

The DEVTA trial¹ examined a large, twice-yearly vitamin A supplementation programme but did not find the expected 20–30% reduction in overall child mortality. Its publication was delayed for more than 6 years. The Comment² argues that the contradiction with present assumptions might explain this delay. We agree. In 2011, we completed an individually randomised placebo-controlled trial of vitamin A supplementation delivered at vaccination sessions to more than 7000 children in Guinea-Bissau and identified no overall effect, but strong sex-differential effects. The report remains unpublished. We believe that reviewers and editors have been looking for errors, as did Sommer and colleagues in their response to DEVTA.³

The existing vitamin A supplementation policy, which is implemented in more than 100 low-income countries, is 20 years-old. It is based on eight trials which were not flawless. Since then, many new interventions have been introduced that could modify the effect of vitamin A supplementation. With the only two recent trials (DEVTA and our unpublished trial) both suggesting no effect, vitamin A supplementation might have become less beneficial. In a reanalysis of one of the original eight trials, the beneficial effect was limited to unvaccinated children and there were strong sex-differential effects of vitamin A supplementation in vaccinated children.⁴ Hence, the roll-out of the vaccination programme might be one environmental factor that has modified the effect of vitamin A. Although vitamin A is cheap, delivery is expensive. Instead of making a meta-analysis of the eight trials and DEVTA to assure donors that there is still a beneficial effect,¹ public health needs new randomised trials to assess whether and in which situations vitamin A is value for money.

We declare that we have no conflicts of interest. The unpublished vitamin A trial was funded by an ERC Starting Grant to CSB (243149).

*Christine Stabell Benn,
Ane Bærent Fisker, Peter Aaby
cb@ssi.dk

Research Center for Vitamins and Vaccines, Statens Serum Institut, Copenhagen, Denmark (CSB, ABF, PA); and Bandim Health Project, InDEPTH Network, Bissau, Guinea-Bissau (CSB, ABF, PA)

- 1 Awasthi S, Peto R, Read S, Clark S, Pande V, Bundy D, and the DEVTA (Deworming and Enhanced Vitamin A) team. Vitamin A supplementation every 6 months with retinol in 1 million pre-school children in north India: DEVTA, a cluster-randomised trial. *Lancet* 2013; **381**: 1469–77.
- 2 Garner P, Taylor-Robinson D, Sachdev HS. DEVTA: results from the biggest clinical trial ever. *Lancet* 2013; **381**: 1439–41.
- 3 Sommer A, West KP Jr, Martorell R. Vitamin A supplementation in Indian children. *Lancet* 2013; **382**: 591.
- 4 Benn CS, Aaby P, Nielsen J, Binka FN, Ross DA. Does vitamin A supplementation interact with routine vaccinations? An analysis of the Ghana Vitamin A Supplementation Trial. *Am J Clin Nutr* 2009; **90**: 629–39.

For epidemiologists, demographers, and those working in household registration systems, the results and interpretation of the DEVTA study¹ are surprising. The reader is left asking why the study—which was certainly large—included neither a surveillance system, nor at minimum a periodic or full household survey before and after implementation of the intervention, to ensure complete and accurate assessment of the primary outcome, mortality. The teams double-checking deaths reported by community workers only verified reported deaths, while leaving unreported deaths entirely unidentified. Deaths are known to be greatly under-reported in certain areas of India,² and our colleagues have shown that even India's Surveillance Registration System under-reported infant mortality compared with a household registration system in southern India, where under-reporting was believed to be scarce.^{2,3} Can the DEVTA study, on the basis of randomisation of the intervention with such inaccurate assessment of the outcome, truly be deemed a clinical trial, much less "a watershed for best practice in research to inform international development"?⁴ Some objective demonstration of the

completeness or incompleteness of both the intervention and outcome data is needed before drawing such strong and global conclusions.

Nutritional status does shift over time (for better and worse) and vitamin A supplementation does not affect child mortality equally in all settings. Is this understanding novel? Does it undermine conclusions based on a multitude of well conducted clinical trials?

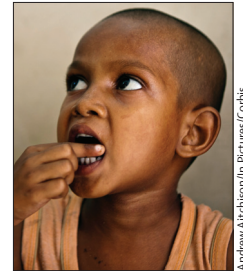
What DEVTA and the ever-growing misinterpretation of meta-analyses that erroneously aggregate data across settings irrespective of their crucial differences (in nutritional status or methodological strengths and limitations, or both) should stimulate is a demand for the same rigor in implementation that Richard Peto recommended for adequate study design many years ago.⁵ Drawing broad conclusions on the basis of unconvincing data and weak methods should be carefully avoided lest we become complacent in our quest for evidence-based medicine, the foundation of which is adequately rigorous and sensitive implementation of clinical trials and their assessments, including in meta-analyses.

We declare that we have no conflicts of interest.

*Nancy L Sloan, Satinda Nath Mitra
nlsloan@gmail.com

Mailman School of Public Health, Columbia University, New York, NY 10025, USA (NLS); and Mitra and Associates, Dhaka, Bangladesh (SNM)

- 1 Awasthi S, Peto R, Read S, Clark S, Pande V, Bundy D, and the DEVTA (Deworming And Enhanced Vitamin A) team. Vitamin A supplementation every 6 months with retinol in 1 million pre-school children in north India: DEVTA, a cluster-randomised trial. *Lancet* 2013; **381**: 1469–77.
- 2 Jha P. Reliable mortality data: a powerful tool for public health. *Natl Med J India* 2001; **14**: 129–31.
- 3 Goudar SS, Carlo WA, McClure EM, et al. The maternal and newborn health registry study of the global network for women's and children's health research. *Int J Gynaecol Obstet* 2012; **118**: 190–93.
- 4 Garner P, Taylor-Robinson D, Sachdev HS. DEVTA: results from the biggest clinical trial ever. *Lancet* 2013; **381**: 1439–41.
- 5 Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. *BMJ* 1976; **2**: 1525–36.



Andrew Aitchison/In Pictures/Corbis