Vitamin A fortification of wheat flour: Considerations and current recommendations

Rolf D. W. Klemm, Keith P. West, Jr., Amanda C. Palmer, Quentin Johnson, Philip Randall, Peter Ranum, and Christine Northrop-Clewes

Abstract

Background: *Vitamin A deficiency is a major public health nutrition problem, affecting an estimated 190 million preschool-aged children and 19 million pregnant and lactating women globally, and 83 million adolescents in Southeast Asia alone. Its consequences (disorders) include xerophthalmia (the leading cause of early childhood blindness), increased severity of infection, anemia, and death. Because vitamin A deficiency is largely due to chronic dietary insufficiency of preformed vitamin A and proactive carotenoids, food fortification can offer an effective approach to prevention.*

Objective: *To provide guidance on fortifying wheat and maize flour milled in industrial rollers for national fortification programs in countries where vitamin A deficiency is considered a public health problem.*

Methods: *Critical review of the literature on the dietary gap in vitamin A intake and levels of wheat flour intake among risk groups as a basis for determining vitamin A fortificant levels. Additional review of efficacy evidence, safety and cost considerations, and country experiences related to wheat-flour fortification with vitamin A.*

Results: *Mill-rolled wheat flour is a technically fortifiable, centrally processed food vehicle that, where routinely and adequately consumed by target groups, should be considered a candidate for fortification. Vitamin A can be stable in flour under typical, ambient conditions, with processing losses estimated at approximately 30%, depending on source and premix conditions.*

Conclusions: *Factors to guide a decision to fortify flour with vitamin A include the extent of deficiency, availability of other food vehicle options, the centrality of milling, market reach and population intake distributions of the flour products, the dietary vitamin A intake required, and associated costs. Large gaps persist in knowledge of these factors, which are needed to enable evidence-based fortification in most countries, leaving most decisions to fortify guided by assumptions. Where flour can and should be fortified, guidelines are given for providing nearly 25% of the Recommended Dietary Allowance for vitamin A to vulnerable groups consuming varying ranges of flour products. The costs will vary according to the level of fortification.*

Key words: Dietary intake, food fortification, vitamin A deficiency, wheat flour

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Introduction

Wheat consumption is rising on a per capita basis in many developing countries where vitamin A deficiency remains a public health problem. Wheat flour fortification, therefore, may provide a growing opportunity to improve vitamin A intake of the poor [1]. Many low-income countries import wheat, either through commercial channels or as food aid; the latter route tends to self-target the poor and, therefore, presumably the most vitamin A deficient [2, 3]. Imported wheat is often milled at a limited number of private (e.g., Philippines and Indonesia) or government (e.g., Sri Lanka, Egypt) mills prior to national distribution, making centralized wheat flour fortification feasible. On the other hand, fortification of wheat flour may be less feasible in countries with large numbers of dispersed small mills, or where home-based milling is commonly practiced, because of challenges such decentralized milling poses to maintaining quality control.

The goal of a vitamin A fortification program is to prevent vitamin A deficiency. Its objectives are to increase vitamin A intake and to improve vitamin A status among population groups whose daily dietary needs for vitamin A are not routinely met, while minimizing the risk of overconsumption among groups whose vitamin A status is normal. For wheat flour to be a suitable vehicle, however, target groups should routinely consume a minimum amount of centrally processed wheat flour, preferably within a definable intake range. This requirement is not met in many low-income countries, particularly by poorer groups for whom foods other than wheat flour may serve as staples (e.g., maize, rice, sorghum, millet, and roots and tubers). In many developing countries, wheat-based foods are consumed primarily by the upper and upper middle socioeconomic groups, who tend to be vitamin A sufficient [4]. In some countries, such as the Philippines, there is also wide geographical and urban–rural variability in wheat flour consumption, even among poor communities [5], posing challenges to setting effective and safe fortification ratios.

Vitamin A deficiency: Magnitude of the problem

On a global scale, countries with per capita annual incomes under US$15,000 per year are considered to harbor most populations at risk for vitamin A deficiency [6]. Within low-income countries, the groups at greatest risk, and thus the primary target groups for prevention, are preschool-aged children, school-aged children through adolescence, and women of reproductive age, especially during pregnancy and lactation. These groups should, therefore, be given careful consideration in the design and evaluation of the public health impact of vitamin A fortification initiatives.

Preschool-aged children

An estimated 190 million children, or approximately 33% of all children under 5 years of age in low-income countries, are vitamin A deficient (**table 1**) [6], with the prevalence being highest among children in Southern Asia (50%) and sub-Saharan Africa (44%) and lower in the Region of the Americas (16%), based on distributions of serum retinol concentrations below 0.70 μmol/L (< 20 μg/dL) [6]. These figures are based on data to 2005, although the results of periodic, more recent studies are consistent with the extent of risk across regions [7–10]. Nearly 1% of preschoolers, or approximately 5 million, have xerophthalmia [6], which in its severe form (keratomalacia) remains the leading preventable cause of childhood blindness [1]. Approximately 11% to 14% of a typical low-income population is composed of children under 5 years of age [11], providing a target of considerable risk and size for intervention, such that adequately reaching this group with vitamin A can have a substantial public health impact. Supplementation trials conducted over the past 20 years, including one that tested the impact of vitamin A–fortified monosodium glutamate (MSG) in Indonesia, have reported reductions in preschool child mortality of, on average, 23% to 34% [12, 13], attributed to reductions in severity and fatality from infections such as measles, diarrhea, malaria, and other febrile illnesses [14]. Although control is largely achieved in young children through direct, high-potency vitamin A supplementation [1], the demonstrated effectiveness of vitamin A fortification of some food items, such as sugar [15, 16] or MSG [17, 18], in improving vitamin A status and reducing xeropthhalmia, anemia,

