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Vitamin A supplementation and fortification programs in India: need for review

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Vitamin A and its metabolism

Night blindness is possibly the first nutritional deficiency disorder discovered and treated with either topical application to the eye, or ingestion of cooked animal liver[1]. Subsequent studies identified the active principles, vitamin A (*all trans* retinol) and its related compounds collectively referred as the "retinoids", with biological activity of retinol. Therefore, in a general sense vitamin A (VA) is a broad term that refers to a group of compounds which include retinol, retinal, and retinoic acid. All these retinoids are fat-soluble and hence are accumulated in the body, especially in the liver and adipose tissue. This property is beneficial because low intake of VA is not immediately associated with clinical symptoms; but there is also the potential risk that over-accumulation of the vitamin can lead to adverse effects.

VA is an essential nutrient that must be provided as part of the diet, as humans lack the ability for *de novo* VA synthesis. Vitamin A is available in diets either as *preformed* retinyl esters (RE) and retinol from animal sources or as provitamin A (PVA) carotenoids from plant sources that are converted to VA in the body[2]. Provitamin A carotenoids such as β-carotene, α-carotene, and β-cryptoxanthin produced in plants (coloured fruits and vegetables) are primary dietary sources of VA. Milk and dairy products, as well as meat and meat products, eggs and egg products and fish are the principal contributors of preformed VA in the diet. Among the dietary sources, carotenoids are the largest contributors to the VA intakes in general population. During gastrointestinal digestion, the dietary RE or PVA carotenoids are emulsified and packed into micelles prior to their absorption in intestinal cells, via a facilitated saturable transport process[3]. The retinol, either derived from RE or PVA carotenoids, is then re-esterified, packed into chylomicrons and egressed via the lymphatic system. Although the specific lipid transporters mediating PVA carotenoid transport are unequivocally established, the specific transporter of retinol, and the precise mechanism of its absorption remain unclear[3, 4]. Absorption of PVA carotenoids is increased if the diet is rich in fats, since micelle formation helps the absorption of fat-soluble VA in the small intestine[5]. In addition to fat, some micronutrients such as zinc are also needed for the mobilization and absorption of the vitamin[6]. Retinol is absorbed via both lymphatic (RE) and portal circulation (passive diffusion of free retinol), the latter being the major route at pharmacological doses[4]. Interestingly, while the absorption of PVA carotenoids and their conversion appears to be dependent on the dose administered and the VA status of the host[7], a similar regulatory pathway for RE appears to be absent, as 50-80% of administered RE has been shown to be retained in the body when supplemented at high doses (1000-6000 µg)[8]. Because of this divergence in absorption and regulatory mechanisms, plant-based PVA carotenoids remain the preferred and safe source of VA in diets. There is now ample evidence to show that PVA carotenoids are converted into VA in many tissues including the liver.

The liver is the main site of VA storage in humans, and most of the stored VA is in the form of RE. From the liver, the retinol is transported bound to retinol binding protein-4 (RBP4), and delivered to the target tissues[9]. RBP4 is synthesized and secreted by the liver, and this process is regulated partly by VA status (liver retinol stores) and partly by other factors. For example, in zinc and protein deficiency, RBP4 is accumulated in the liver despite sufficient stores being available, while inflammation induces the renal clearance of RBP4, leading to a pseudo-deficiency if assessment of VA status is based on blood VA concentration[9]. Despite the fact that RBP4 is the sole carrier of retinol in the blood, humans with mutations in the RBP4 gene that hamper its secretion from the liver as well as experimental animals in which RBP4 has been knocked out (in both conditions the plasma retinol, a marker of VA status, is non-detectable) survive without signs of developmental abnormalities, but their vision is affected[10, 11]. This suggests that there are efficient surrogate mechanisms for retinol transport, such as RE derived from lipoproteins[11]. However, the retina depends on RBP4 derived retinol, and this explains the predominant ocular symptomatology linked to VA deficiency (VAD). VA is mainly oxidized to VA metabolites, and is excreted through the urine and bile; this daily loss has to be replaced through the diet in order to maintain VA homeostasis[12].

Functions of Vitamin A

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It has long been known that VA is the vital component of the light-sensitive visual pigments in the photoreceptors in the retina; over time studies have shown the involvement of VA and its metabolites in a wide variety of biological activities ranging from embryonic development to mediating the immune system[13] and maintenance of overall health. Vitamin A is required for the regulation of several important biological processes including vision, maintenance of epithelial surfaces, immunity, reproduction, embryonic growth and development[2, 6]. Retinol is the precursor for two or more essential biologically active molecules: all-trans retinoic acid as the ligand of nuclear receptors (such as retinoic acid receptors), and 11-cis-retinal which is required in the maintaining normal vision.

