Vitamin A policies need rethinking

**Summary of research**

**Location:** Global

**What we know:** Vitamin A deficiency (VAD) remains prevalent worldwide. Periodic (6 monthly) high dose distribution of VA has been the primary intervention since the 1990s.

**What this article adds:** A narrow focus on one intervention has hampered progress on VAD. The impact of high dose VA distribution on mortality has only recently been directly measured (DEVTA trial, India) and shows no mortality impact – disease patterns (diarrhoea and measles) have changed, high dose VA has minimal impact on sub-clinical VAD which carries risk beyond mortality and infectious disease. Increasing frequent low-dose vitamin A consumption among deficient populations should be prioritised with concurrent reduction in a high dose approach. Policy change is underway in India.

Vitamin A (VAD) deficiency, defined by the World Health Organisation (WHO) as low serum retinol (<20 mcg/dl), affects around 30% of children throughout low- and middle-income regions, and this prevalence is decreasing only slowly. This poor progress is despite periodic high-dose supplementation that is reported to cover more than 80% of the total child population in low-income countries. The rate of improvement has been about 0.3 percentage points (ppts)/year, e.g. a prevalence change from 30% to 25%. At this rate, it will take another 100 years to eliminate the problem. In contrast, the rate of change in iodine deficiency prevalence is three times higher and, if this rate continues, iodine deficiency will be eliminated in the next decade.

A recently published paper argues that this failure to make more progress on VAD is not due to lack of evidence-based effective interventions, but might be ascribed to a failure to adequately apply scientific knowledge to policy making. One intervention, 6-monthly distribution of high-dose vitamin A capsules aimed at reducing child mortality, has largely displaced alternatives since the 1990s. It is argued that this narrow focus on one intervention and one objective misses the opportunity to reduce widespread mild-moderate (‘sub-clinical’) VAD in children and women, which periodic high-dose Vitamin A does not ameliorate, but which contributes significantly to risk of disease, in children and in women.

Vitamin A interventions first addressed corneal damage and blindness, starting in the 1970s. Trials and programme evaluations showed that high doses of vitamin A (200 000 IU) at intervals of 6 months to children (usually aged 1–5 years) substantially reduced or eliminated clinical eye signs, after one or more years of intervention Then an unexpected and large effect of 6- monthly high-dose Vitamin A on mortality in children was found in Indonesia, further tested in five prospective trials of 4–6-monthly high-dose vitamin A supplementation. Meta-analyses of these results (plus two with daily or weekly vitamin A supplements of lower dose) at the time (1993) estimated the average reduction of mortality ascribed to vitamin A in children in this age range at 23%. This was apparently due to reduction in measles and diarrhoeal mortality, with no effect on mortality linked to respiratory tract infections (RTIs) or malaria. This finding focused attention on the potential for a major impact on child mortality by 6-monthly high dose vitamin A supplementation for 1–5-year-old children. Since the 1990s, nearly 8 billion vitamin A capsules (VACs) have been distributed to children in over 100 low and middle income
countries (LMICs).

However, the impact of this extensive programme, launched in the 1990s, was never directly assessed until recently. Many claims were made of numbers of lives saved, but these were all calculated from the coverage and the expected (i.e. 23%) reduction derived from the early efficacy studies (meta-analysis of eight clinical trials (1986-93)). Thus no direct impact evaluations were done until the ‘DEVTA’ trial in India (1999–2004). These results were first reported at a meeting in 2007, and finally published in 2013. This massive study with about 2 million children showed no mortality impact \( P=0.22 \), mortality ratio 0.96, relative risk 95% confidence intervals (CIs) 0.89–1.03. Recently (2010), the meta-analysis was repeated, adding nine newer studies carried out from 1994–2002 (dropping one which involved fortification), for a total of 16 studies. The analysis did not take into account the possible changes in epidemiological patterns in the time between the studies; since the weight ascribed to the newer studies was only 11%, it is not surprising that the conclusion was not altered. What is surprising is that it was not stressed that from 1994 on, only one study showed a mortality effect compared with the no-intervention comparison group \( P<0.01 \), relative risk (RR)¼0.57, 95% CI¼0.42–0.77; no effect was shown when compared with nutrition education. The others showed no effect (95% CIs all spanned 1.0). In this light, the DEVTA result is less surprising.

