See corresponding editorial on page 769 and article on page 854.

Vitamin A deficiency among children younger than 5 y in India: an analysis of national data sets to reflect on the need for vitamin A supplementation

G Bhanuprakash Reddy,[1] Raghu Pullakhandam,[1] Santu Ghosh,[2] Naveen K Boiroju,[1] Shalini Tattari,[1] Avula Laxmaiah,[1] Rajkumar Hemalatha,[1] Umesh Kapil,[3] Harshpal S Sachdev,[4] and Anura V Kurpad[2]

[1]National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, India; [2]St John's Medical College, Bengaluru, India; [3]Institute of Liver and Biliary Sciences, New Delhi, India; and [4]Sitaram Bhartia Institute of Science and Research, New Delhi, India

ABSTRACT

Background: Biochemical vitamin A deficiency (VAD) is believed to be a serious public health problem (low serum retinol prevalence >20%) in Indian children, justifying universal high-dose vitamin A supplementation (VAS).

Objective: To evaluate in Indian children younger than 5 y the risk of biochemical VAD from the Comprehensive National Nutrition Survey, as well as dietary vitamin A inadequacy and excess over the tolerable upper limit of intake (TUL) from national and subnational surveys, factoring in fortification and VAS.

Methods: Child serum retinol data, corrected for inflammation, were examined to evaluate national- and state-level prevalence of VAD. Simultaneously, dietary intakes from the National Sample Survey Office and the National Nutrition Monitoring Bureau were examined for risk of dietary vitamin A deficiency against its average requirement (AR) derived for Indian children. Theoretical estimates of risk reduction with oil and milk vitamin A fortification were evaluated along with the risk of exceeding the TUL, as well as when combined with intake from VAS.

Results: The national prevalence of biochemical VAD measured in 9563 children was 15.7% (95% CI: 15.2%, 16.3%), and only 3 states had prevalence significantly >20%. The AR of vitamin A was 198 and 191 μg/d for boys and girls; the risk of dietary inadequacy was ∼70%, which reduced to 25% with oil and milk fortification. Then, the risk of exceeding the TUL was 2% and 1% in 1- to 3-y-old and 4- to 5-y-old children, respectively, but when the VAS dose was added to this intake in a cumulative 6-mo framework, the risk of exceeding the TUL rose to 30% and 8%, respectively.

Conclusion: The national prevalence of VAD risk is below 20% in Indian children. Because there is risk of excess intake with food fortification and VAS, serious consideration should be given to a targeted approach in place of the universal VAS program in India. *Am J Clin Nutr* 2021;113:939–947.

Keywords: vitamin A, vitamin A deficiency, vitamin A supplementation (VAS), children younger than 5 y, India

Introduction

Vitamin A is an essential nutrient that must be provided in the diet as it cannot be synthesized by humans. Young children are more vulnerable to its deficiency. In low- to middle-income

Funding: AVK is supported by the Wellcome Trust/DBT India Alliance through its Margdarshi Fellowship. GBR is supported by grants from the Department of Biotechnology, the Science and Engineering Research Board, and the Indian Council of Medical Research.

Supplementary Figures 1–3 and Supplementary Material are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Present address for AVK: Department of Physiology, St John's Medical College, Bengaluru, India.

Present address for HSS: Department of Pediatrics and Clinical Epidemiology, Sitaram Bhartia Institute of Science and Research, New Delhi, India.

Address correspondence to AVK (e-mail: a.kurpad@sjri.res.in) or HSS (e-mail: hpssachdev@gmail.com).

Abbreviations used: AR, average requirement; BRINDA, Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia; BW, body weight; CNNS, Comprehensive National Nutrition Survey; CRP, C-reactive protein; CU, consumption unit; EFSA, European Food Safety Authority; GM, geometric mean; GSD, geometric SD; IOM, Institute of Medicine; LLOQ, lower limit of quantitation; NNMB, National Nutrition Monitoring Bureau; NSSO, National Sample Survey Office; RAE, retinol activity equivalent; SES, socioeconomic status; TUL, tolerable upper limit of intake; VAD, vitamin A deficiency; VAS, vitamin A supplementation.

Received July 7, 2020. Accepted for publication October 7, 2020.

First published online December 16, 2020; doi: https://doi.org/10.1093/ajcn/nqaa314.

countries such as India, it is widely accepted that micronutrient deficiencies are highly prevalent because of inadequate dietary intake, infections, and/or chronic inflammation, which could lead to poor absorption of the nutrient or increased catabolism. Vitamin A deficiency (VAD) along with nutritional blindness was prevalent in India in the 1950s and 1960s. In 1970 the National Prophylaxis Program Against Nutritional Blindness, providing high doses of vitamin A, was initiated to prevent nutritional blindness due to keratomalacia. Later, with studies reporting a beneficial impact of high-dose vitamin A supplementation (VAS) in reducing all-cause mortality by 23% (1), the focus of this program shifted to decreasing mortality rates, although this move is widely debated (2, 3).

The question now remains: in a broader context, is VAD still a significant public health problem in India that requires VAS? This seems a reasonable question, given national progress with reduction of infant and child mortality rates (4), immunization coverage (5), poverty reduction (6), and recent initiation of oil and milk fortification with vitamin A (7), underpinned by an almost complete reduction in clinical signs of VAD in children (8–10).

The primary assessment of population VAD is performed by examining for signs of clinical deficiency and serum retinol concentrations, which is a status biomarker. Until recently in India, no nationwide survey examined serum retinol concentrations simultaneously with inflammatory biomarkers in young children. The Comprehensive National Nutrition Survey (CNNS, 2016–2018) now offers this primary evidence for assessing VAD across India in 1- to 5-y-old children (11). In addition, the dietary intakes of the population need to be assessed. Dietary inadequacy of vitamin A can be evaluated by comparing the distribution of intakes with the distribution of requirement. This analysis is problematic when the distribution of the requirement is not explicitly defined. The requirement of vitamin A in India is presently available only as a single value called the RDA (12), while measuring the risk of dietary inadequacy requires definition of the requirement distribution and the average requirement (AR) (13).

The CNNS serum retinol data, in conjunction with dietary intake assessments and the recently mandated cooking oil and milk fortification with vitamin A (14), offer an opportunity for a critical assessment of VAD and the need for the VAS program in India. We evaluated biochemical VAD on a national level in 1- to 5-y-old Indian children, in parallel with their risk of dietary deficiency measured against a factorial estimate of the distribution of vitamin A requirements. The risk was also evaluated with theoretical enhanced vitamin A intakes coming from fortification. Finally, an evaluation of the risk of excess intake of retinol from fortification and VAS over 6 mo was made against the tolerable upper limit (TUL) of intake.