TABLE 1. Prevalence and numbers of cases of preschool-aged child and antenatal vitamin A deficiency and xerophthalmia by region

	Children < 5 yr				Pregnant women			
	Serum retinol < 0.70 μmol/L		Xerophthalmia		Serum retinol < 1.05 μmol/L		Night-blindness	
Region	%	No. (millions)	%	No. (millions)	%	No. (millions)	%	No. (millions)
Africa	44.4	56.4	2.0	2.55	13.5	4.2	9.8	3.02
The Americas	15.6	8.7	0.6	0.36	2.0	0.2	4.4	0.50
South/Southeast Asia	49.9	91.5	0.5	1.01	17.3	6.7	9.9	3.84
European Region	19.7	5.8	0.8	0.24	11.6	0.7	3.5	0.22
Eastern Mediterranean	20.4	13.2	1.2	0.77	16.1	2.4	7.2	1.09
Western Pacific	12.9	14.3	0.2	0.26	21.5	4.9	4.8	1.09
Total	33.3	190	0.9	5.17	15.3	19.1	7.8	9.75

Source: WHO [6].

or mortality reflects the potential that can be achieved when food items regularly consumed by this age group are fortified with vitamin A.

School-aged children

Data remain scant on the burden of vitamin A deficiency in school-aged children and adolescents, although the few reports available suggest mild-to-moderate vitamin A deficiency to be widespread in this age group in low-income countries. Based on the measurement of hyporetinolemia (< 0.70 μmol/L) and liberal extrapolation, 83 million children (~ 23%) 5 to 15 years of age in Southeast Asia are estimated to be vitamin A deficient, of whom 2.6% or 9 million have mild xerophthalmia (night-blindness or Bitot's spots). Corneal xerophthalmia in this age group appears to be negligible [19]. Sporadic reports from South Asia [20, 21], Africa [22, 23], and Latin America [24] are consistent with a 10% to 15% prevalence of vitamin A deficiency among school-aged children and adolescents. Although the health consequences are largely unreported, vitamin A deficiency in this age group could predispose young women to vitamin A deficiency during pregnancy and lactation [25, 26]. Since vitamin A supplementation programs do not extend beyond the preschool years, school-aged children and adolescents in undernourished societies represent large target groups to reach with food fortified with vitamin A. In the Philippines, a pilot trial revealed increased apparent liver stores of vitamin A (by a modified relative dose–response test) among school-aged children consuming vitamin A–fortified wheat flour used in making local bread (*pandesal*) [27], demonstrating proof of principle in this target-aged population.

Women of reproductive age

Recent updated figures from the World Health Organization (WHO) suggest that approximately 19 million pregnant and lactating women (15%) in low-income countries are vitamin A deficient, based on serum retinol concentrations < 0.70 μmol/L, of whom nearly 10 million (~ 8%) have night-blindness. According to the WHO report, the highest-risk regions for maternal deficiency exist in the Western Pacific (21%), South and Southeast Asia (17%), and the Eastern Mediterranean (16%), with a far lower prevalence estimate, at present, given for the Region of the Americas (~ 2%) [6]. Subnational reports from Southern Asia [28–30] and Africa [23, 31–33] tend to support the persistence of maternal vitamin A deficiency in these major regions, while representative data for this group in Latin America remain sparse. The health consequences of vitamin A deficiency during pregnancy include night-blindness [25, 34], anemia [25, 28], and, in some remote and undernourished settings, increased morbidity and mortality [35, 36]. Many countries have policies to reduce maternal vitamin A deficiency through one-time, high-potency, postpartum vitamin A supplementation, but coverage tends to be low. Further, this approach is not designed to raise the overall vitamin A status in a population, leaving a need for more sustainable, broader approaches such as can be afforded by fortification, when feasible. Breastmilk vitamin A has been shown to increase after fortification of sugar [16] and MSG [17] with vitamin A in Central America and Indonesia, respectively, providing evidence of public health potential among women of reproductive age with this intervention.

The dietary gap in vitamin A

Low serum vitamin A distributions (< 0.70 μmol/L) can be assumed to reflect chronic dietary inadequacy of vitamin A from preformed and proactive carotenoid sources. However, status data do not provide information about the size of the dietary deficit, or gap, in requirements to meet via fortification or other dietary strategies. One set of indices that can be used to assess dietary adequacy are the Dietary Reference Intakes (DRIs), including the Estimated Average Requirement (EAR), Recommended Dietary Allowance (RDA), and, for safety purposes, the Tolerable Upper Intake Level (UL), that have been developed by the Institute of Medicine in the United States with appropriate caveats about their applicability to undernourished populations [37]. One estimate of dietary gap is the added amount of vitamin A (in micrograms of retinol activity equivalents [μg RAE]) required to shift the intake distribution to the right of the EAR so that only approximately 3% remain below that level in an age group. A second approach is to estimate the amount of vitamin A required to bring the mean of the population to the level of the RDA. Either estimate serves to represent the extent to which fortification should increase vitamin A intake to minimize the risk of deficiency. Both require quantified dietary intake data, preferably collected by repeated 24-hour recalls from a representative sample of a target population, assumptions of normality of usual intake distributions, and an adequate food composition database. Few data of this nature, caliber, and specificity exist.