One explanation for this apparent change in impact of VAC through time is the shift in disease patterns since the 1980s. Results support the hypothesis that changing disease patterns (diarrhoea and measles) may have altered the effectiveness of VACs. It seems very likely that the overall effect of VACs on young child mortality has decreased over time, and by the 2000s became negligible. Since the 1980s, measles immunisation has all but eliminated measles as a public health problem, including in Africa. Mortality from diarrhoeal disease has decreased with control measures including improved oral rehydration, the use of zinc and expanded rotavirus immunisation in some parts of the world. Thus it is plausible that because the causes of VAC-sensitive child mortality, measles and diarrhoea have been greatly reduced, the recent studies are reflecting the situation on the ground. Finally, the postulated effect (if any) in the DEVTA trial highlights the issue of the age range investigated, which was 1–5 years in most studies and 1–6 years in DEVTA. From the deaths reported in the DEVTA study, only 20.8% of the total under-5 deaths were in the target group, aged 1–6 years. In less developed regions overall, it is estimated that 32% of the under-5 mortality rate (U5MR) was in 1–4 year old children in 1990–95, and 29% in 2010–15. Thus this huge effort in VAC coverage is directed (e.g. in India by DEVTA) to only one-fifth of the U5MR; a reduction of possibly 10%, as suggested in the DEVTA paper, amounts to only 2% of the U5MR, and probably less. The broader estimates (29–32%) imply, at 10% reduction of 1–5 MR, that about 3% of the total U5MR would be prevented.

WHO formally re-defined VAD as low serum retinol (SR) in 2002, emphasising that the problem was much wider than clinical VAD (which now has a prevalence of less than 1% in children) and likely to extend well beyond VAC-sensitive child mortality. Vitamin A status thus came to be defined by SR levels, with a cut-point of 20mcg/dl referred to as ‘low’, indicating mild-moderate deficiency, and below 10 mcg/dl referred to as ‘severe’ deficiency. High-dose VACs every 6 months have a transient and minor impact on prevalence of low serum retinol, and thus on ‘sub-clinical’ or mild-moderate VAD. Early studies, for example in India (1971) and the Philippines (1979) and a number since, showed this lack of an effect on SR after about two months after administration.
Re-examination of the original results on vitamin A and mortality from Aceh, Indonesia, suggests that the mortality impact itself is largely restricted to the first two months after dose. If so, two 6-monthly doses per year is far from the ‘full protection’. There is extensive evidence that SR can readily be raised by frequent low doses of vitamin A. In addition, a recent review of the literature on the impact of food-based approaches (outside the context of fortification) was conducted involving 27 papers published since 1992 documenting results from trials of the impact of 38 foods. It found that 25 had a net positive impact on SR and 18 on serum beta-carotene. In fact, the only common vitamin A intervention that does not have this positive effect on SR is periodic high dose VACs. This was indicated from studies in the Philippines, where prevalence of low SR continued to stagnate or increase, even when VAC distribution reached high coverage: here a national programme of distribution of VACs to children every 6 months, started in 1992 and reaching an estimated 90% from the three national surveys of 1993, 1998 and 2003, showed prevalence of low SR (<20 mcg/dl) in children increasing over this period, from 36% to 38% and then 41%. Closer examination of the data indicated that a transient and small increase in SR (e.g. reducing prevalence by about 10 ppts—from 42% to 32% for the overall sample) could be detected at 1–2 months after the dose, then returning to pre-dose levels, which explained the findings. Studies of vitamin A metabolism give supporting evidence on limited retention of vitamin A from high-dose VACs.