Methods

Surveys used in this analysis

Three surveys were used in the present analysis: the CNNS for serum retinol and specific rounds of dietary surveys from the National Nutrition Monitoring Bureau (NNMB) and the National Sample Survey Office (NSSO) for dietary intake assessments.

The CNNS (11) was conducted in 30 states and Union Territories of India from 2016 to 2018, using a multistage stratified probability proportion to size sampling design, and collected data in children aged 1 to 5 y. The number of children with serum retinol measurements was 9563; among these, 3978 (41.6%) had received VAS within the past 6 mo, but the exact date of receipt was not available. Their mean age was 38.1 mo; 52.6% were boys and 47.4% were girls. The prevalence of low weight for age [underweight, weight for age z score (WAZ), ←2 SD] was 26.2%, and that of low height for age [stunted, height for age z score (HAZ), ←2] was 28.5%. The children were from both urban and rural areas, as well as from a wide range of socioeconomic statuses. Serum retinol concentrations were measured by reverse-phase HPLC (11). No details were provided about the instrument used, the lower limit of quantitation (LLOQ) and upper limit of quantitation, or the inter- and intra-assay precision. Serum retinol concentrations were used as the biomarker for defining VAD (serum retinol <20 μg/dL) in this population, along with adjustments for C-reactive protein (CRP), as a marker of inflammation (**Supplementary Figure 1**). The CRP measurements were performed with 2 different methods of varying resolution, nephelometry and particle-enhanced immunonephelometry (11), where the latter high-resolution method had a LLOQ for serum CRP of 0.2 mg/L, whereas the equivalent value for the former method was 3 mg/L. Most measurements were made by the former, low-resolution method. The proportion of observations that were left-censored due to the LLOQ for both assay methods was 60%. Inflammation adjustment was made through censoring those values associated with high CRP concentrations (≥5 mg/L) from the data set, correction of serum retinol values through the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) method (15), or a new probability method, as defined below.

A diet and nutrition survey (9) was carried out by the NNMB in 10 Indian states in 2011–2012: Andhra Pradesh, Gujarat, Karnataka, Kerala, Madhya Pradesh, Maharashtra, Orissa, Tamil Nadu, Uttar Pradesh, and West Bengal. The survey covered 2400 households in rural areas for socioeconomic status and nutritional assessment, as well as 800 households for dietary assessment in each state. A 1-d individual 24-h dietary recall was collected from children from each household to yield their reported vitamin A intakes as retinol activity equivalents (RAEs)/d (**Supplementary Figure 2**). To evaluate and clean the dietary data for underreporting, the recorded energy intake [expressed per kilogram of body weight (BW)] was compared with the age- and sex-specific total daily energy requirement per kilogram of BW for 1- to 5-y-old children. The distribution of the ratio of the energy intake and energy requirement (per kg/d) was inspected to identify its lower 3-sigma limit at 0.55; values below these were used for identifying and censoring underreporters from the database.

The NSSO survey (16) covered the entire territory of India (29 states and 6 Union Territories) from 2011 to 2012 across all socioeconomic strata, in 7469 villages and 5268 urban blocks, and collected data on monthly per-capita expenditure on household food purchases of 223 food items with a recall period of 30 d (**Supplementary Figure 3**). The quantities of different foods purchased by the household were converted to their vitamin A equivalent as RAEs/d, using the Indian Food Composition

Table (17), and this was adjusted for the number of members in the household and the use of consumption units (CUs) for individual quantity of intake (18). For children aged 1–3 y and 4–5 y, the CUs used were 0.5 and 0.7, respectively, to obtain the vitamin A intake (RAE) per CU per day. To clean the data of underreporters, because BW and age were not available, the lower 0.5% of these data were censored, corresponding to an energy intake of <1050 kcal/caput/d.

It is important to note that all the surveys described above were performed before the regulations on the mandatory vitamin A fortification of cooking oil and the voluntary vitamin A fortification of milk were notified by the Indian government in 2018 (14).

Assessment of serum retinol values in 1- to 5-y-old children

Serum retinol values were adjusted for the CRP concentration by the probability method of correction for inflammation (19), which is a modification of the BRINDA correction approach (15). Unlike the CRP-based exclusion method, these approaches allowed for the inclusion of all serum retinol measurements, irrespective of the presence of inflammation or infection. The CRP measurements in the CNNS were performed with 2 different kit-based methods of varying sensitivity as described above. Using the original BRINDA correction approach could lead to overestimation of the prevalence of low serum retinol due to the left-censored CRP data arising from the less sensitive method. Therefore, a probability method of correction for inflammation with censored data was devised (19). Briefly, it was an extension of the BRINDA concept and used a Monte Carlo simulation-based regression technique to estimate the true probability distribution accounting for random interindividual variability in serum micronutrient biomarkers while eliminating any systematic component due to relatively deterministic processes such as infection/inflammation that was measured by relevant biomarkers. The prevalence of VAD was calculated from the area under the estimated probability distribution curve of the true random variability of serum retinol across individuals below the defined cutoff for deficiency. The estimated probability distribution was adjusted for survey weights within the regression method.

The prevalence of VAD was estimated at the national and state levels, based on the risk of deficiency cutoff for serum retinol (<20 μg/dL). VAD in a population is considered a serious health problem when this prevalence is ≥20% (20). However, there are uncertainties of point estimates of prevalence due to sampling; therefore, national and state prevalence of VAD was considered ≥20% only if the lower CI was also ≥20%. It was deemed critical to obtain estimates of VAD that had ≥95% certainty of being above 20% because of the potential health consequences of the risk of excess intake from both supplementation and fortification (see below), particularly in the broader context of improved health indicators.

Assessment of risk of dietary inadequacy of vitamin A in 1- to 5-y-old children

The risk of dietary inadequacy of vitamin A among children was assessed using dietary intakes from the NNMB and NSSO surveys. These were calculated as the sum of preformed retinol in the diet and that coming from the transformation of β-carotene in foods (total RAEs, μg/d), using a conversion of 8:1, based on the Indian RDA estimation (12). The risk of inadequacy of vitamin A intake was calculated by comparing the distribution of intakes with the distribution of requirement of vitamin A (as described below), for any specific age group, using the probability approach (13). Ideally, the distribution of intakes should be corrected for the intraindividual variability of intake; because this was not reported in the NNMB data, a surrogate value was used from another similar dietary survey in the state of Uttar Pradesh (21), where the within-week intraindividual variability of vitamin A was measured on 100 children aged 1 to 5 y (∼10% of that sample); here, the intraindividual intake variability accounted for ∼20% of the total intake variability (value kindly provided by Tinku Thomas). This surrogate value was used to correct the total intake variability recorded in the NNMB survey for intraindividual variability (22).

