Barts and The London
Queen Mary's School of Medicine and Dentistry

Centre for Primary Care and Public Health
Barts and The London School of Medicine and Dentistry
Queen Mary, University of London
58 Turner Street
London E1 2AB
United Kingdom

Tel: +44 (0)207 882 2551
Fax: +44 (0) 207 882 2552

a.martineau@qmul.ac.uk

22nd September 2015

Professor Hilary Powers, BSc PhD RNutr
Chair, Vitamin D Working Group
Scientific Advisory Committee on Nutrition

sacn@phe.gov.uk

Dear Hilary,

Re: **Draft Vitamin D and Health report**

I am writing in response to the call for comments on the above report.

I would like to congratulate you and your working group on the production of a comprehensive report. In particular, I welcome SACN's acknowledgement that sunlight is insufficient to reliably provide adequate year-round vitamin D to the UK population, and the subsequent recommendation that a reference nutrient intake (RNI) of 10 micrograms vitamin D per day should now be extended to the UK adult population. If successfully implemented, this will have very significant positive effects on the UK population's health.

My own reading of the literature suggests that we should be aiming to elevate serum 25(OH)D concentrations >50 nmol/L (a threshold for adequate vitamin D status that is more broadly accepted internationally), rather than the more modest 25 nmol/L threshold that the Working Group proposes. Consequently, my preference would have been to see a RNI of 15 micrograms vitamin D or more in the adult population, to bring UK recommendations into line with those in the US. However, I welcome SACN's recommendation as a significant move in the right direction, and I anticipate that it will act as a driver towards introduction of effective vitamin D fortification in this country.

I have a few specific comments on the report, most of which relate to my field of primary interest, namely the effects of vitamin D on immune function:

Paragraph 9: Methodology. Were Mendelian randomisation studies included in the review? These studies can provide strong evidence for / against causality, as they are much less subject to confounding than other observational studies. They may have particular value in guiding recommendations where clinical trials may be impractical conduct, e.g. in the prevention of multiple sclerosis. [1] I would therefore urge the Working Group to make an explicit commitment to considering evidence from such studies in your final report.

Paragraph 437: 'Autoimmune disease is characterised by the production of antibodies against the body's own tissues'. Not all autoimmune disease is antibody-mediated – this is just a sub-set of autoimmune disease. Many of the autoimmune diseases cited in the report are T cell-mediated for example.

Paragraph 438: Asthma is not an autoimmune disease – it is an allergic / atopic disorder.

Paragraphs 457-60, Multiple sclerosis: here and elsewhere the report does not seem to have taken account of Mendelian randomisation studies. I would like to highlight one such study in particular, as it has been published since your Draft Report was issued. [1]

Paragraph 471: Liu *et al* (and indeed other investigators, including myself) have not demonstrated that cathelicidin kills *Mycobacterium tuberculosis*; rather, it restricts growth of the bacillus. [2]

Paragraph 475: 'Evidence is lacking on whether vitamin D supplementation can influence the risk of developing infectious disease.' I would question this statement; for example, 22 RCTs enrolling a total of 10,717 patients have now investigated the question of whether vitamin D can prevent acute respiratory infection (ARI).[3-24]

We have recently conducted an individual patient data meta-analysis of these trials, for which the manuscript is in preparation. Key findings are that vitamin D is protective against ARI in all participants (OR 0.88, 95% CI 0.80 to 0.95, P=0.003), and that protective efficacy is greater among individuals with baseline 25(OH)D concentrations <25 nmol/L (OR 0.56, 95% CI 0.41 to 0.76, P<0.001), and on those who receive daily/weekly dosing vs. less frequent dosing (OR for daily/weekly dosing sub-group 0.81, 95% CI 0.72 to 0.91, P<0.001). Preparation of this manuscript is underway, but I would hope that Results may be citeable, at least in abstract form, in time for the publication of your definitive report. Do let me know if you would like to cite this work in the final report.

