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Commentary

Commentaries on 'Vitamin C for preventing and treating the common cold' with responses from the review author

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These are commentaries on a Cochrane review, published in this issue of EBCH, first published as: Douglas RM, Hemilä H, Chalker E, Treacy B. Vitamin C for preventing and treating the common cold. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD000980. DOI: 10.1002/14651858.CD000980.pub3.

Further information for this Cochrane review is available in this issue of EBCH in the accompanying EBCH Summary and Characteristics and Key Findings Tables.

Larissa Shamseer and Sunita Vohra's Commentary

Despite dozens of clinical studies with conflicting or inconclusive results, vitamin C is frequently touted as the natural 'fix' for upper respiratory tract infections (URTI). In their recent Cochrane systematic review, Douglas *et al*. (1) report that while prophylactic vitamin C did not significantly reduce the incidence or severity of the common cold, it reduced mean cold duration by 8% in adults [95% Confidence Intervals (CI) 3–13%] and 13.6% in children (95% CI 5–22%). When used as treatment, vitamin C was reported to have no significant effect on duration or severity of URTI.

The common cold affects people worldwide and is likely the most common illness known. There is no known cure and it is associated with substantial economic loss (2). The incidence and prevalence of the common cold are difficult to estimate as most affected do not seek medical care, making tracking through health care utilization difficult. While the use of conventional over-the-counter medications may be easily measured using financial reports, utilization of natural health products (NHPs) is more challenging since a given product may have multiple potential clinical indications. In Canada, NHPs are defined as vitamins, minerals, herbal remedies, homeopathic remedies, traditional medicines, probiotics and other products like amino acids and essential fatty acids that are manufactured, sold, or represented for use in the diagnosis, treatment or prevention of a disease or disorder, for restoring or correcting organic functions or for modifying organic functions in a manner that maintains and/or promotes health (3). NHPs are most often used by the public as self-care and interest into their safety and efficacy is increasing: to date there have been at least five published Cochrane protocols or completed reviews on NHPs for the common cold (1,4–7).

This large and timely review addresses the important question of whether oral doses of 0.2 g or more daily of vitamin C reduce the incidence, duration or severity of the common cold when used either as continuous prophylaxis or after the onset of symptoms. To aid in interpretation of these findings, we would like to draw attention to three key variables in the review: study inclusion criteria, choice of databases searched, and the generalizability of the included studies. The authors' decision to limit included trials to those that could be 'methodologically assessed using the Jadad quality score' is unusual, since virtually any trial should be assessable using the Jadad scale. Although they state that 'study quality was not used as an exclusion criterion', nor were any trials excluded on this basis, it is worth noting that 46 out of 56 included studies were on the mid-high end of the quality continuum with Jadad quality ratings ≥ 3 (8). Choice of included studies is difficult to interpret due to the absence of assessment or discussion of publication bias.

Publication bias is particularly important to assess in studies of complementary and alternative medicine (CAM), an umbrella term which includes NHPs.

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Unlike conventional medicine, in which high quality, positive findings are most frequently published in leading, high-impact journals (9), the reverse occurs in CAM research: high quality, negative studies are more likely to get published in the same journals (10–12). Further, it is well-known that CAM journals are less likely to be indexed in mainstream databases, such as those examined in this review, than conventional medical journals (13). In fact, one study examining publication location of CAM RCTs found that the Commonwealth Agriculturall Bureaux (CAB Health), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Allied and Complementary Medicine Database (AMED) databases contain unique material not available from MEDLINE and EMBASE (14). None of the included studies in this review are from CAM journals; all are from conventional medical journals, the majority of which are higher impact journals. This may mean that more studies with negative results have been systematically included for analysis, thereby contributing to the lack of significant positive effect for all but one primary outcome. The authors also failed to mention whether foreign language studies were sought, identified, or included in the review, also potentially contributing to publication bias. Unfortunately, the absence of a funnel plot to delineate if and where publication bias exists, and the choice of databases searched for this review renders its findings difficult to interpret.