In this process, 11-cis retinal binds to opsin to form rhodopsin which upon absorbing light leads to isomerization as *all-trans* retinal, and is finally released from opsin. The excited intermediate of rhodopsin amplifies light, resulting in generation of the nerve impulses for vision. *All-trans* retinoic acid is the most biologically relevant compound of VA.

In addition to its involvement in vision in the form of 11-cis-retinal, retinol is also a cofactor in several enzymatic processes, and *all-trans* retinoic acid exerts different functions by binding to nuclear receptors with the subsequent regulation of genetic expression[6]. Retinoic acid binds and activates several nuclear receptors including retinoic acid receptors (RARs) and retinoid X receptor (RXR), thereby initiating gene transcription of about 500 target genes[2, 6]. Nuclear receptors are transcription factors that are activated upon ligand-binding, and can modulate the target gene expression through direct interaction with DNA. Although 48 families of nuclear receptors have been reported to date in humans, RAR and RXR are the main retinoid receptor families and the expression of these receptors is tissue-specific[6]. The main difference between the RAR and RXR families lies in the ligand-binding domain structure, which determines ligand specificity. *All-trans* retinoic acid is a high-affinity ligand for RAR and it can also activate RXR, whereas the 9-cis-retinoic acid binds to RXR with highest affinity[6]. In addition, another family of receptors called peroxisome proliferative activated receptors (PPARs) has also been shown to interact with retinoids. The discovery of the interaction between *all-trans* retinoic acid and PPARs explains the proliferative effect of retinoic acid in keratinocytes and its involvement in insulin sensitivity and energy homeostasis[6].

Daily vitamin A requirements for Indians and the tolerable upper limit of intake

It is important to find out the requirement of different nutrients for individuals of different physiological groups. One of the widely used methods is to assess nutrient intakes in normally nourished healthy people, use these to assess population dietary inadequacies, and formulate nutrition education messages as well as public health policies (such as supplementation and fortification strategies) to minimise the risk of deficiencies. Estimated Average Requirement (EAR) refers to the average daily nutrient intake level estimated to meet the requirements of half of the healthy individuals in a particular life stage and gender group. It is used primarily to evaluate populations or groups. The Recommended Dietary Allowances (RDA) refers to the daily dietary nutrient intake level that is sufficient to meet the nutrient requirements of nearly all (97–98%) healthy individuals in a particular life stage and gender group. This is derived from the EAR as the mean plus 2 standard deviations (SD) of the distribution of requirements. RDA is useful in evaluating levels of nutrient intake which will ensure every individual gets adequate intake of the nutrient. However, RDA is inappropriate for dietary assessment of groups as it represents an intake level that exceeds the requirement of a large proportion of individuals within the group. Tolerable Upper Limit (TUL) refers to the highest average daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the TUL, the risk of adverse effects will increase. The TUL is derived from the toxicological framework and is defined as the safe upper limits of nutrient intakes at which there is no identifiable toxicity. The 2010 ICMR-RDA provided only the RDA, while recent ICMR-NIN Nutrient Requirements of Indians 2020 provided EAR, RDA, and TUL for nutrients including VA[8].

The dietary requirement of VA is primarily derived by the factorial computation of losses from the body, to which additional requirements, estimated using a factorial approach, are added to meet the requirements during growth in children and pregnancy and lactation in women.[8, 14]. The VA requirements, RDA and TUL for Indians are given in **Table 1** (from ICMR-NIN, EAR-RDA, 2020[8]). The EARs for VA indicated in Nutrient Requirement of Indians 2020[8] are lower than the previous single-value recommendations (RDA for Indians 2010) by about 50%. There is also evidence from VA balanced studies that the previous Institute of Medicine (IOM, USA) factorial VA requirements might have been overestimated[15].

The TUL for VA was adopted from the IOM recommendations, due to paucity of Indian data. The adopted TUL is shown in **Table 1**. The current recommendation is that all individuals with high VA intake in their diets should be monitored using blood RE and tests for liver function abnormalities. Some of the recent studies on dietary adequacy analysis performed on Indian children indicate that children whose habitual dietary intake of VA is adequate, and who receive massive dose VA supplementation (MDVAS) and also consume milk and oil fortified with VA might be exposed to excessive VA intakes beyond TUL[14]. Currently, there are no published data in India on the extent of VA-induced bone toxicity or fasting plasma RE levels. There is a need to undertake studies on VA levels in children who are receiving VA through multiple programmes (fortified oil, fortified milk and MDVAS).

