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Why Do Children Become Vitamin A Deficient?[1,2]

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ABSTRACT Vitamin A deficiency is very prevalent and contributes substantially to morbidity and mortality among young children in developing countries. We identify and quantify three causes of vitamin A deficiency in young children based on data available in the literature: maternal vitamin A deficiency resulting in low concentrations of vitamin A in breast milk, inadequate dietary intake of vitamin A during and after weaning and prevalent illness. We developed a set of recursive equations to estimate the amount of vitamin A in the liver as a function of age over the first 2 y of life. To apply the equations, we selected a best estimate value for each input parameter as the most representative of a typical child in a developing country. Because of the great variability that exists for each variable, we also carried out sensitivity analyses, substituting more extreme values for input parameters. We then estimated stores, assuming a child in a developing country also receives the newly revised vitamin A supplementation regimen recommended by the World Health Organization. Without supplementation, a typical child in a developing country is not able to attain and maintain "minimally adequate" liver vitamin A stores. To overcome this deficit by eating fruits and vegetables alone, the child would need to increase portion sizes about 10-fold. If the child receives the new supplementation regimen, his or her liver stores will still be far short of the average American child (i.e., exceedingly far from toxic levels). However, our estimates indicate that the new supplementation regimen will permit a typical child in a developing country setting to attain minimally adequate vitamin A stores during the first 2 y of life. J. Nutr. 132: 2867S–2880S, 2002.

KEY WORDS: • *vitamin A deficiency* • *children* • *liver stores* • *vitamin A supplementation* • *dietary intake.*

Vitamin A deficiency affects > 127 million preschool children (1,2). Improving the vitamin A status of young children in developing countries reduces child death rates by 20–50% (3), which suggests that a substantial portion of their mortality is attributable to vitamin A deficiency. Considering that a large number of foods contain provitamin A carotenoids, many of which are accessible and inexpensive even for the very poor, why is vitamin A deficiency a widespread worldwide problem, especially among young children?

Children become vitamin A deficient for two main reasons: *1*) their mothers are deficient and produce breast milk low in vitamin A and *2*) they are weaned onto diets that provide too little vitamin A. A third contributing factor is that they spend a substantial part of childhood being sick, when anorexia, malabsorption and increased catabolism further deteriorate their vitamin A status.

In this article, we examine these causes in detail. We then quantify their combined effect on the vitamin A stores of a typical child living in a developing country over the first 2 y of life. Each of these three factors (breast-milk vitamin A intake; dietary vitamin A intake; and the burden of disease and its effect on vitamin A consumption, utilization and loss) has been measured and reported in the literature for populations that live under a variety of geographic and cultural conditions. Thus, sensitivity analyses are presented to reflect these ranges of reported values. Next, we estimate the amounts of com-

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monly available foods that contain vitamin A such a child needs to eat to overcome his or her deficiency. Finally, we present estimates of vitamin A stores, assuming the child receives the newly revised vitamin A supplementation regimen recommended by an informal technical consultation of the World Health Organization (WHO)[4] (4).

WHY CHILDREN BECOME VITAMIN A DEFICIENT

Mothers of poor children are often deficient themselves and produce breast milk low in vitamin A. The first cause of childhood vitamin A deficiency is maternal vitamin A deficiency. Until recently, the magnitude and implications of vitamin A deficiency among reproductive-aged women were relatively unappreciated and unaddressed compared with the problem among young children, primarily because the dramatic clinical signs of xerophthalmia are very rare in women. However, data reported over the past decade indicate that xerophthalmia, as an indicator of vitamin A deficiency, may be even more common among women than in children (1,5,6). This causes substantial maternal and infant mortality (7–9) and maternal morbidity (10). Moreover, deficient mothers produce breast milk with very low concentrations of vitamin A (11), which puts the next generation at risk.

Mothers in developing countries are commonly vitamin A deficient for two main reasons: they consume diets low in vitamin A and they experience high fertility with prolonged breast-feeding. The new U.S. recommended dietary allowance (RDA) established by the Institute of Medicine (IOM) (12) for nonpregnant, nonlactating women, aged 19–50 y is 700 μg of vitamin A per day. This increases to only 770 μg/d during pregnancy but nearly doubles to 1300 μg/d during lactation. Median intakes by American women in the Third National Health and Nutrition Examination Survey (NHANES III) (13) were 583, 691 and 1054 μg/d among nonpregnant, nonlactating; pregnant; and lactating women, respectively, meeting 75–90% of their RDA. In addition, an estimated 44% of American women aged 20–39 y take a daily supplement (14), which contributes another 1400 μg of vitamin A per day (13). During pregnancy, most American women take a daily prenatal supplement containing 1000 μg of vitamin A (13). These data can be compared with a median dietary intake of 403 μg/d by rural Bangladeshi women (15), which provides 57% of their RDA if they are not pregnant or lactating and only 31% of their RDA during lactation.

