Meta-analysis on vitamin C and the common cold in children may be misleading

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We are authors of a large Cochrane review on vitamin C and the common cold [1]. Our review includes 63 parallel comparisons of vitamin C and placebo reported in 44 publications [1]. We drew several conclusions from the large set of trials. However, there may be issues that we did not cover, and further analysis of the large set of data is welcome. In this journal, Vorilhon et al. reported a meta-analysis in which they examined the effect of vitamin C on common cold in children [2]. However, we do not consider that their conclusions are valid. Our main concerns are summarized below. We include further issues and details in a supplementary file.

1. The authors stated "*All trials ... comparing the use of vitamin C against placebo were selected*" [2]. However, one of the included trials administered vitamin C with echinacea and propolis [3]. That trial showed significant preventive effects in Vorilhon's Figure 2, and by far the greatest effects on the duration of colds in their Figure 3. However, there is no basis to attribute the observed benefits to vitamin C specifically. For example, one review concluded that "*prophylactic treatment with Echinacea products was associated with a reduced risk of experiencing a cold ... P < 0.001*" [4]. Propolis may also influence the immune system. A meta-analysis on vitamin C should be restricted to trials of vitamin C only [1].

2. Vorilhon wrote that "*All trials qualifying as randomized clinical trials (RCTs) ... were selected.*" However, Coulehan (1974) used alternative allocation rather than randomization: "*All children were assigned alternately, from an alphabetical listing by classroom, to one of two study groups*" [5, p 7]. In the Cochrane Handbook, which was also cited by Vorilhon [2], alternative allocation is classified as an "*inadequate method of sequence generation*" [6]. Thus, if the meta-analysis is restricted to randomized trials, Coulehan (1974) should be excluded. If the Coulehan (1974) study is included, the review should not state that it was restricted to randomized trials.

3. Ludvigsson et al. reported two separate controlled trials [7], but Vorilhon [2] did not include the smaller "pilot" trial, although the number of participants was higher (N = 158) in that excluded trial than in three other trials that were included (N = 39 to 88). In the supplementary file by Vorilhon, the Coulehan (1976) study [8] is both excluded and included; and in their Figure 2 it is included whereas in their Figure 3 it is excluded although Coulehan published the outcomes shown in both figures. No justification is given for these inconsistencies [2].

4. Vorilhon [2] gave SD values for three comparisons from two trial reports [5,9] without any description of the source of those SD values. The original reports did not publish SD values. Although it is appropriate to impute SD values [6], the methods should be described if imputation is used. Furthermore, for the Ritzel trial Vorilhon gave SD values that led to P = 0.238 in their Figure

3. However, Ritzel stated that the study groups significantly deviated one from another with ”*P < 0.05; t-distribution*” [9]. Thus, the SD values used by Vorilhon are incompatible with the Ritzel trial report.

5. In the Results section, Vorilhon wrote: “*the duration of URTI was decreased by 1.6 days (26%) in the vitamin C group*” [2]. The calculation of this result was not reported. Figure 3 is the forest plot for the analysis of cold duration on the SMD (standardized mean difference) scale, which means the calculation of the vitamin C effect in SD units. However, the effect in SD units does not transform to an effect in days or %-units.

6. The assessment of methodological quality was inconsistent. In Table 2, Vorilhon put a question mark for “incomplete outcome data” for the Ludvigsson trial, which indicates that there is potential bias. Ludvigsson reported that 96% (615/642) of participants who took part, continued to the end of the “main” trial [7]. In contrast, Vorilhon did not question the Coulehan (1974) trial, which reported “*Six hundred and forty-one of the 666 children (96 per cent) completed the entire 14-week study period*” [5, p. 7]. These two trials had identical dropout rates, but they were assessed differently.

7. Vorilhon et al. allege our 2013 review [1] had limitations. In the introduction [2, p. 304], they refer to our review as follows: ”*A meta-analysis from 2013 assessed the efficacy of vitamin C for prevention and treatment of the common cold, but the review had limitations: ... it included one trial that contained manifestly incorrect data.*” However, Vorilhon did not explain what they meant by that statement, which particular trial “contained manifestly incorrect data”, or how the data was incorrect. This is a strong accusation about the validity of our review which we consider is unjustified.

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