Preschool Child Vitamin A Deficiency Prevention

A strategic crossroads

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Key messages

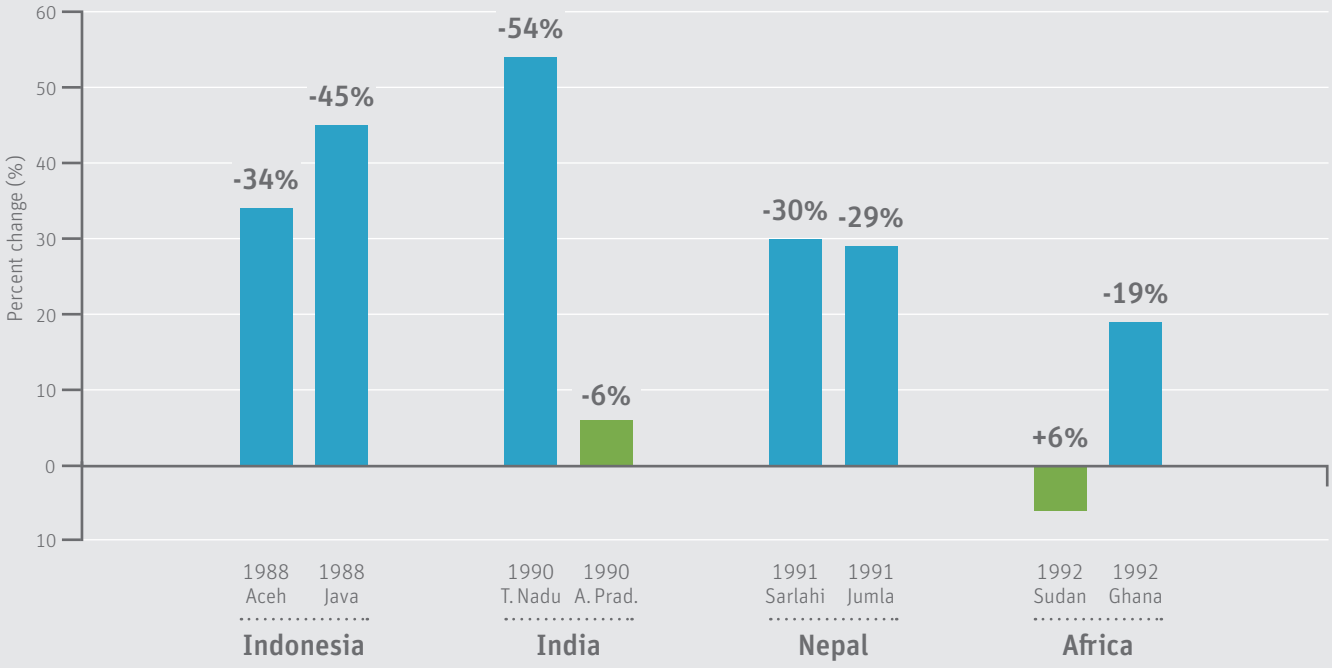
- Childhood vitamin A deficiency (VAD) is a major facet of hidden hunger, with 80 million deficient preschoolers in Africa and Southern Asia alone.
- Multiple strategies exist to prevent VAD, including periodic, high-dose vitamin A supplementation (VAS), food fortification, dietary change and biofortification.
- VAS prevents xerophthalmia, blindness, child mortality and hearing loss, but does not normalize serum retinol, which is only achievable by diet.
- While new, inexpensive measures of vitamin A status are needed, serum retinol remains an interpretable, valid and comparable indicator for population use.
- VAS can be curtailed once fewer than 10% of children (with 95% confidence) are vitamin-A-deficient, and evidence supports improved dietary intake of vitamin A in target populations.