Paragraph 476: The cited study by Reid *et al* [25] reports effects of knee surgery on 25(OH)D levels; its findings have questionable relevance (if any) for the field of infectious diseases. Studies in infectious disease have suggested that 25(OH)D levels do not fluctuate in response to infection. [26]

Paragraph 477: ‘A person exposed to TB will not necessarily develop the disease as the immune system is usually able to destroy the bacteria’. The evidence supporting this statement is very limited. It would be more accurate to say that ‘a minority of individuals may be able to resist infection’. [27]

Paragraph 478: ‘No RCTs of vitamin D supplementation for the prevention of active TB in those with a latent infection could be identified’. One such trial is in progress: https://clinicaltrials.gov/ct2/show/NCT01798680 . One trial has been conducted to determine whether vitamin D can prevent LTBI. [28] One n=8,020 Phase 3 RCT testing this hypothesis is currently recruiting: https://clinicaltrials.gov/ct2/show/NCT02276755

Paragraph 481: the cited study by Arnedo-Pena *et al* [29] investigated acquisition of latent TB infection, not incidence of TB (which is universally understood to mean active TB disease as opposed to latent TB infection). The wording here therefore needs correction. There are at least two prospective studies examining the association between vitamin D status and subsequent risk of active TB which could be cited. [30 31]

Paragraph 482: this would be the appropriate place to cite the study by Arnedo-Pena et al, currently mentioned in paragraph 481. [29]

P83, ‘Respiratory tract infections’ should be retitled ‘acute respiratory tract infections’ (tuberculosis is a chronic respiratory tract infection, but is dealt with in a different section)

Paragraph 485: the authors might want to mention the vocal cords as being classically regarded as the cut-off between URI and LRI.

Paragraph 488: it’s not clear to me why the Rees study is cited specifically here – there are 22 published trials in this field, some positive, some null and some negative. See above for reference list and results of a recently completed meta-analysis.

Paragraph 495: There are at least two observational studies which investigate whether vitamin D status associates with risk of COPD. [32, 33]

.

Paragraph 496: this paragraph does not acknowledge the large volume of RCTs of vitamin D for the prevention of acute respiratory infection in the general population – see above.

Paragraph 497: ‘autoimmune disease risk’ – do the authors mean ‘infectious disease risk’ here?

Paragraph 498: this statement does not acknowledge the existence of the RCT by Ganmaa et al.[28]

Paragraph 500: There are observational studies which investigate whether vitamin D status associates with risk of COPD. [32, 33]

It's not clear to me why COPD has been included in the infectious diseases section: it's a non-communicable disease caused primarily by exposure to smoke.

I hope these comments are of some use, and I look forward to reading the final report next year.

Best wishes

Adrian Martineau, B Med Sci, MB BS, DTM&H, MRCP(UK), PhD
Professor of Respiratory Infection and Immunity