Carotenoid conversion and its implications in the dietary adequacy assessment

The consumption of animal foods provides preformed VA, whereas in a plant-based diet carotenoid molecules are converted to VA in the body. In India, diets are predominantly vegetarian; therefore, it

Table 1: Vitamin A daily requirements for various physiological groups in India[8]

Physiological group	Reference Body weight (kg)	RDA 2020		TUL (µg/day)
		EAR (µg/day)	RDA (µg/day)	
Adult-Male	65	460	1000	3000
Adult-Female	55	390	840	3000
Pregnant	55.0+GWG	406	900	3000
Lactating[π]	55	720	950	3000
Infants (0-6 mo)	5.8	-	350*	600[$]
Infants (6-12 mo)	8.5	170	350	600[$]
Children (1-3y)	12.9	180	390	600[$]
Children (4-6y)	18.3	240	510 (300)	900[$]
Children (7-9y)	25.3	290	630 (350)	900[$]
Boys (10-12y)	34.9	360	770	1700
Girls (10-12y)	36.4	370	790	1700
Boys (13-15y)	50.5	430	930	2800
Girls (13-15y)	49.6	420	890	2800
Boys (16-18y)	64.4	480	1000	2800
Girls (16-18y)	55.7	400	860	2800

RAE: Retinol Equivalents (µg/day); GWG: Gestational weight gain. *Adequate intake; [$]Adopted from IOM; [π]Additional EAR required for lactating women: 325(µg/day)

is important to assess the retinol activity equivalence (RAE) of carotenoids to determine to what extent VA requirements are being met. This, in turn, requires the derivation of a conversion factor[8]. Notionally, one molecule of β-carotene produces two molecules of retinol (RAE, 1:2), while α-carotene and β-cryptoxanthine yield one molecule of retinol (1:1). The intact carotenoids are both absorbed and converted to VA in multiple tissues. However, due to multiple food matrix and physiological constraints, only a fraction of ingested dietary carotenoids is absorbed and converted to retinol. This results in a variable inefficiency, such that typical conversion ratios ranging from 6:1 to 16:1 (β-carotene to VA) were reported, much lower than the theoretical 1:2 ratio. However, recent knowledge on PVA carotenoid speciation, digestion, metabolism and its conversion[5] enables derivation of a local context-specific conversion factor. The carotenoid conversion ratio depends on the dose administered (the higher the intake, the lower the conversion) and the VA status of subjects (the higher the status, the lower the conversion). These factors are taken into consideration while deriving the carotenoid conversion ratios for Indian diets[8]. For computing the RAE of dietary carotenoids, and assuming a maximum carotenoid intake of ~3 mg/day in the Indian adult population, a conservative conversion factor of 6:1 was set for β-carotene, while the conversion factors for other carotenoids such as β-cryptoxanthine and α-carotene were set at 12:1.

Vitamin A toxicity and the need to consider an upper limit of daily intake

Vitamin A toxicity was described in isolated cases with chronic high dose ingestion of supplemental VA, manifesting as liver fibrosis and fat deposition. Although liver function tests can predict VA toxicity, they lack specificity. Therefore the concentration of serum RE in the fasting state is used as a marker for diagnosis of VA toxicity; the presence of 10% and 5% of total serum VA (or retinol) as RE is considered a marker of VA toxicity in adults and children, respectively[16]. A more recent study in cadavers of US adults showed that RE concentrations are related to the liver stores, and 7.5% RE of total serum VA was proposed as the diagnostic marker of VA toxicity[17]. A study in US adults and elderly found elevated levels of fasting RE in subjects who were consuming VA supplements (intake 1500-1800 IU) compared to those who did not take supplements (600-900 RAE/day), while the serum retinol levels remained independent of the VA intakes[18]. A dose response of VA intake to fasting RE was reported in this study. A series of studies in children and pregnant women from South Africa (habitual intake of sheep liver and VA supplementation (VAS)), Guatemala, Malawi, USA, Zambia (fortified foods and VAS) showed that consumption of VA from multiple sources was associated with VA toxicity, characterized by high liver stores of VA or high fasting blood RE concentrations[19].

In addition to liver damage, bone damage may also occur. Excess VA intakes have been reported to increase the risk of bone fracture as a result of increased bone resorption[20, 21]. Supplementation of high dose VA (>7.5 mg/day) or low dose (2.7 mg/day) in animal models led to bone fracture and thinner bones, respectively. Further, the adverse effects on bone were higher in younger compared to older animals, which is of relevance considering that Indian children are already at risk of poor bone density and accretion due to low calcium and vitamin D intakes. A few observational studies reported that when intakes of VA were closer to the EAR, but lower than that of TUL[21-24], there was an association between VA intake or serum retinol levels and an increased risk of osteoporosis and fractures in the elderly. Case control studies in adult women in Sweden found higher odds (OR, 2.1) of hip fracture with retinol intakes >1500 µg/day compared to those with intakes <500µg/day[25].

Yet another cause of concern regarding VA toxicity in India is that the risk of VA toxicity or elevated blood RE have been reported in subjects with familial hypertriglyceridemia, even at modest VA intakes[26, 27]. Analysis of data from the Comprehensive National Nutrition Survey (CNNS)[28] showed a prevalence of 20-25% hypertriglyceridemia in 5–19-year-old children[29]; this might be relevant as a factor that could potentiate the risk of VA toxicity.