In addition to consuming diets low in vitamin A, women in developing countries spend a substantial proportion of their lives breast-feeding, when vitamin A requirements are very high. In industrialized countries, women have, on average, 1.6 babies (16) and breast-feed them for 5 mo (17). Thus, these women spend 8 mo, or 2.2% of their 30 reproductive years (ages 15–45) breast-feeding. However, in the world's least developed countries, women have an average of 5 children and breast-feed each one for 2 y (16,17). Hence, rural Bangladeshi women spend one-third of their reproductive years breast-feeding, when their dietary intake of vitamin A provides less than one third of their RDA.

Maternal vitamin A deficiency seems to have little impact on fetal status, when even well-nourished women transfer very little vitamin A to the baby (18). However, during lactation, well-nourished women transfer about 250 μmol (71,500 μg) of vitamin A [130 L of breast milk consumed (19,20) containing 1.92 μmol of vitamin A per liter (55 μg/dL) (18)], whereas women in developing countries transfer only about half that amount, because average milk vitamin A concentrations are about 1.05 μmol/L (30 μg/dL) (18). Thus, all babies are physiologically vitamin A "depleted" at birth, having little in the way of vitamin A stores in their livers. Young infants in developing countries have even less vitamin A stores. But during lactation, breast-fed babies of well-nourished women accrue adequate stores, whereas breast-fed babies of vitamin A-deficient women remain depleted. Furthermore, if weaning foods are lower in vitamin A than the breast milk they partially replace (as they usually are), the child's risk of deficiency increases further when breast-feeding stops.

Children's diets provide too little vitamin A. The second reason children become vitamin A deficient is that their diets during and after weaning contain insufficient vitamin A. Dietary vitamin A reference intakes for infants and young children established by IOM (12) in the United States and by the Food and Agricultural Organization (FAO) (21) are shown in **Table 1**. Taken together, recommended or "safe" intakes range from 350 to 500 μg/d for infants and from 300 to 400 μg/d for 1- to 6-y-old children.

Food contains vitamin A in two forms: as retinyl esters in animal foods (e.g., milk, eggs, liver) and as provitamin A carotenoids—β-carotene being the most common and biologically active—in plant foods (e.g., dark-green leafy vegetables

TABLE 1

Dietary vitamin A reference intakes for children from birth to 6 y of age[1]

	Age groups		
	<1 y	1–3 y	4–6 y
	μg		
FAO (21)			
Basal requirement	180	200	200
Safe intake	350	400	400
IOM (12)			
Adequate intake			
0–6 mo	400	—	—
6–12 mo	500	—	—
Estimated average requirement (EAR)	—	210	275
RDA	—	300	400

[1] Basal requirement is defined as the minimum daily intake of vitamin A needed to prevent the appearance of clinical signs of vitamin A deficiency (xerophthalmia) and to permit normal growth. Safe intake is defined as the amount of vitamin A needed to meet basal needs and other vitamin A-dependent functions and maintain a minimally adequate liver vitamin A store of 20 μg/g for the median person plus 2 sd; thus, safe intake meets these needs for 97–98% of all healthy people. Adequate intake is the calculated mean vitamin A intake of full-term infants exclusively fed human milk by healthy well-nourished mothers; it is the level that will meet the needs of nearly all healthy infants. It is calculated for infants instead of the RDA (which is based on the EAR) because IOM deemed there are no functional criteria of vitamin A status that reflect response to dietary intake in infants, which makes it impossible to calculate an EAR. EAR is defined as the amount of vitamin A needed to meet basal needs and other vitamin A-dependent functions and maintain a minimally adequate liver vitamin A store of 20 μg/g in half of all healthy people. RDA is defined as the EAR + 2 sd; thus, the RDA meets the needs for 97–98% of all healthy people.

[4] Abbreviations used: EAR, estimated average requirement; FAO, Food and Agricultural Organization; ICU, intensive care unit; IOM, Institute of Medicine; IU, international units; IVACG, International Vitamin A Consultative Group; NHANES III, Third National Health and Nutrition Examination Survey; NCRSP, Nutrition Collaborative Research Support Program; RAE, retinol activity equivalent; RDA, recommended dietary allowance; RE, retinol equivalent; UNICEF, United Nations Children's Fund; WHO, World Health Organization.

and deep-yellow fruits and vegetables). In general, young children in industrialized countries receive most of their vitamin A from animal sources, whereas poor children in developing countries consume most of their vitamin A from the less expensive plant sources (22). For example, the median intake of retinol (preformed vitamin A in animal sources) by 1- to 3-y-old children in NHANES III (13) was 404 μg/d, which exceeded their RDA of 300 μg/d by 35%. In studies of preschool children in Egypt, Mexico, Kenya (23), and India (24) median intakes of animal sources of vitamin A were 174, 119, 50 and 33 μg/d, respectively, providing only 11–58% of the RDA and leaving these children largely dependent on plant sources. In a study of Bangladeshi children, virtually the only source of preformed vitamin A consumed was breast milk; weaned children consumed only negligible amounts of vitamin A from animal sources (15).