These diet surveys were performed before the Indian regulation in 2018, for the fortification of oil and milk with vitamin A. In this regulation, all cooking oils in the country were mandated to be fortified at the manufacturing stage with retinol at a concentration of 6.0 to 9.9 μg/g oil (14). In addition, the fortification of milk was allowed in a voluntary manner by manufacturers, at a concentration of 27 to 45 μg/100 mL milk (14). At present, both are scaling up rapidly, and for the latter, the majority of milk federations (22 of 25) and producer companies across India are fortifying milk with retinol (23). To calculate a theoretical reduction of the risk of dietary inadequacy when fortified vitamin A intakes were present, the oil and milk consumption of children were estimated in the NSSO survey at the national level (16) and then multiplied into their fortified retinol content, respectively, to evaluate the additional preformed retinol intake. The theoretical risk of dietary inadequacy was calculated with either fortified oil alone or with fortified oil- and milk-based intake added to the dietary vitamin A intake, which was calculated as RAEs (μg/d).

Vitamin A requirement of 1- to 5-y-old children

The distribution of the requirement of vitamin A was not available for Indian children, and only a single Indian RDA value is provided at present (12). Therefore, the distribution of requirements, along with an estimation of the AR and the RDA for this age group, was estimated using the factorial approach described by Olson (24), which is also used by the Institute of Medicine (IOM), the Indian RDA, and the European Food Safety Authority (EFSA) with some variations (12, 25, 26).

In the factorial method, 2 primary factors were considered: the daily loss of vitamin A as a function of the minimum acceptable body store and the efficiency with which the loss could be replaced from the dietary intake (24). The former is based on the product of 5 additional factors: first, the percentage of the vitamin A store lost daily; second, the minimum acceptable liver store concentration of vitamin A; third, the liver weight to BW ratio; fourth, the reference weight for the specific age and sex group; and fifth, the proportion of the liver vitamin A store to the total body vitamin A store. Among these factors, specific values were assumed for the BW and liver size in the Indian context (**Supplementary Material**). An additional multiplicative factor was needed in children, to account for retinol utilization during

growth, and was based on a growth factor calculated from tissue accretion rates at those ages (27).

As the requirement was a multiplicative factorial method, the distribution of the requirement was derived assuming symmetry at log scale (lognormal). The mean and SD of all factors at log scale were calculated assuming lognormal distributions (as the reported CVs of some of the factors were >10%). Fixed values were assumed for some factors when the CV was unavailable. The mean and SD of requirement distribution (at log scale) were estimated by combining all factors additively, assuming them to be independent, and this yielded the AR and RDA as the median and the 97.5th percentile of the distribution (Supplementary Material).

Risk of exceeding the TUL of intake in 1- to 5-y-old children

The risk of toxicity with supplementary vitamin A through VAS and mandatory fortification at a national level was also assessed separately in 1- to 3-y-old and 4- to 5-y-old children in the NSSO survey. This was because of different TUL values; the TUL for vitamin A in 1- to 3-y-old and 4- to 5-y-old children was assumed to be 600 and 900 μg/d, respectively (25). The habitual dietary and additional preformed retinol intake that came from fortification was calculated as detailed above. An additional consideration was also made of the risk of excess from the VAS dose (28) in a cumulative framework. The VAS provides 60,000 μg of preformed vitamin A once in 6 mo. When added to the preformed retinol intake from habitual and fortified food over 6 mo, the theoretical exposure risk of exceeding the cumulative 6-mo TUL (108,000 and 162,000 μg/6 mo for 1- to 3-y-old and 4 to 5-y-old children, respectively) can be calculated by the probability method (13). The calculations of risk of excess were made for all children from the NSSO survey as well as for quintiles of socioeconomic status (SES) within that survey.

Statistics

Serum retinol values are presented as mean and 95% CIs. The estimated daily intake was presented as geometric mean (GM) and geometric SD (GSD), owing to the skewed nature of the distribution. The risk of inadequate and excess dietary intake of an individual was defined as the area under the requirement distribution curve below and above the average daily intake by the individual, respectively. The probability of inadequate intake for the population was then defined as the average of the individual risk of inadequate intake (13). Other statistical considerations are provided in the sections above. All analyses were performed using R version 4.0.2 (R Core Team).

Results

Risk of VAD from serum retinol analyses

These analyses pertain to serum retinol values corrected for inflammation by the probability method described above. The geometric mean of serum retinol in the national group was 31.2 μg/dL (95% CI: 30.9, 31.6 μg/dL), and the prevalence of VAD, based on the cutoff of 20 μg/dL, was 15.7% (95% CI: 15.2%, 16.3%). When compared with the method of censoring those serum retinol values associated with high serum CRP values, the precision was lower and the VAD prevalence was 17.5% (95% CI: 15.3%, 20.0%). The BRINDA method was not used here because of the high proportion of left-censored CRP values in the survey, and all subsequent subanalyses were made using the probability method of correction. There were very few children (0.4%; $n = 35$, normal CRP) with serum retinol values <10 μg/dL. There were no significant differences in serum retinol values between urban and rural children, and boys and girls, or in the prevalence of VAD between them, even after stratification at yearly intervals for sex (**Table 1**). VAD prevalence in children who reported receipt of VAS within the previous 6 mo was 11.3% (95% CI: 10.5%, 12.1%), and in those who did not, the prevalence was 16.9% (95% CI: 16.2%, 17.7%). The geometric mean of serum retinol concentration was 34.0 μg/dL (95% CI: 33.3, 34.6 μg/dL) in the former group, whereas in the latter, it was 30.4 μg/dL (95% CI: 30.0, 30.8 μg/dL). When disaggregated by geographical state, 7 states had VAD point prevalence ≥20% by the modified BRINDA method (**Figure 1**). Two-thirds of the 35 children with very low serum retinol (<10 μg/dL) came from these 7 states. Of these 7 states, only 3 states, Jharkhand, Mizoram, and Telangana, had a significantly higher than 20% prevalence, that is, the lower 95% CI of the estimated VAD prevalence was >20%.