## References

1. Mokry LE, Ross S, Ahmad OS, Forgetta V, Smith GD, Leong A, et al. Vitamin D and Risk of Multiple Sclerosis: A Mendelian Randomization Study. PLoS Med. 2015; **12**(8): e1001866.
2. Martineau AR, Wilkinson KA, Newton SM, Floto RA, Norman AW, Skolimowska K, et al. IFN-γ- and TNF-Independent Vitamin D-Inducible Human Suppression of Mycobacteria: The Role of Cathelicidin LL-37. J Immunol. 2007; **178**(11): 7190-8.
3. Bergman P, Norlin AC, Hansen S, Rekha RS, Agerberth B, Bjorkhem-Bergman L, et al. Vitamin D3 supplementation in patients with frequent respiratory tract infections: a randomised and double-blind intervention study. BMJ Open. 2012; **2**(6): e001663.
4. Camargo CA, Jr., Ganmaa D, Frazier AL, Kirchberg FF, Stuart JJ, Kleinman K, et al. Randomized trial of vitamin d supplementation and risk of acute respiratory infection in mongolia. Pediatrics. 2012; **130**(3): e561-7.
5. Dubnov-Raz G, Rinat B, Hemila H, Choleva L, Cohen AH, Constantini NW. Vitamin D supplementation and upper respiratory tract infections in adolescent swimmers: a randomized controlled trial. Pediatric exercise science. 2015; **27**(1): 113-9.
6. Goodall EC, Granados AC, Luinstra K, Pullenayegum E, Coleman BL, Loeb M, et al. Vitamin D3 and gargling for the prevention of upper respiratory tract infections: a randomized controlled trial. BMC infectious diseases. 2014; **14**: 273.
7. Grant CC, Kaur S, Waymouth E, Mitchell EA, Scragg R, Ekeroma A, et al. Reduced primary care respiratory infection visits following pregnancy and infancy vitamin D supplementation: a randomised controlled trial. Acta Paediatr. 2014.
8. Kumar GT, Sachdev HS, Chellani H, Rehman AM, Singh V, Arora H, et al. Effect of weekly vitamin D supplements on mortality, morbidity, and growth of low birthweight term infants in India up to age 6 months: randomised controlled trial. BMJ. 2011; **342**: d2975.
9. Laaksi I, Ruohola JP, Mattila V, Auvinen A, Ylikomi T, Pihlajamaki H. Vitamin D supplementation for the prevention of acute respiratory tract infection: a randomized, double-blinded trial among young Finnish men. J Infect Dis. 2010; **202**(5): 809-14.
10. Lehouck A, Mathieu C, Carremans C, Baeke F, Verhaegen J, Van Eldere J, et al. High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2012; **156**(2): 105-14.

11. Li-Ng M, Aloia JF, Pollack S, Cunha BA, Mikhail M, Yeh J, et al. A randomized controlled trial of vitamin D3 supplementation for the prevention of symptomatic upper respiratory tract infections. Epidemiol Infect. 2009; **137**(10): 1396-404.
12. Majak P, Olszowiec-Chlebna M, Smejda K, Stelmach I. Vitamin D supplementation in children may prevent asthma exacerbation triggered by acute respiratory infection. J Allergy Clin Immunol. 2011; **127**(5): 1294-6.
13. Manaseki-Holland S, Maroof Z, Bruce J, Mughal MZ, Masher MI, Bhutta ZA, et al. Effect on the incidence of pneumonia of vitamin D supplementation by quarterly bolus dose to infants in Kabul: a randomised controlled superiority trial. Lancet. 2012; **379**(9824): 1419-27.
14. Manaseki-Holland S, Qader G, Isaq Masher M, Bruce J, Zulf Mughal M, Chandramohan D, et al. Effects of vitamin D supplementation to children diagnosed with pneumonia in Kabul: a randomised controlled trial. Trop Med Int Health. 2010; **15**(10): 1148-55.
15. Marchisio P, Consonni D, Baggi E, Zampiero A, Bianchini S, Terranova L, et al. Vitamin D supplementation reduces the risk of acute otitis media in otitis-prone children. Pediatr Infect Dis J. 2013; **32**(10): 1055-60.
16. Martineau AR, Hanifa Y, Witt KD, Barnes NC, Hooper RL, Patel M, et al. Double-blind randomised controlled trial of vitamin D3 supplementation for the prevention of acute respiratory infection in older adults and their carers (ViDiFlu). Thorax. 2015.
17. Martineau AR, James WY, Hooper RL, Barnes NC, Jolliffe DA, Greiller CL, et al. Vitamin D3 supplementation in patients with chronic obstructive pulmonary disease (ViDiCO): a multicentre, double-blind, randomised controlled trial. The lancet Respiratory medicine. 2015; **3**(2): 120-30.
18. Martineau AR, MacLaughlin BD, Hooper RL, Barnes NC, Jolliffe DA, Greiller CL, et al. Double-blind randomised placebo-controlled trial of bolus-dose vitamin D3 supplementation in adults with asthma (ViDiAs). Thorax. 2015; **70**(5): 451-7.
19. Murdoch DR, Slow S, Chambers ST, Jennings LC, Stewart AW, Priest PC, et al. Effect of vitamin D3 supplementation on upper respiratory tract infections in healthy adults: the VIDARIS randomized controlled trial. JAMA. 2012; **308**(13): 1333-9.
20. Rees JR, Hendricks K, Barry EL, Peacock JL, Mott LA, Sandler RS, et al. Vitamin D3 Supplementation and Upper Respiratory Tract Infections in a Randomized, Controlled Trial. Clin Infect Dis. 2013.
21. Simpson SJ, van der Mei I, Stewart N, Blizzard L, Tettey P, Taylor B. Weekly cholecalciferol supplementation results in significant reductions in infection risk among the vitamin D deficient: results from the CIPRIS pilot RCT. BMC Nutrition. 2015; **1**(7).
22. Tran B, Armstrong BK, Ebeling PR, English DR, Kimlin MG, van der Pols JC, et al. Effect of vitamin D supplementation on antibiotic use: a randomized controlled trial. Am J Clin Nutr. 2014; **99**(1): 156-61.
23. Urashima M, Mezawa H, Noya M, Camargo CA, Jr. Effects of vitamin D supplements on influenza A illness during the 2009 H1N1 pandemic: a randomized controlled trial. Food & function. 2014; **5**(9): 2365-70.
24. Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. Am J Clin Nutr. 2010; **91**(5): 1255-60.
25. Reid D, Toole BJ, Knox S, Talwar D, Harten J, O'Reilly DS, et al. The relation between acute changes in the systemic inflammatory response and plasma 25-hydroxyvitamin D concentrations after elective knee arthroplasty. Am J Clin Nutr. 2011; **93**(5): 1006-11.
26. Newens K, Filteau S, Tomkins A. Plasma 25-hydroxyvitamin D does not vary over the course of a malarial infection. Trans R Soc Trop Med Hyg. 2006; **100**(1): 41-4.
27. Cassidy JP, Martineau AR. Innate Resistance to Tuberculosis in Man, Cattle and Laboratory Animal Models: Nipping Disease in the Bud? Journal of comparative pathology. 2014.