Previously, it was assumed that 6 μg of β-carotene in all plant foods provided the same vitamin A activity as 1 μg of preformed retinol. However, recent data (**Table 2**) reveal that the amount of β-carotene from plant foods, which provides the equivalent vitamin A activity of 1 μg of preformed retinol, is far more than 6 μg and is also highly variable among foods, ranging from 8 μg to as much as 40–45 μg (22,25–30). Based on the new data, IOM now recommends using a conversion factor of 12 μg of β-carotene to 1 μg of retinol for a mixed fruit and vegetable diet (12). They acknowledge, however, that colored fruits and cooked yellow tubers are much more efficiently converted to vitamin A than equal amounts of dark-green leafy vegetables. To clarify dietary calculation, IOM established a unit, the retinol activity equivalent (RAE), which sets 1 μg of all-*trans*-retinol = 12 μg of β-carotene = 24 μg of α-carotene or β-cryptoxanthin. This new assumption makes very little difference in assessing the adequacy of American children's diets, whose intake of animal sources of vitamin A already exceeds their RDA. In addition, an estimated 44% of young American children (1–5 y old) also take a supplement (14), which provides an additional 750 μg of retinol (13). Clearly, American children do not depend on plant sources to meet their vitamin A requirements, so the new conversion factor has no effect on their dietary adequacy. However, for children in Kenya, Egypt, Mexico, India and Bangladesh, whose animal food intake is modest or even absent, this new assumption of β-carotene activity makes an important difference in interpreting their dietary vitamin A adequacy. **Table 3** makes clear that, with the newly accepted conversion factors for dietary β-carotene, mean "vitamin A" intake of children in these developing countries is substantially below their requirements. The percentage of the RDA met by these diets, using the latest corrected assumptions (1 μg of retinol requires 12 μg of dietary β-carotene), is substantially lower than under the older assumptions (1 μg of retinol requires 6 μg of dietary β-carotene). This helps explain why vitamin A deficiency is common among children who consume diets previously thought to meet or nearly meet their vitamin A requirements.

Children spend a large part of their childhood being sick. As we show quantitatively later in this article, inadequate vitamin A intake explains most childhood vitamin A deficiency. However, a third important contributing factor is that children in developing countries are so often ill. The prevalence of diarrhea among young children in developing countries ranges from 10 to 19% (31–34). Thus, a typical child in a developing country spends 36–70 d each year with diarrhea. The prevalence of acute respiratory illness among young children in developing countries is even higher, 25–60% (34). Illness worsens vitamin A status primarily by reducing intake due to anorexia and malabsorption and increasing utilization through greater catabolism and urinary loss. Anorexia is a major determinant of reduced dietary intake during episodes of childhood diarrhea, the condition during which dietary intake has best been studied (35). Diarrhea particularly seems to result in reduced intake of non–breast-milk foods; intake of breast milk is reduced to a lesser degree or not at all. Among infants and young children in Bangladesh who consumed about half their energy intake from breast milk, total caloric intake decreased only 3% during days of diarrhea (36); among breast-fed Peruvian children, intake was reduced by 12% (37). In another study from Peru, children did not reduce breast milk intake at all during days of diarrhea but took 23% fewer calories from non–breast-milk foods (38). Among Guatemalan children who were completely weaned from the breast, energy intakes were reduced by 20% during diarrhea (39). It is probable that reductions in vitamin A intake during illness are similar to reductions in energy; however, primarily for weaned children, vitamin A intake may be reduced proportionately more if milk, fruits and vegetables are particularly avoided during illness.

Malabsorption of vitamin A can occur during diarrheal illness and lower respiratory infection. Sivakumar and Reddy (40) showed that absorption of labeled oily retinol by well children is nearly complete, but it is reduced by about 30% in children with gastroenteritis and respiratory infection. In another study among children with diarrhea, absorption of a 100,000-IU dose of vitamin A was reduced by 17 and 22% when administered in water and oral rehydration salt solution, respectively (41).

Increased catabolism is frequently listed in textbooks as a consequence of illness, but there are limited data quantifying the vitamin A catabolic rate during health or disease. Increased catabolic losses are a result of the acute-phase response to infection, including fever and metabolic breakdown of muscle and adipose tissue (42). Among healthy adults consuming a vitamin A-free but otherwise adequate diet, Sauberlich et al. (43) estimated that 0.5% of total body vitamin A stores were lost daily. Haskell et al. (44) reported that the catabolic rate in rural Peruvian 12- to 24-mo-old children was 2.2%/d. They speculated that the catabolic rate in healthier children might be between the catabolic rate of nongrowing

TABLE 2

Estimated β-carotene (β-C) from various foods with observed equivalency to 1 μg of preformed retinol

Food	Reference	Relative absorption efficiency of β-C in food to β-C in oil	β-C to retinol conversion factor
		%	
Fruit	de Pee et al. (25)	17	12
Carrots	Torronen et al. (27)	26	8
	Micozzi et al. (28)	18	11
Broccoli	Micozzi et al. (28)	11	17
Mixed vegetables	Van het Hof et al. (29)	14	14
Dark-green leafy vegetables	de Pee et al. (26)	4	46
	de Pee et al. (25)	8	26
Spinach	Castenmiller et al. (30)	5	40