Policy statements in the early 1990s stressed the need for a balanced approach of complementary interventions all involving physiological levels of vitamin A provided frequently (usually daily), except for high doses provided 6-monthly by VACs. VACs were seen as a short-term measure, sometimes described as ‘stopgap’ until more sustainable approaches could be implemented. This policy recommendation had little impact; almost all resources and attention began to be directed to VACs and have remained there. Fears expressed at that time of the risks (‘Disadvantages [of supplementation] include . . . risks of inhibiting the development of alternative programmes’) proved to be prophetic. For example, UNICEF reports that around 70% of LMICs—about 150 countries—distribute at least one VAC per year, whereas the Global Alliance for Improved Nutrition (GAIN), the agency taking a lead in fostering fortification, reports that 19 countries have fortification programmes. If policy is now to be changed—or rather, earlier recommendations finally adopted—to replacing VACs with frequent low-dose VA (through supplementation, fortification or dietary change) three questions need to be considered:

- Would there be the benefits of reducing mild-moderate VAD?
- Is this feasible, affordable and good value in promoting health and child development?
- How can VACs be phased out without incurring risks of increasing mortality?

The term ‘vitamin A deficiency disorders’ (VADDs) has been used to emphasize that VAD has important risks beyond mortality, and these go further than infectious diseases to include anaemia, intra-uterine development and birth outcomes, and cognitive development. Thus reducing the prevalence of ‘sub-clinical VAD’, or VADDs, would be expected to have extensive benefit for the health and well-being of at least one-third of the population in LMICs, especially women and children. A further strong argument for the importance of vitamin A in health comes from the recently enlarged understanding of VA’s extensive role in maintaining barriers to infection.
The integrity of epithelia and of the impact of VAD on immune competence in humans, notably in poorer environments. Benefits of vitamin A adequacy to women’s health in general and to that of their unborn children, are almost certain. It is never recommended to give high-dose vitamin A to pregnant women, and thus not to reproductive age women unless pregnancy status is certain—in principle, only during the early weeks after giving birth. Only weekly or daily low doses are recommended otherwise. This is a further strong argument in favour of frequent low-dose Vitamin A intake, so that reproductive-aged women can be included.

The UN in 1993 recommended that ‘a combination of interventions is usually needed to prevent VAD; these include dietary modification, breastfeeding promotion, food fortification, and supplementation’. The mixed approach now needs to be implemented, and monitoring needs to include assessment of SR, which is quite feasible using established methods. One direct means of increasing provision of daily or weekly intakes of vitamin A, through fortification, is now well known. A recent comprehensive review assessed fortification as highly cost-effective in terms of expected health benefits. High-pro-vitamin A carotenoid foods and high-retinol foods are also effective; deworming (treating intestinal worms with periodic medication), and increasing intakes of fats and oils which may increase absorption of carotenoids can also make an important contribution. Why has this policy shift towards a mixed approach not happened? The answer lies in the politics of governments and agencies, and associated reluctance from the scientific community to change earlier recommendations. The funding institutions are not yet aware that substantial change is needed, yet the set of hypotheses supporting the status quo do not stand up to the evidence, and sooner or later a shift must happen.

Many in India, for a long time, have questioned the exclusive VAC approach, and proposals for policy change have been made. GAIN is gathering momentum to promote fortification in a number of countries. This will no doubt go some way to solving the problem. However, this fortification initiative at scale is not coordinated with the VAC programmes, and there is competition for resources. Also worrying is the fact that several countries have rejected the idea of mandatory vitamin A fortification on the grounds that their young children already receive two mega doses annually, and this might cause problems of toxicity.

The authors conclude that the priority for increasing frequent low-dose vitamin A consumption among deficient populations should be heightened, with a parallel or subsequent de-emphasizing of 6-monthly high dose VAC distribution. The DEVTA results have already influenced policy in India. It is time for the rest of the world to follow suit. Many millions of poor and malnourished children would benefit.


Taken from Field Exchange 49

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