28. Ganmaa D, Giovannucci E, Bloom BR, Fawzi W, Burr W, Batbaatar D, et al. Vitamin D, tuberculin skin test conversion, and latent tuberculosis in Mongolian school-age children: a randomized, double-blind, placebo-controlled feasibility trial. Am J Clin Nutr. 2012; **96**(2): 391-6.
29. Arnedo-Pena A, Juan-Cerdan JV, Romeu-Garcia MA, Garcia-Ferrer D, Holguin-Gomez R, Iborra-Millet J, et al. Vitamin D status and incidence of tuberculosis infection conversion in contacts of pulmonary tuberculosis patients: a prospective cohort study. Epidemiol Infect. 2015; **143**(8): 1731-41.
30. Talat N, Perry S, Parsonnet J, Dawood G, Hussain R. Vitamin D deficiency and tuberculosis progression. Emerging infectious diseases. 2010; **16**(5): 853-5.
31. Sudfeld CR, Giovannucci EL, Isanaka S, Aboud S, Mugusi FM, Wang M, et al. Vitamin D status and incidence of pulmonary tuberculosis, opportunistic infections, and wasting among HIV-infected Tanzanian adults initiating antiretroviral therapy. J Infect Dis. 2013; **207**(3): 378-85.
32. Black PN, Scragg R. Relationship between serum 25-hydroxyvitamin D and pulmonary function in the third national health and nutrition examination survey. Chest. 2005; **128**(6): 3792-8.
33. Shaheen SO, Jameson KA, Robinson SM, Boucher BJ, Syddall HE, Sayer AA, et al. Relationship of vitamin D status to adult lung function and COPD. Thorax. 2011; **66**(8): 692-8.