The findings of this review are particularly important to children, given their high prevalence of the common cold and pediatric NHP use in North America. The Center for Disease Control and Prevention estimates that there is an annual loss of 22 million school days due to the common cold in the United States (15). The National Institute of Allergy and Infectious Disease estimates that children experience between 6 and 10 colds per year, likely due to their close proximity in the school setting (16). With regards to NHP utilization, use among children is widespread – up to 35% reportedly use NHPs, most commonly vitamins and botanical products (17,18). By 2005, at least 24 RCTs of vitamin C for illnesses including the common cold had been identified in populations including children (19). Therefore it is quite evident that vitamin C is already of high interest and use in pediatric populations. Douglas *et al*. presented subgroup analysis for children for only one of five primary outcomes (i.e. the effect of vitamin C administered before cold onset on duration), when all would have been of potential interest and relevance to this population.

Finally, it is important to note that the included trials were primarily conducted in developed countries, perhaps representing differences in terminology used to describe the common cold worldwide. Given the differences in nutritional status between developing countries and those included in the review, caution should be applied when generalizing its results.

Overall, the findings of the review demonstrate that in developed countries, vitamin C may not prevent the common cold, but may have a modest effect in reducing cold duration when taken prophylactically. For a benign self-limited condition such as the common cold, careful consideration of the risk : benefit ratio is warranted. Its effect seems most promising in as prophylaxis in very physically active individuals. For the general population, if vitamin C's only effect is a modest reduction in the duration of cold symptoms, and to achieve this effect, a daily prophylactic dose is required, it may not warrant further consideration. A definitive answer may require additional well-designed trials in this area, particularly those that examine for potential dose-effect, as a recurring criticism of NHP research is the study of inappropriate doses, leading to erroneous conclusions about efficacy. Future systematic reviews should include a broader range of databases, inclusion of CAM journals and careful examination for the effects of publication bias. In the absence of such data, given the modest effect sizes currently reported, it is premature to prescribe vitamin C to prevent or treat URTI.

Declaration of Interest

Sunita Vohra receives salary support from the Alberta Heritage Foundation for Medical Research and the Canadian Institutes of Health Research.

Response from the Review Author to the Commentary by Shamseer and Vohra

I share Shamseer and Vohra's concern about publication bias in the leading medical journals. For example, in 1975 the *American Journal of Medicine* published a highly influential review on vitamin C and the common cold by Thomas Chalmers (20). When I became interested in the same topic, I was puzzled by the great discrepancy between the original trial reports and Chalmers' selection and description of them. I wrote a critique of Chalmers' review, but my paper was rejected by the same journal and it was published in a minor journal (21,22). Obviously, the leading journals must be highly selective in the acceptance of papers, but that leads to bias in reports reaching wide readerships.

Nevertheless, I do not agree that publication bias might substantially affect the main conclusions of our Cochrane review (1). We drew several conclusions and they should be considered individually. We concluded that there is strong evidence of heterogeneity in the effect of vitamin C on common cold incidence. Vitamin C halved the number of colds in participants under heavy acute physical stress, but had no effect on the incidence of colds in the general community. How could such heterogeneity be generated by publication bias? Furthermore, based on 30 trials with 9,676

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recorded common cold episodes in all, we concluded that regular vitamin C supplementation shortens the duration of colds. The proposal that this effect is explained by publication bias presumes that several large trials with negative findings remain unpublished, which does not seem a reasonable assumption. Publication bias may affect the point estimates of our analyses, but it is unlikely to affect our main conclusions.

Shamseer and Vohra comment that we might have included more data bases in our literature searches. However, even though MEDLINE and EMBASE can miss some trials published in CAM journals, we also searched the Cochrane CENTRAL which collects trials independent of them being recorded in MEDLINE or EMBASE. Furthermore, we describe in the Cochrane review that I have been actively collecting literature on vitamin C and common cold trials for over two decades. Because of my familiarity with the literature, I pointed out that an extensive literature search (23,24) had missed six placebo-controlled trials (25). If Shamseer and Vohra consider that we may have missed relevant trials, they should search and describe examples instead of just speculating. Furthermore, as described above, our main conclusions are not sensitive to a few unidentified or unpublished trials.

Shamseer and Vohra state that we did not mention whether foreign language trials were sought and included. We did not describe selection by language which means that we selected trials independent of their language. The reference section of our review shows that we found and assessed trials published in Finnish, German, Spanish and Swedish.