Table 2 illustrates the kinds of dietary data from which estimates of vitamin A intake and prevalence of dietary inadequacy could be constructed for the above three high-risk groups: preschool-aged children, school-aged and young adolescent children, and women of reproductive age. For example, in India in the mid-1990s, the National Nutrition Monitoring Bureau collected single 24-hour dietary recalls from rural adolescents across nine states, enabling the estimation of mean vitamin A intakes [38]. Weighting these estimates with population-based dietary studies in other

TABLE 2. Average daily dietary vitamin A intakes in children and adults[a]

Region/country	N	Vitamin A intake (μg RAE[b])		
		Preschool[c]	School-age[c]	Women[c]
EAR [41]		242	445	500
RDA [41]		350	600	700
Southern Asia[d]				
India[e]				
Average vitamin A intake (μg RAE)		158	147	184
Average % of EAR[f]		65%	33%	37%
Prevalence of inadequacy[g]		72%	87%	85%
Dietary gap (vs RDA, μg RAE)		−193	−453	−516
Andhra Pradesh [68]	220	ND	ND	233
Bihar [69]	1,847	150	ND	ND
Delhi [70]	1,328	208	ND	ND
Gujarat [39]	60	ND	ND	124
Kerala [39]	60	ND	ND	61
Rajasthan [71]	209	ND	216	187
Haryana [40]	117	114	ND	ND
Meghalaya [72]	650	ND	ND	137
9 Indian states [38]	2,579	ND	139	224
Indonesia				
Average vitamin A intake (μg RAE)		331	ND	778
Average % of EAR		137%	ND	156%
Prevalence of inadequacy		27%	ND	18%
Dietary gap (vs RDA, μg RAE)		−19.25	ND	78
Central Java [73]	450		ND	1,232
S. Sulawesi [74]	1,500	329	ND	609
S. Kalimantan [74]	2,112	333	ND	494
Philippines				
Average vitamin A intake (μg RAE)		82	ND	459
Average % of EAR		34%	ND	92%
Prevalence of inadequacy		86%	ND	55%
Dietary gap (vs RDA, μg RAE)		−268	ND	−241
National [75]	3,405	82	ND	ND
National [76]	589	ND	ND	494
National [76]	1,215	ND	ND	425
Africa[h]				
Egypt [42]				
Average vitamin A intake (μg RAE)		465	ND	796
Average % of EAR		192%	ND	159%
Prevalence of inadequacy		6%	ND	16%
Dietary gap (vs RDA, μg RAE)		115	ND	96
South Africa				
Average vitamin A intake (μg RAE)		245	ND	363
Average % of EAR		101%	ND	73%
Prevalence of inadequacy		49%	ND	68%
Dietary gap (vs RDA, μg RAE)		−105	ND	−337
National [43]	2,391	245	ND	ND
Northwest Province [44]	99	ND	ND	661
Limpopo Province [45]	46	ND	ND	318
KwaZulu—Natal [77]	475	328	ND	ND
KwaZulu—Natal [46]	291	94	ND	111

TABLE 2. Average daily dietary vitamin A intakes in children and adults[a] *(continued)*

Region/country	N	Vitamin A intake (μg RAE[b])		
		Preschool[c]	School-age[c]	Women[c]
Other countries in Eastern and Southern Africa				
Average vitamin A intake (μg RAE)		227	175	575
Average % of EAR		94%	39%	115%
Prevalence of inadequacy		54%	84%	40%
Dietary gap (vs RDA, μg RAE)		−123	−425	−125
Kenya—Marsabit [78]	300	ND	ND	243
Kenya—Nakuru [79]	716	ND	ND	712
Malawi—Mangochi District [80]	281	526	ND	ND
Malawi—Balaka [81]	144	94	ND	ND
Mozambique—Zambezia [82]	243	181	ND	ND
Namibia—Kaokoland [83]	53	ND	147	ND
Tanzania—Dar-es-Salaam [84]	271	ND	203	195
Zambia—Lusaka [85, 86]	34	107	ND	ND

EAR, Estimated Average Requirement; ND, no data; RAE, retinol activity equivalent; RDA, Recommended Dietary Allowance; RE, retinol equivalent

a. Intakes represent reported mean intakes of vitamin A by 24-hour recall or food records from population studies or surveys.

b. Data reported as micrograms RE have been assumed to have used a 6:1 conversion factor for provitamin A carotenoids. Intakes were converted to micrograms RAE using study- or region-specific estimates for the proportion of vitamin A intake from carotenoids, multiplying that proportion of overall intake by the previous conversion factor, and then dividing by the current bioconversion factor of 12 μg provitamin A carotenoids to 1 μg RAE [41].

c. Ages reported are for any interval of years up through age 5 years for preschool-aged children, 6 to 15 years for school-aged children, and 16 years and above to provide provisional estimates for "adults."

d. Assumes that 80% of vitamin A intake in South Asia [39, 40, 68, 87] and 40% of vitamin A intake in South East Asia is from provitamin A carotenoids [70–74].

e. An average intake for a country represents the mean of the mean estimates from surveys or states sampled; for preschoolers in India, only one survey is represented, and is taken as a provisional national average; for school-aged children, the nine-state survey estimate of 265 μg RAE was multiplied by 9, to which the two other state estimates were added, and the sum was divided by 11 = 280 μg RAE; the same approach was taken for estimating the average intake for adult women and men.

f. Percentage of the age-gender EAR represented by the mean vitamin A intake level; EAR values used are (as micrograms RAE): 242 for children < 5 years, 445 for school-aged children, and 500 for women of reproductive age [41].

g. Based on an estimate that the percent coefficient of variation (%CV) is 60% of the mean from studies using six to eight repeated 24-hour recalls of dietary intakes that were carried out to reduce sampling variation [39, 40], and calculating the probability area below the EAR cutoff assuming intakes follow a normal Gaussian distribution.

h. Assumes that 80% of vitamin A intake in Eastern and Southern Africa is from provitamin A carotenoids [73, 77, 85].

