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Scientific Advisory Committee on Nutrition

Monitoring evidence on Nutrition and COVID-19

June 2021

Contents

Introduction

1. Since the COVID-19 outbreak, a number of academic articles have hypothesised that poor nutritional status could compromise immune function and increase the risk of adverse COVID-19 outcomes; and that supplementation with some micronutrients could improve immune function and vaccine response in relation to COVID-19.

2. This paper:
   - summarises the work of the Scientific Advisory Committee on Nutrition (SACN) on this topic to date;
   - summarises the monitoring of recent evidence on nutrition and COVID-19 and immune and vaccine response;
   - outlines the monitoring process going forward.

Background

Nutrition and immune function

3. In June 2020, SACN produced a general paper on 'Nutrition and immune function in relation to COVID-19 – a rapid scoping exercise' (SACN, 2020a). The scoping exercise was conducted at speed and though it included evidence from high-quality systematic reviews, randomised controlled trials and clinical trials in humans it was not a formal review of the area. It focused on nutrition and acute respiratory tract infections and nutrition and vaccine response.

4. At the SACN meeting in June, the committee concluded that this scoping exercise (SACN, 2020a) indicated a lack of robust evidence to suggest that specific nutrients or nutritional supplements, can reduce either the risk or severity of COVID-19. SACN therefore decided not to undertake a formal risk assessment at this time. This topic was further discussed by SACN at the meeting in November 2020, where it was judged there was a lack of robust evidence to change recommendations and members agreed to continue to keep this topic under review.

Vitamin D

5. In Spring 2020, SACN conducted a rapid review of the evidence on vitamin D and acute respiratory tract infections (ARTI), and this review was then updated in December 2020 (SACN, 2020b).

6. Public Health England (PHE) and SACN also supported the National Institute for Health and Care Excellence (NICE) in reviewing emerging evidence on vitamin D

and the prevention and treatment of COVID-19. In Autumn 2020, the Secretary of State for Health asked NICE and PHE to re-consider the evidence on vitamin D and COVID-19, and an updated COVID-19 rapid guideline was published in December. (NICE, 2020).

Excess weight and obesity

7. In July 2020 PHE published a report Excess Weight and COVID-19 Insights from new evidence (PHE, 2020) that provides evidence-based insights on the relationship between excess weight and COVID-19. The report concluded that the evidence consistently suggests that people with COVID-19 who are living with overweight or obesity, compared with those of a healthy weight, are at an increased risk of serious COVID-19 complications and death.

Monitoring approach

8. In January 2021, the Chair of SACN agreed that the SACN secretariat should provide SACN with an update of emerging evidence on nutrition in relation to immune function, vaccine response and COVID-19 at their March 2021 meeting. SACN subsequently agreed that monitoring should continue and that this issue would be a standing item on the SACN agenda for the foreseeable future.

9. In preparation for the SACN meeting on 10 March 2021, the SACN secretariat summarised the emerging evidence in relation to COVID-19, considering i) vitamin D, focusing specifically on new trials (including pre-prints) published since publication of the NICE rapid guideline (see Annex 1) and ii) other nutrients (see Annex 2), focusing only on systematic reviews and using the PHE COVID Rapid Evidence Service.

10. In order to ensure the committee had a broad picture of the existing literature on diet/nutritional status and immune function and vaccine response, and building on the scoping paper considered in June 2020, the SACN secretariat also carried out a scoping review on diet/nutritional status and immune function and vaccine response not specific to COVID-19 (note it was not possible to include this in the above search with the PHE COVID Rapid Evidence Service). This focused only on systematic reviews, using the PHE Knowledge and Library services and in line with SACN's Framework for the Evaluation of Evidence. This process is outlined in Annex 5.

11. Due to the rapid nature of this work, it was not possible, within the required timeframe, to formally apply the SACN evidence framework and specifically grade the quality of the available evidence. For the vitamin D and COVID-19 summary (see paragraphs 10 to 16), key data regarding the trials were extracted and strengths and limitations of the papers assessed. For the Nutrition and COVID-19 summary (see paragraphs 17 to 31) and the nutrition and immune/vaccine response summary (32

to 41), during full text screening, criteria (based on the AMSTAR 2 criteria quality assessment tool for systematic reviews) was applied to identify review papers with a truly systematic approach. The AMSTAR 2 quality assessment tool was applied to one paper (James et al 2020) which was identified in advance of the monitoring search in January 2021.

Emerging evidence: Vitamin D and COVID-19

12. In order to identify any relevant trials published since the NICE rapid guideline, the COVID Rapid Evidence Service provided fortnightly updates from 26 October 2020 to 1 February 2021 (see Annex 1 for search strategy) on emerging evidence related to COVID-19. This included any evidence on vitamin D and was not limited by study design. It should be noted that this was not considered a fully systematic search due to the use of a semi-automatic process that utilises Endnote Smart groups, which have limitations in their searching capacity.

13. The literature searches identified 180 records. These records were sifted, and reviews, abstracts and research proposals were excluded, and relevant trials were identified.

14. Four relevant published trials were identified Entrenas Castillo et al, (2020); Nogues et al (2020); Murai et al, (2020) and Rastogi et al, (2020). Castillo et al (2020) is included in the NICE-PHE-SACN Rapid Guideline (NICE, 2020), so was not further evaluated and Nogues et al (2020) was subsequently removed from SSRN server due to concerns about the description of the research in this paper, which has led to an investigation into this study.

15. Murai et al (2021) reports a randomised double-blind study (n=240) undertaken in two hospitals in Brazil. Patient groups with severe COVID-19 symptoms at both study sites were given either a single high dose vitamin D (200,000 IU) or a placebo. There was no statistically significant difference in length of hospital stay, admission to ICU, ventilation or mortality between groups. Randomisation and blinding approaches were clearly stated; however limitations included heterogeneous patient groups, lack of clarity regarding the time between randomisation and administering vitamin D and that the secondary outcomes (including mortality, admission to intensive case and mechanical ventilation requirement) and sub-analyses were likely to be underpowered.

16. Rastogi et al (2020) reports a randomised, placebo-controlled trial (n=40) of high dose vitamin D. Patients positive for COVID-19 were given either a daily dose of 60 000 IU of cholecalciferol for 7 days or a placebo. Significantly more participants in the vitamin D intervention group tested negative for COVID-19 after 21 days than participants on placebo. A number of limitations were noted regarding study design,

including small sample size, lack of information on blinding or randomisation, no information on date of initiation of symptoms between patients in the two groups and notable heterogeneity between groups at recruitment.

17. Full details of Murai et al (2020) and Rastogi et al (2020) are provided in Annex 1 Table 1.

Conclusions

18. SACN agreed that, to date, this monitoring exercise has not identified any new trials in relation to vitamin D and COVID-19 that would require the re-review of the NICE/PHE/SACN rapid guideline or that would change current dietary advice.

Emerging evidence: Nutrition and COVID-19

19. The literature search investigating COVID-19 and nutrition in general (not specific to vitamin D) (between 1 January 2020 up to 10 February 2021) identified 137 records. No duplicates were found. The 137 records were screened by title and abstract using Eppi-Reviewer 4. Of these, 46 covered nutritional interventions and COVID-19 outcomes (see Annex 2 for details of the search).

20. Of the 46 records, the full texts of 41 were retrieved and assessed for eligibility while, at the time this paper was written, the secretariat was awaiting the full text of 5 records. A total of 6 out of the 46 publications met the systematic review inclusion criteria described in Annex 2. Four were available only as pre-prints (therefore not peer reviewed) at the census time.

21. One publication (Jolliffe et al, 2020) was included in the December 2020 rapid update of vitamin D and ARTI (SACN, 2020b) and has not been considered here. Seven publications relating to Vitamin D and COVID (4 peer-reviewed publications and 3 pre-printed were excluded). Given the timing of publications, the primary studies would have been picked up by the NICE rapid guideline (NICE, 2020), so these are not discussed here.

22. One publication investigated the effects of micronutrients or conditional amino acids on COVID-19-related outcomes (Rozga et al, 2020) however the studies included in the review did not include COVID-19 patients and so the publication was not included in this paper. Another publication, reviewing the evidence for zinc supplements for the prevention and treatment of COVID-19 (Arentz et al, 2020) reported the results of 118 RCTs. None investigated zinc supplements for prevention or treatment of acute respiratory coronavirus infections and therefore the publication was not included in this paper.

23. The main characteristics of the remaining 2 peer reviewed publications, (Taneri et al, 2020 and BourBour et al, 2020), are presented in Annex 3 Table 3. The publications have not undergone quality assessment.