Shamseer and Vohra argue that we should have constructed a funnel plot to explore the possibility of publication bias. Funnel plot has been popular; however, it is not a valid method. For example, different metrics lead to different shapes of the funnel plot. Furthermore, asymmetry can arise from biological heterogeneity so that asymmetry is no evidence of publication bias. Because of various problems, the use of the funnel plot has been strongly discouraged (26). In fact, our Cochrane review serves as a good example against the funnel plot. The six trials with participants under heavy acute physical stress, which found that vitamin C halved the number of colds, are all small. In a funnel plot of all 30 trials measuring incidence, these six small trials would lead to asymmetry. Thus, the funnel plot would 'explain' the positive findings by publication bias, which would discourage further trials. In contrast, our subgroup analysis in which the positive results are explained by the special participants and conditions suggests direction for further research to test a justified hypothesis.

Shamseer and Vohra notice that we presented subgroup analysis for children for only one of five primary outcomes. In the incidence analysis, statistically significant heterogeneity disappeared when we divided trials to those with participants under acute physical stress and to those with participants of the general community. Trials with children are consistent with the pooled estimates of these two subgroups. The largest trial with children of the general community, by Ludvigsson *et al*. with 615 Swedish schoolchildren (27), found no effect by vitamin C on common cold incidence consistent with the adult trials in the general community. The single trial with children under acute physical stress, by Ritzel at a skiing school in the Swiss Alps (28), found 45% (95% CI: 5–68%) reduction in common cold incidence consistent with five trials with adults. Another outcome was the severity of colds in regular supplementation trials. We divided trials to two subgroups by the outcome: severity measured by a severity score and by the mean days off work or school ($p = 0.004$ for the benefit of vitamin C over placebo in the two subgroups with 15 trials). The complex outcome and the limited number of trials did not allow further subgroup analyses. Two outcomes were restricted to therapeutic trials and we state that 'none of the therapeutic trials examined the effect of vitamin C on children'. Thus, there are clear reasons why we presented subgroup analysis for children for only one of the five outcomes.

I agree with Shamseer and Vohra's comment that generalizing our results is hampered by the fact that most of the trials were carried out in developed countries. On the other hand, a group of four trials in the UK with schoolboys and male students found a 30% (95% CI 19–40%) reduction in common cold incidence by vitamin C supplementation (29). This subgroup is mentioned in our discussion, but two of the trials used doses less than 200 mg/day and were therefore excluded from the Cochrane analyses. Nevertheless, as regards the developing countries, this group of trials is interesting, because at the time of those four trials the dietary vitamin C intake in the UK was substantially lower than in other western countries and might have been suboptimal (29). A Canadian trial with adults also suggested that vitamin C supplementation effect might be modified by dietary vitamin C intake (30). 'Days confined to house per subject' was reduced by 48% in participants who had low intake of fruit juices and by 22% in those who had high intake of juices; vitamin C dosage was 1 g/day regularly and 3 g/day extra during colds (30). Thus, as Shamseer and Vohra suggest, it seems possible that vitamin C might have a greater effect on the common cold and other respiratory infections (31) in developing countries in which low dietary vitamin C intake and high burden of respiratory infections coexist.

Harri Hemilä

Renske Bax, Leo Spee and Marieke Madderom's Commentary

The common cold is an acute, self-limiting, innocent but frequent viral infection of the upper respiratory tract. A variety of agents, ranging from anecdotal folk

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remedies to extensively studied medications have been suggested as therapy. Ascorbic acid (vitamin C) is one of these possible agents. However, its role in preventing and treating the common cold has been controversial for many years. Public interest is high, and vitamin C continues to be widely used as a preventive and therapeutic agent for this condition. Infants and children have more colds and experience more prolonged symptoms compared to adults so might be a group that can benefit from the use of vitamin C.