states (see footnotes to **table 2**), it is possible to derive crude average vitamin A intakes of 158, 147, and 184 μg RAE per day for these three age groups, respectively, representing 65%, 33%, and 37% of the EAR values for preschoolers (using 242 μg RAE as a mid-value for children 1 to 5 years of age), school-aged children and young adolescents (using 445 μg RAE as a mid-value), and women of reproductive age (using 500 μg RAE as a mid-value). Data from studies that collected multiple 24-hour recalls can be used to estimate the variance in usual vitamin A intake: the coefficient of variation is approximately 60% [39, 40]. Applying this estimate to the above average intakes under assumptions of normality, the prevalence of dietary vitamin A inadequacy in these three high-risk groups in rural India is estimated to be 72%, 87%, and 85%, respectively, far in excess of the approximately 3% recommended by the Institute of Medicine [37, 41]. The same calculations suggest that in Indonesia 27% of preschoolers and 18% of reproductive-age women have inadequate vitamin A intakes; for the Philippines, 86% and 55% of individuals in these high-risk groups, respectively, are not meeting the recommended intake levels. These estimates for the prevalence of dietary inadequacy correspond in magnitude, from an ecologic perspective, with the known extent of preschool, adolescent, and maternal vitamin A deficiency across South and Southeast Asia (**table 1**).

If the distribution of dietary vitamin A intake were well-characterized with respect to spread and shape, it should be possible to estimate the amount of vitamin A needed to add via fortification in order to shift the lower intakes of a population above the EAR. In the near-universal lack of such data, an alternative is to estimate the increment to be added as the difference between the mean or median vitamin A intake and the RDA. Thus, in India, for example, this calculation leads to average deficits in the RDA and amounts needed to be delivered via fortification to be 193, 453, and 516 μg

RAE for preschoolers, older children and young adolescents, and women of reproductive age, respectively (using a mid-point RDA estimate of 350 for 1–8-year olds, and 600 and 700 μg RAE for the other two groups, respectively).

Far fewer representative 24-hour dietary recall studies exist in African countries (though **table 2** is not exhaustive) from which to derive estimates of the dietary gap. According to several surveys in Egypt [42], the prevalence rates of inadequate intake in preschoolers and women are 6% and 16%, respectively, based on the EAR, suggesting little need for fortification, which is discordant with estimates of low-to-deficient serum retinol distributions in large subnational groups in the country [42]. Data on vitamin A intakes and status suggest a greater need for added vitamin A in sub-Saharan Africa. For example, nationally representative data from South Africa suggest that 49% of preschool-aged children have inadequate vitamin A intakes [43]. The estimate is 68% among women of reproductive age, based on surveys in selected provinces [44–46]. Published data from other eastern and southern African countries suggest levels of dietary vitamin A inadequacy comparable in magnitude to those in South Africa (**table 1**).

The forgoing provides an approach for estimating a dietary gap to consider in planning a vitamin A fortification initiative. The examples suggest a role for fortification in correcting dietary gaps in vitamin A, although a scarcity of reliable intake distributions makes it difficult to estimate the amount of vitamin A needed to be delivered via food vehicles. If dietary data are in hand, programs exist for calculating the amounts of vitamin A needed to be delivered via fortification that consider requirements and intakes across targeted groups in a population (O. Dary, personal communication, 2008). To date, concentrations of delivered fortificant have been based on ranges of food vehicle intake, efficacy in improving vitamin A status, the possibility that multiple fortified foods could be consumed, and concerns for safety [47, 48]. Most fortification projects and the few national programs that exist have sought to deliver 30% to 60% of an RDA via fortification to specific population groups [47].

Wheat flour as a vehicle for vitamin A fortification

Vitamin A is virtually absent in whole-grain cereals and flours. Nonetheless, flour from cereal grains can be fortified with a dry, powdered form of vitamin A.

Intakes and fortification levels

In considering whether to fortify a food supply with vitamin A, wheat flour should be considered a candidate. Wheat flour is technically fortifiable and is gradually being consumed more over time in low-income populations, although variation is high among countries and among populations (markets) within countries [49]. Thus, countries should first consider whether wheat flour is consumed on a regular basis, within a manageable range, and in amounts by members of different age and societal groups that would allow it to deliver nutritionally significant levels of vitamin A. Too little or irregular intake patterns by the target population can render a product ineffective. Nationally representative, individual wheat flour intake data are rarely available, revealing a fundamental inadequacy in dietary data for planning fortification of flour, and most other potential food vehicles, in low-income countries. Next most useful are per capita consumption estimates of food vehicles derived from national household income and food expenditure survey data that may be available from selected countries in major regions [49], to which intrahousehold weights can be applied to estimate average intakes within age groups. Least useful for estimating individual intake distributions, but most readily available, are country estimates of per capita wheat (or other food) availability based on food balance sheets maintained by the Food and Agriculture Organization (FAO) [50].

On the assumption that ranges of usual wheat flour intake are in hand, **table 3** shows the additional vitamin A intake expressed as micrograms of RAE that could be achieved for a referent adult male and each target group, assuming average fortificant intakes based on relative energy requirements (i.e., weights of 1.00, 0.37, 0.60, and 0.80 units for adult men, preschool children, school-aged children, and adult women, respectively) [49], across the range of wheat flour fortification levels. The estimates assume 30% losses due to transport, storage, and cooking (H. Cori, personal communication, 2009). **Table 3** also displays the corresponding incremental vitamin A intakes expressed as a percentage of the RDA [41] for each group. For example, fortifying wheat flour at 5.9 ppm will provide an additional 207 to 1,652 μg RAE/day, depending on whether average daily flour consumption is very low (< 75 g or ~ 50 g) or very high (> 300 g or ~ 400 g). These values represent 23% and 184%, respectively, of the RDA for adult men. Applying the fractional weights to estimate intakes for other groups, the corresponding ranges of additional intake are 76 to 611, 124 to 991, and 165 to 1,322 for preschoolers, school-aged children, and adult women, respectively, representing 22% to 175%, 21% to 165%, and 24% to 189% of the RDA for each group, respectively. Lower concentrations of vitamin A in wheat flour will deliver corresponding less vitamin A and lower percentages of the RDA, so that for low consumers of wheat (< 75 g/day), negligible amounts of the vitamin are delivered when the fortification level is at 1.5 ppm or lower. Thus, in settings where wheat intake is low

