

## High dose vitamin A capsules – Rusty bullets?

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### Summary

High-dose vitamin A capsules (HDVAC) are distributed to preschool children in low-income countries on the assumption that they reduce mortality and treat vitamin A deficiency. As for other so-called magic bullet approaches, donors and policy makers consider their large-scale distribution highly cost-effective. Consequently, other ways to improve vitamin A status have received less attention; both donors and governments assume HDVAC are doing most of what needs to be done. Yet, the only evidence for an effect on mortality comes from 25-year-old studies and this effect no longer appears to be substantial. Surprisingly, impact evaluations have been absent. The only study that might be considered an effectiveness or impact evaluation found HDVAC had no effect in northern India. It is not widely appreciated that the impact of HDVAC on vitamin A status is limited, temporary and not cumulative over time. Nor can it be given to women except immediately after giving birth, and thus it is an inappropriate intervention for tackling vitamin A deficiency. To ensure that we use limited resources wisely, we need to identify and scale up strategies which combat vitamin A deficiency and reduce mortality.

### Blanket high dose vitamin A supplementation policy

WHO's recommendation for universal blanket high-dose vitamin A supplement distribution to children between 6 months and 5 years of age dates back to 1994 (World Health Organization, 1997), and was originally based on eight trials enrolling preschool children. Six of these trials indicated beneficial effects of vitamin A supplements on mortality and a meta-analysis suggested an overall 23% reduction (Beaton, et al., 1993). Beaton commented that "There was no relationship between the baseline prevalence of xerophthalmia and the relative effect of vitamin A". However, in spite of the poor correlation between baseline vitamin A status and the mortality reducing effect of supplementation, the target population is defined by level of vitamin A deficiency (VAD) (areas where >20% of children aged 6 months-5 years have serum retinol <0.70 µmol/l) (World Health Organization, 2011c). In the absence of biochemical data, under-five-mortality rates have been used as a proxy for VAD (Schultink, 2002). More recently, WHO has been using multiple indicators to evaluate whether VAD is expected to be a problem in a country, including life expectancy at birth, under-five-mortality rates, gross domestic product, malnutrition rates, measles immunisation rates and regional indicators (World Health Organization, 2009). Based on these figures, WHO estimates that VAD affects a large proportion of children in South-East Asia and Africa (44-50%), estimates which are also supported by recent models based on biochemical data (44-48%) (Stevens, et al., 2015). While VAD is associated with higher mortality (Humphrey, et al., 1992), there are examples where distribution of HDVAC does not lower mortality. However, in spite of the heterogeneity of the results of the eight studies, it has been assumed that the 23% lower mortality found by the meta-analysis would reflect the impact of HDVAC in all populations with VAD as a public health problem. I.e., assuming that HDVAC will lower mortality in young children in a population with VAD. Hence, rather than examining whether HDVAC lowers mortality, the research agenda has focused on how an assumed benefit could be optimised, and beyond assessment of coverage, virtually no impact assessment has taken place.

### Extending the benefits of HDVAC

Even children of well-nourished mothers are born with low stores of vitamin A (Humphrey, et al., 2000), and all children therefore depend on vitamin A intake from early life. In well-nourished populations, breast milk is sufficient to meet this demand and build infant stores (Humphrey, et al., 2000). However, since breast milk vitamin A reflects the vitamin A status of the mother (Stoltzfus, et al., 1995; Semba, et al., 2000), the quantity in breast milk in most mothers in low income countries, while not resulting in deficiency, is insufficient to provide infants with liver stores (Humphrey, et al., 2000; Liyanage, et al., 2008). Thus, there have been efforts to extend the expected benefit of HDVAC to children below the age of 6 months.

Marginal vitamin A status in women may be aggravated and lead to night blindness during pregnancy (Christian, et al., 2000), and thus many lactating mothers also have low vitamin A stores. Supplementing the mother with mega-dose vitamin A in the postpartum period was long recommended based on a presumed benefit through improved vitamin A status of both the mother and infant (World Health Organization, 1997). However, meta-analyses of maternal postpartum supplementation has shown no benefit on maternal, neonatal or infant mortality (Gogia, et al., 2010; Oliveira, et al., 2016) and the recommendation to give postpartum VAS has been withdrawn (World Health Organization, 2011d).

