# Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

**ScriptSwitch™ Rapid Update 1 – March 2017**

## Vitamin D to prevent acute respiratory tract infections

There has been considerable interest in the use of vitamin D supplementation to improve other health outcomes beyond its role in maintaining healthy bone; trials looking at whether it can prevent respiratory infections have conflicting findings. This systematic review and meta-analysis set out to draw together all the data from studies looking at the effect of vitamin D on acute respiratory tract infections. The authors argue that the findings show that Vitamin D supplementation protects against colds, flu, bronchitis and pneumonia, and is safe. Patients who were very vitamin D deficient showed the most benefit. The benefits were seen with daily or weekly doses but not large 'one off' doses. The head of nutrition science for Public Health England has advised that these findings are not robust enough to change practice.

**Reference:** Martineau AR, Jolliffe DA, Hooper RL, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ 2017;356:i6583.

### What do we know already?

- In July 2016, new Public Health England (PHE) guidelines on vitamin D recommended taking a daily dietary supplement of 10micrograms of vitamin D for all adults during autumn and winter. People who might not get adequate sun exposure in spring and summer, and certain ethnic groups, should continue taking this all year round. Also children aged one to four years old should be given a daily supplement containing 10micrograms of vitamin D. This is to keep bones, teeth and muscles healthy.
- People can buy single vitamin D supplements or vitamin drops containing vitamin D (for use by under-fives) at most pharmacies and supermarkets. Women and children who qualify for the Healthy Start scheme can get free supplements containing the recommended amounts of vitamin D.
- Randomised controlled trials of vitamin D supplementation for the prevention of respiratory infections have yielded conflicting results. These trials have shown considerable heterogeneity; for example, the definition of respiratory infection outcomes used in the studies varied greatly.
- Individual participant data (IPD) meta-analysis has the potential to reduce heterogeneity, and to identify factors that may explain this heterogeneity, but this had not previously been performed.

### What does this evidence add?

- This study showed an overall protective effect of vitamin D supplementation against acute respiratory tract infection: number needed to treat **(NNT) = 33, duration not stated.**
- Benefit was greater in those receiving daily or weekly vitamin D **(NNT = 20, duration not stated),** and the protective effects against acute respiratory tract infection in this group were strongest in those with profound vitamin D deficiency at baseline **(NNT = 4, duration not stated).**
- Because of the broad range of outcomes, these NNTs may not be as favourable as they at first appear; for example, because there was not enough antibiotic use, pneumonia or hospitalisation events, it is not possible to say if clinically significant outcomes were prevented (the meta-analysis is underpowered for these rarer outcomes).
- The researchers argue that these findings support the introduction of public health measures, such as food fortification, to improve vitamin D status, particularly in settings where profound vitamin D deficiency is common.
- This has been disputed and the nutritional lead from Public Health England has advised that the evidence is still inconsistent, and should not change guidance or lead to greater food fortification. However, people with low vitamin D levels should receive supplementation if the guidance is followed, in any case.

- The main criticisms of this study are: the results still showed heterogeneity, despite the use of individual participant data; it was underpowered for some subgroups; publication bias was an issue; also, data related to adherence to vitamin D were not available.
- Therefore, for present it seems sensible to follow the PHE guidance on vitamin D supplementation. Patients should be informed this is for bone and muscle benefits, and that it remains unclear if this will prevent respiratory infection. This would be highly unlikely to cause harm.
- Large scale randomised controlled studies are still needed to confirm the findings suggested in this study; apparently some of these are underway.

## Study details

**Participants:**

- 720 studies were initially identified from four main data sources.
- After assessment for duplication 532 studies were scrutinised for eligibility and quality.
- A total of 25 eligible randomised controlled trials were identified.
  - These included 11,321 participants.
  - Individual participant data (IPD) were obtained for 10, 933 (96.6%) participants aged 0 to 95 years.
  - These studies were from 14 countries, including three from the UK.
- The body of evidence contributing to this meta-analysis was assessed as being of high quality.

**Intervention and comparison:**

- The eligibility criteria for study selection were randomised, double blind, placebo controlled trials of supplementation with vitamin $D_3$ or vitamin $D_2$ of any duration, which had been approved by a research ethics committee.
- Importantly, data on incidence of acute respiratory tract infection had to have been collected prospectively and pre-specified as an efficacy outcome (not reported as incidental findings).
- Meta-analysis was conducted looking at variables such as baseline vitamin D levels, dosing (one-off/bolus or daily dosing), age, body mass index, asthma, COPD and prior influenza vaccination.

**Outcomes and results:**

- Overall vitamin D supplementation reduced the risk of at least one acute respiratory tract infection among all participants by 12% compared to placebo (adjusted odds ratio 0.88, 95% confidence interval [CI] 0.81 to 0.96; P = 0.003; P for heterogeneity < 0.001; **NNT = 33**, 95% CI: 20 to 101; 10,933 participants in 25 studies).
- **Trial duration was not specified for NNTs** so it is unclear how these were calculated (or how they should be interpreted).
- In subgroup analysis:
  - A protective effect against acute respiratory tract infection was seen where vitamin D was administered using a daily or weekly regimen without additional bolus doses (adjusted odds ratio 0.81, 95% CI: 0.72 to 0.91; **NNT = 20**, 95% CI: 13 to 43; 5,133 participants in 15 studies; within subgroup P < 0.001)**.**
  - No protective effect was seen among participants in trials where at least one bolus dose of vitamin D was administered (adjusted odds ratio 0.97, 95%CI: 0.86 to 1.10; 5,800 participants in 10 studies; within subgroup P = 0.67; P for interaction 0.05).
  - Looking at *all* vitamin D interventions, protective effects were seen in those with very low baseline circulating 25-hydroxyvitamin D (levels less than 25 nmol/L) (adjusted odds ratio 0.58, 95% CI: 0.40 to 0.82, **NNT = 8**, 95% CI: 5 to 21; 538 participants in 14 studies; within subgroup P = 0.002).
  - Looking at *only* daily or weekly vitamin D treatment, the protective effects were greatest in those participants with very low baseline circulating 25-hydroxyvitamin D concentrations (less than 25 nmol/L), (adjusted odds ratio 0.30, 95% CI: 0.17 to 0.53; **NNT = 4**, 95% CI: 3 to 7; 2,234 participants in six studies; within subgroup P < 0.001.
- With regard to safety, use of vitamin D did not influence risk of serious adverse events of any cause (adjusted odds ratio 0.98, 95% CI: 0.80 to 1.20, P = 0.83), or death due to any cause (adjusted odd ratio 1.39, 95% CI: 0.85 to 2.27; P = 0.18) in the 11,224 participants in the 25 eligible studies.

**Level of evidence:**
Level 1 (good quality patient-oriented evidence) according to the **SORT criteria.**

**Study funding:**
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