24. The 4 pre-print papers are listed in Annex 3, Table 4. The main characteristics of only one of these papers (James et al, 2020) have been extracted and the paper was quality assessed. This systematic review was identified by the SACN secretariat (as a preprint) ahead of the search (and subsequently also picked up in the search) and was considered particularly pertinent to committee discussions given the breadth of the review.

Overview of peer reviewed publications

25. Key reported findings from the 2 peer reviewed publications (1 systematic review with meta-analysis (Taneri et al, 2020) and 1 systematic review without meta-analyses (BourBour et al, 2020)) are presented below (to note: the quality and strength of the evidence of these publications has not been fully assessed however some limitations are outlined in Annex 3, Table 3). Overall, there is limited evidence available on nutrition and COVID-19.

26. Taneri et al, (2020) reported pooled means of biomarkers of anaemia and iron metabolism in relation to disease severity in patients diagnosed with COVID-19. They reviewed 189 observational studies with data from COVID-19 patients. Authors reported that compared to moderate cases, severe COVID-19 cases had lower haemoglobin and red blood cell count, and higher ferritin and red cell distribution width. A significant difference in mean ferritin levels was found between COVID-19 survivors and non-survivors, but not in haemoglobin levels. Limitations included: studies were mainly cross-sectional, some study participants could overlap across the included studies and some did not have a complete follow-up.

27. BourBour et al, (2020) reported the effect of nutrients on the immune system and hypothesised on their possible roles in the prevention, treatment, and management of COVID-19 in adults. They reviewed 51 articles, including 14 meta-analyses, but no papers on COVID-19 outcomes were identified. The authors' conjectures that vitamins A, D (in combination with melatonin) and C may be effective in treating and/or preventing COVID-19 are thus not based on direct evidence.

28. No subgroup analyses based on ethnicity were presented for any of these studies.

Summary of pre-print paper: James et al 2020

29. The AMSTAR 2 quality assessment tool was applied to the systematic review component of the pre-print paper by James et al (2020). The review, while comprehensive, was assigned a 'critically low' confidence rating primarily due to not

having undertaken a formal risk of bias or quality assessment of the included evidence. To note, given the review's reliance on evidence from preprints (and the fact that the majority of the included studies were ongoing at the time of writing), the applicability of the AMSTAR 2 tool may be limited at this stage. More detail about the tool and how the assessment criteria were applied to the review can be found in Annex 4.

30. In summary, the paper from James et al (2020):

- reviewed the latest evidence on how 13 nutrition-related components (overweight and obesity; diabetes; protein-energy malnutrition; anaemia; supplementation trials or status assessments for vitamins A, C, D, and E; polyunsaturated fatty acids; iron; selenium; zinc; anti-oxidants, and nutritional support) may influence both susceptibility to, and progression and severity of COVID-19.
- produced landscape and systematic reviews of 13 key nutrition-related components and their potential interactions with COVID-19. Separate systematic searches were conducted in each of the 13 topic areas and included all original research (all study designs, including case reports) conducted in humans (adults and children) and published in English in peer-reviewed journals or as pre-prints. Clinical trial registries were also searched. After full-text screening, 22 published articles, 39 pre-print articles and 79 references returned from clinical trial registries were included in the narrative synthesis. To note 1: the authors included information on only 14 of the 22 studies included (8 retrospective cohorts, 2 cross sectional studies, 1 prospective cohort study, 1 case study, 1 case-series, 1 study protocol). To note 2: almost all the 79 references retrieved from trial registries were of planned or ongoing studies.
- the authors concluded there was limited evidence that therapeutic use of high-dose supplements of micronutrients would either prevent severe disease or speed up recovery from COVID-19.

Conclusions

31. SACN agreed that this monitoring exercise to date has not identified any new evidence to suggest that specific nutrients or nutritional supplements are likely to reduce the risk or severity of COVID-19 or would change current dietary advice. SACN agreed therefore that a formal risk assessment is not currently required.

Emerging evidence: Nutrition, immune function and vaccine response (not specific to COVID-19)

32. The scoping search carried out by the PHE Knowledge and Library services (between 1 Jan 2020 to 12 February 2021) on nutrition and immune and vaccine response returned 844 records. After removal of duplicates, 842 records were screened by title and abstract using Eppi-Reviewer 4. Of these, 20 records covered nutritional interventions and immunity/vaccine response and 47 covered nutritional interventions/exposures and risk, prevention or treatment of infectious disease (including acute respiratory tract infections) in healthy and clinical populations. The remaining 775 records were not considered relevant to the review and were excluded. The full texts of all 20 records covering nutritional interventions and immunity/vaccine response were retrieved and assessed for eligibility.

33. Members agreed that studies on infant feeding should be excluded given the uncertain relevance of indirect data and the minimal impact of COVID-19 for the majority of children in this age group. Members also agreed not to include studies focusing on probiotics following discussion at the SACN meeting in November 2020.

34. SACN noted that there is convincing wider evidence that people with COVID-19 who are living with overweight or obesity, compared with those of a healthy weight, are at an increased risk of serious COVID-19 complications and death as concluded in the Public Health England report Excess Weight and COVID-19 Insights published in 2020 (PHE, 2020). Members were aware that the evidence in this area is being closely monitored by the PHE Obesity and Healthy Weight team and agreed that SACN should not duplicate this work area. If, however evidence was to emerge on a relationship between excess weight and response to COVID-19 vaccines SACN would consider as necessary.

35. Nine out of the 20 full-text publications screened met the inclusion criteria. However, 1 of the 9 publications (Lee et al, 2018) was considered in SACN's rapid scoping exercise in June 2020 and has not been considered here.

36. The main characteristics of the remaining 8 publications are presented in Annex 6 Table 8 for information.

37. The 47 records examining nutritional interventions/exposures and risk, prevention or treatment of infectious disease (including acute respiratory tract infections) in healthy and clinical populations have not been considered further at this stage.

Summary of main findings

38. Of the 8 publications that examined nutritional interventions and immunity/vaccine response, 2 are systematic reviews with meta-analyses (Church et al, 2019) (Fan, 2016), 3 are systematic reviews without meta-analysis (Dhurandhar et al, 2015), (Jayawardena et al, 2020), (Silva & Furlanetto, 2015), 2 are systematic reviews of systematic reviews or meta-analyses (Domnich et al, 2019), (Kelishadi et al, 2017), and 1 is a systematic review with a network meta-analysis (Vedhara et al, 2020) . All 8 systematic reviews and meta-analyses synthesised findings from RCTs or observational studies, including prospective cohort studies.

39. The most common interventions or exposures examined were childhood or adulthood obesity (3 publications) and vitamin D status (2 publications), for which COVID related evidence was available but has been considered elsewhere. Other topics covered were supplementation with: vitamin A and E and beta-carotene, multi-nutrient (zinc and selenium sulphide or beta carotene, ascorbic acid, and vitamin E), multi-nutrient (retinol, beta-carotene, ascorbic acid, vitamin E, cholecalciferol, vitamin K, thiamin, niacin riboflavin, pantothenic acid, pyridoxine, cyanocobalamin, zinc, selenium, iron, copper, magnesium, iodine, calcium, phosphorus, manganese, chromium, molybdenum and silicium) and vitamin E, zinc, zinc plus arginine, selenium, copper (3 publications).

40. SACN noted that the studies identified in relation to nutrition and immune function and vaccine response, not specific to COVID-19, were heterogenous in their study populations and measured a variety of outcomes, and that there is no consistent evidence for how dietary intake and nutritional status/nutrition might relate to immune function and vaccine response. SACN agreed non-COVID-19 specific papers would not be included within the monitoring process going forwards.

Conclusions

41. SACN agreed that this monitoring exercise to date has not identified any new evidence that would change current dietary advice in relation to immune function and vaccine response. SACN agreed therefore that a formal risk assessment is not currently required.

Overall summary and conclusions

42. SACN agreed that the monitoring exercise thus far indicates that current evidence did not support changing existing advice, for the purpose of preventing or treating COVID-19 or supporting immune function or vaccine response. SACN agreed therefore that a formal risk assessment is not currently required.

43. SACN noted that there is an extensive volume of literature on nutrition and immune function in general, and growing for COVID-19 specifically, but it is a challenging area of research. The complexity of this issue was clear in previous SACN risk assessments that included immune function as an outcome of interest (notably the SACN reports on vitamin D and iron and position statements on selenium and trans fats).

44. SACN discussed that future monitoring should not duplicate the work of other organisations:

- The UK COVID-19 Therapeutic Advisory Panel (UK C-TAP) is responsible for reviewing and prioritising suitable compounds based on promising scientific evidence. The Panel is continuing to monitor ongoing COVID-19 related Vitamin D trials.
- Evidence in relation to vitamins D and C in relation to COVID-19 are also being monitored by RAPID-C19, a multi-agency initiative aiming to get treatments for COVID-19 to NHS patients quickly and safely, as well as by the National Institute for Health Research (NIHR) Innovation Observatory (IO) a national medical horizon scanning facility located at Newcastle University.