These studies together indicate the potential for VA excess or hypervitaminosis A when preformed VA is provided through supplementation and/or fortification programmes[19, 30, 31]. In India, there is ongoing fortification of edible oil and milk and also a (MDVAS) programme[14]. There is a need to assess whether there is a risk of VA intakes exceeding TUL in Indians.

Assessment of the deficiency and excess of dietary vitamin A intake in Indian children

In the past, the dietary adequacy of VA (or other nutrients) was assessed by comparing the intake to the RDA. This was because the earlier Indian documents mentioned a single value as the RDA, and the EAR was not defined. Using the RDA as an index of the requirement will grossly overestimate the prevalence of dietary inadequacy in a population, because by its very definition the nutrient requirement of 97.5% of the population is below the RDA; therefore, RDA should only be used with care, to suggest an adequate nutrient intake for an individual.

The revised ICMR 2020[8] nutrient requirements provide estimates of both EAR and RDA. If data of both the nutrient requirement and the nutrient intake of a population are available, a probability approach can be utilized to measure the risk of nutrient inadequacy in the population[14]. The National Nutrition Monitoring Bureau (NNMB) and National Sample Survey Organisation (NSSO) data sets are available in India[32, 33]. The NNMB survey indicates that the average intake of VA was 98.2 µg RAE/day (geometric mean) in 1-5y old children. The risk of inadequate dietary intake of VA, as estimated from the NNMB dietary intakes (using RDA) for 1-5 y old children, was 70%. The risk of VA dietary inadequacy (using RDA) as per the NSSO data was 69%. If it is assumed that in a normal population, the risk of dietary inadequacy will be 50% (or lower), the expected proportion of inadequate intakes, or those with subclinical deficiency, would be about 20%. Indeed, this was close to the observed prevalence of VAD (measured from serum retinol levels) of 16% in this age group from the recent CNNS data[14, 28]. When the intake of retinol from oil fortification alone is added to the daily VA intake, the risk of dietary inadequacy came down to 33% in all children, and with the intake from fortified oil and milk considered together, it dropped to 25%. It is important to note that the CNNS was conducted prior to the introduction of VA fortification of oil and milk which would lower the prevalence of dietary inadequacies.

For 1-3y old children in the NSSO survey, the risk of excess intake of VA, when considering the additional intake from fortified oil and milk, was low (2%) for all children. For those from the lower and upper two SES quintiles, it was 0.2% and 3% respectively. In the case of 4-5y old children, the risk of excess intake was 1%, 1% and 0%, respectively, from the lower and upper two SES quintiles. Since MDVAS is administered once in 6 months, a six-month cumulative framework was considered when assessing the risk of exceeding the TUL. The cumulative 6-month TUL was 108000 µg in 1-3y and 162000 µg in 4-5y old children. In this computation, the supplementary retinol from MDVAS and food fortification together contributed to about 79% and 52% of the cumulative six-month TUL of 1-3y and 4-5y old children, respectively. While the proportion of

1-3y old children at risk of exceeding the TUL in a 6-month period was 30% for all children, for children from the highest and lowest 2 SES quintiles it was 44% and 12%, respectively. In 4-5y old children, the corresponding values were 8%, 16%, and 1%, respectively[14]. Although one might argue that a high excretion of the administered MDVAS in the days soon after its administration will reduce the possibility of toxicity, the exposure framework needs to be considered independent of adaptations that may occur. Here, the VA exposure (intake) suggests a risk of exceeding the TUL in a significant proportion of children.

Vitamin A deficiency (VAD)

Given the myriad functional roles of VA described above, VAD can lead to a spectrum of health problems. VAD is therefore an important nutritional problem. It is predominantly seen in preschool and school-age children because of higher requirements in this group due to a relatively rapid physical growth and low dietary intake. VAD disorders include xerophthalmia, and a range of eye problems from night blindness to clinical conditions such as Bitot spots, and keratomalacia, leading to permanent blindness. In earlier decades there was the added risk of death from infectious diseases such as measles and diarrhoea, especially in preschool children[2, 34, 35]. VAD may increase susceptibility to infections, particularly respiratory infections. The role of VA in maintaining the integrity of the epithelium in the respiratory, gastrointestinal and genito-urinary tracts has been well recognized. It has been demonstrated in animal models that deprivation of VA could bring about extensive keratinization of epithelial tissues in these organs rendering them susceptible to invasion by pathogens[36]. There is also evidence that VAD could compromise immune function by hindering normal regeneration of mucosal barriers impaired by infection, and by interfering with the function of neutrophils, macrophages, and natural killer cells[37]. Further, VA is also required for adaptive immunity and plays a part in the development of both T-helper (Th) cells and B-cells. It is therefore logical to expect that VAD in children could contribute to increased morbidity and mortality among children[38]. Repeated infections in children deplete VA stores due to losses in urine or in the stools due to increased intestinal permeability, or from increased demand for the repair of damaged epithelial tissues[39].