TABLE 3. Intake of vitamin A and %RDA provided at different levels of fortification of wheat flour at the mill and flour intake for adult men (per capita), preschoolers, school-aged children, and adult women[a]

Fortification level—ppm (μg RAE/ g)[c]	Target group	Flour intake (g/day)[b] < 75 RAE consumed (μg)[d]	< 75 %RDA[e]	75–149 RAE consumed (μg)	75–149 %RDA	150–300 RAE consumed (μg)	150–300 %RDA	> 300 RAE consumed (μg)	> 300 %RDA	Fortificant cost (US$/MT)[f]
5.9 (4.13)	Adult man	**207**	**23**	413	46	826	92	1,652	184	
	Adult woman	**165**	**24**	330	47	661	94	1,322	189	8.62
	School-aged	**124**	**21**	248	41	496	83	991	165	
	Preschool	**76**	**22**	153	44	306	87	611	175	
3.0 (2.10)	Adult man	105	12	**210**	**23**	420	47	840	93	
	Adult woman	84	12	**168**	**24**	336	48	672	96	4.38
	School-aged	63	11	**126**	**21**	252	42	504	84	
	Preschool	39	11	**78**	**22**	155	44	311	89	
1.5 (1.05)	Adult man	53	6	105	12	**210**	**23**	420	47	
	Adult woman	42	6	84	12	**168**	**24**	336	48	2.19
	School-aged	32	5	63	11	**126**	**21**	252	42	
	Preschool	16	5	39	11	**78**	**22**	155	44	
0.75 (0.525)	Adult man	26	3	53	6	105	12	**210**	**23**	
	Adult woman	21	3	42	6	84	12	**168**	**24**	
	School-aged	16	3	32	5	63	11	**126**	**21**	1.10
	Preschool	10	3	19	6	39	11	**78**	**22**	

RAE, retinol activity equivalent; RDA, Recommended Dietary Allowance

a. Bolded numbers represent recommended fortification levels for population vulnerable groups consuming wheat flour within specified ranges, providing nearly 25% of the RDA, assuming cooking losses of approximately 30%.

b. Micrograms of RAE consumed and %RDA calculations based on daily flour intake levels of 50, 100, 200, and 400 g considered as adult equivalent intake midpoints within each of the following ranges of intake, respectively: < 75, 75–149, 150–300, and > 300 g.

c. Parts per million (ppm) = μg RAE/g. Figure in parentheses assumes 30% losses due to transport, storage, and cooking and is the value from which micrograms of RAE consumed is calculated. For example, 5.9 × 0.70 × 50 g = 207 μg RAE by the referent adult man in the first cell.

d. Based on adult equivalent units (AEU) for which the AEU equals 1.0, 0.8, 0.6, and 0.37 for adult men, women of reproductive age, school-aged children, and preschoolers, respectively [49].

e. RDA = 900 μg RAE for an adult man. A midrange RDA estimate of 350 μg RAE is used for preschoolers, and 600 and 700 μg RAE are used for school-aged children and adult women, respectively [41].

f. Cost based on an estimate of US$1.46/MT of flour fortified at a level of 1,000 ppm, equivalent to 1,000 μg RAE/kg, at the mill (i.e., before deducting 30% losses).

and the estimated dietary gap is high, wheat flour may not be the vehicle of choice to correct vitamin A deficiency. Alternatively, fortifying wheat flour at, for example, 1.5 ppm can deliver nutritionally effective amounts of vitamin A where flour consumption is moderate (150 to 300 g/day or ~ 200 g/day). The bolded figures in **table 3** show the recommended fortification levels, assuming 30% cooking and preparation losses, required to deliver approximate 25% of an RDA to target groups consuming wheat flour within the specified ranges. The costs of fortification will vary according to the level of the fortificant. The calculations illustrate the utility of incorporating population estimates of daily flour and vitamin A intake into planning a wheat flour fortification initiative with vitamin A.

Efficacy in improving vitamin A status

Pursuing wheat flour fortification with vitamin A for public health purposes presumes prophylactic efficacy, that is, the ability of a selected concentration of vitamin A in wheat flour to protect populations from deficiency at a given level of intake. To date, two efficacy trials have published findings on the efficacy of vitamin A–fortified wheat flour to raise vitamin status (**table 4**). In the Philippines, wheat flour used in making a popular bun called *pandesal* was fortified with vitamin A at a level of 4.5 mg/kg to produce a pandesal product with 2.8 mg vitamin A/kg [27]. Each school day for 6 months, children received a 60-g piece of fortified pandesal, intended to provide 133 μg RAE per bun, or a nonfortified product of identical size and appearance. Daily pandesal intake per child averaged 53.4 g ± 6.4 (SD) in the experimental group, providing 121 μg RAE, and 53.6 ± 6.1 g in the control group, providing no additional vitamin A. Among all children whose vitamin A status was below the median at the outset, those assigned to the fortified bread showed a 0.07 ± 0.03 μmol/L increment in serum retinol over controls after 6 months ($p = .02$). Apparent liver storage of vitamin A was assessed at the 6-month follow-up by a *modified-relative-dose-response* (MRDR) test in children who had exhibited the lowest vitamin A status at baseline (the lowest 20%) in each group. Nearly half of lowest-status children assigned to fortified pandesal had follow-up MRDR values above the ratio cutoff of 0.06 (15.3%), reflecting low liver stores, compared with controls (28.6%, $p = .05$).

