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## Public Health Policy

# Vitamin A policies need rethinking

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### Abstract

The prevalence of vitamin A (VA) deficiency, which affects about one-third of children in developing countries, is falling only slowly. This is despite extensive distribution and administration of periodic (4- to 6-monthly) high-dose VA capsules over the past 20 years, now covering a reported 80% of children in developing countries. This massive programme was motivated largely by an expectation of reducing child mortality, stemming from findings in the 1980s and early 90s. Efficacy trials since 1994 have in most cases not confirmed a mortality impact of VA capsules. Only one large scale programme evaluation has ever been published, which showed no impact on 1–6-year-old mortality (the DEVTA trial, ending in 2003, in Uttar Pradesh, India). Periodic high-dose VA capsules may have less relevance now with changing disease patterns (notably, reductions in measles and diarrhoea). High-dose VA 6-monthly does not reduce prevalence of the deficiency itself, estimated by low serum retinol. It is proposed that: (i) there is no longer any evidence that intermittent high-dose VA programmes are having any substantial mortality effect, perhaps due to changing disease patterns; (ii) frequent intakes of vitamin A in physiological doses —e.g. through food-based approaches, including fortification, and through regular low-dose supplementation—are highly effective in increasing serum retinol (SR) and reducing vitamin A deficiency; (iii) therefore a policy shift is needed, based on consideration of current evidence. A prudent phase-over is needed towards increasing frequent regular intakes of VA at physiological levels, daily or weekly, replacing the high-dose periodic capsule distribution programmes. Moving resources in this direction must happen sooner or later: it should be sooner.

**Key words:** Child malnutrition, vitamin A, child mortality

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### Key Messages

- High-dose vitamin A capsules (VACs, 200 000 IU) given 6-monthly are reported to now be provided to some 80% of 1–5-year-old children in low- and middle-income countries (LMICs), amounting to 8 billion VACs to date, aiming to reduce 1–5-year-old child mortality.
- However, the efficacy trials on which this is based were conducted over 20 years ago; only one programme evaluation has been done (DEVTA in India, 1999–2004) showing no mortality impact; VACs affect diarrhoea and measles mortality, which have dropped sharply with improved coverage of immunizations and oral rehydration; thus current impact is likely to be small (e.g. 2–3% of U5MR) or non-existent.
- VACs 6-monthly do not to reduce vitamin A deficiency itself (VAD, as low serum retinol), which affects about 30% of children in LMICs; VAD can be reduced by increased regular intakes of VA at physiological levels, through improved diets, fortification and frequent (daily or weekly) supplements; these are also safe for reproductive-age women, unlike high-dose VACs.
- Therefore it is proposed that a broader approach to reducing VAD—in line with long-standing policy recommendations—should now be adopted, shifting judiciously from periodic VACs to increasing regular intakes, while monitoring VAD changes.

## Introduction

Vitamin A (VAD) deficiency, defined by the World Health Organization (WHO) as low serum retinol (<20 mcg/dl),<sup>1</sup> affects around 30% of children throughout the low- and middle-income regions,<sup>2</sup> and this prevalence is estimated to be decreasing only slowly.<sup>3</sup> This slow progress is despite periodic high-dose supplementation that is reported to cover more than 80% of the total child population in low-income countries.<sup>4</sup> The trends in VAD since 1990 in low- and middle-income countries (LMICs) are shown in Figure 1;<sup>3</sup> the rate of improvement has been about 0.3 percentage points (ppts)/year; e.g. a prevalence change from 30% to 25% is 5 ppts; in 5 years, 1 ppt/yr. At this rate it will take another 100 years to eliminate the problem. Also shown is the recent trend in iodine deficiency, to illustrate the results of a highly successful programme, in this case salt iodization. Here the rate of change in deficiency prevalence is three times higher and, if this rate continued, iodine deficiency would be eliminated in the next decade.