45. It was therefore agreed that the secretariat should not search for emerging evidence on vitamins D and C, as this was being undertaken by other organisations. The SACN secretariat are in contact with the NICE surveillance team and DHSC colleagues supporting UK C-TAP to ensure complementary approaches.

46. SACN will continue to support NICE with their monitoring of the evidence related specifically to vitamin D. SACN will not be monitoring the evidence in relation to ARTI and vitamin D, but agreed that if NICE were to update their guideline on vitamin D and COVID-19, SACN would consider whether to update the rapid review on vitamin D and ARTI.

47. An update will be provided to SACN at the next meeting in June 2021.

48. The SACN Secretariat will therefore continue to monitor emerging evidence of nutrition, immune function and vaccine response specifically in relation to COVID-19 by carrying out systematic searches of the published and pre-print literature using the PHE Knowledge and Library services. SACN agreed that this issue would be a standing item on the SACN agenda for the foreseeable future. If evidence does

emerge to indicate any clear associations between nutrition, immune function and vaccine response, specifically in relation to COVID-19, SACN will consider whether to undertake a formal risk assessment of all the available evidence.

49. SACN agreed that all study types including meta-analyses, systematic reviews, primary studies, Mendelian randomisation studies and pre-prints should be considered given the rapidly evolving nature of the evidence.

50. SACN highlight that several nutrients are involved with the normal functioning of the immune system and emphasise that most people can get all the vitamins and minerals they need by eating a healthy, balanced diet and do not need to take supplements (other than specific advice around vitamin D). The government therefore continues to advise that during this time everyone follows a healthy, balanced diet, as illustrated by the Eatwell Guide, which is available to view here: The Eatwell Guide - GOV.UK (www.gov.uk).

Annex 1

Evidence monitoring process for Vitamin D and COVID-19

The PHE COVID Rapid Evidence Service produce fortnightly updates on emerging evidence related to COVID-19; this includes any evidence on vitamin D. The search is not limited by study design (i.e. picks up both primary studies, reviews, editorial, comments, etc), and the process is semi-automated. It should be noted that this was not considered a fully systematic search due to the use of a semi-automatic process that utilises Endnote Smart groups, which have limitations in their searching capacity.

If sufficient new evidence is found via this semi-automated process, a systematic search can be run by the COVID Rapid Evidence Service to conduct an Evidence Summary.

Search strategy

Sources
Ovid Medline, Ovid Embase, WHO COVID-19, medRxiv (searched via Covid-19 portfolio https://icite.od.nih.gov/covid19/search/)

Frequency
Fortnightly (Mondays). All records on COVID-19 are downloaded into a Smart Groups Endnote library. This library contains Smart Groups with basic search strategies behind them, so when citations are imported it automatically moves those that match the search terms into the appropriate Group. These are then screened (by a human) for relevance. A spreadsheet is then created which contains these relevant citations with full text links. NOTE: there is no quality assessment of any of the included papers.

Ovid Medline strategy

1. exp coronavirus/
2. exp Coronavirus Infections/
3. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw.
4. (coronavirus* or coronovirus* or coronavirinae* or CoV or HCoV*).ti,ab,kw.
5. covid*.nm.
6. (2019-nCoV or 2019nCoV or nCoV2019 or nCoV-2019 or COVID-19 or COVID19 or CORVID-19 or CORVID19 or WN-CoV or WNCoV or HCoV-19 or HCoV19 or 2019 novel* or Ncov or n-cov or SARS-CoV-2 or SARSCoV-2 or SARSCoV2 or SARS-CoV2 or SARSCov19 or SARS-Cov19 or SARSCov-19 or SARS-Cov-19 or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese* or SARS2 or SARS-2 or SARScoronavirus2 or SARS-coronavirus-2 or SARScoronavirus 2 or SARS coronavirus2 or SARScoronovirus2 or SARS-coronovirus-2 or SARScoronovirus 2 or SARS coronovirus2).ti,ab,kw.

7. (respiratory* adj2 (symptom* or disease* or illness* or condition*) adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw.
8. ((seafood market* or food market* or pneumonia*) adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw.
9. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei or China* or Chinese* or Huanan*)).ti,ab,kw.
10. or/1-9

Table 1: Main characteristics on key trials on vitamin D and COVID

Reference	Methods	Results	SACN Secretariat Comments
Murai et al (2020) Effect of Vitamin D3 Supplementation vs Placebo on Hospital Length of Stay in Patients with Severe COVID-19: A Multicenter, Double-blind, Randomized Controlled Trial.	Randomised double blind study undertaken in two hospitals in Brazil (randomisation and blinding approaches clearly stated) Patient groups with severe COVID-19 symptoms at both study sites were given either a single high dose vitamin D (200,000 IU) or a placebo on same day as randomisation, after admittance to hospital. 240 patients with severe COVID-19 - but not already on mechanical ventilation. Power calculations suggest adequately powered for primary outcome (hospital stay) but may not have been adequately powered for secondary outcomes. Baseline 25(OH)D values averages of 21.0ng/ml and 20.6ng/ml. Co-morbidities and self-reported weight recorded. Outcomes: hospital length of stay, defined as hospital discharge from the date of randomization or death. Secondary outcomes were mortality, admission to ICU, mechanical ventilation requirement, and serum levels of 25-hydroxyvitamin D, creatinine, calcium, C-reactive protein, and D-dimer.	No significant differences between groups for primary or secondary outcomes. Vitamin D3 supplementation significantly increased serum 25-hydroxyvitamin D levels compared to placebo (difference, 24.0 ng/mL [95% CI, 21.0% to 26.9%]; P = .001). No adverse events were observed. Sensitivity analysis patients 25 OHD <30ng at baseline, no between group differences in primary or secondary outcomes. [Authors noted that this analysis likely to be underpowered] “Among hospitalized patients with severe COVID-19, vitamin D3 supplementation was safe and increased 25-hydroxyvitamin D levels but did not reduce hospital length of stay or any other relevant outcomes vs placebo. This trial does not support the use of vitamin D3 supplementation as an adjuvant treatment of patients with COVID-19.” “Collectively, these analyses indicate that a single oral dose of 200,000 IU of supplementation can rapidly increase 25-hydroxyvitamin levels, in agreement with our hypothesis, so that the present null findings cannot be attributed to the	Heterogenous sample receiving range of treatments. Univariate analysis - though no significant differences reported between treatment groups. Mean time between symptoms and randomisation was around 10 days. Time between randomisation and administering D3 unclear. Results not generalisable to early or preventative vitamin D to reduce severity of COVID-19. Secondary outcomes and sub analysis likely to be under powered Consideration 8 patients removed from analysis - 4 in each group and reasonable exclusion (eg withdrew consent, vomited after administering). Measurement time of 25OHD not provided.

Reference	Methods	Results	SACN Secretariat Comments
	Discharge oxygen saturation >93% [similar level to UK admittance to A+E<92-3%].	failure of increasing serum 25-hydroxyvitamin D levels."	
Rastogi et al (2020) Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study)	Randomised, placebo-controlled COVID-19 positive individuals were randomised to intervention (n=16) or control (n=24) group in a tertiary care hospital in north India. Intervention participants were asymptomatic or mildly symptomatic SARS-CoV-2 RNA positive vitamin D deficient (25(OH) D<20 ng/ml) patients. Participants were randomised (randomisation methods not described, blinding not mentioned) to receive daily 60 000 IU of cholecalciferol (oral nano-liquid droplets) for 7 days with therapeutic target 25(OH) D>50 ng/ml (intervention group) or placebo (control group). 25(OH)D levels were assessed at day 7, and cholecalciferol supplementation was continued for those with 25(OH)D <50 ng/ml in the intervention arm. Outcome measures were proportion of patients with SARSCoV-2 RNA negative before day-21 and change in inflammatory markers.	No significant difference between median (interquartile range) age of intervention vs. control groups (50.5 (36-51) and 47.5 (39.3-49.2) respectively. Baseline serum 25(OH)D was 8.6 (7.1 to 13.1) and 9.54 (8.1 to 12.5) ng/ml (p=0.730), in the intervention and control group, respectively Significant difference in proportion of participants who became negative for COVID-19 [assume at day 21] in intervention group: 10 (62.5%) participants with vitamin D compared to the control group 5 (20.8%) (p<0.018) Fibrinogen levels significantly decreased with cholecalciferol supplementation (intergroup difference 0.70 ng/ml; P=0.007) unlike other inflammatory biomarkers.	Small sample size. No details of blinding or randomisation. Authors note differences in taste and consistency between vitamin D dose and placebo. No discussion of date of initiation of symptoms between patients in the two groups. Intervention sample 6/16 male and 10/16 female; Control group 14/24 male 10/24 female with no presentation of statistics for these differences. High dose administered, risks of toxicity Participants were mildly symptomatic and asymptomatic, limiting generalisability to severe cases of COVID-19.

