

## DEVTA: results from the biggest clinical trial ever



In developing countries health resources are short, so it is particularly important that science should inform policy. In *The Lancet*, a landmark trial<sup>1,2</sup> tests two so-called magic bullets of the international health community's armoury: pre-school vitamin A supplementation, assumed to reduce child mortality by a quarter;<sup>3</sup> and intestinal deworming, assumed to improve child nutrition, growth, and cognitive development.<sup>4</sup>

Richard Peto and colleagues taught us in the 1980s to "ask an important question, and answer it reliably" with large, simple randomised trials testing the effects on mortality of practicable treatments for common conditions.<sup>5</sup> DEVTA epitomises this vision. It is the biggest drug trial ever undertaken, with 2 million pre-school children in India consuming four tonnes of vitamin A and eight tonnes of albendazole over 5 years. It is a credit to all participating: the scientists in Lucknow and elsewhere, the field staff, the anganwadi workers, and the mothers and children. DEVTA is of staggering size, but the delay in publication is equally staggering, in view of the important policy implications for India and the rest of the developing world. Data collection was completed in 2006 and preliminary results for vitamin A (but not deworming) were presented at a meeting in Turkey in 2007, with the presentation available online.<sup>6</sup> Then silence until now, punctuated only by calls from us and others for the team to publish.<sup>7,8</sup> Today, the authors reveal that neither intervention showed a significant effect on child mortality in their trial.

Before DEVTA, the randomised evidence base showed that vitamin A reduced mortality by a quarter, based on 17 trials in 194 795 children.<sup>9</sup> DEVTA, with ten times the number of children (although contributing only about twice as much information, because of cluster effects) estimates mortality reduction at 4%, with 95% CIs ranging from an 11% reduction to a 3% increase ( $p=0.22$ ). On the basis of their meta-analysis, the trial authors propose that DEVTA attenuates the global estimates of mortality reduction by half. Their forest plot suggests heterogeneity, confirmed in a sensitivity analysis in the Cochrane review:<sup>9</sup> so an alternative interpretation is that vitamin A does not affect child mortality in all settings all of the time. If we accept the authors' analysis that this trial simply reduces the global estimate of benefit by half, the question still remains as to why the maximum

estimated mortality reduction of 11% is so substantially different from the estimate of the other 17 trials.<sup>9</sup> Since there is clear evidence of vitamin A deficiency in the study site, this finding is unexpected. Had access to preventive and curative health-care interventions improved, as in many developing countries? Perhaps—even in settings of low service access, there have been substantial reductions in mortality due to diarrhoea and the incidence of measles,<sup>10–13</sup> probably the main routes to mortality benefit in earlier trials.<sup>9</sup> The interpretation of these findings in the context of existing research needs further debate, but what is clear is that DEVTA creates uncertainty around this intervention—or at least uncertainty around the effect size that has been attributed to vitamin A up until now. There could be shifting effects in public health nutrition over time; also, controlled trials of vitamin A are probably worthwhile and ethically justified.

For deworming, the results are also somewhat surprising. A community trial of deworming children in Lucknow, completed in 1994, estimated an average weight gain of almost a kilogram.<sup>7</sup> When DEVTA was set up in nearby rural areas, it was reasonable to assume that such effects would translate into long-term health benefits, making the hypothesis that deworming might affect child mortality worth testing. Yet DEVTA shows no significant effect of deworming on pre-school mortality (mortality ratio 0.95, 95% CI 0.89–1.02,  $p=0.16$ ). Furthermore, the annual compliance monitoring in selected centres did not even suggest an effect on

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weight, although worm loads were light. Indeed, in Lucknow, one early trial completed in 1994 did show big effects on weight, but subsequent trials did not; this outcome mirrors trends globally, with older trials in Kenya estimating big effects on weight, but more recent trials showing little or no effect.<sup>7</sup> In the Cochrane review,<sup>7</sup> for most studies, community deworming effects on growth and nutrition have been limited or absent, apart from in isolated communities where worm burdens were high. Although debate about deworming currently centres on whether the intervention affects educational achievement,<sup>14</sup> DEVTA highlights the debate about whether deworming of populations can lead to substantial long-term developmental benefits in the absence of demonstrable health effects.

Why were the results of DEVTA so delayed? Was it because the trial found no evidence of effect?<sup>15,16</sup> The authors shared DEVTA vitamin A results with the research and policy community in 2008, and they state that “feelings ran high”. As a result, the authors wanted to do further checks to ensure they were not “discredited by a malicious attack on details”.<sup>14</sup> Reading the authors’ narrative, it sounds an unnerving experience for them. Belief disconfirmation bias is a recognised phenomenon. When people are faced with evidence that disconfirms their beliefs they subject it to intense critical evaluation; but when exposed to confirming evidence they take the evidence at face value. This phenomenon means that people might reject good science because, put simply, they don’t like the results; and this biased assimilation of evidence leads to polarisation of attitudes.<sup>17</sup> The believers become more entrenched on one side, with the holders of the evidence on the other, and policies are thrown into confusion.

In Hindi, DEVTA means deity or divine being, and the divine signals emanating from this trial should not be lost. No-one would want to waste money on exaggerated benefits, and just the size of DEVTA shakes beliefs in current global policies promoting vitamin A and deworming to the core. Ironically, the largest drug trial in the world hasn’t settled the policy questions, but has generated uncertainties. As an international community of scientists participating in policy, we must ensure that this trial, now its results are published, doesn’t polarise, but becomes part of open, public, transparent debates to ensure the best use of finite resources to contribute to the health of children in developing countries.<sup>18</sup>

DEVTA is a courageous study, and a watershed for best practice in research to inform international development. The delays, the authors have countered, were in part to ensure integrity of the data and because their resources were limited. So funders should invest—and invest heavily—in such studies, and not shy away from funding big trials because DEVTA did not show a difference.

And what can researchers learn from DEVTA? Undoubtedly, the fact that there was no apparent effect detected delayed publication. The best way to underline this lesson for us all is to modify the criteria of a good trial to: “Ask an important question, answer it reliably; and publish the results promptly, irrespective of the findings”.

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