TABLE 1 Serum retinol values and prevalence of vitamin A deficiency among children (aged 1–5 y) stratified based on locality, sex, and age groups[1]

Characteristic	Serum retinol (μg/dL), mean (95% CI)	VAD % (95% CI)
Urban ($n = 4145$)	31.6 (31.0, 32.3)	15.1 (14.0, 16.2)
Rural ($n = 5418$)	31.1 (30.7, 31.5)	16.0 (15.3, 16.6)
Boys ($n = 5034$)	31.1 (30.6, 31.5)	16.1 (15.3, 16.9)
Girls ($n = 4529$)	31.5 (31.0, 31.9)	15.4 (14.6, 16.2)
Stratified by year of age[2]		
Boys (y)		
1 ($n = 876$)	31.0 (29.9, 32.1)	15.5 (13.7, 17.5)
2 ($n = 1228$)	30.5 (29.7, 31.4)	16.3 (14.8, 18.0)
3 ($n = 1419$)	31.1 (30.4, 31.9)	15.3 (13.9, 16.7)
4 ($n = 1511$)	30.2 (29.4, 31.0)	17.0 (15.6, 18.5)
Girls (y)		
1 ($n = 788$)	33.5 (32.3, 34.8)	12.6 (11.0, 14.5)
2 ($n = 1082$)	34.8 (33.7, 35.9)	11.0 (9.8, 12.4)
3 ($n = 1315$)	29.3 (28.5, 30.2)	19.8 (18.1, 21.7)
4 ($n = 1344$)	31.1 (30.3, 31.9)	16.5 (15.1, 17.9)

[1] No significant differences by binomial test for 2 proportions. VAD, vitamin A deficiency.

[2] Age class interval for each year of age represents age for that year until the next year. For example, year 1 represents children from 1 to <2 y.

Vitamin A requirements of children aged 1–5 y

In the present estimation of the requirement, the values used for 2 of the factors in the factorial method were adjusted to reflect those in Indian children; these factors (BW and liver to BW proportion) were used in the calculation of the minimal acceptable liver store from which daily losses occurred. The reference BW was the age- and sex-specific median value of the WHO growth curve (27). The liver weight to BW ratio was

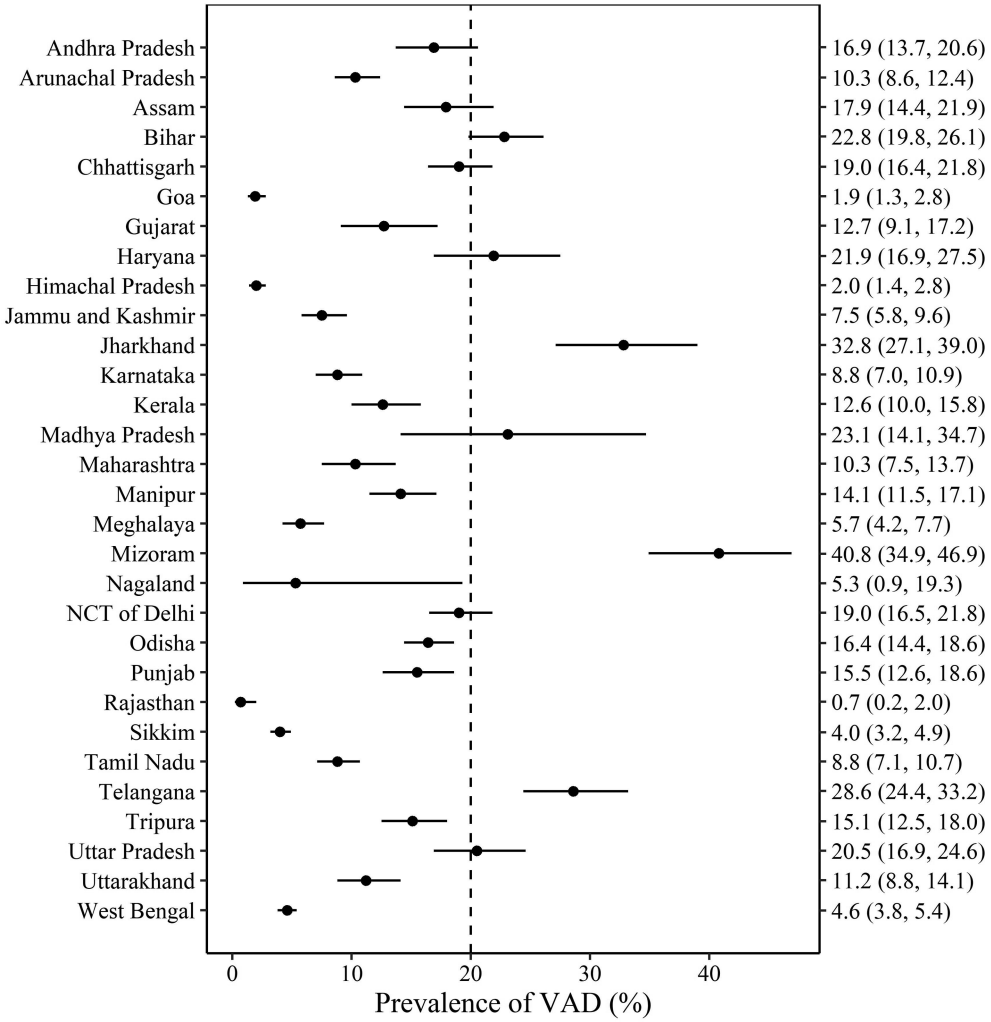

FIGURE 1 Prevalence of vitamin A deficiency among children (aged 1–5 y) across geographical states of India. NCT, national capital territory; VAD, vitamin A deficiency.

taken as 0.034 for Indian children, based on a survey of available literature (see Supplementary Material for a detailed description of the factorial method). The assumed concentration in liver tissue at which no clinical signs of VAD were observed was taken as 20 μg/g liver tissue, at which adequate plasma retinol concentrations are maintained and protection against VAD is provided for ∼4 mo while on a vitamin A–deficient diet (29, 30). These values were multiplied into each other to estimate the size of the minimal acceptable liver vitamin A store. Because the multiplicative structure of the related factors with their respective CV, where available, were reported to be >10%, this required a consideration of the log requirement as the sum of the factors in the log scale. The estimated probability distribution from this assumption was a lognormal distribution that yielded an AR and RDA of 198 and 421 μg/d for 1- to 5-y-old boys and 191 and 409 μg/d for 1- to 5-y-old girls. Effectively, the CV around the AR was 40%.

Risk of dietary inadequacy of vitamin A children aged 1–5 y

The average intake of vitamin A in 1- to 5-y-old children from the NNMB survey was 98.2 μg RAEs/d (GM), with a GSD of 3.34 μg RAEs/d. The risk of inadequate dietary intake of vitamin A calculated from the distribution of NNMB dietary intakes for 1- to 5-y-old children was 70%. When the variability of vitamin A intakes was corrected for the low intraindividual variability of intake, the risk of inadequate intake increased marginally to 72%. The average intake of vitamin A of 1- to 5-y-old children from the NSSO survey was 134.0 (GM) with a GSD of 2.0 μg RAEs/d. This survey had a wider coverage and used a food frequency approach. The average risk of inadequate intake based on the NSSO estimate of usual intake was 69% (**Table 2**). If it is assumed that, in a healthy population, the risk of dietary inadequacy would be 50% (or lower), then in the current CNNS survey, the expected proportion with biomarker-based risk (low serum retinol) would be ∼20%, reasonably similar to the observed biochemical VAD prevalence.