Douglas RM *et al*. (1) systematically reviewed all published trials regarding vitamin C as a prophylactic or as a therapeutic agent on the incidence, the duration and the severity of the common cold. The authors concluded that the prophylactic supplementation of vitamin C did not reduce the *incidence* of the common cold in studies including *a mixed population of adults and children. The therapeutic trials provided inconsistent evidence for an effect of vitamin C on the severity and duration of the common cold.*

The meta-analysis in prophylactic studies on *duration* of common colds was divided into two subgroups: adults and children. *Regarding children, this was the only outcome reported*. All of the participating children were of school age. The authors found an 8% reduction in common cold duration within the adult participants and a 13.6% reduction within the child participants.

The aforementioned reduction in the *duration* of common colds within children was based on 12 prophylactic comparison trials, which include 2,434 episodes of illness. In these trials the dosage of vitamin C varied from 0.2 g to 2.0 g. The pooled effect of 13.6% reduction had a 95% CI 5.6–21.6%. The authors estimated this would result in an average reduction of symptomatic days from about 28 days to 24 days per year per child.

In order to be able to comment on the clinical relevance of these findings we would like to highlight some questions that arise after reading this careful review. The authors found a reduction in the duration of common cold when using vitamin C as a prophylaxis, but did not comment on the compliance of the participating children. Low compliance may have underestimated the effect of vitamin C.

Furthermore, we question the dosages used in the different trials. Adults and children were taking the same dosage of vitamin C. Optimal dosages for children were not studied and we wonder if the differences in dosage for weight could explain the difference in outcome between adults and children. In addition, we wonder if the effect of vitamin C would increase with higher dosages without increasing the risk of adverse events.

The *prophylactic* trials included in the review varied in study period from 2 weeks to 9 months. We consider the duration of these studies too short to get a reliable estimate of reduction in duration of common colds throughout the year, especially because information on the season in which studies were performed was lacking. In addition, generalizability of the study results is questionable because there is no information on the geographic locations of the trials and social economic background or nutritional state of the children, all factors that might be of influence on the results.

Because it is doubtful whether a reduction of 4 days of common cold throughout a year will increase the child's well being, the real beneficial effect of vitamin C prophylaxis in children might well be the reduction in sick leave for the parents. This effect has economic consequences and should be weighted against the costs of taking vitamin C. In order to make a balance between costs and benefit, information on the duration of medication intake is needed. Unfortunately, this information was not presented. Therefore, questions important for clinical decision making, such as: 'how long do you have to take prophylactic vitamin C to achieve an effect?' cannot be answered.

As for now, given the small clinical relevance of the reduction in duration of an innocent ailment we do not recommend vitamin C as a prophylaxis for common cold in children. Compliance, optimal dosage and duration of intake need clarification before important questions about the cost effectiveness of vitamin C intake in children can be answered. In the mean time, we would like to advise parents, recognizing the kiwi as a rich vitamin C source, to take heed to an adapted old saying: 'A kiwi a day keeps the doctor away'.

Declaration of Interest

None.

Response from the review author to the commentary by Bax, Spee and Madderom

I agree with Bax *et al*.'s proposal that the dose per weight may be a fundamentally important variable when considering the effect of vitamin C on colds. However, each scientific report is a compromise between the length and details, and our Cochrane review is already long for an average reader (1). Not all specifics could be discussed, yet the dose-response question was briefly commented on, with the reader being guided to a separate systematic review (32).

In 1999, I divided the vitamin C common cold trials simultaneously by dose: 1 g/day vs. $\geq$ 2 g/day regularly over the trial, and by participants: children vs. adults (32). A major challenge in the analysis was choosing an appropriate outcome. Essentially all trials report the duration of common cold symptoms. However, for the patient and the society, the days off work or school or the subjective severity may be much more relevant outcomes than the length of time for which the nose is running. Vitamin C might have a different effect on different outcomes. For example,

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with 615 Swedish schoolchildren, Ludvigsson *et al.* (27) found that 1 g/day vitamin C shortened the symptoms of upper respiratory tract infection (URI) by just 6% ($P = 0.5$), but the absence from school because of URI was reduced by 14% ($P = 0.016$).