In an unpublished second randomized, controlled trial in Bangladesh, vitamin A–fortified wheat flour (at a concentration of 3,000 μg RAE/kg) was made into chapattis providing approximately 212 μg RAE per two-piece serving [51] plus six other nutrients. Children were fed two chapattis daily for 6 months. The mean serum retinol concentration and percentage of children with values < 0.70 μmol/L at 6 months were higher (1.05 vs 0.94 μmol/L, $p < .05$) and lower (7.4% vs 22.5%, $p < .05$), respectively, in children assigned to fortified than in those assigned to unfortified chapattis. The findings from both trials suggest that vitamin A status can be improved by regular consumption of breads baked with vitamin A–fortified wheat flour; however, to date there have been no studies evaluating the effectiveness of this intervention as a routine program.

Safety considerations

Guidelines exist for gauging the likely safety limits at which foods can be fortified with vitamin A. Life-stage- and sex-specific ULs, published by the Institute of Medicine, are intended to serve as the highest levels of usual dietary intake of a nutrient from all sources that is likely to pose no risk of adverse health to almost all individuals in a healthy, North American population [37]. The UL is specifically not intended to guide vitamin A supplementation or fortification in undernourished populations [41] and should not deter food fortification interventions in countries or regions at risk for vitamin A deficiency [52]. ULs for vitamin A were established on the basis of minimizing the risks of teratogenicity in women of reproductive age, liver abnormalities in all other adults 19 years of age and older (extrapolated to children and adolescent boys), and hypervitaminosis A in infants [37]. The UL for vitamin A set by the Institute of Medicine for adults, including pregnant and lactating women over 18 years of age, is 3,000 μg RAE/day; it has also been set at 2,800 μg RAE/day for adolescents, including young pregnant and lactating women; 1,300 μg RAE/day for 9- to 13-year-olds; 900 μg RAE/day for 4- to 8-year-olds; and 600 μg RAE/day for infants and children under 4 years of age [41]. As another reference, the UK Expert Group on Vitamins and Minerals has set a lower Guidance Level—considered less firm than an Upper Limit—for vitamin A at 1,500 μg RAE/day (half of the UL for adults) in light of observational and animal research linking chronic preformed vitamin A intakes above this level with risk of reduced bone mineral density and fracture [53, 54]. Upper limits can best be avoided by aiming to deliver minimally effective fractions of either an EAR or an RDA to targeted population groups that will also minimize the collateral risks of excessive intake by high consumers of a food vehicle. Sometimes this can also be achieved, in part, by fortifying specific milled streams of wheat flour that self-target the poor or other groups with known narrower intake distributions. Since dietary sources of vitamin A in most regions of the developing world consist of provitamin A carotenoids, it is less likely that individuals in most target populations will exceed the UL on a regular basis.

Stability of vitamin A in premix and flour products

Stable forms of vitamin A palmitate have existed for at least 30 years and have significantly increased the number and kind of foods that can be fortified with vitamin A, particularly cereal grain products [55]. Commercial forms of dry vitamin A as palmitate or acetate are available embedded in a water-soluble matrix (e.g., gelatin, gum acacia, starch) and stabilized with antioxidants. The most common form of vitamin A used to fortify cereal flours is dry stabilized powder-form vitamin A palmitate, generically referred to as Type 250-SD (75,000 µg RAE/g) [56]. This form of vitamin A added to wheat flour to form a premix can remain stable for approximately 15 days, even under hot, humid conditions [57]. Under routinely tested conditions of 30° C and 60% humidity, retention is repeatedly observed to be approximately 90% (H. Cori, unpublished data, 2009), although stability thereafter can vary considerably [57]. Retention studies done to date conclude that a primary factor in vitamin A loss can be premix moisture content (i.e., humidity), but that the different qualities of vitamin A compounds may also underlie wide variability in the vitamin A content of the premix.

Once premix is added at intended ratio concentrations to wheat flour, the stability of vitamin A continues to vary according to temperature, humidity, duration of storage, and other conditions of storage. In the Philippines, approximately 81% of original vitamin A content (500 µg RAE/100 g flour) was retained in fortified wheat flour after 1 month of storage under ambient conditions [58]. Other studies have shown retention rates of fortified, low-extraction wheat flour to exceed 95% for up to a year at temperatures of 40° C [59]. Cort et al. found vitamin A losses to be higher in flour stored at 45° C than in flour stored at room temperature, reaching approximately 30% if the flour was stored for 3 months at higher temperatures [60]. High moisture content, however, may markedly increase losses of stored wheat flour [61].