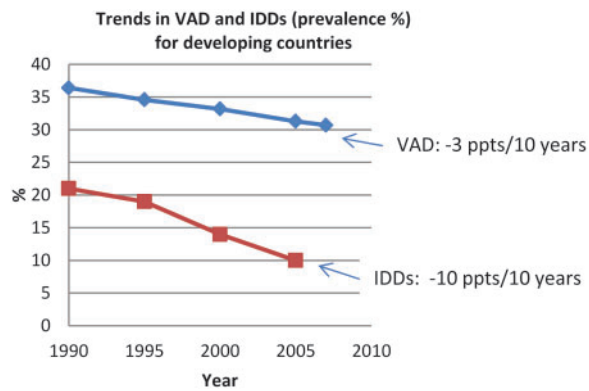
This failure to make more progress is not due to lack of evidence-based effective interventions, but might be ascribed to a failure to adequately apply scientific knowledge to policy making. This stems in part from the complexities of vitamin A's physiological role and metabolism, so that the various potential interventions may have different effects. One intervention, 6-monthly distribution of high-dose vitamin A capsules aimed at reducing child mortality, has largely displaced alternatives since the 1990s.<sup>5</sup> It will be argued here 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 VA does not ameliorate,

but which contributes significantly to risk of disease, in children and in women.

Here we interpret the evidence for the child mortality impact of 6-monthly high doses (200 000 IU) of vitamin A, starting with the results and uses of the original (1980s–90s) trials, and then with the only published large-scale study (DEVTA).<sup>6</sup> Particular note is taken of changing disease patterns and their likely influence. After that we turn to the broader problem of vitamin A deficiency itself (VAD previously 'sub-clinical') measured by serum retinol, and suggest that resources aimed at child mortality should be used to combat VAD itself.

### Vitamin A: 'anti-infective agent'

The importance of vitamin A in human nutrition has long been seen as 'concerned with resistance to infection' (Green and Mellanby, 1928: the paper was entitled 'Vitamin A as an anti-infective agent').<sup>7</sup> VAD was here already linked to damaged membrane barriers to pathogens, notably in epithelial tissues in the respiratory tract and in the intestine and to drying of the eyes, causing xerophthalmia (several types of eye damage are the primary clinical signs). VAD was described in 1965 as 'the most lethal of deficiencies'.<sup>8</sup> The classic *Interactions of Nutrition and Infection*,<sup>9</sup> in the section on vitamin A, said: '...no nutritional deficiency is more consistently synergistic with infectious disease than that of vitamin A. One of the first recognized features of avitaminosis A, increased susceptibility to infection, has had strong confirmation'. In the Institute of Medicine review of 'Prevention of micronutrient deficiencies', Underwood<sup>10</sup> drew the distinction between clinical and sub-clinical deficiencies, noting that low



**Figure 1.** Trends in vitamin A deficiency (VAD), measured as prevalence of low serum retinol (<20 mcg/dl), from 1990; trends in iodine deficiency disorders (IDDs), measured by goitre prevalence, are shown for comparison. Ppts = percentage points.

Sources: VAD, UN-SCN (2010)<sup>3</sup>, Table 5; IDD, calculated from data used for UN-SCN (2010)<sup>3</sup>, Table 13.

tissue concentrations of vitamin A had adverse health consequences, even in the absence of clinical signs.

### Vitamin A and child mortality

Vitamin A interventions first addressed corneal damage and blindness, starting in the 1970s.<sup>11,12</sup> 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 1 or more years of intervention (see Appendix 1, Table A1.1, available as Supplementary data at *IJE* online).<sup>13</sup> Then an unexpected and large effect of 6-monthly high-dose VA on mortality in children was found in Indonesia,<sup>14</sup> 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%.<sup>15</sup> 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 LMICs, and recently the United Nations Children's Fund (UNICEF) gave estimates of children 'fully covered' (with two VACs per year) at more than 80%.<sup>4</sup>

However, the impact of this extensive programme, launched in the 1990s, was never directly assessed until recently. Mortality impact evaluation would have been

