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). All specifics could not be discussed, yet the dose-response question was briefly commented on, the reader being guided to a separate systematic review (2).

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 (2). 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 period the nose is running. Vitamin C might have a different effect on different outcomes. For example, with 615 Swedish schoolchildren, Ludvigsson et al. (3) 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 outcome seemingly most important for the patient, such as days off work or school (2), which made the outcome more relevant but more heterogeneous. In five trials with adults 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% (2,4,5). 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 (2). 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 (4). 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 (4); however, the groups were small and children given the higher dose were older. The most crucial trial testing the dose-dependency administered 3 and 6 g/day of vitamin C to adults randomized to four groups (6); the higher dose caused twice the effect of the lower dose (2.6-8). 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 level increased in the plasma of older children (2) and in the urine of schoolboys (9) given a placebo, suggesting that tablets were exchanged by playful children. The trial by Carr et al. (10) 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 outcome.

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 (1,2). 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 (2,4,5). 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 (6). There was no evidence that the 5-day therapeutic supplementation would be less effective than the regular supplementation (7). 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, and because it is inexpensive and safe and, unlike the antibiotics (11), it does not cause harms on microbial ecology.

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REFERENCES