VAD continues to contribute significantly to the global burden of disease as it is a public health problem in 50% of all countries, particularly affecting resource-constrained countries[40]. While 5.2 million preschool children were estimated to be suffering from night blindness, it has also been estimated that 190 million preschool children, globally have VAD as assessed by low serum retinol concentrations (0.7 µmoles/L)[40]. African and Southeast Asian countries including India are the most affected by VAD[34, 40, 41]. Several studies have found a positive association between VAD and increased respiratory infections, diarrhoea, measles and mortality in Indian children[41]. Prevalence and severity of VAD were significantly higher among children from socio-economically disadvantaged households.

Keratomalacia has not been reported in recent times in most parts of the country, and there has been a sharp drop in the prevalence of Bitot spots (BS) in India over the past three decades; however, the decline in clinical VAD is not uniform (**Table 2**). Recent surveys indicate that the prevalence of BS of >0.5% is limited to population groups which are socio-economically backward, have poor access to health care[32, 42]. One of the reasons for the inter-state variation could be the variations in coverage under the VAS programme. Also, clinical VAD is seen only in certain seasons when green leafy vegetables are in short supply[43, 44]. With the reduction in clinical manifestations of VAD the subclinical VAD, as assessed by serum retinol levels (<20ug/dL), is being used as a marker of VAD. Nonetheless, the acceptability, technical feasibility and performance of serum retinol alone in assessing VAD in communities have been debated. There are many factors that can influence serum retinol levels and hence its validity as an indicator of VAD has been questioned[2, 45]. It is possible that higher prevalence of VAD could be reported based on serum retinol levels. For example, a study conducted between 2002-2005 in eight states reported 62% prevalence of subclinical VAD among rural pre-school children in India[46]. However, the prevalence of BS in this study remained very low (0.8%). Methodological aspects and underlying inflammation which might have been high in rural children might account for the reported differences in this study.

Data from the CNNS, under the Ministry of Health and Family Welfare, Government of India in children and adolescents in India during 2016-2018 have provided recent nation-wide information on VAD in India[28]. This survey carried out a cross-sectional measurement of the prevalence of subclinical VAD (serum retinol <20 µg/dL) among apparently healthy 1-19 year children and adolescents across 30 states of the country, using a multi-stage stratified probability proportion to size sampling design[28]. CNNS also measured serum C-reactive protein (CRP) levels, thereby allowing adjustment for underlying inflammation, an important modulator of serum retinol levels. The overall inflammation-adjusted prevalence of VAD was 15.7%; (95% CI 15.2-16.3) in Indian 1-5 y children at the national level[14].

There were no significant differences in VAD prevalence between urban (15%) and rural (16%) children and between boys (16%) and girls (15.4%)[14]. Children belonging to the highest socio-economic quintile (11%) had lower prevalence of VAD than children of other socioeconomic groups (poorest-26%; poor-18%; middle-18%; high-16.6%). Children from households with access to improved sources of drinking water and basic hand-washing facility had lower rates of VAD prevalence as compared to those who had limited or no such facilities. Children who did not have access to improved sanitation facility had higher prevalence of VAD as compared to those who used improved and unshared toilets[28].

Mothers who consumed eggs ≥3 times/ week had significantly lower VAD than others, and this difference was significant even after adjusting for area of residence, wealth index, caste, religion, mother's schooling and WASH indicators. The prevalence of VAD did not differ in mothers with varying frequencies of consumption of green leafy vegetables or milk. Children who consumed milk had significantly lower VAD than those who did not, and this difference was significant even after adjusting for area of residence, wealth index, caste, religion, mother's schooling and WASH indicators. The

Table 2: Prevalence of Bitot spots among pre-school children[32,42]

States	1975-79	1988-90	1996-97	2002-03	2011-12
Kerala	0.1	0.5	0.1	0	0
Tamil Nadu	2.9	0.6	0.7	0.5	0
Karnataka	2.3	1.1	0.5	0.7	0.6
Andhra Pradesh	3.1	1	0.8	1.2	0.1
Maharashtra	0.4	0.3	3	1.3	1.4
Gujarat	0.9	0.5	0	-	0.2
Odisha	1.5	1.1	0	0.3	0.3
Madhya Pradesh	-	-	-	1.4	-
Pooled	1.8	0.7	0.7	0.8	0.4

prevalence of VAD in the 1-4y age group who had consumed VA-rich foods on the day previous to the test did not show any significant difference as compared to those who had not consumed such foods.