TABLE 3

Vitamin A intake of toddlers in RE and RAE

Country	Retinol intake	β-carotene intake	Total "vitamin A" intake: Assuming 1 μg of RE = 6 μg of β-carotene		Total "vitamin A" intake: Assuming 1 μg of RAE = 12 μg of β-carotene	
	μg/d	*μg/d*	*μg of RE* [μg of retinol/d + μg of β-carotene/d/6]	*% RDA*[1]	*μg of RAE* [μg of retinol/d + μg of β-carotene/d/12]	*% RDA*
Egypt[2] (18–30 mo)	174	786	305	102	240	80
Mexico[2] (18–30 mo)	119	504	203	68	161	54
Kenya[2] (18–30 mo)	50	1920	370	123	210	70
India[3] (18–23 mo)						
Breast-fed	205	433	277	92	241	80
Weaned	35	433	107	36	71	24
(24–29 mo)						
Breast-fed	70	672	182	61	126	42
Weaned	31	672	143	48	87	29
Bangladesh[4] (19–27 mo)						
Breast-fed	100	612	202	67	151	50
Weaned	<1	612	102	34	51	17

[1] RDA = 300 μg of RAE for all groups of children.

[2] Egypt, Kenya and Mexico data were taken from Calloway et al. (23). In this study, vitamin A from animal sources and total vitamin A in μg of RE were reported separately. β-carotene intake was calculated as total intake (μg of RE) − animal intake (μg of RE) × 6 = total μg of β-carotene intake. Total intake in μg of RAE was calculated as β-carotene intake/12 + animal intake.

[3] In the Indian study (24), vitamin A from animal sources (in μg) and from plant sources (in μg of RE) were reported separately for 6-mo age groups. Children 18–23 mo old who were breast-fed were assumed to be taking 550 mL/d, and breast milk was assumed to contain 310 μg of RE/L (1.05 μmol/L); hence, their breast-milk vitamin A intake was estimated to be 170 μg of RE/d. Children 24–29 mo old who were breast-fed were assumed to be taking 320 mL/d, and breast milk was assumed to contain 130 μg of RE/L (0.44 μmol/L); hence, their breast milk vitamin A intake was estimated to be 39 μg of RE/d. These breast milk values were added to intake of non–breast-milk animal sources to obtain total retinol intake by breast-fed children.

[4] In the Bangladesh study (15), dietary intake was assessed for 7 mo only (January to July). For all months, intake from non-breast milk animal sources was negligible. From January through April, the authors reported that non–breast-milk foods contributed less than 1% of the children's RDA, so intake from all non–breast-milk sources (both animal and plant) during these 4 mo was considered nil. For May, June and July, intake was reported as percent RDA consumed and the RDA used was 250 μg for children in the 19- to 27-mo age group. For each of these months, μg of RE consumed from plant sources = percent RDA consumed × 250. These 3 mo were divided by 12 to yield an estimated intake over an entire year. This value was divided by 2 to calculate daily μg of RAE consumption over an entire year. Neither breast-milk volume nor breast-milk vitamin A concentrations were measured in this study. The authors estimated breast milk vitamin A intake assuming volumes of 0.5 L/d for 19- to 24-mo-old children and 0.3 L/d for 25- to 30-mo-old children, and assuming breast milk vitamin A concentration to be 45 μg of vitamin A/65 kcal, equivalent to 45 μg/dL or 1.6 μmol/L across all ages. We considered that the mothers described in this study were probably far too deficient to produce breast milk with this vitamin A concentration; instead, we assumed a breast-milk vitamin A concentration of 0.7 μmol/L in our estimates.

adults (0.5%/d) and that of sick children. Because catabolic rates are applied to existing liver vitamin A stores, absolute losses of the vitamin decline as liver stores diminish (43) and as deficiency progresses (45). Vitamin A is not excreted intact in the urine of normal healthy people, but it can be excreted in substantial quantities during illness. Sixty years ago, Lawrie et al. (46) reported that healthy subjects excreted no vitamin A but that sick patients, especially those with pneumonia, could excrete up to 3.5 μmol (1003 μg) during each day of acute illness. More recently, a research group at the University of Alabama and their collaborators measured urinary vitamin A excretion during infection among adults with sepsis and pneumonia hospitalized in intensive care units (ICUs) in the United States (47) and among sick children in Peru (48) and Bangladesh (49). Although a small number of acutely ill adult patients in ICUs excreted up to 10 μmol (2869 μg) of retinol per day, most excreted much smaller amounts: the geometric mean loss among 29 ICU patients was 0.78 μmol/d (223 μg/d). Similarly, among young children with common childhood infections in Bangladesh, maximum losses were as high as 0.63 μmol/d (180 μg/d), but median losses were <0.007, <0.007, 0.038 and 0.126 μmol/d (<2.0, <2.0, 10.9 and 36.0 μg/d) among children with watery diarrhea, dysentery, pneumonia and sepsis, respectively. More than half the children with watery diarrhea and dysentery had no detectable retinol in their urine at all. Thus, urinary vitamin A loss seems to vary considerably among infections and among children with the same infections. Although some persons can certainly lose enough vitamin A through this route to precipitate xerophthalmia (justifying close monitoring and vitamin A supplementation during acute illness), urinary loss probably has only a minor impact on vitamin A status for the average child during an average day of illness.