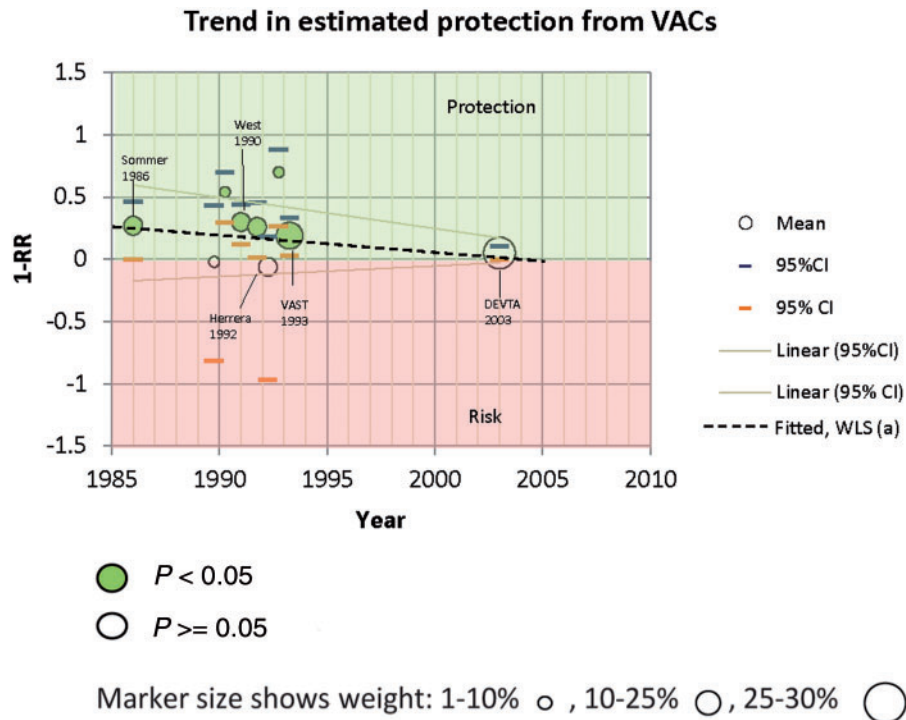
feasible with careful design and a large enough sample, although direct comparisons between deliberately selected treatment and comparison groups would have been unethical. Many claims were made of numbers of lives saved,<sup>16</sup> but these were all calculated from the coverage and the expected (i.e. 23%) reduction derived from the early efficacy studies. The scarcity of evaluation of large-scale programmes is a persistent problem in nutrition; however evaluation is feasible, for example programme impact on young child anthropometry has been plausibly established for a number of programmes.<sup>17</sup>

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,<sup>18</sup> and finally published in 2013.<sup>6</sup> 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].

The initial justification for the periodic high-dose VAC programme was based on the clinical trials, done around 1986–93—these were the eight trials for which the meta-analysis estimated a 23% reduction in mortality in children aged 12–72 months.<sup>15</sup> Recently (2010) the meta-analysis was repeated,<sup>19,20</sup> adding nine newer studies carried out from 1994–2002 (dropping one which involved fortification),<sup>21</sup> 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; moreover 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<sup>22</sup> showed a mortality effect compared with the no-intervention comparison group [ $P < 0.01$ , relative risk (RR) = 0.57, 95% CI = 0.42–0.77], although not compared with nutrition education. The others included by Imdad *et al.*<sup>19</sup> showed no effect (95% CIs all spanned 1.0). In this light, the DEVTA result is less surprising, as we have noted elsewhere.<sup>23</sup>

The change through time is illustrated in Figure 2.<sup>6,14,19,22,24–32</sup> Here, the results of trials quoted in the Imdad *et al.* (2011)<sup>19</sup> meta-analysis are plotted against year of research completion, in terms of the estimated protective effect [1–relative risk, i.e. equivalent to the 23% reduction in mortality widely quoted from Beaton *et al.* (1993)].<sup>15</sup> (Three trials of low weight in the Imdad meta-analysis, omitted also in the DEVTA<sup>6</sup> meta-analysis, are excluded—see notes to Figure 2—which has little effect on the results). One explanation for this apparent change in impact of VAC through time is the shift in disease patterns since the 1980s.

Further analysis of possible effects of disease patterns are given in Appendix 2 (available as Supplementary data at *IJE* online). Results support the hypothesis that



**Figure 2.** Mean protection (1-RR) in child mortality (6 or 12–59 months) from 4- to 6-monthly VACs, by study, with weight assigned in meta-analysis<sup>19</sup>, and  $P$ -value range.

Shaded filled circle:  $P < 0.05$  White filled circle:  $P > 0.05$ . (a) see Appendix 2 (available as Supplementary data at *IJE* online)

Marker size shows weight in meta-analysis: small 1–10%, medium 10–25%, large 25–30%.

Weights shown by marker size are taken from Imdad *et al.*<sup>19</sup>, Figure 3, with DEVTA set to 100. The dashed line is fitted by weighted regression using the weights and datapoints given by Awasthi *et al.*<sup>6</sup>, Web Appendix Table 3 (available as Supplementary data at *IJE* online). Note that data points from Agarwal *et al.* (NS)<sup>24</sup>, Pant *et al.*<sup>22</sup>, and Donnen *et al.* (NS)<sup>25</sup>, quoted by Imdad *et al.*<sup>19</sup>, are not plotted here as they are not included in the DEVTA appendix ( $n = 9$ ) (references are given below). The weighted regression line is very similar whether data and weights from Imdad or from Awasthi are used. Error bars are 95% CIs. The regression results are: mean (1-RR) = 27.032 – (1.347\*(year/100)). Coefficient  $P = 0.068$ ;  $n = 9$ .

