World Nutrition

Commentary
Vitamin A saves lives.
Sound science, sound policy

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Summary

Vitamin A deficiency can cause blindness, impair health, and be an underlying cause of death, in young children. Therefore, responsible debate about its public health importance, and the value of prevention, should be based on reliable evidence of the extent and severity of deficiency, and on the impact of interventions.

In this commentary, we firstly bring attention to sound evidence that vitamin A deficiency remains a major public health problem, affecting about 190 million preschool children, including about 57 million children in India where its importance has been questioned.

Secondly, we summarise the evidence from eight peer-reviewed published community-based vitamin A intervention trials that have been carried out across Southern Asia and in Sub-Saharan Africa, including six which employed large-dose vitamin A supplementation. Based on multiple, independent meta-analyses, the results of these trials are consistent with an overall 23 to 34 per cent reduction in preschool child mortality that can be expected from vitamin A programmes reaching children in undernourished settings. There is also strong evidence from both community and clinical trials that vitamin A prophylaxis and treatment can reduce the severity and fatality from measles and diarrhoea, among other less-well defined infections. No peer reviewed, published data has emerged in recent years to contradict these findings. They thus provide a continuing sound policy basis for governments effectively to control the consequences of deficiency, while at the same time dietary strategies are designed, tested for impact, and scaled up to improve and maintain adequate vitamin A status of child populations.

Repeated representative surveys that reveal a stable, adequate serum retinol distribution, can offer governments the evidence needed to make informed decisions about changing or refining vitamin A deficiency prevention strategies. A carotenoid to vitamin A bioconversion ratio in the body that is half as efficient as previously thought, emphasises the importance of assuring preformed vitamin A, in dietary strategies intended to improve vitamin A status of children.

Finally, rather than being viewed as competitive, we propose that supplementation, fortification and other food-based approaches, once proven effective and sustainable, should be viewed as complementary within the context of national strategies to improve vitamin A intake and status of child populations.

Staying with the science

We appreciate the invitation to contribute to a debate that emerged with the launch of **World Nutrition**, with a previous commentary that called into question the relevance and public health value of vitamin A supplementation as a strategy to reduce child mortality (1).

Our intent is not to further polarise opinion, but to reposition the debate about the continued urgency and options available to prevent vitamin A deficiency, of which vitamin A supplementation is one among a range of other possible interventions that, so far, largely remain unused and untested for public health impact, scalability and sustainability. None are mutually exclusive. They represent choices for prevention, depending upon urgency (breadth, severity and public health consequence) and resources required to mount and maintain.

We hope to move the discussion from views expressing disregard for peer-reviewed research, admixed with anecdotal life experience, to a platform of scientifically derived evidence on which rational discourse can help identify new research needs and inform policy decisions about why, whether and how to prevent vitamin A deficiency, and the public health benefits of doing so. Central to this particular discussion is the value of biannual distribution of a US 2-cent, 200,000 IU capsule of vitamin A to young children in undernourished populations. This approach is based on nutrient liver storage capabilities first suggested by Professor Donald McLaren in 1964 (2,3) and tested in India shortly thereafter (4).

This programme is estimated to cost US $1-2 delivered per child per year. It has, where done well, virtually eliminated nutritional blindness as a public health problem, and has reduced preschool child mortality. This commentary is not, in any way, meant to divert attention, interest or resources away from assuring nutritious diets at all times for all children. Its purpose is to distil and present the research findings behind the need for improving vitamin A status of deficient populations, and the evidence (largely dictated by research design) that vitamin A supplementation is an effective option to reduce childhood blindness and death from this deficiency, while awaiting implementation of food-based solutions proven to accomplish this end.

Deficiency remains a public health issue

We wish to raise three issues, drawing on evidence where it exists, and challenging prejudicial opinions lacking in evidence:

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- Whether childhood vitamin A deficiency remains a significant public health problem in the world.
- Whether vitamin A supplementation safely reduces child mortality.
  And assuming both answers are 'yes':
- Discuss criteria policy makers can employ to judge whether, when and where to change their vitamin A deficiency prevention strategy.

