When should universal distribution of periodic high-dose vitamin A to children cease?

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Vitamin A deficiency (VAD) results in night blindness; continued and severe deficiency leads to more serious forms of xerophthalmia, including corneal ulceration and permanent blindness. VAD also increases the risk of morbidity and mortality from infections, including measles, diarrhea, and respiratory tract infection. Based on the latest Cochrane systematic review, periodic vitamin A supplementation (VAS) among older infants and young children aged 6–59 mo reduced all-cause mortality by 12% (1). The WHO currently recommends periodic VAS among children aged 6–59 mo in settings with a high prevalence of night blindness or VAD. The recommended regimen is 30,000 μg of retinol activity equivalents (RAEs) (i.e., 100,000 IU) once in children aged 6–11 mo, and 60,000 μg of RAEs (i.e., 200,000 IU) for older children every 4–6 mo until the child reaches 5 y (2). VAS has been adopted by over 80 countries to reduce child mortality (3).

The value of continued universal periodic VAS has been debated (4–7). On the one hand, it has been argued that the program no longer has discernible benefits in reducing deaths. The survival benefits of VAS are thought to be primarily through reducing deaths from measles and diarrhea, both of which are less prevalent and better managed in the present time. Studies conducted in more recent years reported small or no effects of periodic VAS on all-cause mortality (1). The DEVTA study, conducted between 1999 and 2004 in Uttar Pradesh, India, is the largest program evaluation of universal VAS and found no benefits on all-cause or cause-specific mortality (8). On the other hand, some have noted that periodic high-dose VAS is still an essential child survival strategy. It has been argued that the recent vitamin A interventional studies were not adequately designed, powered, or implemented to evaluate the impacts of the supplementation on mortality (7). It has also been contended that the program evaluated in the DEVTA study had very poor coverage, which may explain the lack of observed benefits (5).

Periodic high-dose VAS was intended as a temporary solution before more sustainable interventions became widely available. There is, therefore, a consensus that the universal distribution of vitamin A should stop at some point, but the timing of when that can be safely done is contested. Decisions on the timing of discontinuing universal periodic VAS and potentially initiating a targeted approach should be informed by assessments of the vitamin A status in a specific population using repeated, representative surveys. Evidence of adequate vitamin A status sustained over time in a geographic area would lend credence to the discontinuation of the universal delivery in that area. The most commonly used biomarker to monitor vitamin A status at the population level is serum (or plasma) retinol. The assessment of dietary intake provides important additional information to support the biomarker data.

High-dose VAS results in a transient right-shift of the population distribution of serum retinol for 1–3 mo, after which the distribution will return to its level prior to the supplementation (9, 10). Therefore, surveillance of serum retinol should be conducted at least 3 months after supplementation. Also, serum retinol concentrations decrease transiently during the acute-phase response to infection or inflammation (11), so markers of inflammation such as C-reactive protein or α_1-acid glycoprotein should be measured and adjusted for. The population benchmark of VAD prevalence for discontinuing universal VAS is controversial. While the WHO recommends supplementation in settings where the prevalence of VAD is $\geq$20%, others have suggested stopping universal distribution when the prevalence of VAD is $\leq$5% in at least two consecutive years (10). We propose to consider $<$10% as the benchmark for discontinuing universal VAS, as the WHO considers VAD to be of mild public health importance when its prevalence drops below 10% (12).

Using dietary intake to monitor the vitamin A status is comparatively more challenging due to the need for data on the frequency and portion size of foods consumed by at-risk individuals and the availability of accurate food composition tables. This challenge is exacerbated by the increasing consumption of vitamin-A-fortified foods, for which high-quality dietary data are sparse. Whether biomarkers or dietary intake is used, it is critical to ensure that any improvement in vitamin A status is sustained over time. For major global challenges of infectious diseases, elimination is often declared in a region when no local cases are detected in at least three consecutive years (13–15). While it may not be possible to eliminate VAD in children in currently affected countries in the foreseeable future, analogously, the threshold of three consecutive years is worth considering to ensure that the improvement is maintained. In settings with strong seasonality of dietary intake, improved vitamin A status must also be documented across different seasons.

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Two studies published in this issue of *The American Journal of Clinical Nutrition* assessed VAD and VAS in South Asia and sub-Saharan Africa, where the largest burden of VAD is. Reddy et al. used data from national and subnational surveys in India to evaluate whether VAD still presented a serious public health problem among children <5 y of age (16). It was reported that the national prevalence of VAD measured using serum retinol was 15.7% (95% CI: 15.2%, 16.3%) and that only 3 states had a prevalence significantly greater than 20%. Meanwhile, when dietary intake, food fortification, and VAS were considered together, 30% of children aged 1–3 y and 8% of children aged 4–5 y were projected to exceed the tolerable upper limit of vitamin A intake, with the risk greater for children from higher socioeconomic status. In a study in Malawi, Williams and colleagues used the 2015–2016 Malawi Micronutrient Survey (with data on preschool children aged 6–59 mo, among other population groups) to characterize vitamin A status and describe the coverage of vitamin A interventions (17). The results suggest a very low national prevalence of VAD in young children (1.8%; 95% CI: 0%, 4.6%; based on inflammation-adjusted serum retinol) even during a hungry season and with high burdens of infection and inflammation. The Malawi study also reports emerging hazards of vitamin A excess among young children based on elevated fasting serum retinyl esters. Both studies indicate significant reductions in the burden of VAD, raise concerns about the emerging risk of vitamin A excess, and call for a re-examination of the current universal approach to VAS. The important findings of the two studies should be interpreted with several considerations in mind.

