A conversation with Richard Peto and Simon Read on April 10, 2014
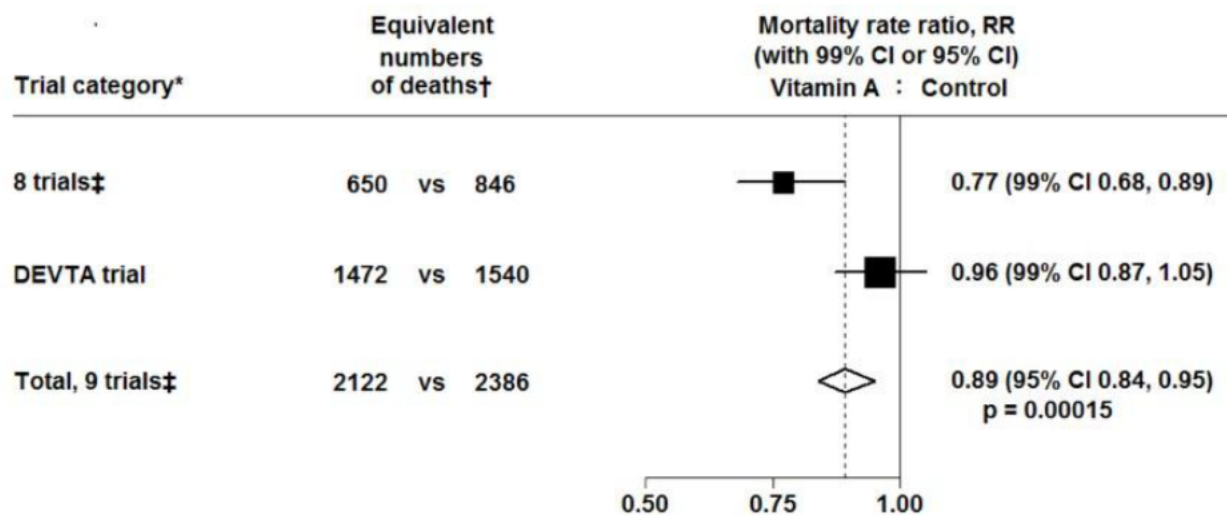
Participants:

- Richard Peto and Simon Read – University of Oxford, UK
- Jake Marcus and Howie Lempel – Research Analysts, GiveWell

Note: This set of notes was compiled by GiveWell on the major points made by Oxford.

Summary

GiveWell (JM, HL) spoke with Oxford (RP, SR) about the Deworming and Enhanced Vitamin A (DEVTA) trial and about GiveWell's draft report on vitamin A supplementation (VAS). For a summary of their view on the effect of VAS, Oxford asked us to direct readers to their response (http://files.givewell.org/files/DWDA%202009/Interventions/Vitamin%20A/DEVTA%20reply,%20as%20published.pdf) to comments on the study in the Lancet. Oxford believe that the best guide to the future impact of vitamin A supplementation is the inverse-variance weighted average of the totality of the randomized evidence (see below the figure from their response), and that we should attribute most of the apparent heterogeneity among the trial results to the play of chance during the randomisation process. This suggests future vitamin A supplementation would lead to reduction in mortality between about 5% and 16%. Oxford also emphasized the safety of vitamin A and believe that its safety is not in any way an open question.

Trial category*	Equivalent numbers of deaths†		Mortality rate ratio, RR (with 99% CI or 95% CI) Vitamin A : Control
8 trials‡	650 vs 846		0.77 (99% CI 0.68, 0.89)
DEVTA trial	1472 vs 1540		0.96 (99% CI 0.87, 1.05)
Total, 9 trials‡	2122 vs 2386		0.89 (95% CI 0.84, 0.95) p = 0.00015

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 8 largest previous trials, the DEVTA trial, and all nine trials

Heterogeneity between RR in DEVTA and in the eight other trials: p=0·001

* 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 numbers 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.

Title and authors' abstract of main report on DEVTA (*Lancet* 2013; 381: 1469-77)

Vitamin A supplementation every 6 months with retinol in 1 million   pre-school children in north India: DEVTA, a cluster-randomised trial
Shally Awasthi, Richard Peto, Simon Read, Sarah Clark, Vinod Pande, Donald Bundy, and the DEVTA (Deworming and Enhanced Vitamin A) team