We conclude with some additional observations.

Deficiency remains a public health problem, including in India

Despite evident global epidemiological and nutritional transitions, with declining child mortality (http://www.who.int/nutrition/nlis/en/index.html), existing data show that vitamin A deficiency remains a global, consequential and preventable public health problem among children in most undernourished societies and, especially relevant to recent correspondence in *WN*, in India.

More accurate, representative and timely data on population risk of deficiency is always needed, and research data is always slower to accumulate than advice, but the most recent estimates from the World Health Organization (WHO), drawn from population-based surveys through 2005, indicate there to be 190 million preschool aged children around the globe with vitamin A deficiency (5). The basis for classifying deficiency is a serum retinol concentration less than 0.70 umol/L, an indicator and cutoff widely regarded to represent deficiency (6,7), below which risks of xerophthalmia, anaemia, severe infection and, likely, mortality rise (8). A review of reported findings on the extent of deficiency at the WHO website raises several notable observations (http://www.who.int/nutrition/databases/en/index.html), when placed into historical context:

Prevalence of (biochemical) deficiency

The current estimated number of 190 million vitamin A deficient children globally, has not discernibly changed from the range of 140 to 190 million children estimated by WHO in the early 1990s (9-11). This surprising lack of 'movement' may still be true and have underlying reasons, as explained below.

Today, 30 per cent of all deficient children are thought to live in Africa, and nearly half in Southern Asia, 60 per cent of whom live in India. Relevant to this latter fraction is our earlier empirical, country-by-country exercise in 2002 that led to a global estimate of 127 million vitamin A deficient preschoolers (12). Because there was no nationally representative data from India, we imputed a prevalence of 31 per cent, adopting an estimate derived from Bangladesh where some population data was available and where high-coverage vitamin A programmes had long been under way.

This appears to have been an under-estimate, by nearly half.   Subsequent data from an 8 state-wide, representative survey of nearly 4000 1-4 year old Indian children, carried out by the National Nutrition Monitoring Bureau of the National Institute of Nutrition in Hyderabad in 2003, reported a prevalence of vitamin A deficiency of 62 per cent (5, 13), with individual states reporting prevalence rates from 55 per cent in Maharashtra (14), to 88 per cent in Madhya Pradesh (15). The overall estimate, if considered a national estimate, translates into about 57 million deficient preschoolers in India, a figure that explains most of the difference noted between the 2002 (12) and 2009 (5) estimates.

While seemingly high, the 62 per cent figure is consistent with earlier, smaller preschool child surveys in the States of Orissa (16) and Andra Pradesh (5) in 2000, where rates of 64 and 52 per cent, respectively, were observed. In the absence of more recent data, these estimates lead to a conclusion that is very different than claimed in earlier commentaries (17, 18): that vitamin A deficiency is not merely restricted to 'pockets', but remains an endemic problem in need of prevention throughout much of India.

Prevalence of xerophthalmia

Unlike the persistent high prevalence of tissue (serum) vitamin A deficiency, the global burden of xerophthalmia appears to have declined over the past three decades. A first, population based (and conservative) estimate of annual incidence of xerophthalmia for Southern Asia was derived by Sommer in the early 1980s. This was of about 5 million new cases of xerophthalmia each year, 10 per cent of which involved the cornea, half of which led to blindness (19, 20).   Extending this finding, one would have expected a global estimate of xerophthalmia to be perhaps twice that number or more. In 1992, based on emerging population based reports from high risk regions, WHO estimated that 13.4 million preschool aged children developed xerophthalmia every year (9, 10).