Annex 2

Evidence monitoring process for Nutrition and COVID-19

The SACN secretariat worked with the PHE COVID Rapid Evidence Service to conduct a scoping search on nutrition and COVID-19. The search was limited to reviews and the search is mainly confined to COVID-19 repositories. The following electronic databases were searched: the preprint server medRxiv, the COVID-19 review repositories WHO covid database and LitCOVID) as well as Ovid Medline, Ovid Embase and Food Science abstracts. The search terms are shown below. Titles and abstracts, followed by full-texts, were screen against the inclusion and exclusion criteria shown in Table 2.

Table 2. Inclusion and exclusion criteria

Category	Inclusion criteria	Exclusion criteria
Study design	Systematic reviews and meta-analyses published in peer-reviewed journals	Primary studies Narrative reviews Animal studies Reviews published in grey literature (such as dissertations, conference proceedings, books/book chapters, opinion pieces, and other non-peer reviewed articles)
Target group	Adults and children (healthy and unhealthy populations)	
Countries	All	
Language	English	Non-English
Interventions	Nutrition, nutrient, nutritional, malnutrition, undernutrition, micronutrient, vitamin, mineral, overnutrition	Non-nutrition interventions Pro/pre/syn/sym-biotics
Outcomes	COVID-19	

During full-text screening it became apparent that some reviews (even if termed ‘systematic’ by their authors) followed a more narrative structure. The secretariat therefore applied the following criteria (based on the AMSTAR 2 criteria quality assessment tool for systematic reviews) to determine whether a publication was a systematic review. A publication was considered a systematic review if it included:

- a research question that incorporated PICO
- a well-defined inclusion/exclusion criteria
- a published literature search strategy, including searches of at least two online databases
- data extraction of included studies (main characteristics etc.)
- Risk of bias/quality assessment of the included studies was considered desirable but not critical (due to rapid nature of field)

Search strategy in Ovid Medline

1. nutrition.tw,kw.
2. malnutrition.tw,kw.
3. nutrient*.tw,kw.
4. vitamin*.tw,kw.
5. zinc.tw,kw.
6. selenium.tw,kw.
7. magnesium.tw,kw.
8. Nutritional Status/
9. exp Malnutrition/
10. exp Nutrients/
11. Zinc/
12. Selenium/
13. Magnesium/
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. exp coronavirus/
16. exp Coronavirus Infections/
17. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw.
18. (coronavirus* or coronovirus* or coronavirinae* or CoV or HCoV*).ti,ab,kw.
19. covid*.nm.

20. (2019-nCoV or 2019nCoV or nCoV2019 or nCoV-2019 or COVID-19 or COVID19 or CORVID-19 or CORVID19 or WN-CoV or WNCoV or HCoV-19 or HCoV19 or 2019 novel* or Ncov or n-cov or SARS-CoV-2 or SARSCoV-2 or SARSCoV2 or SARS-CoV2 or SARSCov19 or SARS-Cov19 or SARSCov-19 or SARS-Cov-19 or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese* or SARS2 or SARS-2 or SARScoronavirus2 or SARS-coronavirus-2 or SARScoronavirus 2 or SARS coronavirus2 or SARScoronovirus2 or SARS-coronovirus-2 or SARScoronovirus 2 or SARS coronovirus2).ti,ab,kw.
21. (respiratory* adj2 (symptom* or disease* or illness* or condition*) adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw.
22. ((seafood market* or food market* or pneumonia*) adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw.
23. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei or China* or Chinese* or Huanan*)).ti,ab,kw.
24. or/15-23
25. 14 and 24
26. limit 25 to "reviews (maximizes specificity)"

Annex 3

Abbreviations

HIC	High-income country
LMIC	Lower- or middle-income country
MA	Meta-analysis
RCT	Randomised controlled trial
SMD	Standardised mean difference
SR	Systematic review
RS	Retrospective cohort
CSS	Cross-sectional study
PCS	Prospective cohort study
CS	Case-study

Table 3: Main characteristics of systematic reviews/meta-analyses on nutrition and COVID (peer reviewed publications)

Reference	Methods	Results	Comments
Anaemia and iron metabolism in COVID-19: a systematic review and meta-analysis **(Taneri et al, 2020)**	Research question: systematic review and meta-analysis of available observational evidence to (i) quantify the mean levels of haemoglobin, ferritin and other biomarkers of iron metabolism, and of biomarkers related to erythrocyte indices in COVID-19 patients, (ii) explore whether the levels would differ by age, sex presence of chronic conditions and severity of COVID-19, and (iii) whether these biomarkers could have clinical and/or prognostic utility in COVID-19. Search criteria *Search dates:* the databases were searched from their inceptions until August 3rd 2020. *Study design:* observational studies (cross-sectional, cohort, and case–control studies), except for case reports and case-series, were included *Population:* adults and children *Intervention/exposure and comparators:* levels of the biomarkers of iron metabolism, erythropoietin and erythrocyte indices, haemoglobin levels or the prevalence of anaemia	Included studies: 189 unique studies, with data from 57,563 COVID-19 patients MA results: Pooled mean haemoglobin and ferritin levels in COVID-19 patients across all ages were 129.7 g/L (95% CI 128.51; 130.88) and 777.33 ng/mL (95% CI 701.33; 852.77), respectively. Haemoglobin levels were lower with older age, higher percentage of subjects with diabetes, hypertension and overall comorbidities, and admitted to intensive care. Ferritin level increased with older age, increasing proportion of hypertensive study participants, and increasing proportion of mortality. Compared to moderate cases, severe COVID-19 cases had lower haemoglobin (WMD −4.08 g/L (95% CI−5.12;−3.05)] and red blood cell count (WMD −0.16×1012 /L (95% CI−0.31;−0.014)), and higher ferritin (WMD,−473.25 ng/mL (95% CI 382.52; 563.98)) and red cell distribution width (WMD, 1.82% (95% CI 0.10; 3.55). A significant difference in mean ferritin levels	Funding information: work was not funded but open access funding provided by University of Bern Limitations: Review restricted to articles in English (potential publication bias), studies mainly cross-sectional, heterogeneity in the definition of moderate and severe cases of COVID-19 patients and in the definition of comorbid patients could have contributed to the heterogeneity observed in the meta-analysis, authors unable to exclude the possibility that some study participants could overlap across the included studies and some studies did not have a complete follow-up,

Reference	Methods	Results	Comments
	Primary outcome: disease severity, admission to intensive care unit, mechanical ventilation, and mortality	of 606.37 ng/ mL (95% CI 461.86; 750.88) was found between survivors and non-survivors, but not in haemoglobin levels Author's summary: This meta-analysis suggests that haemoglobin and ferritin levels vary according to the severity of COVID-19 as well as age, gender and presence of comorbidity among COVID-19 patients. Whether haemoglobin and ferritin can be used for prognostic purposes, or have further implications for identifying novel treatment targets, needs further investigation.	and therefore the stratified analyses by the percentage of survivors should be interpreted with caution.
Nutrients in prevention, treatment, and management of viral infections; special focus on Coronavirus **(BourBour et al, 2020)**	Research question: What is the effect of nutrients and dietary supplements on boosting the immune system on preventing and treating COVID-19 compared to other people who do not get enough nutrients? Search criteria *Search dates:* 1990-2020 *Study design:* RCTs, case-control, in-vivo studies, and meta-analyses on RCTs *Population:* People with or without infection *Intervention/exposure and comparators:* Eating a healthy diet or supplement Primary outcome: Prevention or treatment of coronavirus	Included studies: 51 articles, including 14 meta-analyses (note: all 14 were published before 2019 and report non-COVID 19 outcomes). No direct evidence available for: dietary protein, omega-3 fatty acids, vitamin E, vitamin B1, vitamin B6, vitamin B12, iron, zinc or selenium and their effect on COVID-19. Vitamin A was suggested as an option to the treatment of coronavirus and prevention of the lung infection. Vitamin D: the combined supplementation of vitamin D with melatonin could offer a synergistic alternative for the prevention and treatment of pulmonary infection by COVID 19. Vitamin C may protect against infection caused by coronavirus	All the 14 meta-analyses of RCTs were published before 2019 and report non-COVID 19 outcomes. BourBour did not conduct a meta-analysis as part of this SR. The study was funded by Student Research Committee, Guilan University of medical Sciences Rasht, Iran

Reference	Methods	Results	Comments
		Author's summary: Following an immune-boosting diet is important in order to prevent viral infections such as COVID-19. Supplementation with proper dietary components may also improve the health-related outcome of patients with COVID-19. Lack of clinical trial studies on the effects of the nutrients on COVID-19 and insufficient data on the effects of supplementation in healthy subjects for the prevention of COVID-19. Further studies are needed.	Limitations: the authors did not conduct any meta-analyses themselves). No direct evidence was available for: dietary protein, omega-3 fatty acids, vitamin E, vitamin B1, vitamin B6, vitamin B12, iron, zinc or selenium and their effect on COVID-19. The authors conclusions that vitamin A, D (in combination with melatonin) and vitamin C may be effective in treating and/or preventing COVID-19 are based on general respiratory disease data and plausible mechanisms. Limitations include: a lack of clinical trial studies on the effects of the nutrients on COVID-19 and insufficient data on the effects of supplementation in healthy subjects for the prevention of COVID-19.