First, in the study from India, 42% of the children had received high-dose VAS within the previous 6 mo, with the specific dates of distribution unknown. Given the transient increase in serum retinol concentrations after supplementation (9, 10), the inclusion of those who received supplementation within the past 1–3 mo would have led to an overestimation of serum retinol concentrations and thus an underestimation of the prevalence of VAD. In the Malawi study, the scheduled biannual VAS was intentionally postponed until data collection was completed, so the serum biomarkers were not likely to have been affected by the short-term impacts of VAS.

Second, in the Indian study, the *lower* bounds of the 95% CI of VAD prevalence estimates were compared against the cutoff of 20%. When there is uncertainty in the estimate due to sampling, it is perhaps prudent to make sure the *upper* bound of the 95% CI is below the benchmark to be conservative. Eleven out of 30 states had their upper bounds of VAD prevalence exceeding 20%, and 23 states had their upper bounds exceeding the 10% cutoff we proposed. In the Malawi study, retinol-binding protein (RBP) was used to assess VAD; this indicator has a few challenges, including the inconsistent ratio with retinol across geographic settings and potential impacts of kidney function and overweight and obesity, which is rising in all countries (18). The low prevalence of VAD based on RBP was corroborated through triangulation with alternative measures, including serum retinol, modified relative dose response, and serum carotenoids. However, the sample size available for these other biomarkers was very small for a national sample ($n = 73$). The prevalence of VAD at the national level in Malawi does appear to be fairly low (much lower than the 10% cutoff we have proposed above), although breakdown by regions would also be informative given the expected clustering of VAD in rural and more disadvantaged areas.

Third, even with governmental mandates, vitamin-A-fortified foods may not be immediately available to or consumed by all households, especially those in rural areas or with lower socioeconomic status, who are in the greatest need (19). In India, the surveys were conducted before the national regulation for the fortification of oil and milk with vitamin A was introduced, so the estimated impacts of food fortification are perhaps the maximum theoretical effects rather than depictions of the current situation. In the Malawi study, around 70% of the (mostly rural) households in a nationally representative sample had sugar and oil fortified with retinol.

Fourth, stronger evidence on the approach to assessing vitamin A toxicity is needed. Precise safety thresholds of vitamin A intake among young children are limited, with the lowest-observed-adverse-effect level of 6000 μg/d for children aged 1–5 y being an extrapolation from adults due to the dearth of data (20). Large doses of *daily* supplementation for an extended period (months or years) in young children can result in chronic hypervitaminosis A (21–23); however, the risk of such toxicity under the WHO-recommended periodic VAS regimen and current fortification programs is unclear. Furthermore, although retinyl ester measurement is the most commonly used biomarker to assess vitamin A toxicity, its use has several challenges. These include the need for the samples to be taken while adequately fasted, complications in the interpretation of values in the presence of protein malnutrition and liver disease, and a lack of consensus on the appropriate cutoff for defining hypervitaminosis A (18). In the Malawi study, elevated levels of retinyl esters were also noted among children aged 5–14 y who were not receiving VAS, so it is uncertain to what extent the potential vitamin A excess in young children under 5 y was attributable to the supplementation.

The options for the targeted approach of supplementation should be evaluated critically when considering phasing out universal VAS. Individual targeting based on nutritional backgrounds and socioeconomic status is perhaps less feasible than targeting geographic regions. Given the potential variability in nutritional status and dietary intake within a region, geographic targeting based on subunits (e.g., districts or smaller) would be preferable. The cost-effectiveness of targeted supplementation is also a vital consideration. In the Philippines, for example, VAS targeting high-risk children was projected to be much less cost-effective than universal supplementation (24). The scaling back of VAS from <5 y to include only children younger than 2 or 3 y has also been implemented or suggested in some settings (25).

It is crucial to have an open dialogue on when and how to discontinue well-established public health programs. The detailed assessments by the Indian and Malawian study teams are laudable. We will follow with great interest further evidence on the sustained improvements in vitamin A status among young children in these two countries. As more countries start seeing an improvement in vitamin A status in the era of overlapping vitamin A interventions, there is a critical need to monitor the prevalence of VAD and vitamin A excess in the population. To advance policies and programs, it is imperative that the WHO and UNICEF lead the scientific community in achieving global consensus on the optimal combination of markers and the specific cutoff for each that is indicative of deficiency or excess states. In

the meantime, VAD still poses a serious public health challenge for children in much of the developing world (3). Universal distribution of periodic high-dose vitamin A remains vital in countries where vitamin-A-fortified and vitamin-A-rich foods are not widely available or accessible.

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