Subsequent global reports from 1995 through 2009 suggest a halving of the annual number of xerophthalmic children from these earlier estimates (5), but show no further downward trend. This lack of further reduction could be due to many factors, including differences in reports admitted for calculations and a loss in precision as nationally representative, child eye survey data has become less available over the past decade. Findings from large trials (21, 22) and well-designed evaluations of high coverage programmes (23, 24) have repeatedly found reductions of 75 per cent or more in the rates of mild and potentially blinding childhood xerophthalmia, bringing prevalences below WHO minimum criteria for public health significance (25). Thus, an apparent lack of further global reduction in xerophthalmia could also reflect low vitamin A supplement coverage in some large, high risk populations (26-32) such that xerophthalmia would not be likely to be prevented (33).

Supplementation does save lives

Well-conducted trials conclusively show that vitamin A supplementation is an effective strategy for helping children survive. This has been demonstrated in a variety of undernourished and vitamin A deficient populations. Specifically, several well executed, population-based, mostly randomised and placebo controlled field trials, have been conducted that enrolled and followed about 165,000 children between around 6-12 months through 72 months of age (34-42). The results of these trials are summarised in Table 1.

Table 1
Community-based vitamin A intervention trials to reduce preschool child mortality

Location	Country	Vitamin A supplement	Mortality difference (a)	Reference
Aceh	Indonesia	Large dose every 6 months	-34% *	34
Bogor	Indonesia	Vitamin A fortified MSG	-45% *	35, 36
Sarlahi	Nepal	Large dose every 4 months	-30% *	37
Jumla	Nepal	One large dose with follow-up	-29% *	38
Tamil Nadu	India	Weekly RDA	-54% *	39
Hyderabad	India	Large dose every 6 months	-6% (b)	40
Khartoum	Sudan	Large dose every 6 months	+6 %	41
Kintampo	Ghana	Large dose every 4 months	-19% *	42

MSG = monosodium glutamate; RDA = recommended dietary allowance
a.　　Six months and older at baseline
b.　　As calculated from data reported by authors
* Confidence interval for effect estimate excluded 1.0

The trials have been carried out in diverse, vitamin A deficient populations by a variety of investigative teams, employing a range of study designs and dosage regimens, across Southern Asia (Indonesia, India and Nepal) and Sub-Saharan Africa (Ghana and the

Sudan). Six gave children an encapsulated 200,000 IU dose of vitamin A as the active agent. One, in South India, provided a smaller weekly dose (15,000 IU), more closely approximating a recommended dietary intake of preformed vitamin A (39). Another delivered about one-third of a recommended dietary allowance to children through fortified monosodium glutamate (MSG), which enhances the flavour of meals (35, 36). Primary findings from all of the studies were published in peer-reviewed, high-impact journals.

The trials are well known. They have been thoroughly analysed and interpreted, and have had their findings additionally submitted to multiple, peer-reviewed, published meta-analyses, as shown in Table 2.

Table 2
Meta-analyses of findings from community-based vitamin A intervention trials to reduce child mortality

Location (number) of studies	Relative risk (95% CI)*	Reference
Southern Asia (n=5)	0.70 (0.62, 0.79)	46
Southern Asia (n=6)	0.66 (0.58, 0.75)	44
Southern Asia (n=6) and Africa (n=2)	0.77 (0.68, 0.88)	43
Southern Asia (n=7) and Africa (n=1)	0.70 (0.56, 0.87)	45

* Relative risk in all cause mortality among vitamin A supplemented children relative to controls, with 95 % confidence limits
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These studies and analyses by different authors arrive at the same conclusion. Vitamin A prophylaxis, delivered by different means, reduces child mortality, on average, by 23 to 34 per cent (43-46). An additional supportive finding, often overlooked, is that in Nepal, where vitamin A reduced child mortality by 30 per cent (37), continued vital surveillance showed that deaths in control villages declined to that of the intervention level after the control communities were crossed over to receive vitamin A (47).