A century after its discovery, vitamin A remains a nutrient of intense biomolecular, developmental and curative interest, and there has been a persistent public health focus over the past 50 years to assess and prevent its deficiency and health consequences in the low-to-middle-income world. Deficiency arises from a diet chronically lacking food sources of preformed vitamin A (e.g., breast milk in infancy, animal and fish liver [and oils], whole-fat dairy products and egg) or provitamin A carotenoids (e.g., dark green leafy vegetables and yellow-orange fruits, vegetables and tubers).[1] A diverse diet that provides adequate amounts of vitamin A and its carotenoid precursors is also one that generally meets nutritional sufficiency and promotes health.[2]

> "A century after its discovery, vitamin A remains a nutrient of intense interest"

Public health strategies for preventing vitamin A deficiency (VAD) include efforts to enhance food systems through the fortification of foods with vitamin A and biofortification with provitamin A carotenoids,[3] as well as horticultural, and dairy and fish farming initiatives,[4] coupled with nutrition education and behavior change communication that can expand dietary diversity.[1] Alongside a wide range of food-based and dietary approaches, periodic provision of a large (200,000 IU) dose of vitamin A has become a major, if conceptually interim, approach to protecting preschool-age children from VAD and its health consequences.[5] Suggested by Professor Donald McLaren as a biologically feasible approach to build liver stores and prevent xerophthalmia, and tested shortly thereafter in India in the 1960s,[6] semi-annual vitamin A supplementation (VAS) has evolved over the past five decades into a strategy that, today, is implemented globally.[7] While this approach is not without its limitations[8] and critics,[9] this essay argues for sustained childhood VAS to prevent vitamin A deficiency disorders (VADD) until high-risk countries demonstrate a low prevalence of deficiency, together with corroborative evidence of dietary adequacy, at which point a shift in preventive strategies will be justifiable and

FIGURE 1: Changes in preschool child mortality from population-based vitamin A intervention trials conducted in South Asia and Sub-Saharan Africa in the 1980s and 1990s



Among eight, original, population-based vitamin A intervention trials conducted in South Asia and Sub-Saharan Africa in the 1980s and 1990s, six reported significant 19% to 54% reductions in preschool child mortality (blue bars) while two trials reported no significant effects on mortality (green bars)[1]

safe. Although fortification, biofortification and food diversification strategies are making progress toward raising vitamin A intakes across regions, the lack of reliable data on the prevalence of VAD in most countries[7,11] is concealing their impact and hampering progress. There remains an urgent need for rapid, valid and inexpensive assessment methods that comparably reflect distributions of serum retinol < 0.70 µmol/L, which remains the most widely used and understood indicator and cutoff for classifying population risk of VAD.[10–12]

> "There remains an urgent need for rapid, valid and inexpensive assessment methods that comparably reflect distributions of serum retinol"

Vitamin A deficiency disorders and their response to interventions

Depleted vitamin A nutriture affects a plethora of host defense, hormonal, growth and homeostatic mechanisms that protect phenotypic development, growth, function and survival.[13] VADD comprise "health and physiological consequences attributable to VAD, whether clinically evident (xerophthalmia, anemia, growth retardation, increased infectious morbidity and mortality) or not (impaired iron mobilization, disturbed cellular differentiation and depressed immune response)."[12] VADD can be distilled to consequences of public health importance that respond in whole or in part to vitamin A interventions. In children, VADD include xerophthalmia, involving night blindness, Bitot's spots and corneal disease (xerosis and keratomalacia),[14] anemia, severity of infectious diseases, and consequent mortality,[1] and can include hearing loss following severe middle ear infections.[15] All likely coexist in areas of endemic VAD without adequate prophylaxis.

