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

random error. DEVTA should therefore be considered in conjunction with the previous trials, and they with it, as in the figure (adapted from figure 4 in the original Article).[1]

The Comment[2] and Correspondence about DEVTA do not sufficiently emphasise how much the play of chance during randomisation can affect the apparent mortality findings in trials. The result from a trial (or meta-analysis) is not only the point estimate of the mortality rate ratio but also its CI, which generally includes a much wider range of possible answers.

The figure shows weighted averages of results from eight previous trials of regular vitamin A supplementation of young children in low-income countries, the DEVTA trial, and all 9 trials. From the previous trials, the point estimate of the average proportional mortality reduction was 23%, but the 99% CI ran from 11% to 32%, corresponding to a wide range of purely statistical uncertainty about the average benefit. DEVTA substantially narrows this uncertainty; the point estimate suggested by DEVTA plus previous trials is 11% (95% CI 5–16%), suggesting that the real benefit generally lies around the lower end of the previous range of uncertainty.

Assessment of trial evidence should be wholly separated from advocacy, but most responses to DEVTA are from two groups of advocates. The Comment,[2] coauthored by a critic of routine vitamin A supplementation, over-emphasises the non-significant DEVTA result, somewhat downplaying the meta-analysis. Conversely, correspondents who advocate vitamin A supplementation (or work with organisations delivering it) want to downplay or ignore DEVTA, either by questioning its validity or by using random-effects meta-analyses that give inappropriately little weight to large, statistically reliable trials.[3,4]

Inappropriately, such random-effects meta-analyses would almost ignore any major new trial, no matter how good it was or what it showed. For example, even if DEVTA had been an impeccable individually randomised trial in tens of millions of children with 89 000 versus 100 000 deaths (an 11% risk reduction), a standard random-effects meta-analysis would still inappropriately conclude, based mainly on the far smaller previous trials, that vitamin A reduces mortality by about a quarter.

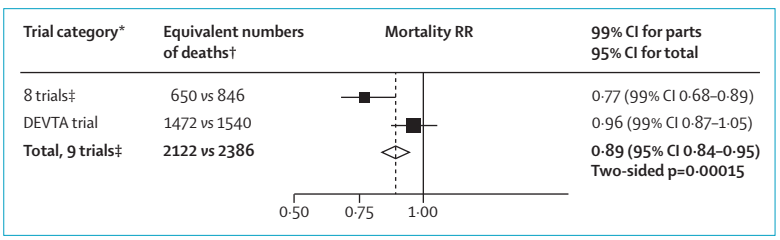

Figure: **Randomised trials in low-income populations of effects of regular vitamin A supplementation on the childhood mortality rate ratio (RR, vitamin A *vs* control); weighted averages of RRs in the eight previous largest trials, the DEVTA trial, and all nine trials**

Heterogeneity between RR in DEVTA and in the eight other trials: p=0·001 (see appendix to DEVTA report[1]). RR=rate ratio. *Cluster-randomised or individually randomised trials of regular vitamin A supplementation with at least 20 child deaths. Most trials were cluster-randomised, and analysed accordingly. Trials were excluded if they recruited patients with disease or gave only single-dose treatment. †Numbers of deaths (vitamin A *vs* control) in a large 50:50 individually randomised trial that would yield the same RR and CI. These are approximately additive when we average different results. ‡We calculated the inverse-variance-weighted average of the log RR values identified in different trials. This does not assume the real risk ratios in different trials are the same, so should not be called a fixed-effects meta-analysis, but is efficient when the risk ratios are similar to each other. If the real risk ratios are dissimilar then a weighted average of the observed RRs provides an efficient estimate of a similarly weighted average of the real risk ratios; its CI describes only the effects of chance during the random allocation, regardless of such dissimilarities.

Sommer and colleagues,[5] whose prompt response is cited by other correspondents, suggest that DEVTA was not a valid trial. As, however, the population studied was vitamin A deficient by conventional criteria, the key methodological issues are whether there was good compliance with the randomly allocated treatment (yes), and whether there was any material bias between the two treatment groups in ascertainment of mortality (no). All else is irrelevant to trial reliability.