Although children who were severely stunted and underweight showed higher prevalence of VAD, the difference was not significant when adjusted for area of residence, wealth index, caste, religion, mother's schooling and WASH indicators. Wasting did not have an association with VAD prevalence. The prevalence of VAD was lower in children who received VAS as compared to the group that did not receive VAS, but the difference was not statistically significant. The presence or absence of MDVA supplementation was not associated with VAD prevalence after adjusting for mother's education, wealth index, incidence of diarrhoea and WASH indicators.

The mega-dose approach to alleviating VAD: WHO policy and guidelines

Massive dose supplementation of VA is administered to elevate hepatic stores and to provide VA for metabolic function. The recommendation was based on the concept that VA is absorbed and stored in the liver effectively in high doses and can provide a reserve during periods of low dietary intake[1]. Considering VAD as a serious global public health problem, particularly in low- to middle-income countries, the WHO strongly recommends mega-dose VA supplementation (MDVAS) to infants and children aged 6–59 months in areas experiencing VAD, including in populations where children may be living with HIV; these include populations in which the prevalence of night blindness is more than 1% in children 24–59 months of age and those in which the prevalence of subclinical VAD is more than 20% in infants and children 6–59 months of age. The WHO recommends a single dose of 100 000 IU VA (30 mg RAE) to infants 6-11 months of age, and 200 000 IU VA (60 mg RAE) at least twice a year to children 12–59 months of age as a public health intervention to reduce VAD-related child morbidity and mortality[47]. This intervention should be used in vulnerable groups along with other strategies to improve VA intakes, such as dietary diversification and food fortification[47, 48].

The MDVAS program in India- history, motivation and achievements

In the 1950s and 60s, many of the states in India reported blindness resulting from keratomalacia due to VAD in children under the age of 5 years[41]. A five-year long field trial conducted by the National Institute of Nutrition (NIN) showed that administration of MDVA once in six months to children between 1-3 years of age, reduced the incidence of corneal xerophthalmia by about 80%[49]. NIN pioneered MDVAS as an approach to prevent and control nutritional blindness, and provided much-needed scientific evidence, long before any other country or agency conceived of the strategy and started it[50].

Based on the recommendations arising from the NIN studies, and in view of the serious problem of blindness in children due to VAD, the *National Prophylaxis Programme Against Nutritional Blindness* (NPPNB) was initiated in 1970, with the aim of preventing nutritional blindness due to keratomalacia. This was launched as a centrally sponsored government scheme[43, 51]. The Programme was initiated in 11 states across the country. Evaluation studies conducted by the NIN in 1976 in two states revealed positive outcomes. In subsequent years, the programme was extended to all the states in the country. In 1994, under the National Child Survival and Safe Motherhood (CSSM) Programme, the age group of eligible children was restricted to 9 to 36 months of age[52]. This target age group for VAS was arrived at in view of the limited supplies of supplements and higher vulnerability of younger children to VAD. Under this scheme, children below 11 months of age were administered 100,000 IU and those between 1-3 years of age received 200,000 IU of VA orally once in six months. During the Eighth Five Year Plan period, in an attempt to improve the coverage, especially of the first two doses, it was decided to link VA administration to the ongoing immunization programme. In 2006, the age group of children eligible to receive the oral prophylactic dose was broadened to 6-59 months after considering recommendations of the WHO, UNICEF and the Ministry of Women and Child Development[53]. Accordingly, given the operational feasibility, one dose of 100,000 IU was administered along with measles immunization to children between 9-11 months of age, and eight doses of 200,000 IU at six-monthly intervals to children in the 1–5-year age group.

Table 3: Prevalence of VAD (%, 95% CI) by state in 1-5 years age group of children