Xerophthalmia responds to the direct provision of vitamin A treatment.[1,14] Twice-annual, high-dose VAS (200,000 IU > 12 mo, 100,000 IU 6–11 mo) reaching ~85% or more of preschoolers virtually eliminates blinding keratomalacia as a public health concern[16] and reduces the prevalence of night blindness or Bitot's spots by ~60% or more.[1,17] Few new trials exist, but generally effectiveness declines markedly as coverage lapses, with little effect on prevalence to be expected below 25% coverage.[5] Fortification of one or more commonly eaten food items can

raise vitamin A status,[18–20] which should also prevent xerophthalmia. While not subjected to trials, epidemiological studies have revealed consistent, dose-responsive, protective associations against xerophthalmia through more frequent breastfeeding[21,22] and intakes of dark green leaves, orange-yellow fruits, vegetables and tubers, egg and dairy products.[1,23,24]

Preschool child mortality is reduced by vitamin A interventions, which is likely achieved by attenuating the severity of certain infectious diseases in undernourished populations. Original population-based, controlled, efficacy trials in Southern Asia and Africa revealed ~0% to 54% reductions in preschool child mortality, providing average reductions via meta-analyses of 23% to 34%, depending on the inclusion criteria,[1,25] when children received vitamin A as a 4–6-monthly high dose,[1,26,27] a weekly low dose (15,000 IU)[28] or a daily fraction of a recommended dietary amount via fortification of a food item[29] (**Figure 1**). Since 2000, a program evaluation in India[30] and a trial in Guinea-Bissau[31] have reported nonsignificant reductions of 4% and 13%, respectively, in preschool child mortality with VAS, but these lower estimates may have been due, in part, to difficulties faced in study design, implementation[30,32] and in preventing controls from receiving vitamin A during a concurrent national VAS program.[31]

> "Supporting the all-cause effect on child mortality is evidence that VAS reduces the fatality of measles"

Supporting the all-cause effect on child mortality is evidence that VAS reduces the fatality of measles, first shown in London in 1931[33] and in several trials a half-century later.[1,25] While increased measles vaccination will reduce this impact of vitamin A, VAS can still lower complication rates and case fatality where measles vaccine coverage falters,[34,35] suggesting a need for caution about prematurely desisting VAS amidst a current resurgence of measles in many areas of the world. WHO also continues to globally recommend VAS as a treatment for measles.[36] Other potentially fatal childhood infectious illnesses that are likely attenuated in severity by vitamin A include diarrhea and dysentery[1,37] and *falciparum* malaria.[38] Correspondingly, VAS has been found to reduce frequencies of early childhood clinic sick visits and hospitalizations as proxies for the severity of illness,[27] although high-dose vitamin A has lessened neither the severity nor the risk of fatality from early childhood pneumonia.[39] It is interesting to note that hospitalized, malnourished children with severe respiratory or diarrheal morbidity have been shown to respond more favorably to a low, daily dose than to a single large bolus of vitamin A,[40] similar to the response seen for child mortality following smaller weekly[28] or daily[29] intakes of vitamin A.

Otitis media, a leading cause of childhood hearing loss, is associated with VAD.[41] Experimental vitamin A depletion exacerbates tympanic membrane damage from middle ear infection, which heals more quickly with vitamin A treatment.[42] In children with acute measles, vitamin A has reduced the risk of otitis media.[43] In Nepal, adolescents who, as preschoolers, developed one or more episodes of purulent ear infection while receiving 4-monthly VAS during a community trial[26] were 42% less likely to be hearing-impaired than early childhood placebo-recipient peers who also had episode(s) of ear discharge.[15] As nearly 20% of children experienced at least one preschool episode of ear discharge, among whom ~20% of control recipients were hearing-impaired, the findings suggest that preschool VAS, beyond impacting xerophthalmia and mortality, can avert 15 cases of permanent hearing loss per 1,000 children per year of age.