After baking, vitamin A retention

TABLE 4. Summary of efficacy trials on the impact of vitamin A–fortified wheat flour

Country	Design and study subjects	Sample size		Food vehicle	Nutrient level	Target daily vitamin A intake from fortified flour product	Results
		Fortified flour	Unfortified flour				
Philippines [27]	Individually randomized, controlled trial Schoolchildren 6–13 yr	396	439	Pandesal	6,000 µg RAE/kg	133 µg (33% RDA)	Mean (± SD) serum retinol (µmol/L) fortified vs nonfortified: Baseline: 1.17 ± 0.33 vs 1.18 ± 0.30 30 wk: 1.32 ± 0.37 vs 1.31 ± 0.40 % low liver stores based on MRDR[a] ≥ 0.06 among subsample of children with lowest baseline serum retinol concentration (n = 72 and n = 77 for vitamin A and no vitamin A) at 30 wk: 29 vs 15*
Bangladesh [51]	Cluster-randomized, controlled trial Schoolchildren 6–15 yr	191	143	Chapatti	3,000 µg RAE/kg plus other nutrients	212 µg (35–55% RDA)	Mean (± SD) serum retinol (µmol/L) fortified vs nonfortified: Baseline: 0.96 ± 0.26 vs 0.98 ± 0.29 3 mo: 1.07 vs 1.04 6 mo: 1.05 vs 0.94* % < 0.70 µmol/L: vitamin A vs no vitamin A Baseline: 13.6 vs 15.4 3 mo: 7.9 vs 16.2* 6 mo: 7.4 vs 22.5*

MRDR, modified relative dose response; RAE, retinol activity equivalent; RDA, Recommended Dietary Allowance
* Between-group differences are statistically significant at $p < .05$.
a. MRDR is an indirect assessment of liver stores that tests the relative responsiveness of serum retinol following receipt of a standard, small dose of vitamin A.

in fortified flour used in traditional Persian breads has been shown to be approximately 70%, alone or when mixed with other nutrients [62, 63]. Cort et al. found no losses of vitamin A when bread was baked or after 5 days of storage compared with the level declared on the product label [60]. Other studies in the past have observed losses of vitamin A of 10% to 20% during baking of bread and 13% and 17% after drying and cooking of long durum wheat pasta, respectively [64].

Vitamin A loss in wheat flour products may vary with inclusion of other nutrients. In the Philippines, vitamin A retention remained greater than 70% after a month of storage in a premix that included iron (45 mg/kg flour) [65]. Further vitamin A losses from premixes with different forms of added iron ranged from 3% to 46% in products such as baked loaves of bread, raw noodles (prepared from hard flour), and biscuits (prepared from soft flour). Losses were higher for loaf bread and noodles (40% and 46%, respectively) when the iron fortificant was ferrous fumarate versus either ferrous sulfate (21% and 28%) or reduced iron (3% and 21%). Vitamin A losses, however, were 20% to 30% in biscuits, irrespective of the type of iron fortificant. Rubin et al. investigated the stability of vitamin A in bread made from flour enriched by six vitamins and four minerals, among which added calcium and magnesium appeared to adversely affect retention during the baking process [66]. The paucity of data on the stability of vitamin A under a myriad of (often adverse) storage and baking conditions, in diverse products without and with many kinds of nutritive and non-nutritive additives, makes it difficult to generalize about retention of vitamin A in premix and finished wheat flour products, and how the available evidence can guide overages. The data available, however, suggest that premix vitamin A retention of about 80% to 90% can be expected within a month of its use, assuming reputable supplies and reasonable protection from high temperature and humidity, and that additional losses of up to 30% can be expected across a range of baked products and conditions.

Organoleptic qualities

Sensory tests have been conducted on flour and wheat flour-based products prepared with vitamin A. Solon et al. [65] found no detectable differences in color or odor of flour fortified with 490 μg RAE/kg until 3 months after fortification. No differences were found in the flavor of pandesal with fortified flour, stored for up to 3 months, and baked under laboratory testing conditions. Neither were there detectable differences in color, odor, flavor, or texture of the flour or the fortified food products when vitamin A–fortified flour had any of three different forms of iron (each added at 45 mg/kg) [65]. School-based programs delivering fortified cookies in Guatemala have added up to 10 mg/kg of vitamin A in flours without sensorial changes (O. Dary, personal communication, 2008). Thus, the data to date suggest that vitamin A fortification of wheat flour has little effect on the organoleptic qualities of the final product.

Country program experiences

Historically, vitamin A has not been added to cereal flours in most industrialized countries, because margarine and milk are the preferred food vehicles and today vitamin A deficiency is no longer a problem of public health significance in such societies. Since 1969, however, cereal flour–based food aid commodities, such as wheat–soy and corn–soy blends, have been fortified with 7 and 10 mg vitamin A/kg, respectively, providing an estimated 80% to 90% of the RDA for school-aged children consuming approximately 75 g/day [3]. Currently 10 low- and low-middle-income countries and two upper-middle-income countries are fortifying or proposing to fortify wheat flour with vitamin A (**table 5**). In the Philippines, wheat flour was selected as a preferred vehicle for fortification because there is relatively high penetration of wheat flour products, even among the poor, and there is no local wheat production, so that all wheat is imported and is milled centrally by 12 millers in the country [58].

TABLE 5. Countries with voluntary or mandatory vitamin A fortification of wheat flour

Country	Product	Mandated level—μg RAE/g (IU/g)
Nigeria	Wheat flour	9.0 (30)
South Africa	Wheat flour (white)	1.68 (5.36)
	Wheat flour (brown)	1.414 (4.712)
	Wheat bread (white)	0.8 (2.664)
	Wheat bread (brown)	0.700 (2.331)
Lesotho	Wheat flour	1.784 (5.947)
Indonesia	Noodles	
Palestine	Wheat flour	1.0 (3.333)
Philippines	Enriched wheat flour	3.0–6.5 (10.0–21.7)
Afghanistan[a]	Wheat Flour	7.078 (23.594)
Bangladesh[a]	Wheat flour	3.3 (11.0)
Venezuela	Wheat flour	2.85 (9.5)
Jordan	Wheat flour	1.5 (5.0)
Ghana	Wheat flour	2.0 (6.666)
Uganda[b]	Wheat flour	2.52 (8.4)

RAE, retinol activity equivalent
Source: Nutriview [88].
a. Managed by the World Food Programme.
b. Voluntary except for World Food Programme–purchased flour

The government passed a law mandating fortification of hard wheat flour with vitamin A in 2000 (Republic Act 8976, 2000), which started to be applied nationally in 2004. Wheat flour is now fortified with SD-250 at a level of 4.5 mg/kg to produce bread products with a vitamin A content of 2.2 μg RAE/g [47]. At an average bread intake of approximately 40 g/day by school-aged children, this level of fortification meets approximately 33% of the Recommended Nutrient Intake (RNI, comparable to the RDA) for this age group [67].