The benefits have long been known

What potentially fatal infections may be attenuated by vitamin A? Scrimshaw, Taylor and Gordon, in their classic and comprehensive 1968 WHO monograph *Interactions of Nutrition and Infection,* concluded from evidence available at that time that vitamin A was noteworthy in its potential to mitigate infection (48).

Measles offers a clear example. In London in 1932, hospitalised cases of severe measles were offered conventional treatment and alternately assigned to receive vitamin A treatment. Case-fatality among children randomised to vitamin A was cut in half (49). Little further was done on this until the late 1980s when trials in Tanzania (50) and South Africa (51-53) reported comparable reductions in fatality and fewer complications following randomised administration of vitamin A to hospitalised cases of severe measles (versus standard treatment or placebo) on admission.

Fawzi and colleagues, in their meta-analysis, estimated the impacts observed in these trials to be consistent with about a 70 per cent reduction in risk of death from measles with vitamin A treatment (45), an effect size that has continued to withstand analytic challenge (54). These findings are remarkably consistent in the degree of protection from measles-related death conferred by periodic vitamin A supplementation trials, in which measles-specific mortality was found to be reduced by 33 to 76 per cent (55). We do not yet understand all the molecular mechanisms that account for this impact (many plausible mechanisms exist). This is common in clinical advances.

Contrary to an argument put forth by Professor Latham, we do wish to point out that only a fraction of all deaths prevented in vitamin A trials have been attributed to measles. An example can be found in our trial in Nepal, where vitamin A reduced all-cause mortality by 30 per cent (37). While the relative risk of mortality from measles in the vitamin A group was 0.24 (a 76 per cent reduction), measles was responsible for only about 4 per cent of all deaths. Other responsive 'causes of death', which were identifiable by an admittedly surrogate 'interview' and assignment process, included wasting malnutrition, diarrhoea/dysentery and other unclassifiable infections (37), similar to the pattern that was observed in South India (39).

However, the coordinated morbidity and mortality intervention trials in Ghana provide perhaps the clearest evidence of the importance of improving vitamin A status in attenuating potentially fatal, if not routine, illness. In that population setting, where vitamin A supplementation reduced all-cause mortality by 19 per cent, an adjacent, concurrent, double-blinded morbidity trial (42) documented no difference in home-reported illness symptoms, a finding that has now been reported elsewhere (56, 57), including a study to which Professor Latham refers (58).

However, the rate of clinic visits for illness (which is likely to reflect greater severity) were significantly lower (by 12 to 27 per cent) and the rate of hospitalisation for severe illness was reduced by 38 per cent. Further, among those hospitalised for diarrhoea, children randomised to vitamin A in the community programme had less severe signs of dehydration than controls (59). These data support other evidence that vitamin A is more likely to attenuate the severity of infectious illnesses, especially measles and diarrhoea, rather than the frequency or duration of milder morbidity.

A modelling exercise using the Lives Saved Tool (LIST) at Johns Hopkins University uses data on consensus cause of death-specific-effect estimates (in this case, diarrhoea) from the original trials, coupled with current estimates of cause-specific mortality and population data. (These data are available on the ChildInfo.org website of UNICEF). From this, it can be estimated that some 360,000 diarrhoea-related deaths, not assigned to other causes, would have occurred in the world's 68 highest risk and priority countries in 2010 had there been no vitamin A programmes. As it is, vitamin A coverage is reported to be reaching about 75 per cent of children in these countries, so a substantial number of deaths from diarrhoea will not have been averted.

There is consistent, firm and repeated evidence that vitamin A interventions can dramatically improve child survival from measles and diarrhoea. On the other hand, there is little evidence that it impacts on deaths from lower respiratory infection (other than broncho-pulmonary disease related to measles). The reasons remain unclear (60). Also, to date effects of vitamin A on risk of *falciparum* malaria are mixed, with supplementation lowering indices of severity in Papua New Guinea (61) but lacking an impact in Ghana (62). Severity of ear infections may be reduced with vitamin A. In the original cohort from our trial in Nepal, we recently observed about a 40 per cent reduction in hearing loss in young adults who during the original trial (37) had purulent ear discharge and were in the vitamin A supplemented group versus those with ear infections but received the placebo (63). These findings will add important new information for considering the public health benefit of vitamin A interventions.