**References.** For data points from left to right: Sommer *et al.*<sup>14</sup>; Vijayraghavan *et al.*<sup>26</sup>; Rahmathullah *et al.*<sup>27</sup> (note: this was weekly dosing, and is included only for consistency with the meta-analyses). West *et al.*<sup>28</sup>; Daulaire *et al.*<sup>29</sup>; Herrera *et al.*<sup>30</sup>; Arthur *et al.*<sup>31</sup>. VAST: Ghana VAST study team, 1993.<sup>32</sup>; DEVTA: Awasthi *et al.*<sup>6</sup>. Not included: Agarwal *et al.*<sup>24</sup>; Pant *et al.*<sup>22</sup>; Donnen *et al.*<sup>25</sup>

changing disease patterns (diarrhoea and measles) may have altered the effectiveness of VACs.

Viewed in this way, 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 immunization has all but eliminated measles as a public health problem, including in Africa;<sup>33</sup> and mortality from diarrhoeal disease has decreased with control measures including improved oral rehydration, plus the use of zinc and expanded rotavirus immunization in some parts of the world.<sup>34</sup> 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.<sup>6</sup> 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.<sup>35</sup> Thus this huge effort in VAC coverage is directed (e.g in India by DEVTA) to only one-fifth of the U5MR; and 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. There must be better priorities.

### The problem of mild-moderate vitamin A deficiency

WHO formally re-defined vitamin A deficiency as low SR in 2002,<sup>1</sup> thus emphasizing that the problem was much wider than clinical VAD (which now has a prevalence of

less than 1% in children)<sup>2</sup> and likely to extend well beyond VAC-sensitive child mortality. Their statement said: 'For the past 15 years, the non-ocular, systemic manifestations of VAD have often been misleadingly referred to as 'sub-clinical'. . .the only biochemical parameter validated and found practical for routine survey use is serum retinol concentration'.<sup>1</sup> Vitamin A status thus came to be defined by serum retinol levels, with a cut-point of 20 mcg/dl referred to as 'low', indicating mild-moderate deficiency, and below 10 mcg/dl, 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)<sup>36</sup> and the Philippines (1979)<sup>12</sup> and a number since (including by J.M.)<sup>37</sup> showed this lack of an effect on SR after about 2 months after administration. Results from a literature review on effects of VACs on SR are given in Appendix 1, Table A1.2 (available as Supplementary data at *IJE* online).

Re-examination of the original results on vitamin A and mortality from Aceh, Indonesia,<sup>14</sup> breaking the mortality rates into 2-month periods, suggests that the mortality impact itself is largely restricted to the first 2 months after dose, see Figure 3.<sup>14</sup> Similar analyses, not shown, from the Jumla results<sup>29</sup> gave a similar picture. If so, two 6-monthly

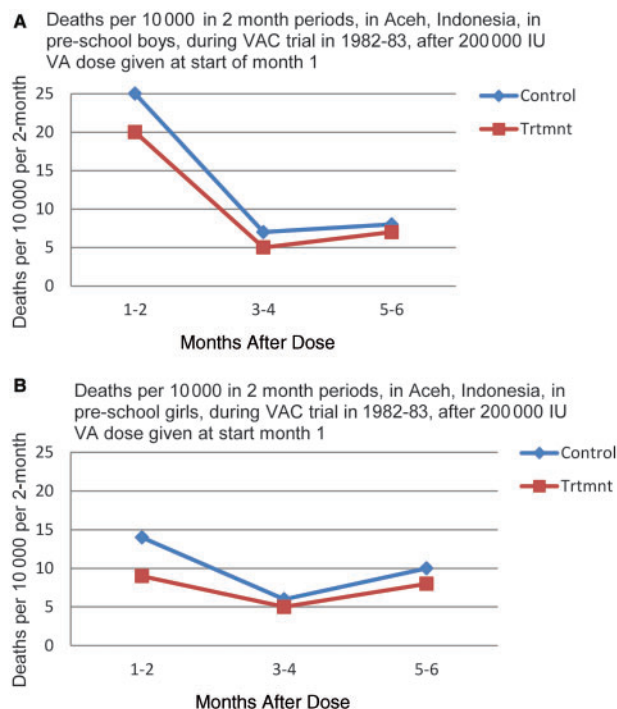
doses per year is far from the 'full protection'.<sup>4</sup> Indeed, the nearly parallel fall in mortality seen in Figure 3 in the without-VA control group (which did not receive a placebo) strongly suggest that there may be an important programme effect from mothers having attention paid to them, which has not been highlighted before in this context.