In 1999, Bangladesh initiated a trial program of vitamin A wheat flour fortification with assistance from the US Agency for International Development and the World Food Programme (WFP). Vulnerable group families were targeted with fortified *atta* in lieu of the usual monthly ration of 30 kg of whole-grain wheat [51]. Program activities included studies to assess organoleptic changes, efficacy, utilization, acceptability, and cost. The findings were favorable with respect to the taste, texture, and appearance of vitamin A–fortified flour; consumer acceptability and utilization relative to the previous whole-grain ration; efficacy in improving vitamin A status (**table 4**); and cost (~ US$5/MT or ~ 1.6% of the retail price of commercial white flour sold in plastic bags) [51]. Efforts are under way in Bangladesh to promote this intervention more broadly, although a national program does not yet exist, except through WFP commodity importation.

In South Africa, fortification of white and brown wheat flour and white and brown bread is mandated. Nigeria has mandated adding vitamin A to wheat flour, as have Jordan and the Palestinian territories. Vitamin A is currently added to the wheat flour provided through the WFP in Afghanistan. Finally, Egypt is considering adding vitamin A to the iron and folic acid premix that is currently being used to fortify its subsidized *baladi* bread flour (82% extraction) [24].

Cost considerations

Cost and commercial viability, rather than public health benefit, can often determine whether vitamin A fortification is a feasible and sustainable option for producers and potential beneficiaries. The benefits of vitamin A fortification need to be convincingly sold to private producers, who face research and development costs as well as potential marketing losses in modifying existing food products. Similarly, the benefits must be marketed to the public to promote the use of fortified products.

Dary and Mora [47] compared the cost of fortifying different foods with vitamin A, considering food consumption patterns and losses of vitamin A during storage, transport, and cooking (**table 6**). A comparison of the costs of vitamin A fortification of oil, cereal flours (including wheat flour), sugar, and MSG shows that vitamin A programs for each of these four food vehicles have the potential to be cost-effective, with annual per person costs ranging from US$0.008 for edible oils to US$0.121 for sugar [47]. On a per person basis, and under a set of comparable consumption and stability assumptions, Dary estimates that vitamin A fortification of wheat flour costs approximately 11 times more than oil fortification (personal communication, 2008). Another important cost consideration is the relative price increase of the fortified food vehicle compared with its unfortified version, because this price will determine the feasibility of production, trade, enforcement, and affordability among the lower-income groups who are often the main targets for food fortification. More comparative cost data are required to establish a reliable database across diverse food production and marketing systems that can adequately inform decisions on candidate food vehicles for vitamin A fortification.

TABLE 6. Comparative cost of vitamin A fortification to supply 180 μg RAE (30% of RDI) with different food vehicles

Food vehicle	Typical consumption (g/day)	Level at households[a] (mg/kg)	Level at stores[b] (mg/kg)	Overage for production[c] (%)	Cost (US$/MT)	% of purchasing price	Annual cost/ person (US$)
Oil or margarine	15	12	15	20	1.87	0.37	0.008
Cereal flours	200	1	1.25	40	1.25	0.26	0.091
Sugar	50	3.5	4.5	100	6.65	1.39	0.121
MSG[d]	0.25	720	900	100	1266	25.32[d]	0.116

MSG, monosodium glutamate; RAE, retinol activity equivalent; RDI, Recommended Daily Intake
Source: Dary and Mora [47].
a. Level = dietary goal (μg RAE/consumption pattern [g/day]).
b. Assuming 25% additional amount to compensate for any losses.
c. Theoretical estimate based on reported stability information and length of product marketing life.
d. The cost of MSG is assumed to be US$5/kg

Recommendations for fortifying wheat flour with vitamin A

Fortification of foods with vitamin A is a potentially effective intervention to prevent or control vitamin A deficiency in low-income countries where undernutrition and poverty coexist. The following recommendations are offered to guide fortification of wheat flour or other potential food vehicles with vitamin A:

» Vitamin A fortification should be motivated and guided by evidence of deficiency as a public health problem. This evidence should be derived from population-based findings of deficient vitamin A status and dietary inadequacy of the vitamin or its food sources.
» Vitamin A deficiency is a public health concern in preschool-aged children, women of reproductive age, and school-aged children and young adolescents.
» Fortification of food with vitamin A should be designed to correct estimated dietary inadequacy in one or more vulnerable groups, that is, to fill a dietary gap.
» Wheat flour is a suitable candidate for vitamin A fortification. Its selection as a vehicle of choice should be guided by estimates of intakes of vitamin A and wheat flour by intended beneficiaries, levels of fortificant required to meet dietary corrective and safety goals, stability under ambient conditions, stability under usual conditions of product preparation (e.g., high temperature and humidity during cooking or baking) and product storage conditions, and comparative costs.
» The form of vitamin A and premix to be used in fortification should be the highest grade, appropriate for the intended food vehicle, stable under ambient conditions and for the duration of expected use, and introduced into the food supply in accordance with industry standards.
» In general, provision of 15% to 50% of the RDA can be expected to meet both nutritional and safety goals. **Table 3** displays the recommended fortificant levels to meet roughly 25% of the RDA for adult women, preschoolers, and school-aged children (using adult men as the referent weight), at mid-range wheat flour intake levels of 50, 100, 200, and 400 g/day.

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