Two childhood diseases, chicken pox and measles, can severely compromise vitamin A status. In a study by Campos et al. (50), children were assessed for vitamin A status and then supplemented with 200,000 IU of vitamin A. Three months later, more than one third of the children came down with chicken pox. Before supplementation, about 40% of the children had deficient liver stores. Six months after supplementation, 90% of uninfected children were still vitamin A sufficient, but only 26% of the infected children had adequate stores. Measles results in markedly depressed circulating vitamin A concentrations (51) and can precipitate xerophthalmia (52,53). Vitamin A supplementation during acute measles consistently and dramatically reduces measles case fatality rates (54,55). Thus, since 1987, both the Expanded Programme on Immunization and the Nutrition Unit of WHO, along with the United Nations Children's Fund (UNICEF) and the International Vitamin A Consultative Group (IVACG), recommend high-dose vitamin A treatment of all

cases of severe measles in places where the measles case fatality rate exceeds 1% (56). Because children get chicken pox and measles only once in a lifetime, we do not include these diseases in calculations later in this article; given the substantial impact of these infections on vitamin A status, however, we would be remiss to exclude them from this discussion.

METHODS

Model for estimating liver vitamin A concentration

The liver contains about 90% of total body vitamin A (57). Thus, liver vitamin A concentration is the best estimate of total body stores and, therefore, the best indicator of vitamin A status. Because little vitamin A is transferred in utero (18), all infants are born with very limited liver vitamin A stores, ~6 μmol total stores, or 0.04 μmol/g,[5] which is less than a 2-wk supply (59). Healthy, well-nourished infants rapidly accumulate liver vitamin A stores, achieving an adult concentration of ~0.07 μmol/g (or about 20 μmol total stores) by 6 mo of age. This liver vitamin A concentration has been suggested as the minimum level that prevents deficiency, provides a suitable reserve for periods of stress and/or low intake and is fully consistent with good health (60).

Liver stores of vitamin A accumulate as a function of the absorbed intake, basal requirements and catabolic losses of the vitamin. Dietary intake depends on the volume and vitamin A content of breast milk, foods and supplements consumed and the percentage absorbed from each source. Basal requirements are primarily influenced by age and body size. Catabolic loss of vitamin A is proportional to existing vitamin A liver stores and the catabolic rate of the vitamin. Illness may affect vitamin A stores by reducing intake, reducing absorption and increasing catabolic rate.

In this section, we develop a set of recursive equations to estimate the amount of vitamin A in the liver as a function of age. The amount of vitamin A in the liver at the end of day t is equal to the amount of vitamin A in the liver on the previous day $(t - 1)$ plus the net change during day $t[\Delta(t)]$. Let $S(t)$ and $S(t - 1)$ represent the micrograms of vitamin A stored in the liver at the end of day t and day $(t - 1)$ after birth, respectively. Then,

$$S(t) = S(t - 1) + \Delta(t) \quad (1)$$

$\Delta(t)$ is equal to total intake less basal needs and catabolic losses. To allow for the complexity consequent to illness, we develop separate equations for the expected net daily change in vitamin A depending on whether the child is healthy or sick during day t.

If the child is healthy during the day, the net daily change is

$$\Delta_0(t) = I_0(t) - U - r_0 S(t - 1) \quad (2)$$

where $I_0(t)$ is the absorbable daily intake of vitamin A for a healthy child [μg of vitamin A or μg of retinol equivalents (RE)]; U is the amount of vitamin A required for basal needs (μg), which is assumed not to vary with age; and r_0 is the fractional catabolic rate (percentage of total body stores lost per day) for a healthy child. The absorbable intake of vitamin A for a healthy child is

$$I_0(t) = b_0(t) + f_0(t) + v(t) \quad (3)$$

where $b_0(t)$, $f_0(t)$, and $v(t)$ are the amounts of vitamin A absorbed from breast milk (μg of RE), food (μg of RAE) and supplements (μg), respectively, during day t for a healthy child. The amount of vitamin A from breast milk is

$$b_0(t) = b_{v0}(t) \times b_{c0}(t) \quad (4)$$

where $b_{v0}(t)$ is the volume of breast milk consumed (mL) and $b_{c0}(t)$ is the absorbable vitamin A concentration of breast milk during day t. $b_{c0}(t)$ is the product of the vitamin A concentration of the breast milk in μg of RE/mL and the percentage of vitamin A absorbed from breast milk.

[5] Approximate liver weights are 125 and 275 g at birth and 6 mo, respectively (58).

