCT04596657	van Helmond The Cooper Health Foundation	First posted: 22 October 2020 Last update: 23 October 2020 Recruitment status: not yet recruiting

Annex B. Evidence tables

Table B.1. Systematic reviews and meta-analyses

Study	Methods	Included	Results	**Limitations** (assessed by authors) **and study conclusions**
Jolliffe et al, 2020 (preprint) **Aim**: to assess the overall effect of vitamin D supplementation on risk of acute respiratory infection (ARTI), and to identify factors modifying this effect. **Study design**: systematic review and meta-analysis of RCTs **Countries**: Afghanistan (2), Australia (3), Belgium (1), Canada (2), Chile (1), Denmark (1), Finland (2), India (3), Israel (2), Italy (1), Japan (5), Mongolia (2), New Zealand (3), Poland (1), Sweden (1), UK (4), USA (7), Vietnam (1) **Funding source**: conducted without external funding. DAJ supported by a Barts Charity Lectureship and ARM by the UK Office for Students. **Declarations of interest**: None	**Search period**: from inception to May 2020 **Databases searched**: Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, ClinicalTrials.gov, International Standard RCT Number (ISRCTN) **Language restrictions**: none **Inclusion criteria**: • randomised double-blind trials • Intervention: vitamin D3, D2 or 25(OH)D • Comparator: placebo or low-dose vitamin D • Data on ARTI incidence collected prospectively and pre-specified as outcome. **Outcome measures**: Primary outcome: proportion of participants experiencing ≥ 1 ARTI Secondary outcomes • incidence of URTI and LRTI analysed separately	**Number of studies:** 45 studies identified; data from 42 studies included in meta-analyses **Study duration**: 8 weeks to 5 years **Study population**: • 47,262 participants from 18 countries (5 continents) • Age: 0 to 95 years **Intervention**: • oral vitamin D3 (41 trials); • 1 administered oral 25(OH)D (1 trial). Vitamin D doses given as: • monthly to 3-monthly bolus (13 studies) • weekly (6 studies) • daily (21 studies) • combination of bolus & daily (2 studies). **Comparator:** • single vitamin D regimen vs placebo (31 studies)	**Primary outcomes:** 1.Proportion of participants experiencing ≥1 ARTI, vitamin D vs placebo (36 studies, n=44,009) • OR 0.91, 95% CI 0.84 to 0.99 (I^2 =37.2%, p for heterogeneity 0.01) 2.Proportion of participants experiencing ≥1 ARTI, higher vs lower dose (11 studies, n=3,047) • OR 0.87, 95% CI 0.73 to 1.04 (I^2 =0.0%, p for heterogeneity 0.496) **Subgroup analyses:** By baseline 25(OH)D concentration (nmol/L) • <25 (OR 0.78, 95% CI 0.53 to 1.16; 19 studies, n=3,617) • 25-49.9 (OR 1.03, 95% CI 0.92 to 1.15;28 studies, n=9,167) • 50-74.9 (OR 0.90, 95% CI 0.76 to 1.06; 29 studies, n=5,417) • ≥75 (OR 0.97, 95% CI 0.81 to 1.16; 25 studies, n=3,014).	**Limitations**: Evidence of publication bias suggesting overall effect size may have been overestimated, meta-analyses were of aggregate (trial-level) data rather than IPD; unable to investigate race/ethnicity and obesity as potential effect-modifiers due to lack of IPD; unable to account for other factors that might modify vitamin D efficacy for ARTI such as taking supplement with or without food, or secular trends that could influence trials such as increased societal use of vitamin D supplements. **Conclusions:** Vitamin D supplementation reduced risk of ARTI. The overall effect size may have been over-estimated due to publication bias. Protection associated with administration of daily doses of 10-25 µg (400-1000 IU)