Summary
Background In north India, vitamin A deficiency (retinol <0. 70 μ mol/L) is common in pre-school children and 2–3% die at ages 1. 0–6. 0 years. We aimed to assess whether periodic vitamin A supplementation could reduce this mortality.
Methods Participants in this cluster-randomised trial were pre-school children in the defined catchment areas of 8338 state-staffed village child-care centres (under-5 population 1 million) in 72 administrative blocks. Groups of four neighbouring blocks (clusters) were cluster-randomly allocated in Oxford, UK, between 6-monthly vitamin A (retinol capsule of 200,000 IU retinyl acetate in oil, to be cut and dripped into the child's mouth every 6 months), albendazole (400 mg tablet every 6 months), both, or neither (open control). Analyses of retinol effects are by block (36 *vs* 36 clusters). The study spanned 5 calendar years, with 11 6-monthly mass-treatment days for all children then aged 6–72 months. Annually, one centre per block was randomly selected and visited by a study team 1–5 months after any trial vitamin A to sample blood (for retinol assay, technically reliable only after mid-study), examine eyes, and interview caregivers. Separately, all 8338 centres were visited every 6 months to monitor pre-school deaths (100 000 visits, 25 000 deaths at ages 1. 0–6. 0 years [the primary outcome]). This trial is registered at ClinicalTrials.gov, NCT00222547.
Findings Estimated compliance with 6-monthly retinol supplements was 86%. Among 2581 versus 2584 children surveyed during the second half of the study, mean plasma

retinol was one-sixth higher (0. 72 [SE 0. 01] *vs* 0. 62 [0. 01] μ mol/L, increase 0. 10 [SE 0. 01] μ mol/L) and the prevalence of severe deficiency was halved (retinol <0. 35 μ mol/L 6% *vs* 13%, decrease 7% [SE 1%]), as was that of Bitot spots (1. 4% *vs* 3. 5%, decrease 2. 1% [SE 0. 7%]). Comparing the 36 retinol-allocated versus 36 control blocks in analyses of the primary outcome, deaths per child-care centre at ages 1. 0‑6. 0 years during the 5-year study were 3. 01 retinol versus 3. 15 control (absolute reduction 0. 14 [SE 0. 11], mortality ratio 0. 96, 95% CI 0. 89‑1. 03, p=0. 22), suggesting absolute risks of death between ages 1. 0 and 6. 0 years of approximately 2. 5% retinol versus 2. 6% control. No specific cause of death was significantly affected.

Interpretation DEVTA contradicts the expectation from other trials that vitamin A supplementation would reduce child mortality by 20‑30%, but cannot rule out some more modest effect. Meta-analysis of DEVTA plus eight previous randomised trials of supplementation (in various different populations) yielded a weighted average mortality reduction of 11% (95% CI 5‑16, p=0. 00015), reliably contradicting the hypothesis of no effect.

GiveWell overview of the Deworming and Enhanced Vitamin A (DEVTA) trial

Oxford co-authored a study on Deworming and Enhanced Vitamin A (DEVTA). Prior to the start of DEVTA, Indian government policy was to distribute vitamin A supplementation (VAS) every six months to populations in need. However, the program was not being fully implemented. The leaders of the DEVTA study wanted to examine whether a large-scale VAS program in India was practicable using existing facilities and whether it saved lives.

Estimation of compliance in DEVTA

The authors of the study estimated that 86% of the eligible children were given vitamin A supplementation at each treatment campaign. It is unlikely that this compliance rate was substantially in error because there were several types of evidence about compliance.

Distribution of VAS

During the study, mothers in the vitamin supplementation areas (which were in rural Uttar Pradesh) generally wanted their children to receive VAS, and study advertising forewarned them of distribution dates. At their monthly meetings, the anganwadi child-care center (AWC) workers received vitamin A capsules for distribution. They had an incentive to attend these meetings because the meetings are where they were paid. The workers were also aware that monitors from the study would visit some villages on the scheduled distribution day, so they had an incentive to distribute the capsules. Monitors also visited 25% of villages within a week after the distribution day to ask mothers and AWC workers whether the capsules had been distributed.

Evidence from the study's census

A census was completed by the DEVTA monitors during the study, which was subsequently used on days when treatment was due to provide a list of names of children who had been included in the census and would still to be in the age range (6-72 months) for treatment. Monitors later determined whether those listed had received treatment recently. This data showed that there was a 96% compliance rate among children who were registered for supplementary nutrition with AWC workers (over half of the population) and a 72% compliance rate among those who were not. Children are required to be below the official poverty line to be registered for supplemental nutrition. Based on the proportions of the population that were registered and unregistered, the authors of DEVTA estimated an overall compliance rate of 86%.

Biomedical evidence

Every year, one randomly chosen village in each of the 72 study areas was visited by a biochemical team to examine a convenience sample of about 20-30 children. Compliance had initially been estimated directly from answers given to the biomedical team by carers. However, this slightly overestimates the compliance rate, since the non-random convenience sampling of children within an AWC included too high a proportion of those registered for supplementary nutrition, and in the published report these compliance estimates were replaced by the census-based estimates above (see Lancet paper).