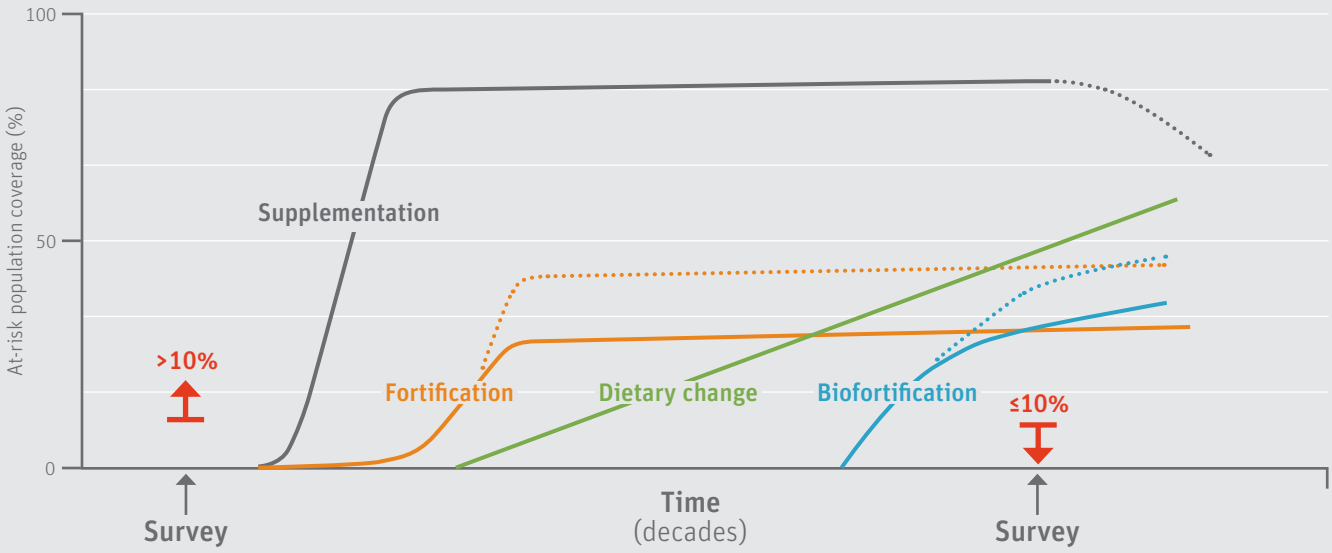
A vast literature reveals the pleiotropic roles of vitamin A, through its metabolites, in regulating innate and adaptive, mucosal/local and systemic, auto- and paracrine to hormonal aspects of immune defense.[1,44,45] These effects on elements of the immune system help to explain the diverse but generally favorable effects of vitamin A in reducing infectious morbidity in populations that are marginal to deficient in vitamin A status.

Vitamin A deficiency and its response to interventions

The vitamin A status of populations is most often evaluated by assaying serum retinol, or its binding protein, among a cache of other methods.[8,46] Serum retinol concentrations below 0.70 µmol/L (20 µg/dL) typically define deficient status,[11] which often reflects combined nutritional and inflammatory stresses that are useful to partition[46] in order to understand different causes and estimate possible responses to interventions. VAD and inflammation are, however, also inseparable, in that infection can increase vitamin A losses[47] and, experimentally, VAD itself is pro-inflammatory.[48] Regardless, hyporetinolemia has been estimated to affect 45%–50% of preschoolers throughout Southern Asia and Sub-Saharan Africa for the past three decades,[10] suggesting there are ~80 million vitamin-A-deficient preschool-age children in these two regions alone.

Vitamin A interventions may exert different effects on serum retinol. Underway for more than four decades,[5] vitamin A supplements are being distributed semi-annually to preschool-age children in 82 countries.[7] While effective in reducing VADD, for poorly understood reasons a 6-monthly pulse of vitamin A only transiently raises serum retinol concentrations or reduces deficiency by this indicator.[8] As a consequence, a serum retinol distribution should not be expected to exhibit a long-term rise following VAS or be used to evaluate this intervention. Rather, target population coverage is the prima facie indicator of performance