The average oil and milk consumption in all children from the NSSO survey (GM ± GSD) was 14.5 ± 1.0 g/d and 83.0 ± 2.3 mL/d, respectively. The theoretical additional intake from these sources was calculated based on the individual intake of oil alone, or oil and milk together, and the resultant total vitamin A intake was then evaluated for the risk of dietary inadequacy in children in each case, by SES quintile (**Figure 2**). With the added intake of

TABLE 2 Risk of inadequacy and excess vitamin A intake with fortification and supplementation in children from the National Sample Survey Office survey (n = 100,547 households)[1]

	Risk of inadequate intake (%)	Risk of excess intake (%)	
Dietary intake	1–5 y	1–3 y	4–5 y
Normal diet[2]	68.8	0.9	0.5
Normal diet + fortified oil[2]	32.5	1.8	0.9
Normal diet + fortified oil and milk	24.9	2.1	1.0
Normal diet + fortified oil and milk + VAS[4]	1.1	30.0	7.8

[1]Risk of inadequate and excess intake was calculated as in the main text. Risk of excess intake was calculated separately for 1–3 y and 4–5 y as tolerable upper limit of intake is different for these age groups. For the VAS condition, risk of excess intake was calculated from the cumulative intake over 6 mo. VAS, vitamin A supplementation.

[2]While estimating risk of excess, only the preformed retinol intake from diet was considered.

[4]Cumulative (6-mo) risk. The VAS provides 60,000 μg retinol/6 mo.

retinol from oil fortification alone, the risk of dietary inadequacy dropped to 33% in all children, and with oil and milk intake considered together, it dropped to 25%. In children from the upper 2 quintiles of SES, it was 16% and 10%, respectively, while in the lower 2 SES quintiles, it was 52% and 45%, respectively.

Risk of exceeding the TUL of intake in children aged 1–3 y and 4–5 y

For 1- to 3-y-old children in the NSSO survey, the risk of excess with oil and milk fortification was low and was 2%, 0.2%, and 3% for all children and those from the lower and upper 2 SES quintiles, respectively (Table 2 and Figure 2). In 4- to 5-y-old children, the corresponding proportions were 1%, 1%, and 0%, respectively (Table 2 and Figure 2). In the 6-mo cumulative framework, the supplementary retinol from VAS and food fortification contributed to ∼79% and 52% of the cumulative 6-mo TUL of 108,000 μg in 1- to 3-y-old and 162,000 μg in 4- to 5-y-old children. Then, the proportion of 1- to 3-y-old children at risk of exceeding the TUL was 30% for all children and 44% and 12% for children from the highest and lowest 2 SES quintiles, respectively. In 4- to 5-y-old children, the corresponding values were 8%, 16%, and 1%, respectively.

Discussion

In 2016–18, the prevalence of biochemical VAD in 1- to 5-y-old children, in a national survey conducted with strict quality control (11) and with correction of serum retinol values for inflammation, was 15.7% (95% CI: 15.2%, 16.3%). In only 3 states, this prevalence estimate was >20% with 95% certainty. The prevalence of VAD was significantly lower than 20%, even in the children who had not received VAS within the previous 6 mo. There are few other contemporary reports of CRP-corrected serum retinol in Indian children; in a New Delhi slum in 2015, the risk of VAD was similar at 17% in 12- to 23-mo-old children (31). In comparison to the estimated AR (198 and 191 μg/d for boys and girls, respectively), the risk of dietary inadequacy of vitamin A from 2 national surveys, conducted in 2011–12, was ∼70%, or effectively, the theoretical proportion of those at risk of clinical or biochemical consequences was ∼20%. Accounting for mandatory (oil) and additional voluntary (milk) fortification introduced in 2018 reduced the risk of dietary inadequacy to 33% and 25%, respectively (meaning no clinical or biochemical consequences), whereas the risk of exceeding TUL was 2% (1–3 y) and 0.9% (4–5 y). Considering simultaneous VAS over a 6-mo cumulative framework, the corresponding dietary risk of exceeding the TUL was 30% and 8%, respectively.

The distribution of vitamin A requirement was explicitly derived using the factorial method with regionally appropriate BWs and proportions. The AR values derived approximated the EFSA estimates (26), but were well below those proposed by the IOM (25) and the single Indian RDA (12), and in line with the recent suggestion on the appropriateness of EFSA values (32). The CV around the AR was ∼40%, in contrast to the 20% assumed by the IOM (23) and 30% assumed by EFSA (26); no formal determination of the multiplicative variance was performed in those guidelines. However, the factorial estimate of the requirement is fragile due to the many assumptions made in its process. For example, it has been recently suggested that the minimal acceptable retinol concentration in the liver should be higher, at 28.6 μg/g liver (33). Equally, liver retinol concentrations in adult South Asians with no apparent liver dysfunction ranged from 5.7 to 85.8 μg/g (34), suggesting uncertainty in the acceptable minimum liver concentration in humans. The efficiency of dietary retinol deposition is based on 1 adult study (34), but in an earlier report in 2- to 10-y-old healthy Indian children, whole-body retinol retention over 4 to 6 d after a 900-μg dose of radiolabeled retinol acetate or palmitate was ∼80% (35).

After the dietary surveys and CNNS were conducted, the mandatory fortification with retinol of all sources of cooking oil was notified in 2018 (14), and milk producers were also encouraged to voluntarily fortify milk. Oil fortification is being scaled up rapidly, with ∼50% of oil manufacturers fortifying oil (36), and the milk fortification is not far behind (∼40%) (23). This significant intake of preformed retinol from fortification will substantially reduce the risk of dietary inadequacy (Table 2), whereas the risk for excess intake begins to appear in those with high oil and milk intake, in the upper SES quintiles (Figure 2). The latter may be an underestimate, as it is possible that children have a higher intake of milk than adults. There is external validity to this; a recent survey of serum retinol in 210 New Delhi urban primary school children, conducted in 2019 after oil and milk fortification had begun, but who are out of the VAS program, documented a biochemical VAD prevalence of 2.3% (study registration: CTRI/2019/09/02,1073; personal

