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Reply to A Hasman et al.

Dear Editor:

In response to Hasman et al., we have the following observations. We agree with their primary observation that targeting or prioritizing vitamin A supplementation (VAS) in place of a universal policy promises a solution to the problems of stagnant coverage and risks of excess intake while increasing the potential for population-level impact. Yet, they go on to advocate universal VAS in younger children, which we believe is incorrect. In our view, the underlying principle of their primary position is correct: that "one size does not fit all." Therefore, countries should formulate their own VAS policy depending on local evidence and circumstances, as we argue below.

In support of universal VAS, Hasman et al. ask several questions stemming from their global perspective. In response, we present the Indian perspective, relevant to the precision that is now critically needed in global public health. First, they ask if there is evidence that VAS can prevent mortality and morbidity in the target population. In Indian children, a meta-analysis of 5 studies of VAS and its effect on mortality showed no significant survival benefit (1). This contrasts with the survival benefit that emerged in the Cochrane analysis of global evidence (2), but it should be noted that the Cochrane analysis included the benefit from much older trials conducted when vitamin A deficiency (VAD) was rife. However, even this estimated global 12% mortality reduction (2) has no practical relevance for the current 6 mo–5 y mortality rate in India, especially with suboptimal programmatic coverage (1). We think this local context is very critical for the definition of VAS-related policy.

Next, they ask if there is evidence that VAS is associated with serious or frequent side effects. We ask in return: do they seek evidence of *harm* or evidence of *risk* (of excess intake)? In support of universal coverage, they go on to state: "although vitamin A excess may occur … there is little evidence about the severity of … excessive vitamin A intake." This statement is astonishing, because no evidence of toxicity is not the same as evidence of no toxicity. In addition, apart from the transient bulging fontanelle with attendant clinical symptoms that cause parental anxiety, it may be the more *chronic* effects (with respect to liver and bone pathology), that are not immediately visible, which are very relevant to later health (3). A letter (4), written in response to this review on acute and chronic vitamin A toxicology (3), noted: "It is sincerely hoped that [this discussion of toxicity] may help to turn the minds of health policy managers toward a safer and more sustainable approach to tackling VAD … by diet diversification and biofortification." Sadly, >15 y later, although fortification has commenced in India (5), diet diversification is still not getting the advocacy it deserves. It is worth reminding ourselves that only small amounts of green leafy or orange vegetables are required to meet the daily β-carotene (and therefore retinol) requirement of young children, and that this is a feasible and economical solution to pursue.

Next, Hasman et al. ask about the costs of VAS. They state that universal delivery is often inexpensive and highly cost-effective. We cannot speak for the rest of the world, but in a large country like India, the targeting of VAS will result in very significant cost savings, which could be better invested in interventions that are likely to improve survival and quality of life.

Finally, they consider the possibility of misclassifying children during the prioritization of VAS and missing those most in need. We have considered this as well and have stated that when moving to a targeted VAS policy, it is critical to conduct sentinel site monitoring of eye signs and to keep a close watch on vital statistics at *all* sites (1). They also question the cutoff used to define toxicity; although we agree with the need for this rigor, we will also add that the same doubt extends to the serum retinol cutoff used to define VAD. The following words, written many years ago with respect to the definition of VAD based on serum retinol concentration, are important (6): "the interpretation of VAD status depends on the availability of reference data, preferably derived from populations known to have adequate vitamin A status, as from 'elite' groups within the population itself."

Hasman et al. end by positing the provision of universal VAS to younger children, who are 6–23 mo old. The contrasting position is that these younger children could actually be the most vulnerable to the risk of toxicity. Their daily vitamin A requirements are lower, and breast-milk feeding ≤6 mo (which often extends through the first year) will also build up their body stores. In support of this position (1, and unpublished data), the prevalence of VAD was higher in 5- to 9-y-old than in 1- to 4-y-old Indian children (19.3% compared with 15.7%). In addition, it is also possible that the exposure to fortified milk or other fortified health beverages could be higher in the first 2 y of life.

We conclude by re-emphasizing that it might be unwise to pursue the "one size fits all" rule for VAS. The sensible, safe, economical, and sustainable solution for vitamin A nutriture is food-based, and it is mystifying why the influential authors of this letter do not advocate for this option, before their advocacy for universal high-dose VAS.

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Reply to Hasman et al.