FIGURE 2: Complementary vitamin A interventions



Following a survey reporting VAD (serum retinol < 0.70 µmol/L) of > 10% in preschool children (**first red line**), a problem of moderate or worse public health significance,[11] interventions are launched: periodic VAS for rapid, sustainable control of VADD (**grey line**), with other strategies gradually implemented: **(a)** fortifying one (**orange line**) or more (**dotted orange line**) foods reaching target markets; **(b)** achieving dietary changes (**green line**) by agricultural, market, subsidy and behavior change approaches; and **(c)** biofortifying one (**blue line**) or more (**dotted blue line**) staple crops with provitamin A carotenoids. As combined approaches increase dietary vitamin A, and a follow-up survey (**second red line**) shows a low prevalence of VAD (< 5%[8] or upper 95% confidence limit < 10%), VAS can be withdrawn (**dotted grey line**).

and public health impact, an inference that has been supported by occasional national evaluations that have revealed high-coverage VAS programs to reduce xerophthalmia[49] and mortality.[50]

Dietary approaches – such as fortifying commonly consumed food items to deliver a significant fraction (e.g., ~⅓) of the Recommended Dietary Allowance as preformed vitamin A – reduce the risks of VADD, reflected by lowered child mortality,[29] and raise serum retinol over the long term,[18–20] thereby sustainably reducing VAD. Feeding children dark green leaves and other vegetable, tuber and fruit sources of carotenoids will raise serum retinol from deficiency although, alone, not fully normalize status.[1] Biofortifying staple crops with provitamin A carotenoids will likely also prevent deficiency, reduce VADD[51,52] and increase serum carotenoids, although only slightly further improve vitamin A nutriture[53] due to the complex determinants of carotenoid bioavailability.[54] Nevertheless, a dietary safety net against VAD can generally be assured with an assorted diet offering adequate preformed vitamin A esters and provitamin A carotenoids.

Choice of interventions to prevent vitamin A deficiency and its deficiency disorders

Countries have at hand an increasing portfolio of strategies to adopt for preventing VAD, depending on its extent and severity, the urgency to avert health consequences, dietary cultures, food system capabilities and economic resources. **Figure 2** provides a conceptual diagram of how preventive strategies of supplementation, fortification and biofortification and approaches to improve dietary diversity can unfold over time. Countries can exist anywhere on this continuum. Supplementation can be scaled up relatively quickly to effectively control VADD (reduce xerophthalmia, severe morbidity and mortality) in young children, but it fails to address dietary causes, sustainably improve status or address other target groups (e.g., neonates, school-age children, adolescents and women of reproductive age). While there are vocal calls for countries to shift away from VAS,[9] any decision to do so should be based on representative data of improved vitamin A status, together with supportive evidence of increased vitamin A intakes that explain the improved status. Effective dietary strategies should both prevent VADD and, with some fraction of retinol equivalency derived from preformed vitamin A (animal or fortified) food sources, normalize serum retinol distributions. Periodic surveys that measure serum retinol as the primary indicator of status can provide comparable and interpretable indicator data. It has been suggested that a basis for shifting from VAS can exist where national surveys have found the prevalence of deficiency (serum retinol < 0.70 µmol/L) among preschoolers to be < 5%.[8]

Alternatively, the estimated prevalence should have an upper 95% confidence limit < 10%, the WHO minimum prevalence for a moderate or worse public health problem.[11] Either way, there should also be supportive evidence of increased availability and intakes of foods rich in vitamin A and carotenoid by children and mothers in vulnerable regions.[8]

"While there are vocal calls for countries to shift away from VAS, any decision to do so should be based on representative data"

Conclusions

VAD remains a major burden in impoverished societies, with significant health consequences. Globally, VAD prevention is at a crossroads of achievement, capability and multisectoral commitment. As with all micronutrient deficiencies, mapping VAD to at-risk target populations is hindered by infrequent assessment. Serum retinol, while less responsive once in a normal range and influenced by infection,[45] provides interpretable data about VAD for public health decision-making and should be used until new assays of vitamin A status are validated, proven reliable and widely available. High-coverage VAS protects children from xerophthalmia, reduces mortality, including measles fatality, and can lower the risk of hearing loss from severe ear infections, but will not resolve the underlying VAD. Only an adequate diet can sustainably raise serum retinol distributions and prevent VAD, which is now achievable via multiple intervention strategies.

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