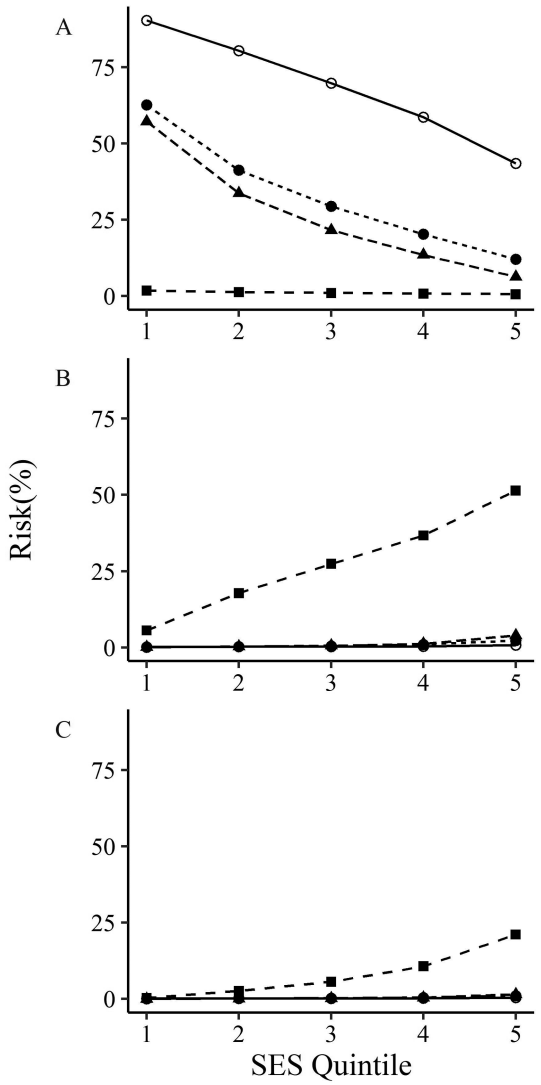

FIGURE 2 Estimates of the risk of inadequacy and excess vitamin A intake, stratified by socioeconomic status quintiles from the National Sample Survey Office survey (9). (A) Risk of inadequacy of vitamin A with habitual diet alone, or with fortified oil and milk, or added VAS. (B) Risk of excess in 1- to 3-y-old children with habitual diet alone, with fortified oil, with fortified oil and milk combined, or all with added VAS. (C) Risk of excess in 4- to 5-y-old children with habitual diet alone, with fortified oil, with fortified oil and milk combined, or all with added VAS. See text for calculation of risk of inadequacy and excess. —●— Habitual diet; - -●- - Habitual diet + fortified oil; - -▲- - Habitual diet + fortified oil + fortified milk; —■— Cumulative (6 mo) risk for habitual diet + fortified oil + fortified milk + VAS. SES, socioeconomic status; VAS, vitamin A supplementation.

communication from the principal investigator Dr RK Marwaha, 2020/06/24).

When the additional intake from VAS was also considered in a cumulative frame, the risk of excess increases to 30% for 1- to 3-y-old. It could be debated that this calculation overestimates the risk, because a large part of the VAS is excreted in the short term (37). Studies in Indian children suggest that nearly 50% of the VAS dose is retained (35, 38); using this value would reduce the risk to ∼10% in 1- to 3-y-old. However, in a toxicologic frame, the risk should be based on the magnitude of exposure, or the intake, and even though the intake here is well below the lowest observed adverse effect level of 6000 μg/d (39), abundant caution is required, as practiced in the setting of the TUL value. These considerations have some external validity. A recent isotopic super-child kinetics study from Guatemala (39), in which sugar and oil had been fortified with retinol for a long period of time, showed that total body vitamin A store was in excess of 1000 μmol, which equates to >300 μg/g liver tissue. Similarly, Zambian children also showed risk for hypervitaminosis when vitamin A supplementation and fortification were combined with high-carotene foods (40).

Survival benefit for children younger than 5 y has been a pivotal argument for the continuation of the VAS program. This has been debated extensively in the Indian context (2, 3, 41), because there was no convincing evidence of benefit in two pre-2000 large studies (42, 43) and the relatively recent trial on a million participants (44). Furthermore, direct extrapolation of pooled survival benefits (12%) from the latest Cochrane review (45) may be inappropriate in the current setting because most included studies were conducted prior to 2000, when VAD was florid or high, and the morbidity and mortality profiles differed. The mortality rate for children younger than 5 y in India has now decreased from 83.1 in 2000 to 42.4 per 1000 live births in 2017, and the neonatal mortality rate has dropped from 38.0 to 23.5 per 1000 live births (4). With an infant mortality rate of 33 per 1000 live births in 2017 (46), a conservative estimate of the 0- to 6-mo mortality can be made, assuming 50% of deaths between 1 and 12 mo occur during 1 to 6 mo. Then, VAS can only intervene for 14 deaths between 6 mo and 5 y (42.4–28.4) per 1000 live births. Thus, even the estimated 12% mortality reduction (45) has little practical relevance currently (absolute risk difference 1.7; 95% CI: 1.0, 2.4 per 1000 live births), especially with suboptimal programmatic coverage (47).

The results of the present analyses have profound implications for continuing the VAS policy in India. The WHO recommends VAS when VAD is a serious public health problem with ≥1% prevalence of night blindness among 24- to 59-mo-old children or ≥20% prevalence of low serum retinol (≤20 μg/dL) in 6- to 59-mo-old children (48). Because neither condition is satisfied in contemporary India (even in those who had not received VAS within the previous 6 mo), the universal VAS to children younger than 5 y should be discontinued forthwith. This is in consonance with the WHO recommendation of a broader health context when considering the implementation of VAS (20), such as mortality and immunization rates and a host of ecologic factors, including data from national dietary surveys. The alternative policy brief by the Global Alliance for Vitamin A, which reduced the VAD prevalence cutoff to 5% or 10% when considering the scaling back of VAS (49), is not considered helpful because an explicit evidence-based framework for this reduction is not apparent, while the potential for harm due to excessive intake from overzealous supplementation is ignored. Indeed, the possibility of hypervitaminosis, with both VAS and recently introduced fortification, is the more urgent consideration. Policy efforts also need to be directed toward sustainable and cheap food-based interventions (e.g., green leafy vegetables), which are needed in small daily amounts with no risk of hypervitaminosis.

Limitations of these analyses include the lack of data on 6- to 12-mo-old infants, but these are unlikely to be substantially different, and continued breastfeeding constitutes a significant

source of vitamin A intake (breast milk contains ∼50–60 μg retinol/dL). An additional limitation is the lack of detailed reporting on the serum retinol and CRP assays. The triangulation of dietary intakes and serum retinol from the same data set would have been desirable, but this was unavailable.

