Could child vitamin A supplementation have long-term health effects?

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Mason et al. raise issues concerning the widely implemented high-dose vitamin A supplementation programme for young children in low-to-middle income countries, because the programme may no longer be having the beneficial effects on child mortality seen in randomized controlled trials 20 years ago.¹ The high-dose vitamin A supplementation programme was originally instituted after vitamin A was unexpectedly found to protect against child death as well as vision loss.¹ However, the mechanism by which vitamin A reduced child mortality was never specifically identified, so vitamin A could be protecting against something which is no longer relevant to child mortality in low-to-middle income countries. For example, vitamin A protects against specifically diarrhoeal disease and possibly measles, but not pneumonia,² when control of childhood infectious diseases has improved in low-to-middle income countries over the past 20 years.¹ These issues concerning short-term effects may well be addressed by the next review of the high-dose vitamin A supplementation programme due in 2016.³ What might perhaps also be relevant is whether high-dose vitamin A supplementation has any long-term effects.

When the high-dose vitamin A supplementation programme was started, vitamin A and its precursor β-carotene, like many vitamins and minerals, were seen as potentially protective against a broad range of diseases affecting children and adults in low- and high-income countries, including infections,⁴ cardiovascular disease⁵ and cancer,⁶ so there was no reason to think that vitamin A would be anything other than beneficial. However, for adults in high-income countries these observed protective effects have now largely been refuted by randomized controlled trials which instead suggest that high doses of vitamin A could increase mortality.⁷ Moreover, since David Barker re-ignited interest in early-life processes connected with chronic diseases,⁸ chronic diseases are much more seen as products of exposures throughout life. Taking these two developments together raises the question as to whether high-dose vitamin A supplementation in young children in low-to-middle income countries could have long-term effects on susceptibility to the adult chronic diseases which are now becoming more common globally.⁹ Vitamin A has pleiotropic effects and plays a physiological role in many processes connected with chronic diseases, such as atherosclerosis,¹⁰ lipids,¹¹ hormones¹²,¹³ and obesity,¹⁴ which might also need to be taken into account in any evaluation of the costs and benefits of a vitamin A supplementation programme. Whether these effects are in any way related to mode of delivery—increased intake of relevant foods such as...
We agree with Mason et al. that time is ripe to rethink vitamin A policies.1 We recently published the results of the first individually randomized placebo-controlled trial testing the World Health Organization (WHO) policy of providing high-dose vitamin A capsules (VAC) at vaccination contacts to children after 6 months of age in vitamin A deficiency-endemic countries.2 In Guinea-Bissau, from 2007 to 2010, we found no overall beneficial effect, the overall effect being a non-significant mortality reduction of 9% (−41–41%).2 This result is in line with the only other recent assessment of VAC, a cluster randomized open Indian trial from the early 2000s.3 Hence, though a recent meta-analysis based on older VAC trials from the late 1980s and early 1990s concluded that VAC are associated with a 24% reduction in overall mortality, 4 like Mason et al. we speculated that the effect of VAC may have changed over time.2

However, in contrast to Mason et al., we do not believe that VAC can be phased out and replaced by more regular low-dose vitamin A intake without further studies. The effect of VAC may be very different from the effect of regular low doses of vitamin A. Vitamin A affects the immune system in many ways5 and there is increasing evidence that the high vitamin A content of VAC—more than 100 times the recommended daily allowances—has immune-modulating effects. Our recent trial is a good example: we found a strong interaction between VAC and sex. VAC were associated with a 55% (13–76%) reduction of overall mortality in females, but at the same time VAC were associated with a borderline significant 92% (−2–275%) increase in mortality in males.2 The prevalence of vitamin A deficiency (VAD) is high and similar in males and females in Guinea-Bissau,6 hence the effect of VAC...