Table 4: List of shortlisted pre-print systematic reviews/meta-analyses on nutrition and COVID

Ref (First author, date)	Title	Link
(Andrade, 2020)	Vitamin A and D deficiencies in the prognosis of respiratory tract infections: A systematic review with perspectives for COVID-19 and a critical analysis on supplementation	here
(Hunter et al, 2020)	Benefits and risks of zinc for adults during covid-19: rapid systematic review and meta-analysis of randomised controlled trials	here
(James et al, 2020)	Could nutrition modulate COVID-19 susceptibility and severity of disease? A systematic review **(note: summary of paper included in main body of this paper)**	here
(Oghenekome & Ralph, 2020)	Should zinc be used for COVID-19 prophylaxis or treatment? A rapid review	here

Annex 4

The AMSTAR 2 assessment and tool

Table 5 presents the AMSTAR 2 assessment of James et al 2020.

To note that the tool has been applied to the systematic review component of the paper and not the landscape reviews included in the paper.

The critical domains have been highlighted in grey and marked with an asterisk (*).

Table 5. AMSTAR 2 assessment

Domains		Comments
1. PICO	YES	
2. Protocol*	YES	Published on Prospero reference CRD42020186194
3. Study design	NO	To note that this criterion was considered not applicable for the report on lower carbohydrate diets for adults with T2D as the search included only MAs of RCTs/PCS; and SMCN's Feeding young children aged 12-60 months report because most SRs included multiple study designs
4. Search strategy*	YES	
5. Study selection duplicate	YES	
6. Data extraction duplicate	YES	No details given about the duplication process and how disagreements between reviewers were resolved.
7. Excluded studies*	NO	
8. Evidence tables	Partial yes	Minimum data extracted for a subset of studies in supplementary materials or described in the narrative of the review
9. RoB tool*	NO	Formal RoB assessment not undertaken due to rapid nature of the review and expected heterogeneity of study types, exposures and outcomes
10. Funding of included studies	NO	

11. Statistical analysis*	N/A*	
12. Impact RoB assessed	NO	No quality assessment
13. RoB discussed*	NO	
14. Heterogeneity discussed	NO	
15. Publication bias*	N/A*	
16. DOI	YES	
OVERALL CONFIDENCE RATING	Critically low	Review is comprehensive (comprised of 13 systematic reviews) but no RoB assessment or grading of the evidence was undertaken – review conclusion is appropriately cautious and inconclusive

Abbreviations used in the table above: MA (meta-analysis), PICO (population, intervention, control or comparator, outcome(s)), RoB (risk of bias), DOI (declarations of interest)

* N/A (not applicable) applies to criteria relevant in cases where a statistical/quantitative synthesis is performed

The AMSTAR 2 tool is a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of interventions (NRSI), or both.

The AMSTAR 2 tool has 16 questions, each with a number of criteria to support reviewers in assessing the quality of a systematic review in relation to the corresponding question (see www.amstar.ca/Amstar_Checklist.php for the checklist). Depending on which criteria are met, the systematic review is assigned a 'yes', 'partial yes' or 'no' (or non-applicable [N/A], where relevant) for that question.

The AMSTAR 2 authors have identified 7 of the 16 questions that can critically affect the validity of a review and its conclusions and have called these 'critical domains'. The AMSTAR 2 authors recognise that these 7 critical domains will not always be regarded as critical and will be affected by the nature of evidence under review.

The authors of AMSTAR 2 proposed a scheme for interpreting weaknesses detected in critical and non-critical questions to rate overall confidence in the results of the review:

Table 6. Rating overall confidence in the results of the review

High	**No or one non-critical weakness**: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.
Moderate	**More than one non-critical weakness*:** the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.
Low	**One critical flaw with or without non-critical weaknesses:** the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.
Critically low	**More than one critical flaw with or without non-critical weaknesses:** the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence.

The critical domains suggested in AMSTAR 2 are questions 2, 4, 7, 9, 11, 13, 15. These may vary depending on the research question.

Annex 5

Evidence monitoring process for Nutrition and immune and vaccine response

PHE Knowledge and Library services conducted a scoping search. Titles and abstracts, followed by full-texts, were screen against the inclusion and exclusion criteria shown in Table 7.

Table 7: Inclusion and exclusion criteria

Category	Inclusion criteria	Exclusion criteria
Study design	Systematic reviews and meta-analyses published in peer-reviewed journals	Primary studies Narrative reviews Reviews published in grey literature (such as dissertations, conference proceedings, books/book chapters, opinion pieces, and other non-peer reviewed articles)
Target group	Adults and child over 11 (healthy and unhealthy populations)	Children under 11 Pregnant women
Countries	All	
Language	English	Non-English
Interventions	Nutrition, nutrient, nutritional, malnutrition, undernutrition, micronutrient, vitamin, mineral, overnutrition	Non-nutrition interventions Pro/pre/syn/sym-biotics
Outcomes	Immune function/response, immunity, immune, vaccine response, vaccine, vaccination	Outcomes specific to certain countries

During full-text screening it became apparent that some reviews (even if termed ‘systematic’ by their authors) followed a more narrative structure. The secretariat therefore applied the following criteria (based on the AMSTAR 2 criteria quality assessment tool for systematic reviews) to determine whether a publication was a systematic review. A publication was considered a systematic review if it included:

- a research question that incorporated PICO
- a well-defined inclusion/exclusion criteria
- a published literature search strategy, including searches of at least two online databases
- data extraction of included studies (main characteristics etc.)
- Risk of bias/quality assessment of the included studies was considered desirable but not critical (due to rapid nature of field)

Search strategy

The systematic review question was ‘Are there systematic reviews or meta-analyses investigating nutrition (including individual nutrients, undernutrition, micronutrient deficiencies and overnutrition) and the effect on immune function and/or vaccine response in general (not COVID-19 specific)?’. The search terms were based on this question. This search strategy was intentionally broad in terms of outcomes and focused on systematic reviews (SR) and meta-analyses (MA) published since 2000. The search terms are presented below. The search was conducted on 10 February 2021.

Limits applied:

Age group	Language	Publication type	Time limit
N/A	English	N/A	2000-2021

Summary of resources searched and results

Source	No. of results before deduplication	No. of results after deduplication
Citation searches: James et al backward & forward citation search for systematic reviews and meta-analysis papers Jayawardena et al backward & forward citation search for systematic reviews and meta-analysis papers	18 16	18 14
Cochrane	7	7
Embase 1974 to 2021 February 10	190 (Search 1) 446 (Search 2) = 636	96 (search 1) 206 (search 2) =302
Ovid Emcare 1995 to 2021 Week 05	62	54
Ovid MEDLINE(R) ALL 1946 to February 10, 2021	40 (Search 1) 399 (Search 2) =439	37 348 (search 2) =385
medRxiv	9	9
PubMed	78	46
Web of Science	32	9
TOTAL	**1297**	**844**

Note:

- Search 1 was a preliminary search, carried out on Medline and Embase.
- Search 2 included the six major nutrients, carried out on Medline and Embase. Details can be found in the Appendix.

Disclaimer

Although every effort has been made to ensure this information is accurate, it is possible it may not be representative of the whole body of evidence available. Both articles and internet resources may contain errors or out of date information. None of the resources have been critically appraised. No responsibility can be accepted for any action taken on the basis of this information.

Citation search

Backward and forward citation searches carried out on the following reference papers:

- James, P. T., Ali, Z., Armitage, A. E., et al. 2020. Could nutrition modulate COVID-19 susceptibility and severity of disease? A systematic review. *medRxiv* 2020.10.19.20214395.
- Jayawardena, R., Sooriyaarachchi, P., Chourdakis, M., et al. 2020. Enhancing immunity in viral infections, with special emphasis on COVID-19: A review. *Diabetes Metab Syndr* 14(4) 367-382.