Study	**Methods**	**Included**	**Results**	**Limitations** (assessed by authors) **and study conclusions**
To note that this paper was available as a preprint when the literature search was conducted, but that a peer-reviewed version of this paper was subsequently considered, as available on MedRxiv as v3 (https://www.medrxiv.org/content/10.1101/2020.07.14.20152728v3).	• incidence of Emergency Department attendance and/or hospital admission for ARTI • death due to ARTI or respiratory failure • use of antibiotics to treat an ARTI • absence from work/ school due to ARTI • incidence of serious adverse events • death due to any cause • incidence of potential adverse reactions to vitamin D (hypercalcaemia and renal stones) **Statistical analysis**: Random-effects model to obtain pooled odds ratio (OR) with a 95% confidence interval (CI). Heterogeneity evaluated by I^2 statistic and its p-value. Publication bias assessed with funnel plots. 2 comparisons: 1) vitamin D vs placebo and 2) higher- vs lower-dose vitamin D. Additional analyses for primary comparison: Prespecified subgroup analyses: baseline serum	• higher dose, lower dose and placebo arms (4 studies) • higher vs lower dose regimens of vitamin D (7 studies) **Author's evaluation**: Risk of bias (RoB) (Cochrane RoB tool): - 4 trials, unclear RoB due to high loss to follow-up. - All other trials, low RoB. Quality assessed using GRADE - Evidence of publication bias or small-study effects - For primary efficacy outcome and major secondary outcomes, body of evidence considered to be of moderate quality.	By age (years) • significant protective effect for ages 1 to 15.9 (OR 0.71, 95% CI 0.57 to 0.90; 15 studies, n=11,871) • not significant in ages <1 (OR 0.95, 95% CI 0.82 to 1.10; 5 studies, n=5,697), 16 to 64.99 (OR 0.97, 95% CI 0.93 to 1.09; 21 studies, n=9,603), ≥ 65 (OR 0.96, 95% CI 0.90 to 1.02; 16 studies, n=16,983) By dosing frequency: • significant protective effect where vitamin D given daily (OR 0.75, 95% CI 0.61 to 0.93;18 studies, n=4,005) • Not significant when given weekly (OR 0.97, 95% CI 0.88 to 1.06; 6 studies, n=12,756) or monthly to 3-monthly (OR 0.98, 95% CI 0.93 to 1.03;12 studies, n=27,248). By dose size: • significant protective effect when vitamin D given at daily doses of 10-25 µg (OR 0.70, 95% CI 0.55 to 0.89; 10 studies, n=2,305) • Not significant for daily doses <10 µg (OR 0.65, 95% CI 0.31 to 1.37; 2 studies, n=2,308), >25-50 µg (OR 0.97, 95% CI 0.92	vitamin D for up to 12 months.

Study	Methods	Included	Results	**Limitations** (assessed by authors) **and study conclusions**
	25(OH)D concentration, age at baseline, vitamin D dosing regimen, dose size, trial duration and presence of airway disease. Exploratory analysis restricted to studies with optimal dosing frequency, dose size and duration also performed. Multivariable meta-regression analysis on trial-level characteristics (dose frequency, dose size and trial duration). Sensitivity analyses two for primary comparison: 1 excluded RCTs where risk of bias unclear; the other excluded RCTs in which incidence of ARTI was not the primary outcome.		to 1.03; 15 studies, n=31,702), >50 µg (OR 1.05, 95% CI 0.84 to 1.31; 7 studies, n=6,906). By duration**:** • significant protective effect with ≤12 months (OR 0.82, 95% CI 0.72 to 0.93; 29 studies, n=9,255) • Not significant for >12 months (OR 0.99, 95% CI 0.95 to 1.04; 7 studies, n=34,754). By presence of airway disease**:** • significant protective effect in trials not restricted to participants with asthma or COPD (OR 0.91, 95% CI 0.84 to 0.99; 30 studies, n=42,799) • not significant in trials of participants with asthma (OR 0.73, 95% CI 0.36 to 1.49; 4 studies, n=795), or COPD (OR 1.01, 95% 0.68 to 1.51; 2 studies, n=415). **Exploratory analysis**: placebo-controlled trials on effects of daily dosing at 10-25µg (400-1,000IU) and ≤12 months: (OR 0.58, 95% CI 0.45 to 0.75; I^2=0.0%, p for heterogeneity 0.67 (8 trials, n=1232). **Meta-regression analysis:**	