Supplementation is effective and safe

Vitamin A supplementation programmes do effectively and safely reduce child mortality. This is a sound conclusion, within the inferential limits of designs available to most programme evaluations.

For example, in Nepal after two trials in the south and far west showed 30 per cent reductions in child mortality, the country launched a semi-annual vitamin A campaign-style programme that now regularly reaches more than 85 per cent of eligible children nationally. Subsequent evaluation, through sequential national family health surveys,

confirmed that the programme was likely to be achieving a substantial reduction in child mortality (64).

Other programme evaluations have reported results consistent with declines in mortality, severe morbidity or xerophthalmia that would be expected with vitamin A programme activity, for example in the Philippines (24), India (23, 65), the Yemen (66) and South Africa (67). But evaluations of programmes are fraught with difficulty, as historical trends are influenced by variations in climate, rains, harvests, economies and the like. For these reasons, randomised community trials remain the gold standard, as they define what can be achieved when all other aspects remain comparable except for providing vitamin A.

With respect to safety, most public health interventions carry minor risks, and vitamin A supplementation is no exception. Among preschool children receiving the large, semi-annual dosage of vitamin A, 5-10 per cent may experience one or more transient, self-limiting symptoms of nausea, vomiting, headache or fever, usually not lasting more than 24-48 hours (68). Still, these kinds of side effects in even a small fraction of children can create difficulties with programmes, should staff not be adequately trained and the community not informed of such risks.

When to begin and to end supplementation

Why and when should vitamin A supplementation begin, be maintained, and then be phased out?

When to begin

Essential criteria exist for initiating a preschool vitamin A prophylaxis programme in a country. Vitamin A deficiency should exist at a level of public health significance, defined by WHO in terms of minimum prevalence criteria for any stage of xerophthalmia or for deficiency reflected by a serum retinol concentration (which is, more than 15 per cent below 0.70 umol/L, or 20 ug/dL) (69). While other vitamin A status indicators exist, these are currently the two firm and long-established mainstays for informing public health policy. It is best that both be measured in a population. Exceeding either the clinical or biochemical cut-offs merits intervention.

Health risks, including increased severity of infection and excessive mortality, can occur in a population without ocular signs of deficiency. It is therefore incorrect to assume, without serological data, that the absence of xerophthalmia indicates the population is risk-free. Studies have repeatedly shown that the reduction in childhood mortality accompanying a vitamin A intervention greatly exceeds the excess mortality

attributable to xerophthalmia, which begins to rise before earliest eye signs become present (8).

The choice of intervention to improve vitamin A status depends upon the urgency with which the condition needs to be addressed. This is reflected by the extent of xerophthalmia or biochemical deficiency, plus the extent of negative health outcomes it causes, especially infant and child blindness and mortality. The decision also must take into account available resources, infrastructure, and cultural determinants.

Typically, semi-annual vitamin A supplementation is considered a first choice when

- Vitamin A deficiency exceeds its minimum public health threshold criterion (based upon a representative population sample).
- Preschool child mortality is high (for example, when a UNICEF-defined U5MR (under five mortality rate) is more than 50 per 1000 live births),
- There are few dietary options widely available for reliably raising vitamin A intakes within a reasonable time period among young children.

Equally important, is the concurrent planning of longer term, food based solutions to prevent vitamin A deficiency, and infection control approaches that can preserve a child's nutritional reserves to support activity, growth and development.