Cochrane

ID	Search	Hits
#1	MeSH descriptor: [Malnutrition] explode all trees	4256
#2	MeSH descriptor: [Micronutrients] explode all trees	5786
#3	MeSH descriptor: [Vitamins] explode all trees	4741
#4	MeSH descriptor: [Minerals] explode all trees	3862
#5	MeSH descriptor: [Overnutrition] explode all trees	14024
#6	((nutrition or malnutrition or micronutrient* or vitamin* or mineral* or overnutrition)):ti,ab,kw	70204
#7	#1 or #2 or #3 or #4 or #5 or #6	85366
#8	MeSH descriptor: [Immunity] explode all trees	3991
#9	MeSH descriptor: [Immunosuppression] explode all trees	2053
#10	MeSH descriptor: [Immune System] explode all trees	12029
#11	(immun*):ti,ab,kw	122690
#12	#8 or #9 or #10 or #11	127695
#13	MeSH descriptor: [Vaccines] explode all trees	12986
#14	MeSH descriptor: [Vaccination] explode all trees	2533
#15	((vaccin*)):ti,ab,kw	25933
#16	#13 or #14 or # #15	25967
#17	MeSH descriptor: [Systematic Reviews as Topic] explode all trees	22
#18	MeSH descriptor: [Meta-Analysis as Topic] explode all trees	322
#19	(systematic review or meta-analysis):ti,ab,kw	24191
#20	#17 or #18 or #19	24192
#21	#7 and #12 and #16 and #20	9

Embase

Search 1:
Database(s): Embase 1974 to 2021 February 10
Search Strategy:

#	Searches	Results
1	exp Malnutrition/	163381
2	exp Micronutrients/	41481
3	exp Vitamins/	648443
4	exp Minerals/	43953
5	exp Overnutrition/	548544
6	(nutrition or malnutrition or micronutrient* or vitamin* or mineral* or overnutrition).tw.	719171
7	exp Immunity/	1539165
8	exp Immunosuppression/	208428
9	immun*.tw.	3166386
10	exp Immune System/	2170092
11	exp Vaccines/	338688
12	exp Vaccination/	172586
13	vaccin*.tw.	372545
14	exp "Systematic Review"/	283097
15	exp Meta-Analysis/	208677
16	(meta-analysis or systematic review).tw.	342642
17	1 or 2 or 3 or 4 or 5 or 6	1748590
18	7 or 8 or 9 or 10	4840874
19	11 or 12 or 13	485488
20	14 or 15 or 16	464725
21	17 and 18 and 19 and 20	198
22	limit 21 to (human and english language and yr="2000 -Current")	189

Search 2:
Database(s): **Embase** 1974 to 2021 February 10
Search Strategy:

#	Searches	Results
1	exp Carbohydrates/	931992
2	exp Lipids/	1582149
3	exp Proteins/	468568
4	exp Vitamins/	648443
5	exp Minerals/	43953
6	exp Water/	475683
7	exp Malnutrition/	163381
8	exp Micronutrients/	41481
9	exp Overnutrition/	548544
10	(nutrition or carbohydrate* or lipid* or protein* or vitamin* or mineral* or water or malnutrition or micronutrient* or overnutrition*).tw.	5587560
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	7783080
12	exp Immunity/	1539165
13	exp Immune System/	2170092
14	(immune function* or immun*).tw.	3166386
15	12 or 13 or 14	4786054
16	exp Vaccines/	338688
17	exp Vaccination/	172586
18	vaccin*.tw.	372545
19	16 or 17 or 18	485488
20	exp "Systematic Review"/	283097
21	exp Meta-Analysis/	208677
22	(meta-analysis or systematic review).tw.	342642
23	20 or 21 or 22	464725
24	11 and 15 and 19 and 23	508
25	limit 24 to (human and english language and yr="2000 - Current")	445

Emcare

Database(s): Ovid Emcare 1995 to 2021 Week 05
Search Strategy:

#	Searches	Results
1	exp Malnutrition/	40722
2	exp Micronutrients/	9494
3	exp Vitamins/	119755
4	exp Minerals/	13400
5	exp Overnutrition/	161543
6	(nutrition or malnutrition or micronutrient* or vitamin* or mineral* or overnutrition).tw.	177950
7	exp Immunity/	174300
8	exp Immunosuppression/	24724
9	immun*.tw.	323947
10	exp Immune System/	237339
11	exp Vaccines/	61618
12	exp Vaccination/	38394
13	vaccin*.tw.	58837
14	exp "Systematic Review"/	131609
15	exp Meta-Analysis/	67302
16	(meta-analysis or systematic review).tw.	126685
17	1 or 2 or 3 or 4 or 5 or 6	408038
18	7 or 8 or 9 or 10	527620
19	11 or 12 or 13	81847
20	14 or 15 or 16	174032
21	17 and 18 and 19 and 20	68
22	limit 21 to (human and english language and yr="2000 -Current")	62

Medline

Search 1:
Database(s): Ovid MEDLINE(R) ALL 1946 to February 10, 2021
Search Strategy:

#	Searches	Results
1	exp Malnutrition/	123673
2	exp Micronutrients/	665472
3	exp Vitamins/	326930
4	exp Minerals/	170614
5	exp Overnutrition/	220155
6	(nutrition or malnutrition or micronutrient* or vitamin* or mineral* or overnutrition).tw.	562896
7	exp Immunity/	347477
8	exp Immunosuppression/	61141
9	immun*.tw.	2425140
10	exp Immune System/	1169945
11	exp Vaccines/	233302
12	exp Vaccination/	87313
13	vaccin*.tw.	325815
14	exp "Systematic Review"/	145248
15	exp Meta-Analysis/	126381
16	(MEDLINE or (systematic and review)).ti,ab. or meta-analysis.pt.	336920
17	1 or 2 or 3 or 4 or 5 or 6	1434869
18	7 or 8 or 9 or 10	3196920
19	11 or 12 or 13	394419
20	14 or 15 or 16	341461
21	17 and 18 and 19 and 20	47
22	limit 21 to (english language and humans and yr="2000 - Current")	40

Search 2:
Database(s): Ovid MEDLINE(R) ALL 1946 to February 10, 2021
Search Strategy:

#	Searches	Results
1	exp Carbohydrates/	1589373
2	exp Lipids/	1178261
3	exp Proteins/	6448633
4	exp Vitamins/	326930
5	exp Minerals/	170614
6	exp Water/	180857
7	exp Malnutrition/	123673
8	exp Micronutrients/	665472
9	exp Overnutrition/	220155
10	(nutrition or carbohydrate* or lipid* or protein* or vitamin* or mineral* or water or malnutrition or micronutrient* or overnutrition*).tw.	4679596
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	10173023
12	exp Immunity/	347477
13	exp Immune System/	1169945
14	(immune function* or immun*).tw.	2425140
15	12 or 13 or 14	3177108
16	exp Vaccines/	233302
17	exp Vaccination/	87313
18	vaccin*.tw.	325815
19	16 or 17 or 18	394419
20	exp "Systematic Review"/	145248
21	exp Meta-Analysis/	126381
22	(MEDLINE or (systematic and review)).ti,ab. or meta-analysis.pt.	336920
23	20 or 21 or 22	341461
24	11 and 15 and 19 and 23	464
25	limit 24 to (english language and humans and yr="2000 - Current")	399

medRxiv

9 Results
for term "nutrition AND immun* AND vaccin*
In category: Nutrition
[Variation words also searched: nutrition, micronutrient* malnutrition, vitamin*, mineral* overnutrition]

PubMed

Search: (nutrition OR malnutrition OR micronutrient* OR vitamin* OR mineral* OR overnutrition) AND (immunity OR immunosuppress* OR immun*) AND (vaccine* OR vaccination*)
Filters: Meta-Analysis, Systematic Review, English, from 2000/1/1 - 2021/2/28

Web of Science

(AB=(nutrition OR malnutrition OR micronutrient* OR vitamin* OR mineral* OR overnutrition) AND AB=(immunity OR immunosuppress* OR immun*) AND AB=(vaccine* OR vaccination*) AND ALL=(systematic review OR meta analysis)) *AND* LANGUAGE: (English)

Refined by: [excluding] DOCUMENT TYPES: (PROCEEDINGS PAPER OR EDITORIAL MATERIAL)

Indexes=SCI-EXPANDED, SSCI Timespan=2000-2021

Annex 6

Abbreviations

BMI	Body mass index
CS	Cross-sectional study
HAI	Hemagglutination-inhibition assay
HIC	High income country
LMIC	Lower- or middle-income country
MA	Meta-analysis
NMA	Network meta-analysis
OR	Odds Ratio
PCS	Prospective cohort study
SC	Seroconversion rate
SP	Seroprotection rate
SR	Systematic review