Lower dose supplementation to women of reproductive age has also been attempted. While one early report suggested this might reduce maternal mortality (West, et al., 1999), later controlled trials failed to confirm this (Kirkwood, et al., 2010).

Vitamin A supplementation of the newborn child looked like a promising strategy based on an Indonesian trial from 1996 (Humphrey, et al., 1996) – but further evidence failed to confirm that as well. A meta-analysis of 12 trials indicated no benefit of neonatal vitamin A supplementation on survival in infancy (Haider, et al., 2017). Similarly, HDVAC to children between 1-5 months has not been associated with a beneficial effect (Imdad, et al., 2016).

Hence, in spite of VAD being present in children younger than 6 months (Humphrey, et al., 2000), supplementation in neonates, 1-5 month old children and women (for their own sake or for the young infant) has not been shown to reduce mortality and thus are no longer recommended (World Health Organization, 2011b; a).

### Current evidence for HDVACs

In contrast, due to the assumed almost universal benefit, the HDVAC programme for preschool children has obtained a status where it has practically been considered unethical to question the programme. When the update to Beaton's meta-analysis was published in 2011, the reported 24% (17-31%) mortality reduction was based on only trials conducted before 1995 (Mayo-Wilson, et al., 2011). Nevertheless, the new meta-analysis reinforced the recommendation for HDVAC to children 6 months to 5 years in populations at risk of deficiency and the accompanying editorial underlined that the research efforts needed were to find new ways to cover all, not to evaluate its impact (Thorne-Lyman, et al., 2011).

In a more recently published meta-analysis (Imdad, et al., 2017), two later trials were included. In one of these, the impact of HDVAC was tested in the huge DEVTA cluster randomised trial in India. One million children with a population level deficiency of approximately 60% were cluster randomised to HDVAC or nothing, and no impact on mortality was found (Awasthi, et al., 2013). In an individually randomised trial from Guinea-Bissau, there was also no overall mortality benefit of vitamin A supplementation (Fisker, et al., 2014). Including these trials in the meta-analysis, the estimated benefit of HDVAC was reduced to 12% (7-17%) but the conclusion remained "In populations with documented vitamin A deficiency, it would be unethical to conduct placebo-controlled trials" (Imdad, et al., 2017).

However, it should be noted that the study results were highly heterogeneous, suggesting that a pooled analysis including all trials conducted between 1981 and 2010 is not necessarily meaningful. When the estimates of the mortality impact for the individual trials are plotted over time, the impact has clearly declined (Mason, et al., 2015). Including the two recent trials in the meta-analysis with the pre-1995-trials, may therefore not answer the question about what effect from HDVACs can be expected today. Furthermore, trials as DEVTA, with a million children over a 5-year period may rather be considered an effectiveness trial and better reflect the estimated impact under real life conditions.

Provision of HDVAC in campaigns has been judged cost-effective based only on the assumed, not measured mortality impact. However, bi-annual vitamin A campaigns are inevitably diverting resources from routine

health services (Cavalli, et al., 2010) and exerting relatively high opportunity costs on countries with weak health sectors.

To lower implementation costs, integrating HDVAC with other health care is recommended. To piggy back the VAS programme on another successful programme achieving high coverage, WHO recommends integration of vitamin A with immunisation services (World Health Organization, 1999). While providing VAS with routine vaccines could provide an assumed beneficial intervention to young children and – based only on modelling would affect mortality (Kupka, et al., 2016), it would not reach high coverage rates beyond 12-24 months where no vaccines are scheduled.