For info and background only:

The overall prevalence of Bitot's spots was 3-4%, which shows that by conventional criteria these populations were sufficiently vitamin A deficient to require supplementation. The prevalence of Bitot's spots was approximately halved in the vitamin A arm, confirming that the treatment was delivered, and was biologically active when delivered.

The overall levels of blood retinol show unequivocally that this was a vitamin-A-deficient population by current standards.

The highly significant differences in blood retinol between treatment and control arms show unequivocally that the trial treatment was effective, and was reaching the children.

In the second half of the study the biomedical team questioned each child's carers on whether treatment had been received at the last treatment campaign and the responses were used to estimate the compliance fractions presented at a meeting of international experts convened in Oxford in November 2008 by the DEVTA investigators to seek advice on the interpretation of their then-unpublished methods and findings. After criticism at this meeting that the biomedical subjects were not randomly selected from each AWC, which was readily conceded, an in-depth analysis of the much more extensive compliance data available (based on listings extracted from the mid-study census) confirmed that the biomedical team's compliance estimates had been slightly over-optimistic, quantitatively explained by the increased fraction of children registered for supplementary nutrition in the biomedical data (as explained in the Results section of the eventual Lancet paper.)

Estimation of child mortality in the DEVTA study

For the most part, deaths were recorded accurately in the trial. Some deaths of infants may not have been recorded, but infant mortality was not a study outcome (and the infant mortality that was found was approximately similar to the rural average in UP at that time).

A monitor would visit each village every six months to inquire about deaths of children that had occurred in the past year. An average of one new death at ages 1.0-6.0 was reported for every four village visits. The monitor would interview the villagers on the details of the death. A different monitor would visit the village six months later to repeat the process and correct any mistakes by the first monitor. The monitors had an incentive to be accurate in their counts because they knew that their results would be reviewed.

Each death should have been reported twice. The Lucknow office staff eliminated these duplicate death records by manual matching, but about 1% of the remaining records were later found to be duplicates using computerized matching of possible duplicates followed by manual investigation of all these possible duplicates. These few real duplicates were removed prior to publication, but this did not affect the risk ratio estimates from the study.

Heterogeneity between the proportional reductions in child mortality in DEVTA and in the 8 main previous population-based trials of vitamin A supplementation (VAS)

The degree of heterogeneity between the results of DEVTA (where the treatment group's reduced child mortality was not statistically significant) and the results of the 8 main previous trials of VAS (which found large decreases in child mortality due to VAS) was surprising, with a *p*-value for heterogeneity of approximately 0.001. Because of the improbability of the result, the authors of the DEVTA trial searched thoroughly for differences between their trial and other trials that could have led to this heterogeneity. They convened a meeting of researchers who had performed the previous main trials on VAS, at which they compared the methodology of the trials. However, they found nothing that could explain the discrepancy. The discussions from the meeting were not published.

Explanations for the heterogeneity that have been considered include:

Population estimation

One possibility considered at the meeting was that there had been inaccuracy in counting the number of children per block (sub-district in India, unit of randomization in the trial). To address this, the data were reanalyzed using the number of deaths per AWC. AWCs are all approximately village size and the number of AWCs in each block is known, but the mortality risk ratio (aka relative risk) was virtually unaltered. Duplicate death records were also searched for and removed. Again, this did not change the relative risk in DEVTA.

GiveWell: Could differences in baseline child mortality rates between VAS trials have explained the differences in results?

The DEVTA study sites had slightly higher child mortality than the average in rural UP. This is because the DEVTA trial used AWCs to deliver VAS, and AWCs generally serve

populations that are somewhat needier than average. However, AWCs are common in rural India, so the difference was not great.

The VAS trials that preceded the DEVTA study were performed in the 1980s and early 1990s, when mortality rates for children under 5 years of age were about twice as high as they are today. This decline in under-5 mortality rates is expected to continue.

Changing child mortality rates should not much affect the risk ratios seen in trials that compare treatment versus concurrent control arms. For risk ratios in old or new VAS trials derive from the few children who, without treatment, would die from infection or malnourishment, and are therefore not greatly affected by the overall child mortality rate.

Although it is possible that the causes of child mortality have changed in ways that are of some relevance (eg, deaths from measles have decreased due to widespread measles vaccination), most deaths in the DEVTA study were, as in the previous trials of VAS, due to preventable infections (such as measles, diarrhea, and pneumonia). If VAS is effective, it should be relevant to these causes of death, so the decreasing levels of child mortality should not materially affect the mortality risk ratio, treatment versus control.