In conclusion, evidence from national surveys on serum retinol and dietary vitamin A intakes, as well as an analysis of survival benefit, indicates the need for serious consideration for adopting a targeted approach instead of continuing with the universal VAS in India. This should be accompanied by careful monitoring of 6-mo to 5-y mortality trends through the ongoing Sample Registration System (50), keratomalacia caseload data from ophthalmic hospitals or sentinel sites, and serum retinol and retinyl esters from repeat national surveys or regional studies in high-burden states if cost is a limitation. Continuing universal VAS, along with recently introduced fortification, is likely to result in the risk of exceeding the TUL of vitamin A intake in a proportion of children, especially those in a higher SES, as well as wastage of scarce financial and logistic resources.

The CNNS study was conducted by the Ministry of Health and Family Welfare, Government of India, and UNICEF, with support from the Mittal Foundation. The data were provided to Indian researchers after a data user workshop conducted by UNICEF, India. All authors except SG, NKB, and ST were part of a committee constituted by the Ministry of Health and Family Welfare of the Government of India, cochaired by AVK and UK, to evaluate vitamin A and D deficiency in India with specific reference to the CNNS. The authors acknowledge the discussions that took place in this committee with regard to the interpretation of the analyses reported here. However, the views expressed here by the authors are in their individual capacity and should not be construed as the views or recommendations of that committee or of the institutions the authors belong to. The authors also are grateful to R. K. Marwaha for his input on the unpublished 2019 serum retinol study on in New Delhi primary school children and K. V. Radhakrishna for critical comments. The manuscript drafting assistance provided by Srishti Sinha, St John's Research Institute, Bengaluru, is gratefully acknowledged.

The authors' responsibilities were as follows—GBR, RP, SG, NKB, RH, AVK, and HSS: performed initial statistical analyses on the CNNS data, with further comments and iterations involving all authors; AL: provided the NNMB raw data of individual-level vitamin A intake; AVK and SG: analyzed the publicly available NSSO dietary intake data; GBR, RP, SG, NKB, ST, and AL: performed the initial iteration of the estimation of distribution of requirements and analyses of dietary inadequacy; and all authors: read and approved the final manuscript.

HSS designed the draft protocol of the CNNS with consultancy support from UNICEF, India. HSS, AL, UK, and AVK were members of the Technical Advisory Committee of the CNNS, constituted by the Ministry of Health and Family Welfare of the Government of India, to oversee its conduct and analysis. HSS is a member of the World Health Organization Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health and a member of Expert Groups of the Ministry of Health and Family Welfare on Nutrition and Child Health. AVK is a nutrition adviser to the Tata Trusts. SG has consultancy support for statistical analyses from UNICEF, India. AVK is an associate editor of the journal. All other authors report no conflicts of interest.

Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon reasonable request to the corresponding authors.

References

1. Beaton GH, Martorell R, Aronson KJ, Edmonston B, McCabe G, Ross AC, Harvey B. Effectiveness of vitamin A supplementation in the control of young child morbidity and mortality in developing countries. Nutrition Policy Discussion Paper No. 13. Toronto: University of Toronto; 1993.
2. Greiner T, Mason J, Benn CS, Sachdev HP. Does India need a universal high-dose vitamin A supplementation program? Indian J Pediatr 2019;86:538–41.
3. Kapil U, Sachdev HP. Massive dose vitamin A programme in India—need for a targeted approach. Indian J Med Res 2013;138:411–7.
4. Dandona R, Kumar GA, Henry NJ, Joshua V, Ramji S, Gupta SS, Agrawal D, Kumar R, Lodha R, Mathai M, et al. Subnational mapping of under-5 and neonatal mortality trends in India: The Global Burden of Disease Study 2000–17. Lancet 2020;395:1640–58.
5. International Institute of Population Science. National Family Health Survey India 2015–2016: India fact sheet. Mumbai: Ministry of Health and Family Welfare, Government of India; 2016.
6. Economic Division, Department of Economic Affairs. Economic survey 2016–17. New Delhi: Ministry of Finance, Government of India; 2017.
7. Alae-Carew C, Bird FA, Choudhury S, Harris F, Aleksandrowicz L, Milner J, Joy EJ, Agrawal S, Dangour AD, Green R. Future diets in India: a systematic review of food consumption projection studies. Global Food Security 2019;23:182–90.
8. National Nutrition Monitoring Bureau (NNMB). Prevalence of vitamin A deficiency among rural preschool children. Report No. 23. Hyderabad: National Institute of Nutrition, Indian Council of Medical Research; 2006.
9. National Nutrition Monitoring Bureau (NNMB). Diet and nutritional status of rural population, prevalence of hypertension and diabetes among adults and infant and young child feeding practices—3rd Repeat Survey. Hyderabad: National Institute of Nutrition, Indian Council of Medical Research; 2012.
10. Laxmaiah A, Nair MK, Arlappa N, Raghu P, Balakrishna N, Rao KM, Galreddy C, Kumar S, Ravindranath M, Rao VV, et al. Prevalence of ocular signs and subclinical vitamin A deficiency and its determinants among rural pre-school children in India. Public Health Nutr 2012;15:568–77.
11. Comprehensive National Nutrition Survey (CNNS). CNNS National Report 2016–18. New Delhi: Ministry of Health and Family Welfare (MoHFW), Government of India, UNICEF and Population Council; 2019.
12. Indian Council of Medical Research. Nutrient requirements and recommended dietary allowances for Indians. Hyderabad: Indian Council of Medical Research National Institute of Nutrition; 2010.
13. Institute of Medicine, National Academy of Sciences. Dietary reference intakes: the essential guide to nutrient requirements. Washington (DC): National Academies Press; 2006.
14. Food Safety and Standards Authority of India (FSSAI). Gazette of India: notification, part-2: standards on fortification. New Delhi (India): Ministry of Health and Family Welfare; 2018.
15. Larson LM, Namaste SM, Williams AM, Engle-Stone R, Addo OY, Suchdev PS, Wirth JP, Temple V, Serdula M, Northrop-Clewes CA. Adjusting retinol-binding protein concentrations for inflammation: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project. Am J Clin Nutr 2017;106(suppl_1):390S–401S.
16. National Sample Survey Office. Nutritional intake in India: 2011–12, NSS 68th round. New Delhi: National Statistical Organization, Government of India; 2014.
17. Longvah T, Ananthan R, Bhaskarachary T, Venkaiah K. Indian food composition tables. Hyderabad: National Institute of Nutrition, Indian Council of Medical Research; 2017.
18. Thimmayamma BVS, Rau P, Damayanti K. Dietary assessment as part of nutritional status.In: Bamji MS, Krishnaswamy K, Brahmam GNV, editors. Textbook of human nutrition. 4th ed. New Delhi (India): Oxford & IBH Publishing Pvt Ltd.; 2016:121–51.
19. Ghosh S, Sachdev HPS, Kurpad AV, Thomas T. Using censored inflammatory markers when correcting for infection in estimations of biomarker based micronutrient deficiency. Am J Clin Nutr 2021;113(1):47–54.