There is extensive evidence that serum retinol can readily be raised by frequent low doses of vitamin A; results of a literature review are summarized in Appendix 1, Table A1.3 (available as Supplementary data at *IJE* online). In addition, one of us (T.G.) has recently reviewed the literature on the impact of food-based approaches (outside the context of fortification):<sup>38</sup> of 27 papers published since 1992 documenting results from trials of the impact of 38 foods, 25 had a net positive impact on serum retinol 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 prevalences of low serum retinol 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, reaching an estimated 90% from the three national surveys of 1993, 1998 and 2003, showed prevalences of low SR (<20 mcg/dl) in children increasing over this period, from 36% to 38% and then 41%.<sup>39</sup> Closer examination of the data indicated that a transient and small increase in serum retinol (e.g. reducing prevalences 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.

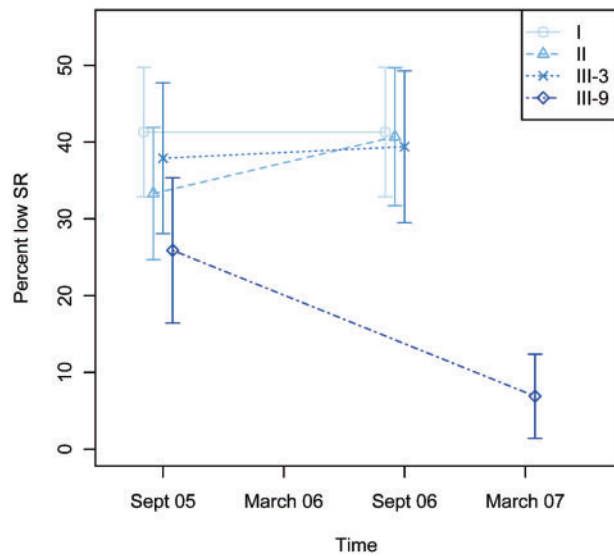
Studies of vitamin A metabolism give supporting evidence on limited retention of vitamin A from high-dose VACs. The time that a single VA dose persists in animals is measured in hours or days (not months), in normal or deficient rats.<sup>40</sup> The dose, likely to be 50% absorbed,<sup>41</sup> is stored primarily (but not only) in the liver. Standard estimates in children are that the catabolic rate for retinol is 2.2% per day,<sup>41</sup> which is 50% in 30 days—if so, the effect of a dose might be expected to last up to 1–2 months, in line with other observations discussed here. The only exception is for protecting eyes from clinical VAD, where 6-monthly VACs are usually effective (see Appendix 1, Table A1.1, available as Supplementary data at *IJE* online).

A trial of 3-monthly VACs, 6-monthly VACs and 6-monthly VACs plus promotion of VA-fortified cooking oil gave results shown in Figure 4.<sup>37</sup> Neither 6- nor 3-monthly VACs changed SR, but the group receiving promotion of fortified oil had a greatly reduced prevalence of low SR.<sup>37</sup> This fortified oil effect was expected (the group



**Figure 3.** Results showing the child mortality reduction estimated after 200 000 IUs vitamin A capsule (VAC) dose for boys (A) and girls (B), replotted into rates per 2-month periods from the original data (Sommer *et al.*)<sup>14</sup>

Source: replotted from Figure in Sommer *et al.*<sup>14</sup>



**Figure 4.** Changes in prevalence of vitamin A deficiency (VAD: measured as serum retinol < 20 mcg/dl) after 12–18 months provision of either vitamin A capsules 6-monthly, 3-monthly or 6-monthly plus promotion of VA-fortified vegetable oil; in cluster randomized trial in Leyte, Philippines.<sup>37</sup>

CIs (90%) shown. Group I: 6-monthly VACs (200 000 IUs). Group II: 3-monthly VACs. Group III-3: 6-monthly VACs with 3 months fortified oil promotion. Group III-9: 6-monthly VACs with 9 months fortified oil promotion. In Group III-9, paired *t*-test on children's serum retinol measured in September 2005 and again (same children) in March 2007 gave  $P=0.000$ ; change in prevalences between groups III-3 and III-9 different with  $P=0.000$  (<sup>16</sup>, Table III).