State	1-3 y	4-5 y	1-5 y	State	1-3 y	4-5 y	1-5 y
National	14.5 (13.6-15.4)	16.6 (15.8-17.4)	15.7 (15.2-16.3)	Manipur	13.2 (9.7-17.5)	14.7 (10.9-19.3)	14.1 (11.5-17.1)
Andhra Pradesh	16.9 (12-22.8)	17.1 (13-22)	16.9 (13.7-20.6)	Meghalaya	3.8 (2.1-6.5)	7.1 (4.8-10.2)	5.7 (4.2-7.7)
Arunachal Pradesh	8.4 (6.2-11.2)	11.9 (9.4-14.9)	10.3 (8.6-12.4)	Mizoram	36.5 (28.1-45.7)	43.4 (35.6-51.5)	40.8 (34.9-46.9)
Assam	17.2 (11.5-24.6)	18.6 (14.2-23.6)	17.9 (14.4-21.9)	Nagaland	2.2 (0-40.8)	8.1 (1-32)	5.3 (0.9-19.1)
Bihar	20.5 (16-25.8)	24.8 (20.6-29.3)	22.8 (19.7-26.1)	NCT of Delhi	21.7 (17.5-26.4)	16.4 (13.4-19.9)	19 (16.5-21.8)
Chhattisgarh	21.6 (17.5-26.2)	17 (13.8-20.7)	19 (16.4-21.8)	Odisha	17.7 (14.4-21.4)	15.2 (12.7-18)	16.4 (14.4-18.6)
Goa	1.8 (0.8-4)	2 (1.3-3.2)	1.9 (1.3-2.8)	Punjab	17.2 (12.6-22.8)	13.5 (10.2-17.5)	15.4 (12.6-18.6)
Gujarat	17.9 (11-27.2)	8.8 (5.4-13.6)	12.7 (9.1-17.2)	Rajasthan	0 (0-0)	2.3 (0.6-6.8)	0.7 (0.2-2)
Haryana	20.3 (12.6-30.3)	22.5 (16.4-29.8)	21.9 (16.9-27.5)	Sikkim	3.7 (2.8-5)	4.3 (3.2-5.7)	4.0 (3.3-4.9)
Himachal Pradesh	0.9 (0.5-1.6)	4.0 (2.4-6.6)	2.0 (1.4-2.8)	Tamil Nadu	8.4 (5.9-11.7)	9.1 (7-11.6)	8.8 (7.1-10.7)
Jammu & Kashmir	7 (4.7-10)	8 (5.6-11.2)	7.5 (5.8-9.6)	Telangana	26.4 (19.5-34.4)	30.5 (25-36.4)	28.6 (24.3-33.2)
Jharkhand	31.3 (22.7-41)	33.5 (25.9-41.7)	32.8 (27.1-39)	Tripura	18.2 (14.1-23.1)	11.7 (8.6-15.5)	15.1 (12.5-18)
Karnataka	7.2 (5-10)	10.4 (7.7-13.9)	8.8 (7-10.9)	Uttar Pradesh	17.9 (12.9-24)	22.4 (17.5-28)	20.5 (16.9-24.6)
Kerala	10.3 (7.1-14.4)	14.8 (10.6-19.8)	12.6 (10-15.8)	Uttarakhand	11.3 (7.8-15.8)	11.5 (8.3-15.5)	11.3 (8.9-14.1)
Madhya Pradesh	21.2 (7.8-42.7)	26.3 (14.6-41.4)	23.2 (14.1-34.7)	West Bengal	3.0 (2.2-4)	4.7 (3.7-6)	4.6 (3.8-5.4)
Maharashtra	9.8 (5.5-16)	10.9 (7.4-15.5)	10.3 (7.5-13.7)				

The objectives of the MDVAS programme as it was originally conceptualized in India were considered to be '*no more than a crutch*'[50], primarily to prevent blindness due to severe VAD. Later, however, based on the global evidence that VAS may lead to reduction in mortality in under-five children, the intervention was advocated for child survival[54]. UNICEF considered that Millennium Development Goal-4 could be achieved by including young children in a package of conventional child survival interventions along with VAS and therefore recommended VAS in 61 countries with high under-five mortality rates (>70/1000 childbirths)[55].

Survival benefit with MDVAS: Indian context

Is the purported child survival benefit of MDVAS relevant in the Indian context in the current era? The survival benefit documented in the initial studies in 1980s and 90s pertained to a time when VAD was common and was often seen in association with measles and diarrhoea[54, 56]. Better immunisation coverage has resulted in lower incidence of measles and diarrhoea is being better managed. Two trials reported after the year 2000, notably the DEVTA trial in one million children from Uttar Pradesh[35, 57], when under-five mortality rates and clinical VAD had declined, did not reveal any evidence of survival benefit with VAS. The updated Cochrane Meta-analysis[58] reported a mortality reduction of 12% (RR 0.88, 95% CI 0.83 to 0.93), which is unsurprising considering the weightage given to older studies[56]. When the analysis was restricted to the five Indian studies of MDVAS included in this meta-analysis[35, 59-62], there was no evidence of a survival benefit (RR=0.96; 95% CI: 0.89, 1.03; P=0.23). Considering the 2017 mortality rates for India, even the estimated 12% mortality reduction from the Cochrane review[58] has little practical relevance (absolute risk difference 1.7; 95% CI: 1.0, 2.4 per 1000 live births), especially with suboptimal programme coverage[14]. With further reduction in mortality rates in 2018 and later, it becomes even more irrelevant.

The MDVAS Policy for India: What next?