If the child is sick during day t, the net daily change is

$$\Delta_1(t) = I_1(t) - U - r_1 S(t - 1) \quad (5)$$

and

$$I_1(t) = b_1(t) + f_1(t) + v(t) \quad (6)$$

where the components of eqs. 5 and 6 are defined analogously to eqs. 2 and 3.

We define $p(t)$ to represent the probability that a child is sick during day t. Then, the expected net daily change in vitamin A levels is a weighted average of eqs. 2 and 5, where the weights are determined by $p(t)$. That is,

$$\Delta(t) = p(t)\Delta_1(t) + [1 - p(t)]\Delta_0(t) \quad (7)$$

Various models could be postulated for the probability of illness, $p(t)$. The simplest model is to assume that the probability a child is sick on day t is constant, such as 0.10. More complex models can also be developed to allow the probability a child is sick on day t to depend on age or even the amount of vitamin A in the liver the preceding day. The reason for considering such a model is that, as vitamin A stores decrease, the probability of illness may increase, which further negatively affects vitamin A stores, creating a negative feedback loop.

Regardless of the model that is chosen for $p(t)$, these equations can be solved recursively for a given set of input parameters as follows. The initial value of vitamin A in the liver at birth is specified—for example, $S(0) = 6$ μmol (1700 μg). The expected net daily change in vitamin A is calculated from eq. 7 by using eqs. 2–6. Then, eq. 1 is used to estimate expected levels for the following day. These equations are then used recursively to obtain the expected vitamin A levels at each day of age.

Input parameters

To apply the equations developed in the preceding section, values for the input parameters must be specified (**Table 4**). For each variable we selected a best estimate value as the most representative of a typical child in a developing country based on the available literature. These values were used in the primary analysis. However, recognizing the great variability that exists for each of these variables reflecting true between-individual variability and imprecision in their measurement, we also carried out sensitivity analyses substituting more extreme values for the input parameters. These sensitivity analyses demonstrate both the likely range of liver vitamin A stores among children living under various conditions in developing countries around the world and the robustness of our model in answering the key question: why do children become vitamin A deficient?

Vitamin A stores in the liver on day t[S(t)]. We estimated that liver vitamin A stores at birth are 6 μmol (1700 μg) based on available autopsy data from developed and developing countries (61,62).

Basal need (U). In our primary analysis, we used 180 μg/d as the amount of vitamin A required for basal needs, or U, and assumed U to be constant over the first 2 y of life. This is the amount defined by FAO/WHO (21) as the minimum daily intake of vitamin A needed to prevent the appearance of clinical signs of vitamin A deficiency and to permit normal growth among children 0–1 y of age. FAO/WHO stated that infants fed by vitamin A-deficient mothers whose milk provided 120 ± 15 μg of RE/d grow normally and do not show clinical signs of vitamin A deficiency. They then increased this value to 180 μg/d to account for variability in growth rate. Therefore, in a sensitivity analysis, we used the 120 μg/d values for U. However, it should be noted that subclinical vitamin A deficiency may begin to significantly increase morbidity and mortality risk before growth is impaired or clinical eye signs or symptoms appear (63).

Catabolic rate (r_0). The fractional catabolic rate is the percentage of total body stores lost per day. There are limited data in the literature estimating this quantity. In a small volunteer sample of eight adult males, the catabolic rate was estimated to be 0.5%/d (43) and is probably too low for infants whose turnover of liver vitamin A stores is expected to be higher to support growth (64). In rural Peru, among children aged 12–24 mo (n = 105), a rate of 2.2%/d was calculated with data on plasma retinol kinetics (44,64). Because of the uncertainty in this measurement, we selected an intermediate value (1.5%/d) for our primary analysis, but, in sensitivity analyses,

TABLE 4

Input parameters

Variable	Description	Specified age (d)	Primary analysis		Sensitivity analyses			
$S(0)$	Stores at day 0 (μg)	0	1700					
U	Basal need[1] (μg of RE)	0–730	180		120			
r_0	Healthy catabolic rate (%/d)	0–730	1.5		0.5[2], 2.2[3]			
$b_{v_0}(t)$	Breast milk intake[4] (mL/d)		Exclusively breast-fed, birth–180 d; Partially breast-fed 180–730 d		Partially breast-fed birth–730 d			
		0	50		50			
		7	600		510			
		45	714		617			
		135	784		663			
		225	660		660			
		540	549		549			
		730	0		0			
$b_{c_0}(t)$	Absorbable breast milk vitamin A concentration[5] (μg of RE/dL) (0.9)		Breast milk vitamin A conc (μg of RE/dL)	Absorbed breast milk vitamin A conc (μg of RE/dL)	Very low breast milk vitamin A		Adequate breast milk vitamin A	
		0	50	45	35	32	90	81
		7	50	45	35	32	90	81
		30	30	27	20	18	50	45
		730	30	27	20	18	50	45
$f_0(t)$	Absorbable non-breast milk vitamin A intake (μg of RAE)		Kenya[7]		India[7]			
		0	0		0			
		180	0		0			
		450	146		54			
		730	205		76			
$p(t)$	Probability of illness	0-730	0.10		0.20, no illness			
$v(t)$	Vitamin A supplementation				Newly recommended WHO regimen		Current WHO regimen	
	Infant doses				Absorbed dose[8] (μg)		Absorbed dose (μg)	
		42			7500		0	
		70			7500		0	
		98			7500		0	
		180			15,000		15,000	
		365			30,000		30,000	
		548			30,000		30,000	
		730			30,000		30,000	
	Mother doses				Dose transferred to infant via breast milk[9] (μg/dL), increase to $b_{c_0}(t)$			
		0			9			
		7			9			
		30			9			
		180			8			
		210			6			
		300			0			
		730			0			

