Vitamin A deficiency has plagued human society throughout history. It will not disappear until vulnerable populations have achieved normal vitamin A status by sustained changes in dietary vitamin A intake. We must all strive to improve the diets of those who are now vulnerable. Until then, periodic large-dose vitamin A delivery has a vital public health role in protecting child health and survival.

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References

Reply to West et al. Vitamin A policies need rethinking

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We have the following points to make in response to the commentary by Dr West and his distinguished colleagues.1

The first premise in our paper was that response to vitamin A capsule (VAC) intervention (as with most others) depends on context, in this case on disease patterns and prevention, especially immunizations. For example, Prentice et al. state: ‘Vitamin A provides a good example of how supplementation may have quite different effects in different..."
age groups or against different disease backgrounds'. This context has incontrovertibly changed since the efficacy trials of the 1980–90s. Therefore it is reasonable to question whether effectiveness of large-scale distributions of VACs can still be assumed. In the commentary, this premise is not addressed, concerning either diseases or immunizations. Thus we stand by our position, which appears not to be directly questioned.

It is not correct to state that DEVTA is the only negative result. First, if the trials included in the meta-analyses are examined (e.g. Beaton et al.,4 Imdad et al.5), it will be seen that several showed no benefit: in Beaton et al.,4 of the six trials of 4–6-monthly VACs, four showed significant impact, two did not; among the 15 trials quoted by Imdad et al.,5 (see their Figure 3, omitting the Tamil Nadu results which should not be included being weekly VA), seven had significant results and eight did not. Second and more important, both DEVTA from India (1999–2004) and a study in Guinea-Bissau (2007–09), published in August 2014,6 showed similar negative results; further, a re-analysis of the Ghana VAST trial showed that the mortality effect of that study was confined to unvaccinated children.7 The criticisms of the DEVTA study suggest that it should be viewed as (indeed) the only effectiveness trial of a large-scale programme that we have. One of the co-authors of Dr West’s letter (J.H.) has cogently argued for the distinct uses of efficacy and effectiveness results;8 when seen in this light, implementation problems (on which presumably we have to follow the published descriptions from the trial investigators3,9 until otherwise agreed) are crucial to include in the assessment. The unavoidable conclusion is that distribution of VACs did not work in the context of Uttar Pradesh, India.

In situations of uncertainty it seems important to be very clear on what is evidence and what is not. For example in West et al.’s letter, reference 3 is not a research report; reference 5 is to a meeting in February 2012 whose report still has not been issued after nearly 3 years (promised in 201410 and then in 201511). West et al. reject the DEVTA results, which was a trial aiming to measure the mortality impact of VAC, although elsewhere they suggest that it ‘is really a programme evaluation’.12 We agree it should be used as a programme evaluation. Their references 9–11 may be ‘consistent with’ effects, but association is not evidence of cause, particularly at aggregate level when there is no agreed mechanism. When the under-5 mortality rate is falling anyway, inferences are vulnerable to ecological fallacies, particularly with highly aggregated data. Reference 9 calculates mortality from assumed relative risks from the literature, not from new estimates. Reference 11 also primarily calculates impact from assumed relative risk and coverage; it does not assess the actual risk, beyond noting that mortality changes and VAC coverage are associated in that they were moving in the same directions at national level in two countries; the authors comment that ‘Many factors may have contributed to these (mortality) declines’. The references as described, like the assertions we refer to in our third paragraph above, seem to give an impression of consistency when it is the inconsistency that is striking, suggesting effects dependent on context, as might well be expected. This agrees with Fawzi’s comment: ‘Finding consistency in the effects of vitamin supplementation in trials around the world may be less likely than it would be for other interventions, because [of] the differences in the nutritional backgrounds and the infectious disease burdens in different countries and the different social settings within countries’.13

Improved understanding of the mechanisms involved in the mode of action of high doses of vitamin A and of associated problems is now emerging. Prentice and others state: ‘Although universal vitamin A supplementation is now accepted policy, the need for scientific clarity concerning its basic mode of action has never been greater’.13 The work of Benn, Aaby and colleagues6,14,15 has suggested that the inconsistent responses to VAC (themselves a sign of complex interactions) relate to vaccination status, age, gender and other contextual factors including those mentioned in our first paragraph. Further, some results suggest increased mortality effects in certain groups, with significant VAC/gender interactions. As to mechanisms, ‘One possibility is that high-dose vitamin A supplements bypass the normal physiological controls on the availability of vitamin A to the immune system. Iron supplementation regimens face a similar conundrum with regard to adverse interactions with malaria infection’.16

It seems worth reiterating that the proportion of total under-5 mortality rate possibly reduced by VACs provided to 1–5-year-old children is now less than 5%, as we note in our paper. Should not this alone be forcing a reconsideration of policy?

In view of all this, it seems probable that if the evidence were reviewed in its totality today, the advisability of providing hundreds of millions of children with VACs would be questioned. Added to this, consideration is needed of the considerable expense and undoubted opportunity costs, for example by continuing to distribute VACs through monthly child health days;17,18 these were originally primarily for supplementary immunizations, which are now winding down and may be less frequent (e.g. every few years for supplementary immunization activities for measles).15 Do we think there is a benefit for the majority of children who have normal vitamin A status [e.g. the 70% with serum retinol (SR) > 20 μg/dl], in giving them an additional large dose of vitamin A? There are indications of risk for some groups of increased mortality (as suggested by Benn et al.;6,14) why would we risk this, at least for well-nourished children who
are unlikely to benefit? Where is ‘first do no harm’? This issue is also being raised specifically concerning fortification—is it safe to fortify when there are 6-monthly large doses being given?20

Surely we need an independent, objective review of overall policies for tackling vitamin A deficiency, and we should no longer drag our feet. This must be broader than the 2012 GAVA meeting to which Dr West refers (his ref 5), whose new policy recommendations (as far as can be ascertained) seem in practice much like the old ones, adding assessment of serum retinol; by these guidelines, VACs will be ‘needed’ for the next century. This independent review is needed soon; what institution has the status and demonstrated independence to convene it?

References