Dear Editor:

We agree that an open dialogue about modifying universal vitamin A supplementation (VAS) programs, suggested by researchers at Harvard (1) and supported by UNICEF (2), is needed. The goal of universal VAS programs is prevention of mortality and morbidity (3), given the role of vitamin A in immune functions (4). The Global Alliance for Vitamin A (GAVA) has a framework for evidence-based decision making to scale back universal VAS, and the decision tree outlined in the GAVA framework starts with a determination of the vitamin A status of a population using biochemical indicators (5). We recognize that the resource requirement, government commitment, and agency coordination required to collect and synthesize population-based vitamin A biochemical data are not trivial. Here, we describe the experience in Malawi by the government and partners to collect and analyze vitamin A biomarker data during the 2015–16 National Micronutrient Survey, as well as a pilot to test a new distribution model for VAS.

The Government of Malawi regularly assesses their national vitamin A status, completing national surveys that collected vitamin A biomarker data in 2001, 2009, and 2015–16. In early 2019, planning discussions for the next national micronutrient survey were interrupted by the coronavirus disease 2019 pandemic. Survey planners anticipated low vitamin A deficiency (VAD) in 2015–16 (6), given the trend of decreasing VAD between 2001 and 2009 and the implementation of multiple, overlapping vitamin A interventions. Thus, survey planners decided a priori to collect sufficient serum for analyses of multiple vitamin A biomarkers. After the main vitamin A survey results of the modified-relative-dose response and retinol binding protein were disseminated, due to low levels of VAD a decision was made to also analyze retinyl esters, carotenoids, and retinol using back-up serum.

In 2020, when the complete vitamin A data from the 2015–16 survey became available, the Government of Malawi organized a workshop to review findings to inform how national vitamin A programs may need to be modified. In preparation for this workshop, government agencies collated data on performance and coverage of vitamin A programs (i.e., VAS, sugar and cooking oil fortification, micronutrient powders, biofortified foods, and supplementary feeding for low-income households), dietary intake, and biomarkers (i.e., retinyl esters, carotenoids, retinol, modified-relative-dose response, and retinol binding protein). The workshop was organized in accordance with the GAVA framework that states "decisions to scale back or shift from universal VAS should be based on information that verifies that vulnerable populations have an adequate and sustained vitamin A status from dietary sources and other interventions" (5). Malawi is unique to have this wealth of data; yet, at the conclusion of the workshop, data gaps precluded decisions to scale back VAS.

Key data gaps that were identified included the need for more granular biomarker data by age group (children aged 6–11, 12–24, 25–36, and 37–59 months) and geography (7), which translates to a larger sample size. Furthermore, vitamin A biomarker data may need to be collected in a season when vitamin A–rich fruits and vegetables are less accessible (7). More comprehensive dietary intake data among infants and young children were also needed (7).

Survey data that collected information on individual intakes in the past 24 hours or household expenditures did not provide the distinctions necessary to determine regular intake patterns and intra-household food consumption. Modeling household expenditure data suggested that children aged 6–59 months in the lowest-wealth categories may not have access to sufficient vitamin A–rich foods or vitamin A–fortified foods (oil and sugar). Triangulating program coverage, quality, and adherence data with the age groups of the populations reached by programs was proposed as a follow-up activity from the workshop deliberations (7).

A separate but related activity to pilot a modified VAS delivery system was tested in 2019. Since 2004, Malawi has achieved >90% VAS coverage for children aged 6–59 months using a Child Health Day campaign delivery platform (8). Malawi concluded that separate delivery of VAS and routine immunizations may be inefficient, both financially and with health worker shortages (8).

Considering that immunization and VAS target the same children and are delivered by the same health workers, the Ministry of Health piloted the distribution of VAS within the Expanded Program on Immunization in 10 districts to assess feasibility and assess VAS coverage using routine delivery (8). The target for VAS coverage within the pilot program was 80% for children aged 6–11 months and 50% for children aged 12–59 months, which was exceeded as of June 2020, with all children aged 6–11 months reached and 54% coverage among children aged 12–59 months (8). The VAS delivery

The International Micronutrient Malnutrition Prevention and Control team (IMMPaCt) program at the CDC provided technical support in the design and implementation of 3 national micronutrient surveys in Malawi (2001, 2009, and 2015–16). IMMPaCt/the CDC also collaborates technically in certain Global Alliance for Vitamin A (GAVA) activities, including the development of the GAVA scaling back framework and related workshops.

The findings and conclusions in this letter are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Abbreviations used: GAVA, Global Alliance for Vitamin A; VAD, vitamin A deficiency; VAS, vitamin A supplementation.