[1] FAO/WHO (21).
[2] Sauberlich et al. (43).
[3] Haskell et al. (44).
[4] Intake at 0 and 7 d estimated from Neville (65). Intake at 45 d and older estimated for developing country children exclusively breast-fed through 6 mo of age and partially breast-fed thereafter or partially breast-fed through 2 y of age (17).
[5] 90% of vitamin A from breast milk and animal sources is absorbed and 12 μg of β-carotene = 1 μg of retinol.
[6] Vitamin A intake at 450 d was extrapolated from intake at 730 d, which was estimated with data from 18- to 30-mo-old Kenyan children (n = 100) (23).
[7] Estimated from 12- to 48-mo-old Indian children (24).
[8] We assumed that 50% of the infant dose of vitamin A is absorbed.
[9] We assumed that 12% of the total vitamin A dose given to the mother is transferred over 9 mo to the infant via breast milk. We estimated the concentration of the maternal vitamin A supplement in breast milk by assuming median breast milk intake for a developing country infant if exclusively breast-fed for the first 6 mo and partially breast-fed thereafter (17).

we substitute the higher and lower values, 0.5%/d and 2.2%/d. In all analyses, we assumed the rate to be constant from birth through 2 y.

Absorbable intake [$I_0(t)$]. The daily intake of vitamin A from breast milk, food and supplements varies substantially among children and with age. Thus, we used age-specific mean intake data reported in the literature to plot breast milk intake (dL), breast milk vitamin A concentration (μg/dL) and dietary vitamin A intake (μg of RAE) as a function of age and then constructed a continuous curve by connecting the data points with straight lines. We assumed 90% of the vitamin A from breast milk and animal sources is absorbed and used. The new IOM conversion factor for β-carotene of 12 μg of β-carotene to 1 μg of retinol in mixed vegetable diets is used.

Breast milk intake [$b_{v0}(t)$]. Brown (17) compiled quantitative information from the literature on breast milk consumption by children and estimated the daily mean volume (mL/d) of breast milk consumed by age group and exclusivity of breast-feeding. In our primary analysis, we used the values estimated by Brown for children in developing countries who are exclusively breast-fed from birth through 6 mo and partially breast-fed from 6 mo of age through 2 y; we plotted the mean breast milk intake, or b_{v0}, by the median age of the specified age group. With these data, we plotted intake values at 45, 135, 225 and 540 d. For the amount of colostrum and early milk consumed, we estimated the intake during days 1 and 7 to be 50 and 600 mL, respectively (65). We assumed that children are completely weaned from the breast by 24 mo of age [b_{v0} (730) = 0 mL]. For $b_{v0}(t)$, we constructed a continuous curve by connecting the age-specific data points for breast milk consumption with straight lines. In a sensitivity analysis, we used breast milk intake values for children partially breast-fed from birth through 2 y (17), assuming intake during day 1 and day 7 to be 50 and 510 mL, respectively.

Breast-milk vitamin A concentration [$b_{c0}(t)$]. In our primary analysis, we estimated mature breast milk vitamin A concentration to be 1.05 μmol/L (30 μg/dL), an average value for several developing country studies (18). Because the vitamin A concentration of colostrum is greater than that of mature milk (11), we estimated the vitamin A content of breast milk from birth through 7 d to be 1.75 μmol/L (50 μg/dL). In two sensitivity analyses, we substituted breast milk vitamin A concentrations representative of women who are frankly deficient (mature milk = 20 μg/dL, colostrum = 35 μg/dL) and of women whose milk is considered to be vitamin A adequate (mature milk = 50 μg/dL, colostrum = 90μg/dL). In all analyses, we assumed the concentration of vitamin A in colostrum (0–7 d) and mature milk (>30 d) to be constant with age. For the period between 7 and 30 d, we constructed a straight line between two concentrations, representing a continuous decrease in the vitamin A content of transitional milk. In all analyses and over all time periods, we assumed that absorption of vitamin A from breast milk was 90%.