Study	Methods	Included	Results	**Limitations** (assessed by authors) **and study conclusions**
			No interaction between allocation to vitamin D vs placebo and dose frequency, size or trial duration were identified. **Sensitivity analyses:** • After exclusion of 4 trials with unclear RoB: OR 0.93, 95% CI 0.86 to 1.0 (33 studies, n=43,626) • After exclusion of 17 trials where ARTI secondary outcome: OR 0.89, 95% CI 0.77 to 1.03 (18 studies, n=7,537)	
Wang et al, 2020 **Aim**: to assess effects of providing micronutrients singly through oral means, on cold incidence, and/or management (in terms of cold duration and symptom severity) in healthy adults from systematically searched randomized controlled trials. **Study design**: systematic review and meta-analysis of RCTs **Countries**: Australia (1), Canada (1), Finland (1), Japan (1), New Zealand (1), Netherlands (1), US (2)	**Search period**: to August 2018 **Databases searched**: Pubmed, Cochrane Library, Embase and Scopus **Language restrictions**: none **Inclusion criteria**: • Study design: randomised controlled trials of healthy individuals (without chronic conditions, comorbidities, non-hospitalised) aged between 18 and 65 years • Intervention: oral supplementation with a single micronutrient.(• Comparator: placebo or no intervention	**Number of studies**: 8 RCTs relating to vitamin D **Study duration**: 2 to 18 months **Study population**: • 2312 healthy adults • Mean age: 19 to 61y **Intervention**: Vitamin D3: • 10-50 µg (400-2000 IU)/day (6 studies) • 250 µg (10,000 IU)/week (1 study) • 5000 µg (200,000 IU)/month for initial 2 months and 2500µg (100,000 IU) for remaining months (1 study).	**Primary outcomes:** (no significant findings) <u>Risk of cold incidence</u> • RR 0.95; 95% CI 0.90 to 1.01 (I^2=13%, p for heterogeneity 0.33) (8 studies, n=2204) (GRADE: very low) <u>Cold duration</u> • Mean difference 0.14 days; 95% CI −0.48 to 0.20 (I^2=0%, p for heterogeneity 0.65) (5 studies, n=1022) (GRADE: very low) <u>Cold severity</u>: No difference between vitamin D and placebo group in severity scores (5 studies, meta-analysis not conducted)	**Limitations**: Cold episodes self-reported. Outcomes grouped into 'colds' but included a range of outcomes; cold incidence, URTI and ARTI. Additional limitations: low external validity of results (in terms of the type and form of micronutrients used as well as the limited populations involved) and very low certainty in the results. **Conclusions:** Vitamin D supplementation, may not prevent cold incidence or reduce symptom severity among healthy adults.

Study	Methods	Included	Results	Limitations (assessed by authors) and study conclusions
Funding source: Ministry of Defence [of Singapore], grant number N-608-000-065-001. **Declarations of interest**: not specified aside from "the funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results".	**Outcomes**: • Primary outcomes: Incidence, duration, or severity of common cold • Secondary outcomes: community acquired pneumonia **Statistical analysis**: For cold incidence: fixed effects model, risk ratio (RR) with 95% CI For cold duration: random effects model, weighted mean difference with 95% CI. Statistical heterogeneity evaluated by I^2 statistic and Cochran's Q test. Publication bias assessed with contoured funnel plots for outcomes with >2 studies.	**Comparator:** placebo control group **Author's evaluation**: RoB (Cochrane RoB tool): - 2 studies, low risk for all criteria, 1 study, 'unclear' risk for 2 criteria (incomplete outcome data and 'other' bias) - 5 studies, high risk for at least 1 criteria, including blinding for outcome assessors, group comparability and 'other' bias) Quality assessed using GRADE - Heterogeneity not significant for cold prevention (I^2=0%,p >0.05) and cold duration (I^2=0%, p=0.65) - Publication bias strongly suspected for cold prevention outcome. - GRADE certainty of evidence for vitamin D administration for both cold prevention and reduction of duration was very low.		