In India, there has been considerable criticism about the continuation of universal MDVAS as a permanent solution to VAD, and more specifically for the principal improvement of child survival[43, 48, 63, 64]. During the last four decades, child health indicators have shown substantial improvements in most states in the country. The prevalence of severe undernutrition has come down significantly[28, 65, 66]. The ICDS, which covers 80% of rural India, provides nutritional supplements to children under six years of age and nutrition education to mothers, besides facilitating the delivery of VA supplements. Developments in infrastructure have led to better access to health care facilities. Food availability in India has improved in the last 30 years. All these factors would have led to improvement in the VA status of children and led to reduction in the prevalence of VAD in the country[32, 42, 43, 48, 63]. In spite of these improvements in the health and nutritional status, the biannual VAS which was envisaged by Dr. Gopalan as a short-term measure to combat blindness due to VAD, and not as a quasi-permanent or long-term solution to VAD[50], threatens to become just that.

Apart from the cost of the micronutrient supplement, the programme also consumes precious human and material resources meant for delivery of primary health care. Also, VA is toxic in high doses. The MDVAS (200000 IU) given to children is many-fold higher than the RDA (350-400 µg/day). Children hospitalized for acute infectious diseases with low VA status benefit from high-dose supplements given at the time of admission, but no such benefit was observed among those with adequate preadmission VA status[67]. It is, therefore, inappropriate to administer a pharmacological dose of VA to a child whose VA status is adequate. The potential adverse effects of administering a pharmacological dose of VA to a child who is not suffering from deficiency have not received due attention.

The prevalence of subclinical VAD among states is shown in **Table 3**. According to the WHO, the prevalence of subclinical VAD >20% signifies a public health problem. Based on a probability method of correction of serum retinol, there were only 7 states which had VAD prevalence ≥20% (**Table 3**). However, there is uncertainty about point estimates, as the 95% CI would fall on either side of the cut-off value of 20%. A more robust estimate of the VAD prevalence comes from considering *the lower confidence limit* as the cut-off wherein the entire confidence interval lies to the right of the cut-off prevalence of 20%. Based on this, only 3 states, Telangana, Jharkhand and Mizoram, had a VAD risk ≥20%[14].

Currently, the major contributory factor for the reported prevalence of VAD is low amounts of VA in diets. Therefore, it is necessary to ensure enhanced VA intake among the vulnerable groups through horticultural intervention to produce foods rich in the micronutrient, thereby improving availability, access and utilization of locally available VA-rich foods. Horticultural strategy coupled with behaviour change communication will be a sustainable approach to control VAD. A 3-year study conducted by NIN demonstrated that home gardening along with effective nutrition communication in villages in backward districts of Andhra Pradesh increased the availability and consumption of vegetables rich in β-carotene at household level[68]. Further, a study conducted by NIN in rural areas of Andhra Pradesh demonstrated the effectiveness of a social marketing strategy in communicating nutrition messages to prevent VAD thereby highlighting the need to adopt innovative strategies to communicate nutrition messages[69].

As a medium-term strategy, fortification of one or more commonly consumed foods with VA was also considered as a cost-effective means of preventing VAD, particularly in countries where improvements in dietary intakes among rural communities is unlikely in the conceivable future. Mandatory fortification of hydrogenated fats with VA has been in vogue for several decades[48]. Other strategies are (i) improvement in the VA intake in children and in pregnant and lactating women by encouraging local production and homestead gardening of green leafy vegetables and other VA rich foods, and (ii) creating awareness about the importance of preventing VA deficiency among the women attending antenatal clinics and immunization sessions, as well as among women and children registered under the Integrated Child Development Services (ICDS) programme[48].

Conclusion

Evidence from national surveys on dietary VA intakes, the biochemical indicators of VAD, and an analysis of survival benefit suggest the need for seriously considering a targeted approach instead of continuing with the universal VAS in India. This should be accompanied by meticulous monitoring of a) U5MR trends through the ongoing Sample Registration System[70]; b) keratomalacia case-load data from ophthalmic centres or sentinel sites; and c) monitoring serum retinol and REs from repeat national surveys or, if cost is a limitation, at least through regional studies in high-burden states. Vitamin A deficiency, iron deficiency anaemia and iodine deficiency disorders are public health problems which need to be addressed through a comprehensive approach that includes promoting optimal IYCF practices, horticultural interventions, dietary diversification, and public health measures including nutrient supplementation and food fortification[71]. These are very much in tune with public health policy approaches to VAD visualized by Dr. C Gopalan, who was the Father of Nutrition Science in India.

The authors of this review agree with his views wholeheartedly, and these reflections are a tribute to Dr Gopalan.

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FOUNDATION NEWS

Dr. Prema Ramachandran Director NFI participated and made presentations in the webinars organised by Lady Irwin College Delhi and Avinashilingam University during the POSHAN Maah

The 2nd Dr. C. Gopalan Memorial Webinar 'Child growth and nutrition - recent NFI studies' will be held on 01.10.2021. During the webinar presentations will be made on secondary data analysis of large scale surveys on nutritional status of children carried out by NFI. Presentations will also cover community based longituidinal studies on nutritional status of pre-school children and explorations on intra-family differences in nutritional status carried out by NFI.