When to phase out

Supplementation programmes can sensibly be phased out, when there is clear evidence that vitamin A deficiency in the target population is no longer a problem. This can be taken to mean that its prevalence is well below the minimum public health thresholds, both for xerophthalmia and serum retinol, for an extended period of time, in order to be sure of sustained, satisfactory status. Collateral evidence should also document that preschool child mortality is also in decline. The reasons that both clinical and biochemical indicators should be met is because they provide different and complimentary evidence of status.

Periodic vitamin A supplementation has a direct, immediate and clear impact on the risk of xerophthalmia. With regular high coverage, xerophthalmia, as the most specific and clinically detectable consequence of vitamin A deficiency, will be controlled.

Semi-annual vitamin A delivery fails to do two things: It does not correct the dietary causes of deficiency, and alone never normalises (except for a limited period, around 2 months) the serum retinol distribution of a deficient population (70-71). What shifts the serum retinol distribution in a population in the right direction, and stabilises it within a normal range, are diets and therefore food systems that are adequate all year round in vitamin A, as has been amply shown through food fortification (35, 72-75).

Presumably, this can occur when diverse food- based interventions routinely increase the availability and intakes of food sources of vitamin A over the long term, as suggested by some (76, 77) though not all (78, 79) pilot projects evaluated.

The intransigence of the serum retinol distribution to respond to periodic vitamin A delivery, but its responsiveness to a steady, adequate dietary intake, sustained over time, can guide policy makers in their decisions to maintain or to change programme options (72).

As long as a substantial fraction of any population has deficient serum retinol levels, emphasis should be placed on finding ways to improve dietary vitamin A intake in sustainable ways, while continuing to supplement children until that occurs. Once serum retinol surveys repeatedly begin to indicate that serum retinol distribution has shifted in the right direction, and is adequate in the vast majority of young children, in a sustained manner, dietary adequacy and vitamin A sufficiency has probably been assured, and vitamin A supplementation can be safely withdrawn (72).

However, policy makers must remain alert to unusual changes in economically marginalised populations, as occurred in South Asia in the 1990s and globally in 2008 (80, 81). These adverse changes can severely undermine nutritional well being and possibly vitamin A intake and status (82). In such circumstances, policy makers need to be prepared to re-intervene with shorter term measures to prevent resurgent vitamin A deficiency when this occurs.

Concluding remarks

In this commentary we have focused on vitamin A supplementation because of the nature of the original attack made by Professor Latham, We have attempted to give an objective view of the basis for global policy specifically to prevent vitamin A deficiency, reinforced by numerous studies, without minimising the importance of nutritious diets for young children.

There is much more that can be stated about dietary intervention strategies; for example, the implications of the inefficiencies of bio-converting plant carotenoid precursors to retinol (83). In the past decade, this has led the US Institute of Medicine in to change its estimate of the beta-carotene to retinol bioconversion ratio from 6:1 to 12:1 (84). The implication of this new knowledge, based on numerous clinical studies, is that children need to consume diets containing far more beta-carotene from plant foods than previously supposed, or else need some preformed vitamin A from animal foods, in order to assure adequacy.

There is also much that can be said about staple food product fortification, as a promising and rising strategy, as well as bio-fortification as a future contributor to deficiency prevention. We view dietary diversity, food fortification and supplementation as complementary, each with their strengths, efficacies and limitations (8).

We see little relevance in using the term 'Vitamin A Fiasco' in the current debate. There is no valid parallel with the 'Protein Fiasco' about which Donald McLaren wrote in 1974 (2). With vitamin A deficiency, there is ample evidence of its singular importance and the specificity of health benefit from its prevention in children. There are ways and means to tackle vitamin A deficiency along a continuum of short-acting to longer term strategies.

If there is any 'fiasco', it is the sad fact that food-based strategies to prevent malnutrition have not yet properly been developed, tested, implemented, taken to scale, and proven adequately to solve the dietary deficits of the world's poorest populations . We stand among those continuing to work toward these solutions.

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