In spite of having been recommended for >20 years, neither the effect in controlled settings nor the impact in programme settings of providing VAS alongside vaccines was measured. Based on studies which indicated that there were no major adverse effects and that immunity against measles was not impaired if 100,000 IU vitamin A was given with measles vaccine at 6-11 months of age, it was judged safe to give HDVAC with vaccines after 12 months (Semba, et al., 1995; Benn, et al., 1997; Semba, et al., 1997; Arya, et al., 2000). However, the effect of providing HDVAC with vaccines on overall child health was unknown.

In the first randomised placebo-controlled trial of vitamin A given at vaccination contacts on mortality (Fisker, et al., 2014), in spite of two thirds of the more than 7500 children being vitamin A deficient, no overall beneficial effect of HDVAC was found: a 9% non-significant reduction in mortality. However, as has been seen in other studies (Benn, et al., 2005; Benn, et al., 2008; Benn, et al., 2009; Benn, et al., 2010), opposing effects were seen in boys and girls; boys had a 92% (-2-275%) increase in mortality while mortality in girls was lowered by 55% (13-76%). Hence, the assumption that providing HDVAC to children with vaccinations after 6 months of age can never have a negative effect on child mortality may not be correct.

#### [HDVAC may interfere with more effective methods of improving vitamin A status](#)

HDVAC is recommended in areas with high rates of vitamin A deficiency. However, the impact on serum retinol is small and its effects are always transient, raising serum retinol above deficient levels for only 1-3 months (Mason, et al., 2015).

Initially, HDVAC policy was intended only as a stop-gap solution for the short term, and was to be replaced by more sustainable solutions in the longer term (World Health Organization, et al., 1994). Indeed it was specified in the original policy papers that with the integration HDVACs into the immunisation programme, countries “should plan from the outset to provide a food based solution within a defined time period such as five years” (World Health Organization, et al., 1994). However, due to the presumed magic bullet properties of HDVAC, some observers have reported that policy makers and donors (including those funding HDVAC) may be misled into thinking HDVAC is all that needs to be done—or that it is so effective that other approaches can safely be given low priority (Greiner, 2012). Similarly, we have experienced that some government policymakers express an unwillingness to mandate fortification with vitamin A out of fear that children receiving HDVAC might suffer from excessive doses.

HdVACs are being promoted based on their assumed impact on mortality but the target populations are defined on the basis of the level (or expected level) of VAD and the expected impact is assessed on the basis of coverage (Bhutta, et al., 2013). In addition, VAD frequently co-exists with other deficiencies and can be as prevalent in pregnant and lactating women as in young children. Thus, other approaches must be sought. However, based on its assumed impact on mortality, HdVAC has long been ranked as one of the world's most cost-effective interventions (Horton, et al., 2008; Bhutta, et al., 2013), giving the feeling that little attention is needed to other, more complex, interventions. While mandatory vitamin A fortification could solve the problem of VAD deficiency in a low cost way, its implementation has been slow with the nearly universal HdVAC approach. Though now implemented at a wider scale than 10 years ago, a third of countries providing HdVAC to children do not have fortification programmes (Wirth, et al., 2017).

Though other approaches to combat VAD, e.g. food-based interventions exist and are efficacious (Greiner, 2013), in many low-income countries, once HdVAC are in place, government funds are inadequate to allow more to be done for vitamin A. Though we have heard many policymakers say they would prefer food-based approaches over HdVAC, we know of no cases where they were given that option in the use of donor funds. Since the mid-1990s, choosing food based approaches over HdVAC would have been considered unethical. Yet for women, where HdVAC is not a solution, and the efficacy of high carotene foods like carrots and papaya has been clearly shown (Ncube, et al., 2001), no large-scale programs have been implemented as far as we know.

If the approach for phasing out HdVAC proposed by the Global Alliance for Vitamin A (two nationally representative surveys finding <5% with serum retinol < 0.70  $\mu\text{mol/l}$ ) (GAVA, 2014) were to become WHO guidance, there may never be a chance to stop HdVAC. Therefore, a stand on whether blanket HdVACs is an adequate solution has to be made by the international players, in particular WHO. If WHO is to formulate guidelines on strategies for reducing VAD applicable for a wide range of countries, evidence that the interventions are associated with overall beneficial effects also under varying conditions are needed. In our opinion, current evidence does not support the case for universal HdVAC. Apparently that notion is not shared by UNICEF and some funders who still find it justified to model impact, based on averages of effects on mortality seen in research 25 years ago and no effect today (Kupka, et al., 2016).