Table B.2. Randomised controlled trials

Author (year) **Country**	**Population** (participants, number, age)	**Intervention/ Duration**	**Baseline 25(OH)D concentration** (nmol/L)	**Post intervention 25(OH)D concentration** (nmol/L)	**Outcome**	**Results**
Ganmaa et al (2020) Mongolia	8,851 children Mean age: 9.4±1.6 years	1. 350 µg (14,000 IU) vitamin D3 per week 2. placebo Duration: 3 years	29.7±10.5	1. 77.5 2. 26.7 Mean difference between groups: 50.7 (95% CI, 49.7 to 51.5)	Primary: incidence of tuberculosis disease Secondary: serum 25(OH)D concentration; ARTI incidence	Retention: 92% (n=8,117); ITT analysis No significant difference in proportion of children: • hospitalised for ≥ 1 episode of ARTI (adjusted RR 0.86; 95% CI 0.52 to 1.40) • with ≥ 1 episode of ARTI (adjusted RR 1.00; 95% CI 0.98 to 1.02) • who received ≥ 1 course of antibiotics for treatment of ARTI (adjusted RR 0.99; 95% CI 0.93 to 1.05)

Annex C. Comparison of reviews by Martineau et al (2017) and Jolliffe et al (2020)

	Martineau et al (2017)	Jolliffe et al (2020)
STUDY CHARACTERISTICS		
Studies	• 25 trials (11,321 participants) from 14 countries • IPD obtained for 10,933 participants • Study duration ranged from 7 weeks to 1.5 years • Mean baseline 25(OH)D concentrations (reported in 19/25 trials) ranged from 19 to 89 nmol/L. • All trials administered oral vitamin D3 in intervention arm	• 45 trials (73,384 participants), from 18 countries • Data for primary outcome obtained for 46,331 participants in 42 trials • Study duration ranged from 8 weeks to 5 years • Mean baseline 25(OH)D concentrations (reported in 34/42 trials) ranged from 19 to 91 nmol/L. • All trials administered oral vitamin D3 in intervention arm except for 1 which gave oral 25(OH)D
Populations	Out of the 25 included RCTs: • 10 (40%) in populations with pre-existing disease (including asthma, chronic obstructive pulmonary disease, pneumonia) • 1 (4%) in low birthweight infants • 1 (4%) in older care home residents with range of comorbidities (including asthma, chronic obstructive pulmonary disease, congestive heart failure, diabetes, dementia).	Out of the 42 included trials: • 13 (31%) in populations with pre-existing disease (including asthma, chronic obstructive pulmonary disease, pneumonia) • 1 (2.4%) in low birthweight infants • 2 (4.8%) in preterm infants • 1 (2.4%) in older care home residents with range of comorbidities (including asthma, chronic obstructive pulmonary disease, congestive heart failure, diabetes, dementia).
Vitamin D dosing regimens	Vitamin D administered: • daily (12 RCTs; 7.5 to 100µg; 7 weeks to 13 months) • weekly (3 RCTs; 35 to 500 µg; 8 weeks to 6 months) • bolus (10 RCTs; once, monthly, 2-monthly, 3-monthly; 750 to 5000 µg; 3 to 18 months) • 3 of the studies that administered bolus doses combined this with daily vitamin D supplementation. • In 2 studies, the control group also received vitamin D	Vitamin D administered: • daily (21 trials; 7.5 to 100µg; 7 weeks to 2 years) • weekly (6 trials; 35 to 500 µg; 8 weeks 3 years) • bolus (13 trials; once, monthly, 2-monthly, 3-monthly; 750 to 5000 µg; 3 to 3 years). • 2 studies - bolus doses combined with daily vitamin D supplementation