Table 8. Main characteristics of eligible systematic reviews or meta-analyses on nutrition and immune and vaccine response

Reference	Methods	Results	Comments
'Interventions to improve oral vaccine performance: a systematic review and meta-analysis' **(Church et al, 2019)** Study design SR with MA Funding/declarations of interest Wellcome Trust, Bill & Melinda Gates Foundation, UK Medical Research Council, WHO Polio Research Committee	Research question A systematic review and meta-analysis of interventions to increase oral vaccine efficacy or immunogenicity in LMICs [lower- and middle-income countries] Search criteria Search dates: up to Oct 23 2017 Study design: RCTs, cluster-RCTs, non-randomised trials and meta-analyses assessing ≥1 interventions Population: no restrictions on age or setting (even though review is targeted at children in LMICs) Intervention/exposure and comparators: interventions to improve oral vaccine performance Primary outcome **Oral vaccine performance** (defined as either vaccine efficacy or immunogenicity)	Included studies 87 studies (74 RCTs, 13 non-RCTs) included in qualitative synthesis, including 15 on micronutrients, 6 on withholding breastfeeding 66 studies included in the meta-analysis (5 on zinc, 5 on vitamin A, 5 on withholding breastfeeding) Most common oral vaccines studied: poliovirus, rotavirus, cholera, typhoid Study population - Infants to adults from 38 countries, mostly in Africa, South Asia, South-East Asia, South America - Vitamin A studies included in the MA: 4 estimates in children aged 0.8 months to 4.3 months from South Asia, Asia and Africa and 1 estimate in adults from South Asia - Zinc studies included in the MA: 6 estimates in children aged 0.3 to 40 months from South Asia - Withholding breastfeeding studies included in the MA: 6 estimates in children aged 1.4 to 14 months in South Asia and Africa Author's summary	Evidence aimed for application to infants and young children living in LMICs, even though 11/87 studies were conducted in adults Limitations from the review authors - Considerable heterogeneity (study design, interventions, sample characteristics, settings, vaccine types) - Vitamin A and zinc deficiency vary with age and setting and true deficiency may have been under-represented in the included trials - Limitation of using seroconversion as the primary outcome for the MA – does not always correlate with protection from disease - Potential publication bias identified in seven intervention categories (not including vitamin A, zinc and withholding breastfeeding) Limitations from the secretariat - Funding of primary studies not reported or considered

Reference	Methods	Results	Comments
		No evidence of effect for zinc, vitamin A, withholding breastfeeding. Overall, there was considerable heterogeneity between studies. -Zinc & withholding breastfeeding: significant residual heterogeneity not explained by vaccine type - Zinc: effect on vaccine response was significantly greater for older than for younger children (p=0.002).	

Reference	Methods	Results	Comments
'Interaction of obesity and infections' **(Dhurandhar et al, 2015)** Study design SR Funding/declarations of interest Lead author is a holder of several patents relating to viruses and viral obesity methods	Research question To review the available literature identifying infections that potentially contribute to greater body mass index BMI) and differential responses of overweight and obese persons to infections. Search criteria Search dates: January 1980 to July 2014 Study design: human studies Population: not specified Intervention/exposure and comparators: effects of infection/ effects of obesity Primary outcome **- Obesity status** (including body weight, fat mass, waist -circumference, waist to hip ratio) **- Immune response to antibacterial or vaccination, severity of infection, re-hospitalisation, wound infection etc.**	Included studies 343 studies included in qualitative synthesis (study design not reported) Study population Adults, adolescents and children Author's summary - Viral infection by human adenovirus Ad36 and antibiotic eradication of *Helicobacter pylori* were followed by weight gain. - People with overweight or obesity had higher susceptibility to developing post-surgical infections, H1N1 influenza and periodontal disease - More severe infections tended to be present in people with a larger BMI - People with a higher BMI had a reduced response to vaccinations and antimicrobial drugs • Obesity independently associated with poorly sustained seroconversion in response to vaccines - Higher doses of antibiotics were more effective in obese patients. - Infections may influence BMI, and BMI status may influence response to certain infections as well as to preventive and treatment measures.	Limitations from the review authors None identified Limitations from the secretariat - Consideration not given to the role of sex, socioeconomic status, settings, as potential confounders or independent risk factors - Analyses were not conducted separately on children and adults - No quality/risk of bias assessment of included studies

Reference	Methods	Results	Comments
'Mapping host-related correlates of influenza vaccine-induced immune response: an umbrella review of the available systematic reviews and meta-analyses' **(Domnich et al, 2019)** Study design SR of SRs and MAs Funding/declarations of interest The lead author is a full-time employee of Seqirus, an influenza vaccine company, although no financial support for this project was received from Seqirus or any other external source.	Research question To analyse the available systematic evidence on the host factors able to modify influenza vaccine-induced immunogenicity. Search criteria Search dates: up to 2 July 2019 Study design: systematic reviews and meta-analyses (or both) of experimental and observational studies (cohort and case control) Population: no restrictions Intervention/exposure: influenza vaccines (IV) of any type in individuals with a given health condition that could modify the IV-induced immune response Comparator: healthy controls who received a vaccine Primary outcome - **Influenza vaccine-induced immunogenicity.** Humoral immune response as measured by hemagglutination-inhibition assay (HAI) and associated statistical parameters: geometric mean titers (GMTs), seroconversion rate (SC), seroprotection rate (SP) The review authors also carried out their own meta-analyses based on primary data from the included studies.	Included studies 28 systematic reviews/meta-analyses or both experimental and observational studies (PCS and case-control) covering **vitamin D supplementation/deficiency** (1 review) among other (non-nutrition) topic areas Study population Children and adults.The SR with MA on vitamin D was conducted in individuals through the life-course. Author's summary **Vitamin D deficiency** - 1 SR with MA found that vaccinated subjects with vitamin D deficiency had a lower probability of being seroprotected against A/H3N2 and B (sub)types; no other significant (SP against A/H1N1 and SCs against all three strains) results emerged	1 SR on vitamin D (Lee et al 2018) was considered in SACN rapid scoping exercise in June 2020 Limitations from review authors - AMSTAR 2 ratings of included SRs/SRMAs were moderate to low Limitations from the secretariat - Consideration not given to the role of weight status in modifying immune response

Reference	Methods	Results	Comments
'Hepatitis B vaccine response in obesity: A meta-analysis' **(Fan et al 2016)** Study design MA Funding/declarations of interest None reported **(Fan et al, 2016; Parsons et al, 1999)(Fan et al, 2016; Parsons et al, 1999)(Fan et al, 2016; Parsons et al, 1999)(Fan et al, 2016; Parsons et al, 1999)(Fan et al, 2016; Parsons et al, 1999)**	Research question To further characterise the available evidence on the relationship between obesity and immune response to hepatitis B vaccine. Search criteria Search dates: January 1973 to November 2015 Study design: human studies Population: humans vaccinated with recombinant Hepatitis B vaccine, obese and non-obese Intervention/exposure: recombinant Hepatitis B vaccine given to humans, BMI used as a surrogate marker of obesity, vaccination programme with no less than 2 doses, administered intramuscular or intradermal injection only and immune response measurement Comparator: studies must include both obese and non-obese subjects Primary outcome **Immune response to hepatitis B vaccine with anti-HBs P10 IU/L (seroprotection)**	Included studies 16 studies: 3 cross-sectional studies, 7 cohort studies and 6 RCTs. Study population 5/16 studies conducted in healthcare workers (HCW), 1 study in children aged 12 years, the remaining in adults and/or children/adolescents from America, Oceania, Asia, Europe and Africa. Author's summary - Extracted data from 7 studies with uniform BMI cut-off value (BMI < 25, BMI: 25–30 and BMI > 30) found that individuals with a BMI of more than 25 were less prone to respond to Hepatitis B vaccination compared to those people with a BMI of less than 25. Risk of non-responsiveness of Hepatitis B vaccine among obese people increased with BMI values (p for the trend test: 0.003). - Extracted data from 3 studies with direct obtained OR values, that found non-responsiveness of Hepatitis B vaccination was significantly associated with obesity even after adjustment for testing time interval, ethnicity, sex, alcohol use, age, smoking status (adjusted OR: 2.46, 95% CI: 1.50–4.03). - Significant heterogeneity possibly explained by criteria of population selection and obesity definition. - No evidence of publication bias	Limitations from review authors - Inability to examine differences in vaccine response between children and adults - Did not examine vaccine response in infants Limitations from the secretariat - All MAs pooled data from mixed study designs – Impact of risk of bias of included studies in the MAs not investigated