Source: calculated from data used for Mason *et al.*<sup>37</sup>

was included initially as a positive control), following the many studies (Appendix 1, Table A1.3, available as Supplementary data at *IJE* online) which have shown results of similar magnitude from a variety of fortified products, including an earlier comparison in the Philippines of 6-monthly VAC with fortification.<sup>12</sup>

## Policy considerations

Policy statements in the early 1990s stressed the need for a balanced approach of complementary interventions—all for 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 from the 159 governments participating in the International Conference on Nutrition,<sup>42</sup> from WHO and from elsewhere in the United Nations (UN) system<sup>43</sup> 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 develop-

ment of alternative programs’<sup>43</sup>) proved to be prophetic. For example, UNICEF reports that around 70% of LMICs—about 150 countries—distribute at least one VAC per year,<sup>44</sup> whereas the Global Alliance for Improved Nutrition (GAIN), the agency taking a lead in fostering fortification, reports that 19 countries have fortification programmes. A recent review of fortification opportunities, covering 48 LMICs, suggested new or expanded plans for fortification programmes, implying that national coverage had not been achieved for these.<sup>45</sup>

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 association of vitamin A deficiency with increased risks of infection and blindness were the main concerns up to the 1980s, as discussed earlier. Sommer and West in 1996<sup>46</sup> summarized as follows: ‘A vast array of relevant data have become available over the past two decades... These data provide overwhelming evidence that vitamin A status alters the incidence and/or severity of a variety of infections, particularly diarrhoea, measles, urinary tract infection, and probably some forms of respiratory disease’. At the same time it became clear that the effects of supplementation were on disease severity (and hence also case-fatality).<sup>47</sup> The recent (2010) Cochrane meta-analysis<sup>19</sup> showed effects of vitamin A supplementation on incidence of diarrhoea ( $P < 0.00001$ ), measles ( $P < 0.00001$ ) and malaria ( $P = 0.0013$ ). The association of vitamin A with respiratory tract infections (RTIs) is inconsistent, some studies showing increased risk of RTIs with VA supplementation.<sup>48</sup> A possibly clarifying finding was that VA supplements (weekly, low-dose) were protective against acute lower RTI incidence in underweight children, but increased the incidence in normal weight children.<sup>49</sup>

The term ‘vitamin A deficiency disorders’ (VADDs) has been used<sup>1</sup> 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.<sup>50</sup> 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.<sup>48,49,51</sup>

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 (integrity of epithelia) and of its multifaceted role in the immune system, its hormone-like action and its role in control of gene expression. Many studies have begun to elucidate the mechanisms, and others the impact, of VAD on immune competence in humans, notably in poorer environments.<sup>52–54</sup>

Maternal mortality was substantially reduced by low-dose VA supplementation in one controlled trial, where nearly a halving of maternal mortality was reported.<sup>55</sup> These results were not replicated in studies in Bangladesh<sup>56</sup> (where all night-blind women in the study were given VA, possibly mitigating the effect<sup>57</sup>) nor in Ghana.<sup>58</sup> A meta-analysis of results of the three studies concluded that there was little evidence for the maternal mortality impact.<sup>59</sup> Nonetheless, 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,<sup>60</sup> 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 VA intake, so that reproductive-aged women can be included.

It is now quite implausible that low serum retinol is compatible with normal physiology and good health (even if we are still learning the details). Vitamin A is still a key factor in resisting and recovering from infectious disease, just as Mellanby and others said nearly a century ago,<sup>7</sup> and the mechanisms are becoming progressively better understood.