In the 1999 analysis, when several outcomes were published in a trial report, I selected the outcomes seemingly most important for the patient, such as days off work or school (32), which made the outcomes more relevant but more heterogeneous. In five trials with adults who were administered 1 g/day of vitamin C, the mean decrease in cold duration was only 7%, whereas in two trials with children administered 2 g/day the mean decrease was four times higher, 26% (32–34). Children administered 1 g/day and adults administered $\geq$ 2 g/day were in the middle with mean effects of 13% and 20%, respectively. The pattern of results supports dose dependency, given also the lower average weight of children (32). Nevertheless, the conclusions must be cautious, because the outcome is heterogeneous.

One trial with children tested different vitamin C doses for separate groups using the same outcome definition (33). Compared with the placebo group, colds were 12% shorter in children administered 1 g/day of vitamin C and 29% shorter in those administered 2 g/day (33); however, the groups were small and children given the higher dose were older. The most crucial trial that tested dose-dependency administered 3 and 6 g/day of vitamin C to adults randomized to four groups (35); the higher dose caused twice the effect of the lower dose (25, 32, 35, 36). So far, there is no definite evidence to claim dose-dependency in the region of high doses, but the described trends are consistent with such a conception.

Bax *et al.* suggest that low compliance might have been a problem in trials with children. In fact, there is empirical evidence to support their proposal. During the trial, vitamin C levels increased in the plasma of older children (33) and in the urine of schoolboys (37) given a placebo, suggesting that tablets were exchanged by playful children. The trial by Carr *et al.* (38) with twins aged 14 to 64 years (mean 25 y) is also interesting inasmuch as a significant reduction in common cold duration was observed in twins living apart (-35%, $P < 0.01$), but no effect was seen in twins living together (0%), who probably swapped their tablets to a great extent - not so easy for twins living apart. Thus, in some trials with children the mischief of the subjects may have confounded the results and the observed difference may underestimate the true physiological effect.

Bax *et al.* claim that in our Cochrane review "there is no information on the geographic locations of the trials." However, our table "Characteristics of included studies" describes for each included trial the country in which the trial was carried out (1).

Although Bax *et al.*'s advice to give children kiwi as a source of vitamin C is a pleasant ending to their commentary, evidence and consideration of cost effectiveness should be required for such an advice, too. One gram of vitamin C cost pennies, but corresponds to some half kilograms of kiwi (about 200 mg vitamin C/100 g fruit) which has a substantially higher cost. Thus, if we assume that vitamin C is the important substance in the kiwi fruit, it is much more cost effective to use pure vitamin C. Moreover, if we assume that it is not vitamin C that is beneficial in kiwi, then we should require evidence indicating that kiwi in general is effective for some health outcomes.

Based on our Cochrane review, regular vitamin C supplementation to prevent the common cold in ordinary children and adults should be discouraged. On the other hand, given the evidence that vitamin C reduces the incidence of colds in children and adults under heavy acute physical stress, it seems reasonable to test the effect of vitamin C at an individual level for children who exercise heavily and have a concomitant problem of frequent respiratory infections.

The consistent effect of regular vitamin C supplementation on the duration and severity of colds indicates a biological effect. With such an effect on common cold symptoms, it would appear reasonable to administer vitamin C therapeutically, starting immediately after the first symptoms; however, no therapeutic trials have been carried out in children (1,32). The lack of therapeutic trials with children may justify a conclusion that vitamin C should not be recommended for treating colds in children, because there is no direct evidence of benefit.

On the other hand, there is indirect justification to test vitamin C for treating colds in children. Two trials with children administered 2 g/day vitamin C regularly, and they found a 26% reduction in common cold duration (32–34). A single trial has compared the effect of regular and therapeutic (5 days during colds) vitamin C supplementation (3 g/day) on common cold duration (35). There was no evidence that the 5-day therapeutic supplementation would be less effective than regular supplementation (36). Consequently, the 26% effect on children given 2 g/day vitamin C regularly may serve as a crude estimate for the benefit of a similar therapeutic dosage for children. Furthermore, the result of a controlled trial is always an average for a group. Accordingly, vitamin C is much more (and much less) effective for some individual people than suggested by a single trial, or by the pooled results of a meta-analysis. Thus, there seems to be a justification to test therapeutic vitamin C at the individual level for children who have problems with respiratory infections, because there is strong evidence that vitamin C differs from placebo, it is inexpensive and safe and, unlike the antibiotics (39), it does not cause harms on microbial ecology.

Harri Hemilä

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