Reference	Methods	Results	Comments
Enhancing immunity in viral infections, with special emphasis on COVID-19: A review (Jayawardena et al, 2020) Study design SR Funding/declarations of interest The authors received no external or internal funding for this study.	Research question: a systematic review to evaluate the highest quality evidence from clinical trials for both the prevention and treatment of viral diseases by means of nutritional interventions Search criteria Search dates: the databases were searched from their inceptions until 23rd March 2020 Study design: SR of RCTs Population: Humans Intervention/exposure and comparators*:* nutrition-based interventions (vitamin A, vitamin D, vitamin E, vitamin C, multi-nutrient supplements, zinc, selenium, copper, magnesium, nutraceuticals supplements,) Primary outcome: viral diseases (with special emphasis on respiratory infections)	39 RCTs were included (13 on vitamins, 8 on minerals, 18 on nutraceuticals) On the basis of the 39 studies, the authors concluded that vitamins A and D showed a potential benefit, especially in deficient populations, and that selenium and zinc had favourable immune-modulatory effects in viral respiratory infections. The authors concluded that taking high doses of vitamin C and E were inefficient in enhancing immunity, with the possible exception of vitamin E for viral hepatitis. They noted that most of included studies reported adverse effects of vitamin E supplementation on immune response. Author's summary: In addition to treating malnutrition and weight reduction in obese healthy subjects, this review highlights the potential preventive and therapeutic application of few vitamins, trace elements, and several nutraceuticals. In the current global context with limited movements, it is difficult to obtain a balanced and varied diet. Therefore, achieving recommended amounts of calories and micronutrient will be a challenge and elective micronutrient supplementations may be beneficial especially for vulnerable populations such as the elderly.	Limitations from review authors: meta-analysis was not been performed due to heterogenicity of studies, (especially in relation to reported outcomes). A large quantum of research on supplementation of different nutrients for patients with HIV infection was excluded as authors believed including clinical trials on HIV may dilute the message of the review. Quality assessment using the Jadad scale identified 13 studies (54%) had a score >3, indicating acceptable/good methodological quality. Reviewing the effects of exercise and stress on immune function was considered beyond the scope of the review.

Reference	Methods	Results	Comments
'Association of Childhood Obesity and the Immune System: A Systematic Review of Reviews' **(Kelishadi et al, 2017)** Study design SR of SRs Funding/declarations of interest None to declare	Research question - How does childhood obesity affect the immune system and the immune-mediated diseases, for example, asthma and allergy? How does it influence the functions of immune system? - How does childhood obesity affect the immune system protein products, for example, cytokines, and how changes of cytokines might affect different organs or different cells in the body? - How does childhood obesity affect the immune cells? - How does obesity-induced inflammation or other problems caused by obesity change the physiological state in the children's body to pathological state? Search criteria *Search dates:* October to December 2015. *Study design:* reviews (systematic, narrative or meta-analysis) *Population:* children, adolescents and/or mothers *Intervention/exposure and comparators:* relationship between childhood obesity/overweight and immunological factors. Primary outcome	Included studies 24 studies: 17 narrative reviews and 7 SR and MA (of PCS, CC, CS) Study population 7 SR and MA: children from birth to 18 years; countries/settings not reported 17 narrative reviews: age and settings not reported Author's summary - Obesity and overweight in infants and children might greatly affect the immune system by changing the immune cell responses and levels of cytokines. In turn, it may reduce the immune response to antigens or vaccines, or may alter the immunological response and inflammatory processes in a way that causes or worsens diseases or their symptoms, such as asthma and other related disorders - Obesity and overweight in infants and children might be associated with reduced immunological response and inflammatory processes, which might be related to worsening diseases or their symptoms such as asthma.	Limitations from review authors None reported Limitations from the secretariat - Studies examining relationship between obesity and immunogenicity to vaccines not specific to paediatric population, as some were conducted in adults - Potential confounders and independent risk factors not considered or discussed

Reference	Methods	Results	Comments
	Association of childhood overweight/obesity with the immune system.		
'Does serum 25-hydroxyvitamin D decrease during acute-phase response? A systematic review' **(Silva & Furlanetto, 2015)** Study design SR Funding/declarations of interest National Council for Scientific and Technological Development, Brazil; no conflicts of interest to declare	Research question To review the longitudinal studies that evaluated the association of acute-phase response with serum 25(OH)D levels during an inflammatory state. Search criteria *Search dates:* until January 2014 *Study design:* longitudinal studies *Population:* humans *Intervention/exposure and comparators:* acute inflammatory response (caused by a medical procedure or an acute illness) Primary outcome **Serum 25(OH)D** (at least 2 measurements (the first prior to the inflammatory insult or at its beginning and the second during follow-up)	Included studies 8 longitudinal studies (most were prospective, number not reported) C-reactive protein concentrations used as inflammatory markers in almost all included studies. Study population Population characteristics or settings not reported Author's summary - 25(OH)d dropped after an inflammatory insult (6 studies); this decrease was abrupt in the studies that measured 25(OH)D early after the insult - No change of 25(OH)D during the course of the disease, but baseline levels were measured in both after days of symptoms onset (2 studies) - Haemodilution decreased 25(OH)D, with no effect on inflammation (1 study) The metabolic meaning and functional importance of these changes are unknown. In light of the current evidence, the 25(OH)D measured during acute-phase response should be interpreted with care.	Limitations from the review authors - Heterogeneity: serum 25(OH)D measured at different moments, acute inflammatory response due to several causes - Possible selection bias as only studies published in English, Spanish and Portuguese were considered Limitations from the secretariat - No risk of bias/quality assessment of the included studies - No consideration of potential confounding by ethnicity, weight status, setting

Reference	Methods	Results	Comments
'Effects of non-pharmacological interventions as vaccine adjuvants in humans: a systematic review and network meta-analysis' **(Vedhara et al, 2020)** Study design SR and NMA Funding/declarations of interest Wellcome Career Re-entry Fellowship and Elizabeth Blackwell Institute for Health Research (University of Bristol) Wellcome Trust Institutional Strategic Support Fund	Research question To examine the effects of non-pharmacological adjuvants on vaccine effectiveness as measured by antibody responses to vaccination. Search criteria *Search dates:* up to 6 February 2018 *Study design:* comparative studies (randomised and non-randomised) *Population:* human adult, child and infants receiving any type of vaccine (in standard doses) *Intervention/exposure and comparators:* any intervention that targets a non-pharmacological parameter (e.g. diet, physical activity, mood) known to affect immunity Primary outcome **Antibody response to vaccination** (antibody titres, seroconversion, sero-protection)	Included studies 57 trials of dietary/nutritional interventions: - Vitamin and/or mineral treatments – mostly vitamin A and zinc (41 trials) - Nutritional formulae (6 trials) - Fatty acids (2 trials) - Other (8 trials) Only RCTs included in NMA. Study population Infants, children, adults, older adults (countries not reported) - Subgroup analyses were conducted based on age throughout the life-course and whether participants were at high or low risk of vaccination failure Author's summary 52% of trials reported some evidence of a statistically significant improvement in the antibody response to vaccination in the intervention vs control groups 42% of trials showed no significant effect 6% of trials showed evidence that their intervention significantly impaired/reduced antibody response NMA **Antibody titres** (SMD)	Limitations from the review authors - High heterogeneity in interventions and population characteristics - Subgroup analyses, meta-regression and sensitivity analyses unable to reduce heterogeneity - Considerable variability in ways the primary outcome (antibody response) was measured and at what time points - Not possible to determine participant adherence or intervention fidelity in some trials Limitations from the secretariat - Publication bias not investigated - Funding of primary studies not reported or considered - Did not consider the influence of weight status in modifying immunogenicity - Did not consider the role that baseline nutritional status might have in modifying effect of nutritional supplementation on vaccine response

Reference	Methods	Results	Comments
		- Vitamins & minerals -0.14 (95% CI -0.68 to 0.39) - Nutritional formulae 0.99 (95% CI -0.09 to 2.08) • In those at high risk of vaccine failure 1.303 (95% CI 0.01 to 2.62) **Seroconversion** (log OR) - Vitamins & minerals 0.08 (95% CI -0.20 to 0.37) - Nutritional formulae 0.30 (95% CI -0.39 to 1.08) • In those at high risk of vaccine failure 0.77 (95% CI 0.10 to 1.44) **Sero-protection** (log OR) - Vitamins & minerals -0.07 (95% CI -0.47 to 0.31) - Nutritional formulae 1.37 (95% CI -0.16 to 2.99) The NMA found no evidence that the effects of (all explored) non-pharmacological interventions varied significantly between different vaccines or age ranges although this may be due to insufficient data.	

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