### Implementing the mixed approach to VAD: a shift is needed towards policies long agreed

The landmark conference on 'Ending Hidden Hunger' (Montreal 1991) recognized '...three basic approaches .. diet diversification and quality improvement, fortification of food and other vehicles, and direct and targeted supplementation.'<sup>61</sup> The 1992 International Conference of Nutrition called on governments to 'formulate and implement programmes to correct micronutrient deficiencies and prevent their occurrence, promoting the dissemination of nutrition information and giving priority to breastfeeding and other sustainable food-based approaches that encourage dietary diversification through the production and consumption of micronutrient-rich foods, including appropriate traditional foods'.<sup>42</sup> The UN in 1993 recommended

that 'a combination of interventions is usually needed to prevent vitamin A deficiency; these include dietary modification, breastfeeding promotion, food fortification, and supplementation'.<sup>43</sup> Fifteen years later, the only indicator for vitamin A used by UNICEF is still VAC coverage.<sup>62</sup> The mixed approach now needs to be implemented, and monitoring needs to include assessment of serum retinol, 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. As examples, margarine was fortified with vitamin A in the UK during World War II; in Central America in the 1970s, the impact of fortifying sugar on the serum retinol of the population was clearly demonstrated.<sup>63</sup> The substantial effect of fortified coconut oil on SR in the Philippines was recently shown by J.M. and colleagues,<sup>37</sup> see Figure 4. A recent comprehensive review<sup>45</sup> assessed fortification as highly cost-effective in terms of expected health benefits. High-provitamin 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.<sup>38</sup>

Why has this policy shift not happened? The answer lies in the politics of governments and agencies, and associated reluctance from the scientific community to change earlier recommendations. The (incorrect) idea in policy makers' minds, that a simple cheap fix is being successfully used to address the issue, has probably prevented faster adoption of effective measures. A self-reinforcing cycle of assertion of success and appeal for wider and more implementation, to save more children's lives, led to more funding for VACs. Objective evaluation would have acted as a brake, but there was virtually none.

What is needed may not be quite a paradigm shift—the issue is perhaps not of that magnitude—but does have some common features. The funding institutions are not yet aware that substantial change is needed. Assertions of humanitarian success are presented in one-sided terms ('how can you justify stopping a proven life-saving intervention?' is a direct quote) to support the status quo. Moreover, high-profile commitments of funds have been explicitly not fungible; they have to be spent on capsules.<sup>64</sup> However, the set of hypotheses supporting the status quo is not standing up to the evidence, and sooner or later a shift must happen.

### Proposals for policy change

Many in India, for a long time, have questioned the exclusive VAC approach, and proposals for policy change have

been made.<sup>65,66</sup> Recently, the late Michael Latham made the case under the title of the ‘great vitamin A fiasco’,<sup>5</sup> echoing the title of an earlier policy issue, ‘the great protein fiasco’.<sup>67</sup>

The Global Alliance for Improved Nutrition (GAIN), founded in 2002 with support from the Bill and Melinda Gates Foundation and others, is gathering momentum to promote fortification in a number of countries. This will no doubt go some way to solving the problem, provided due attention is given to ensuring that foods eaten by the most vulnerable are included: for the poorest who purchase only cheap foods, for infants and young children who do not yet eat much adult food, and for women, especially in pregnancy. But even this fortification initiative at scale is not coordinated with the VAC programmes, and there is competition for resources. For example, GAIN is not a member of the Global Alliance for Vitamin A, and has not been represented—nor has fortification been on the agenda—in recent considerations of vitamin A supplementation.<sup>68</sup> Also concerning 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 megadoses annually, and this might cause problems of toxicity.<sup>69</sup>

The evidence is clear enough to use available resources to finally have a major impact on vitamin A deficiency, with likely broad benefits for health. This would at last begin to meet the now-forgotten World Summit for Children goal of eliminating VAD by the year 2000 (VAD actually declined from 36% 1990 to 31% 2007, see figure 1). Vitamin A deficiency never explicitly made its way into the Millennium Development Goals. There has been much confusion over the goal of eliminating VAD—with mortality conflated with deficiency, and the wider problem of milder VAD ignored. This should now change.

In sum, a strategy for effectively reducing VAD, i.e. prevalences of low serum retinol, needs clear policy directions, to establish the importance of such an objective and to bring together options for reaching it. 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. One of us (T.G.)<sup>69</sup> has outlined detailed steps that could be taken to achieve this in a low-risk manner. WHO has been instrumental in setting standards, and the decision to retire the concept of ‘sub-clinical VAD’ and define VAD as measured by low serum retinol has extensive policy implications—most importantly for effective intervention and monitoring—and this process now needs to be completed.

The DEVTA results have already influenced policy in India.<sup>65,66</sup> It is time for the rest of the world to

follow suit. Many millions of poor and malnourished children would benefit.

## Supplementary Data

Supplementary data are available at *IJE* online.

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## Commentary: Vitamin A policies need rethinking

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