20. World Health Organization. Serum retinol concentrations for determining the prevalence of vitamin A deficiency in populations. Geneva (Switzerland): Vitamin and Mineral Nutrition Information System, World Health Organization; 2011.
21. Larson L, Thomas T, Kurpad A, Martorell R, Hoddinott J, Swaminathan S, Neufled L. (P12-065) Anemia in women and children in Uttar Pradesh: a path analysis of the associations between nutritional, environmental, infectious, and genetic determinants. Curr Dev Nutr 2018;2:nzy039.
22. National Research Council (US) Subcommittee on Criteria for Dietary Evaluation. Nutrient adequacy: assessment using food consumption surveys. Washington (DC): National Academies Press; 1986.
23. National Dairy Development Board. Milk fortification to tackle malnutrition in India [Internet]. 2019. Available from: https://www.ndb.coop/node/1812.
24. Olson JA. Recommended dietary intakes (RDI) of vitamin A in humans. Am J Clin Nutr 1987;45:704–16.
25. Food and Nutrition Board, Institute of Medicine. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington (DC): National Academies Press; 2001.
26. EFSA Panel on Dietetic Products, Nutrition & Allergies. Scientific opinion on dietary reference values for vitamin A. EFSA J 2015;13:4028.
27. World Health Organization. WHO child growth standards—length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age—methods and development. Geneva (Switzerland): World Health Organization; 2006.
28. Family Planning Programme, Fourth Five-Year Plan. Maternal and child health scheme for prophylaxis against nutritional blindness in children caused by vitamin A deficiency. Technical Information: MCH No. 2. New Delhi: Government of India; 1970.
29. Hicks VA, Gunning DB, Olson JA. Metabolism, plasma transport and biliary excretion of radioactive vitamin A and its metabolites as a function of liver reserves of vitamin A in the rat. J Nutr 1984;114:1327–33.
30. Loerch JD, Underwood BA, Lewis KC. Response of plasma levels of vitamin A to a dose of vitamin A as an indicator of hepatic vitamin A reserves in rats. J Nutr 1979;109:778–86.
31. Houghton LA, Trilok-Kumar G, McIntosh D, Haszard JJ, Harper MJ, Reid M, Erhardt J, Bailey K, Gibson RS. Multiple micronutrient status and predictors of anemia in young children aged 12–23 months living in New Delhi, India. PLoS One 2019;14:e0209564.
32. Allen LH, Carriquiry AL, Murphy SP. Perspective: proposed harmonized nutrient reference values for populations. Adv Nutr 2020;11:469–83.
33. Tanumihardjo SA, Russell RM, Stephensen CB, Gannon BM, Craft NE, Haskell MJ, Lietz G, Schulze K, Raiten DJ. Biomarkers of Nutrition for Development (BOND)—vitamin A review. J Nutr 2016;146:1816S–48S.
34. Haskell MJ, Handelman GJ, Peerson JM, Jones AD, Rabbi MA, Awal MA, Wahed MA, Mahalanabis D, Brown KH. Assessment of vitamin A status by the deuterated-retinol-dilution technique and comparison with hepatic vitamin A concentration in Bangladeshi surgical patients. Am J Clin Nutr 1997;66:67–74.
35. Reddy V, Sivakumar B. Studies on vitamin A absorption in children. Indian Pediatr 1972;9:307–10.
36. Food Safety and Standards Authority of India (FSSAI). Media upload—fortification touches 47% in packaged edible oil, 36.6% in milk [Internet]. 2019. Available from: https://fssai.gov.in/upload/media/FSSAI_News_Fortification_MoneyControl_28_08_2019.pdf.
37. Kalz F, Schafer A. Vitamin A serum levels after ingestion of different vitamin A preparations. Can Med Assoc J 1958;79:918–9.
38. Kusin JA, Reddy V, Sivakumar B. Vitamin E supplements and the absorption of a massive dose of vitamin A. Am J Clin Nutr 1974;27:774–6.
39. Ford JL, Green JB, Haskell MJ, Ahmad SM, Mazariegos Cordero DI, Oxley A, Engle-Stone R, Lietz G, Green MH. Use of model-based compartmental analysis and a super-child design to study whole-body retinol kinetics and vitamin A total body stores in children from 3 lower-income countries. J Nutr 2020;150:411–8.
40. Tanumihardjo S, Gannon B, Kaliwile C, Chileshe J. Hypercarotenodermia in Zambia: which children turned orange during mango season? Eur J Clin Nutr 2015;69:1346–9.
41. Vijayaraghavan K. National control programme against nutritional blindness due to vitamin A deficiency: current status & future strategy. Indian J Med Res 2018;148:496–502.
42. Vijayaraghavan K, Radhaiah G, Surya Prakasam BS, Sarma KVR, Reddy V. Effect of massive dose vitamin A on morbidity and mortality in Indian children. Lancet 1990; 336:1342–5.
43. Agarwal DK, Pandey CM, Agarwal KN. Vitamin A administration and preschool child mortality. Nutr Res 1995;15:669–80.
44. Awasthi S, Peto R, Read S, Clark S, Pande V, Bundy D. Vitamin A supplementation every 6 months with retinol in 1 million pre-school children in North India: DEVTA, a cluster-randomised trial. Lancet 2013;381:1469–77.
45. Imdad A, Mayo-Wilson E, Herzer K, Bhutta ZA. Vitamin A supplementation for preventing morbidity and mortality in children from six months to five years of age. Cochrane Database Syst Rev 2017;3:CD008524.
46. Sample Registration System, Vital Statistics Division. SRS Bulletin (Vol 52, No.1). New Delhi: Office of Registrar General, Ministry of Home Affairs, Government of India; 2019.
47. International Institute of Population Sciences. National Family Health Survey (NFHS-4), 2015–16. Mumbai (India): IIPS; 2017.
48. World Health Organization. Guideline: vitamin A supplementation in infants and children 6–59 months of age. Geneva (Switzerland): World Health Organization; 2011.
49. Global Alliance for Vitamin A (GAVA). Conditions for scaling back universal preschool vitamin A supplementation: policy brief [Internet]. 2019. Available from: http://www.gava.org/content/user_files/2019/05/GAVA-Brief-Scaling-Back-VAS-EN-May-10.pdf.
50. Office of the Registrar General & Census Commissioner, India. Sample registration system [Internet]. Available from: https://censusindia.gov.in/vital_statistics/SRS_Bulletins/Bulletins.html.