The report of DEVTA[1] was the 44th published trial of vitamin A.[2] The effect on its primary outcome, mortality, is noticeably smaller than the results of 15 previous trials including more than 200 000 participants.[3] In view of problems with the delivery of the intervention in DEVTA,[4] meta-analyses of previous high-quality trials might more accurately show the efficacy of vitamin A.

In a meta-analysis using a fixed-effect model, DEVTA accounts for 65% of the weight and reduces the average effect by half (risk ratio [RR] 0·88, 95% CI 0·84–0·94; I^2=64%),[2] consistent with the meta-analysis reported by Awasthi and colleagues.[1] Using random-effects, which might be a more appropriate model in view of differences between the included trials, DEVTA accounts for 14% of the overall effect, which suggests a 26% average reduction in mortality (RR 0·74, 95% CI 0·64–0·87). Since model choice meaningfully changes the outcome, both averages should be interpreted with caution.

Continued research to improve the delivery of vitamin A remains important, but further trials are not needed. Because of the size of DEVTA and the stability of previous estimates, average effects are highly unlikely to change. We believe that the meta-analysis by Awasthi and colleagues underestimates the effect of vitamin A when delivered faithfully to children at high risk of deficiency; however, their report affirms that vitamin A supplementation prevents death, illness, and blindness for children who are deficient and cannot obtain enough vitamin A through diet alone. It would no longer be ethical to compare vitamin A with a placebo or with a nutritional intervention that lacks this essential nutrient. DEVTA should be the last trial of this kind.

We declare that we have no conflicts of interest.

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The DEVTA trial[1] of vitamin A supplementation was large and well organised, but did not show the 20–30% reduction in mortality in children aged 1–6 years that had been shown in earlier trials, even though adverse effects were absent. Supplementation might have reduced mortality but only by between 0% and 10%. A meta-analysis with data from other vitamin A supplementation trials showed mortality reductions of 11% (95% CI 5–16; p=0·00015). Methodological errors in the management of the trial were unlikely but non-methodological factors could have confounded this particular trial. For example, were samples from the batches of the pharmaceutical capsules supplied checked for vitamin A content and activity to exclude deterioration of their contents, or possible adulteration, somewhere along the supply chain?

Another possible confounder is hypovitaminosis D. Vitamin D induces bactericidal cathelecidin secretion, reducing childhood respiratory infection risks,[2] but vitamin A antagonises vitamin D.[3] Furthermore, higher vitamin D status was inversely associated with lung cancer mortality in non-smokers, an effect lost in those with excessive circulating vitamin A or taking vitamin A or β-carotene supplements. Since children living in northern India have a high prevalence of vitamin D deficiency despite abundant sunshine,[4] large doses of vitamin A might lose apparent effectiveness by antagonising vitamin D. Since lifestyles might reduce vitamin D status more in Indian girls than boys, the benefits of vitamin A could be reduced in girls, as suggested earlier,[5] and outcomes might be shown to vary with sex in children, from the age of puberty in the DEVTA study.

I declare that I have no conflicts of interest.

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Authors' reply

DEVTA[1] was a well conducted cluster-randomised trial of the effects of allocation to twice-yearly vitamin A supplementation on pre-school child mortality in a population with low blood retinol, some Bitot's spots, but little xerophthalmia. It had good compliance (about 86%), unbiased assessment of outcome (mortality at ages 1–6 years), and appropriate analysis (as 36 clusters *vs* 36 clusters). Its effective sample size was twice that of all previous trials combined, but its findings are still subject to some