### [Interactions between HdVAC, vaccines, and the immune system](#)

Of the original eight vitamin A trials, HdVAC was tested in six, and in four of those six trials there was evidence of a beneficial effect. Based on these trials and the trials testing whether there was benefit to younger children, a hypothesis was put forward in 2003: That the effect of HdVAC depends on other immunologic stimuli at the time of supplementation, in particular vaccines (Benn, et al., 2003).

Accumulating evidence indicates that vaccines, in addition to inducing a specific protective effect, leaves imprints on the immune system, altering the response to unrelated pathogens often in a sex-differential manner (Benn, et al., 2013). Vitamin A and vitamin A metabolites also may have far-reaching effects on the immune system. It was recently shown that vitamin A in vitro induces epigenetic changes at the monocyte level, which can lead to fundamental alterations of the innate immune system, with potential consequences for the response to a large range of pathogens (Arts, et al., 2015). Through acting as immunomodulators, HdVAC may have varying effects, dependent on the situation in which it is given.

Potentially, interactions with vaccines could help explain the contrast between a possible beneficial effect in the late 1980s and early 1990s, and little or no effect today. If HDVAC is beneficial when co-administered or given close to with live vaccines, but detrimental when given with inactivated vaccines (Benn, et al., 2003), that could explain why VAS is not beneficial in children below 6 months who around the same ages receive the inactivated diphtheria-tetanus-pertussis vaccines, but may be beneficial later in life when the live measles vaccine is given. Vaccines are not the only immune-stimuli that could potentially alter the effect of HDVACs. In addition to vaccination status and sex, the effect of HDVACs may also depend on previous receipt of HDVAC and on season (Benn, et al., 2015).

The explanation for the lack of impact of HDVAC today, may also be explained by a change in the diseases which are known to have some interaction with vitamin A status (Mason, et al., 2015). Measles is effectively controlled through vaccination and diarrhoeal deaths have declined through vaccination, improved water and sanitation and improved treatment. Regardless of why the effect of blanket vitamin A supplementation with HDVAC has changed, HDVAC may not have an overall beneficial effect – and evidence indicates that it likely harms subgroups.

### Ignore or explore?

Almost no post-implementation evaluation of HDVAC has taken place, partly because many consider it unethical to test the policy, at least in ways that involve withholding an intervention from some children that is assumed to be beneficial. However, evidence is growing that the context within which HDVAC was efficacious 25 years ago has now changed. In the light of the very heterogeneous effects of HDVAC, further effectiveness trials are justified. Indeed, to clarify under which circumstances HDVAC reduces mortality, has no effect, and when it may even increase mortality, further trials are needed.

In light of the accumulated evidence that HDVAC is not uniformly beneficial, we cannot justify continuing to provide biannual HDVAC to millions of children in 82 countries (UNICEF, 2017). We must acknowledge that policies are made based on the best evidence or interpretation of evidence at the time of formulating policy, but that does not mean that the policy reflects an unchangeable truth, especially when relevant circumstances change. The scientific evidence will have to be gathered to make better policies; clear and “implementable” messages are worth striving for, but a simple policy itself is not the final objective: focus must remain on the distal objective, to improve child health. When conditions change, so may the effects of interventions and so must policy.

### Stop modelling and start testing!

To identify to which subgroups HDVAC is beneficial we need large randomised trials. A two-armed study comparing HDVAC and placebo may help formulate better HDVAC policy, but it will not provide sufficient evidence to formulate the optimal vitamin A policy. Ideally, the effect of HDVAC in populations with VAD should be compared to other means of improving vitamin A status, such as low weekly doses, fortification and food based approaches.

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