GiveWell: Could poor quality of vitamin A capsules in the DEVTA trial explain the lack of effect on child mortality?

This is unlikely. The capsules were manufactured by Roche and delivered yearly, so they would not have degraded over time. In addition, the effects on Bitot's spots and blood retinol levels demonstrate that vitamin A deficiency (VAD) decreased as expected.

GiveWell: Could inaccuracy in the census have affected results?

The mortality risk ratio is not affected by the inaccuracies in our census, which include:

- The spelling of fathers' names (though the first 3 letters were generally accurate)
- Some individuals were missed by the DEVTA census. Infants, particularly below the age of two months, were often not recorded, due to the high infant mortality. Oxford estimates that only about 75% of infants (under the age of 1) were recorded by the census, though almost all children over the age of 1 were recorded.
- Estimation of the ages of individuals, some of which were noted if that child was contacted some time later for other purposes.
- Some villages entirely lacked records that we could use for our census.

However, even if minor inaccuracies in the census had affected population estimates, it would affect only the estimates of absolute risk. The relative risk (aka risk ratio) depends only on the number of deaths per AWC, which is wholly unaffected by any inaccuracy in population estimates.

GiveWell: Is it possible that people who were not recorded by the census were disproportionately unlikely to receive VAS?

It is possible, but people who were not recorded by the census were probably disproportionately unlikely to be VAD as well. The census was done mainly through AWC workers, who are generally more familiar with people below the poverty line who are on the AWC registers. This population is probably both more likely to be VAD and more likely to receive supplements. Anyway, this is irrelevant to the calculation of mortality ratios, which do not depend at all on the census records.

Richard Peto's explanation for the heterogeneity between DEVTA and previous trial results

Speaking as a professor of medical statistics, Richard Peto believes that the heterogeneity between the results of DEVTA and the average of the results of the 8 main previous trials was due mainly to the play of chance, despite the p-value of 0.001 for heterogeneity. There have been other instances of striking heterogeneity between the results from different trials of much the same therapeutic question.

Opposition to VAS

There has been some literature strongly opposing VAS. The debate on VAS is polarized between people who believe that it reduces child mortality by 20-30% and those who believe that it is ineffective or unsafe. Oxford holds an intermediate position: that while VAS is safe and reduces child mortality, the reduction is probably only about 5%-16%, as indicated by the CI for the average of DEVTA and the other trial results (see figure, above).

Some Indian pediatricians were opposed to Alfred Sommer, one of the major proponents of VAS. Some of them believed that VAS was eclipsing more important forms of pediatric healthcare. Some were also sensitive to foreigners administering VAS programs in India.

The safety of VAS

Some deaths of children a few days after receiving VAS in non-trial mass treatment in India have been unjustifiably attributed to VAS, even though there was no comparator group without VAS to help assess how many deaths should have been expected without VAS. The VAS program in the Indian state of Assam was halted due to these safety concerns. There was a court case on the safety of VAS, in which the government of Assam was made to compensate the parents of children who had died after receiving VAS.

However, the evidence from DEVTA shows that there is no material increase or decrease in mortality immediately after VAS. In the week before treatment was due to be administered in DEVTA, there were 356 deaths of children who would have been due for VAS (consistent with the annual mortality rate), while in the week starting on the day VAS was to be given there were 354 such deaths (suggesting that no excess mortality was caused in Assam).

Comment: Any mass treatment or mass vaccination program is likely to encounter the same apparent safety issues. There will always be children who die of natural causes shortly after receiving treatment, and often these deaths will be blamed on the treatment.

Oxford's comments on GiveWell's report on VAS

The Oxford investigators believe that some of the quotes in the references of the report are not supported by strong evidence, and they disagree with many of Dr. Sommer's criticisms.

In particular, they believe that reference 89 may be misinterpreted by readers not familiar with DEVTA. The reference says, "In 2005–06, shortly after DEVTA ended, only 6.1% of children aged 6–59 months in Uttar Pradesh were reported to have received a vitamin A supplement in the previous 6 months according to results from the National Family Health Survey, a national household survey representative at national and state levels."

The reference implies that the DEVTA program did not achieve the compliance it had reported. However, DEVTA was completed in autumn 2004, a significant amount of time before the National Family Health Survey. Additionally, DEVTA operated in only 7 out the 70 districts in UP and provided VAS in only 3% of the blocks (sub-districts) in UP. Among those blocks, VAS was distributed only from ones that had functioning AWCs. [This response will be added to the reference].

All GiveWell conversations are available at http://www.givewell.org/conversations