The direct evidence we cited of good compliance (despite claims by various correspondents) is supported by airline delivery records of 6 million Roche vitamin A capsules (1·2 million in November, 1998; October, 1999; January, 2001; December, 2001; and October, 2002; all used in DEVTA). Individual child deaths in the past year were sought from several sources at 6-monthly visits to each village, so most deaths were recorded twice; confirming relatively few were missed twice, DEVTA mortality rates slightly exceeded those recorded by the Registrar-General of India for the whole state. The low cost per child (miscalculated tenfold by Sommer and colleagues[5]) merely reflected efficiencies of design and scale.

As DEVTA had surprisingly unpromising results we convened a meeting of other vitamin A trialists to discuss their studies and ours, seeking explanations for any heterogeneity. There were no agreed proceedings, but that 2008 meeting engendered for the DEVTA publication extensive further data checks and more robust statistical analysis methods; these did not, however, change the mortality rate ratio.

We conclude that the apparent discrepancy between DEVTA and previous trials was probably due mainly to the play of chance (despite being significant, p=0·001). If so, it is medically and statistically appropriate for DEVTA to have twice the weight of all other trials combined when averaging trial results to guide implementation strategies.

As indicated in the figure, the real risk reduction could well be about 11% both in the circumstances of DEVTA and in those of some previous trials. To assess such moderate differences

Andy Crump, TDR, WHO/Science Photo Library

reliably, large-scale randomised evidence was needed, and DEVTA has contributed substantially to this. Arguments for or against routine vitamin A supplementation should now be based on appropriate assessment of all mortality trial results, without unduly selective exclusions.[3]

We declare that we have no conflicts of interest.

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Iran and science publishing: an open letter

I believe—or used to believe—that dissemination of research data for the benefit and betterment of all crosses borders.

I was rather astonished and saddened after reading an email from *The American Journal of Cardiology* to one of my colleagues informing him of the rejection of his article on the grounds of nationality and employment status of the author—ie, an employee of the Government of Iran—and mentioning that the review process was withheld because of the Iranian nationality of the authors (long after the submission of the article). The correspondence states that "As a result of OFAC [US Office of Foreign Assets Control] sanctions, all US owned journals are unable to handle scientific manuscripts which are authored by Iranian scientists, employed by the Government of Iran. Based on this OFAC regulation and that *The American Journal of Cardiology* is a US owned journal we are unfortunately unable to handle your manuscript."

Almost all scientific journals in the world, even in the USA, publish Iranian authors' scientific results irrespective of their nationality. According to Scopus database, in 2012, Iranian academic communities contributed about 40 000 scientific publications, including 23 000 articles in the field of medicine.

The US sanctions state that handling (ie, editing or publishing) scientific manuscripts from Iran violates the trade embargo on this country. I was unaware that researchers traded findings, but rather that we all shared research results with a view to improve health worldwide. As an example, the article I was referring to was about non-preventable diseases, which once reviewed and if acceptable, could have contributed potentially to improving human health.

The American Geophysical Union stated that they do not consider publishing to be a trade issue, and accept paper submissions from anywhere in the world, a view shared by the American Society of Mechanical Engineers and the American Association for the Advancement of Science.

Iranian scientists and academics have substantially contributed to scientific achievements, leading to increased communications and collaborations between international scientific institutions and bodies above and beyond politics and differences between governments. Surely, this is the way it should be.

At a time when several countries —even the USA, despite important differences of opinions—are trying to reduce tensions with Iran (eg, withdrawal of sanctions on items such as computer software and hardware, mobile phones, food, and medicine), discriminatory action against scientific publishing is difficult to understand.

All of us need to stand above race, ethnic origin, and nationality when results of our work relate to others, whoever and wherever they might be.

As surgeons and physicians, if we face patients from different nationalities requiring urgent care, surgery or treatment, could we hesitate to provide care, knowing someone's life depends on it?

Please voice and share your opinions and views—I look forward to them.

I declare that I have no conflicts of interest.

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Editors' reply

The Lancet welcomes the submission of research from scientists in all nations, including Iran. We are disappointed that some publishers have created the impression that work from Iran should be discriminated against. This attitude is contrary to the spirit and values of global science. We are currently working to deepen our relationship with Iranian medical and public health scientists, and we look forward to publishing the results of that collaboration, which, we hope, will include Iran's Ministry of Health.

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