	Martineau et al (2017)	Jolliffe et al (2020)
		• In 7 studies, the control group also received vitamin D. • In 1 study, intervention group also given co-intervention of vitamin D and calcium and the control group was given placebo
METHODS		
Search date	up to 31 December 2015	up to 1 May 2020
Synthesis method	IPD analysis performed for each outcome	Trial level data analysis
Comparisons	vitamin D vs placebo	1) vitamin D vs placebo 2) higher vs lower dose vitamin D
Subgroup analyses	• Baseline 25(OH)D <25 nmol/l vs ≥25 nmol/l • Vitamin D dosing regimen: daily or weekly without bolus vs ≥1 bolus of ≥750µg • Dose size (daily eq): <20 vs 20 to <50µg vs ≥50µg • age: ≤1 year vs 1.1-15.9 years vs 16-65 years vs >65 years • presence compared absence of asthma, COPD and previous influenza vaccination **Not in 2020 version:** • BMI: <25 vs ≥25	• Baseline 25(OH)D <25 vs 25-49.9 vs 50-74.9 vs ≥75nmol/l (stratified analysis) • Vitamin D dosing regimen: daily vs weekly vs monthly or less frequent • Dose size (daily eq): <10 vs 10-25µg vs >25-50µg vs >50µg • age: ≤1 year vs 1.1-15.9 years vs 16-64.9 years vs >65 years • presence of airway disease (trials restricted to participants with asthma vs those restricted to participants COPD vs those in which participants without airway diseases were eligible) Not in 2017 version: • trial duration: ≤12 months vs >12 months

	Martineau et al (2017)	Jolliffe et al (2020)
RESULTS		
Overall results	• 1 step analysis - Vitamin D reduced proportion of participants experiencing at least 1 ARTI (OR, 0.88; 95% CI, 0.81 to 0.96; p=0.003; p for heterogeneity <0.001; 25 RCTs, 10,933 participants). • 2 step analysis - Vitamin D reduced proportion of participants experiencing at least 1 ARTI (OR, 0.80; 95% CI, 0.69 to 0.93; p=0.004; I^2=53.3%, p= for heterogeneity 0.001; 24 RCTs, 10,899 participants).	• Compared to placebo, vitamin D supplementation reduced the proportion of participants experiencing at least 1 ARTI (OR, 0.91; 95% CI, 0.84 to 0.99; I^2=37.2% p for heterogeneity =0.014; 44,009 participants, 36 studies). • No statistically significant difference for secondary comparison of higher vs lower dose of vitamin D (OR 0.87, 95% CI 0.73 to 1.04 (I^2 =0.0%, p for heterogeneity 0.496; 3,047, 11 studies))
Sensitivity analyses	• Excluding the 2 studies at unclear risk of bias: (OR, 0.82; 95% CI, 0.70 to 0.95; 10,744 participants, 23 studies). • Restricting to trials where ARTI a primary or coprimary outcome: (OR, 0.82; 95% CI, 0.68 to 1.00; 5,739 participants, 14 studies).	• Excluding the 4 studies at unclear risk of bias: (OR, 0.93; 95% CI, 0.86 to 1.00; 43,626 participants, 33 studies). • Restricting to trials with ARTI as a primary or coprimary outcome: no significant protective effect (OR, 0.89; 95% CI, 0.77 to 1.03; 7,537 participants, 18 studies).
Subgroup analyses	• Dosing frequency: protective effect of vitamin D when given daily or weekly vitamin D supplements (OR, 0.81; 95% CI, 0.72 to 0.91; p<0.001; 15 RCTs, 5133 participants) but not bolus doses (OR, 0.97; 95% CI, 0.86 to 1.10; p=0.67; 10 RCTs, 5800 participants). • Baseline 25(OH)D concentration: protective effect of vitamin D in those with baseline 25(OH)D <25 nmol/L (OR 0.58, 95% CI, 0.40 to 0.82, p=0.002; 14 RCTs; 538 participants) but not in those with 25(OH)D >25 nmol/L (OR, 0.89; 95% CI, 0.77 to 1.04; p=0.15; 19 RCTs; 3634 participants).	• Dosing frequency: significant protective effect of vitamin D when given daily (OR 0.75, 95% CI 0.61 to 0.93, 4,005 participants, 18 studies) but not weekly (OR 0.97, 95% CI 0.88 to 1.06, 12,756 participants, 6 studies) or monthly to 3-monthly (OR 0.98, 95% CI 0.93 to 1.03, 21,248 participants, 12 studies) • Baseline 25(OH)D concentration: no significant effect in any of the subgroups