Non–breast-milk vitamin A intake [$f_0(t)$]. In the primary analysis, we assumed exclusive breast-feeding from birth to 6 mo and then we assumed a complementary food diet was started that was similar in vitamin A content to that of the Kenyan children in the Nutrition Collaborative Research Support Program (NCRSP) study (23). We assumed the vitamin A intake at 24 mo (730 d) of age to be the same as that of the 18- to 30-mo-old children studied (205 μg of RAE/d) (23), and we estimated the intake during day t by using $f_0(t)$ (see below). In a sensitivity analysis, we assumed the complementary diet begun at 6 mo was similar to that of the 12- to 48-mo-old Indian children studied by Ramakrishnan et al. (24). Using their data, we estimated the intake of 15-mo (450-d)-old children to be the same as that of the 12- to 17-mo-old study children (54 μg of RAE/d) and the intake of 1-y (365-d)-old children to be the average of the 18- to 23-mo and the 24- to 29-mo-old children studied (76 μg of RAE/d). For $f_0(t)$, we plotted the Indian data and connected the points with straight lines. In the sensitivity analysis examining the effect of partial versus exclusive breast-feeding during the first 6 mo of age, we assumed that weaning foods replacing breast milk before 6 mo of age (such as water, porridge, juice and tea) contain negligible amounts of vitamin A.

Impact of illness. In our primary analysis, we assumed the probability of illness on any given day t, $p(t)$, is constant, and we conservatively estimated a value of 10% from the low end of the range for the prevalence of diarrhea among young children in developing countries. During a day of illness, we assumed that breast milk volume remains the same, but absorption of vitamin A from the breast milk is reduced by 30%. Thus,

$$b_1(t) = 0.7[b_0(t)] \quad (8)$$

For intake of vitamin A from food, we assumed that the amount of intake is 20% less due to anorexia and that, of this reduced intake, there is 30% reduced absorption. Thus,

$$f_1(t) = 0.56[f_0(t)] \quad (9)$$

There are no data, as far as we know, that compare the catabolic rate during illness with the catabolic rate when healthy. However, we do know that, in general, catabolism increases during illness (42). We have approximated that the catabolic rate increases by 150% during illness compared with the rate for healthy persons. Thus,

$$r_1 = 1.5(r_0) \quad (10)$$

In a first sensitivity analysis, we estimated the prevalence of illness to be 20%, the high end of reported ranges. In a second sensitivity analysis, we estimated vitamin A stores for an atypical child living in a developing country who is not sick at all during the first 2 y of life. In a third sensitivity analysis, we considered that, in addition to being acutely ill 10% of the time, the child is also infected with helminths from 6 mo of age onward, which results in a 20% reduction in vitamin A absorbed from all sources.

Vitamin A supplementation [$v(t)$]. The vitamin A supplementation regimen for mothers and children newly proposed by a WHO informal technical consultation (4) is as follows. **Mothers:** two doses of 200,000 IU within the first 6 wk postpartum. The two doses should be given at least 24 h apart. **Infants:** three doses of 50,000 IU between birth and 6 mo; 100,000 IU at 6 mo; and 200,000 IU every 4–6 mo from 12 mo onward.

Maternal vitamin A supplementation increases the vitamin A content of breast milk, b_{c0}, with a greater increase in concentration closer to the time of supplementation (Table 4). We assumed that 12% of each maternal dose was transferred to the infant through breast milk (0.12 × 200,000 IU = 24,000 IU = 25 μmol = 7200 μg) (59) over 9 mo (66). Infant vitamin A supplementation, or $v(t)$, increases I_0 during the day the infant receives the dose. On days when no supplement is given, $v(t) = 0$. We assumed that 50% of each high-dose supplement was absorbed (43,67), and the three doses of 50,000 IU were given at 42, 70 and 98 d; the 100,000-IU dose was given at 180 d; and the 200,000-IU doses were given at 365, 548 and 730 d.

Model for estimating the quantity of dietary vitamin A from non–breast-milk food sources that must be consumed over a given period of time to replete vitamin A stores

An additional question of interest is: How much vitamin A does a child need to consume from non–breast-milk foods to achieve a desirable amount of liver stores? To answer this question, we can use the recursive equations developed to estimate the vitamin A stores in the liver and solve for the amount of vitamin A needed from food. Specifically,

$$f_o(t) = \frac{S(t) - S(t-1) - p(t)A - (1-p(t))B}{0.56p(t) + (1-p(t))} \quad (11)$$

where $A = 0.7b_0(t) + v(t) - u - 1.5r_0S(t-1)$, $B = b_0(t) + v(t) - u - r_0S(t-1)$, and recall that $b_0(t) = b_{v0}(t)b_{c0}(t)$. Required inputs are $S(t)$, $b_{v0}(t)$, $b_{c0}(t)$, $v(t)$, u, r_0 and $p(t)$.

RESULTS

In this section, we apply the model developed in the second section and present our results.

Estimated liver vitamin A stores among children in developing countries during the first 2 y of life

We now estimate the combined effect of low breast-milk vitamin A concentration, inadequate dietary vitamin A intake

and prevalent illness on resulting liver vitamin A stores for a typical child in a developing country with the values defined in Table 4 for "primary analysis." In brief, this child begins life with 6 μmol (1700 μg) of vitamin A in his or her liver, has a basal requirement of 180 μg/d, loses 1.5% of total vitamin A stores each day due to normal catabolism of the vitamin, is exclusively breast-fed until 6 mo of age from a marginally vitamin A-deficient mother producing mature breast milk that

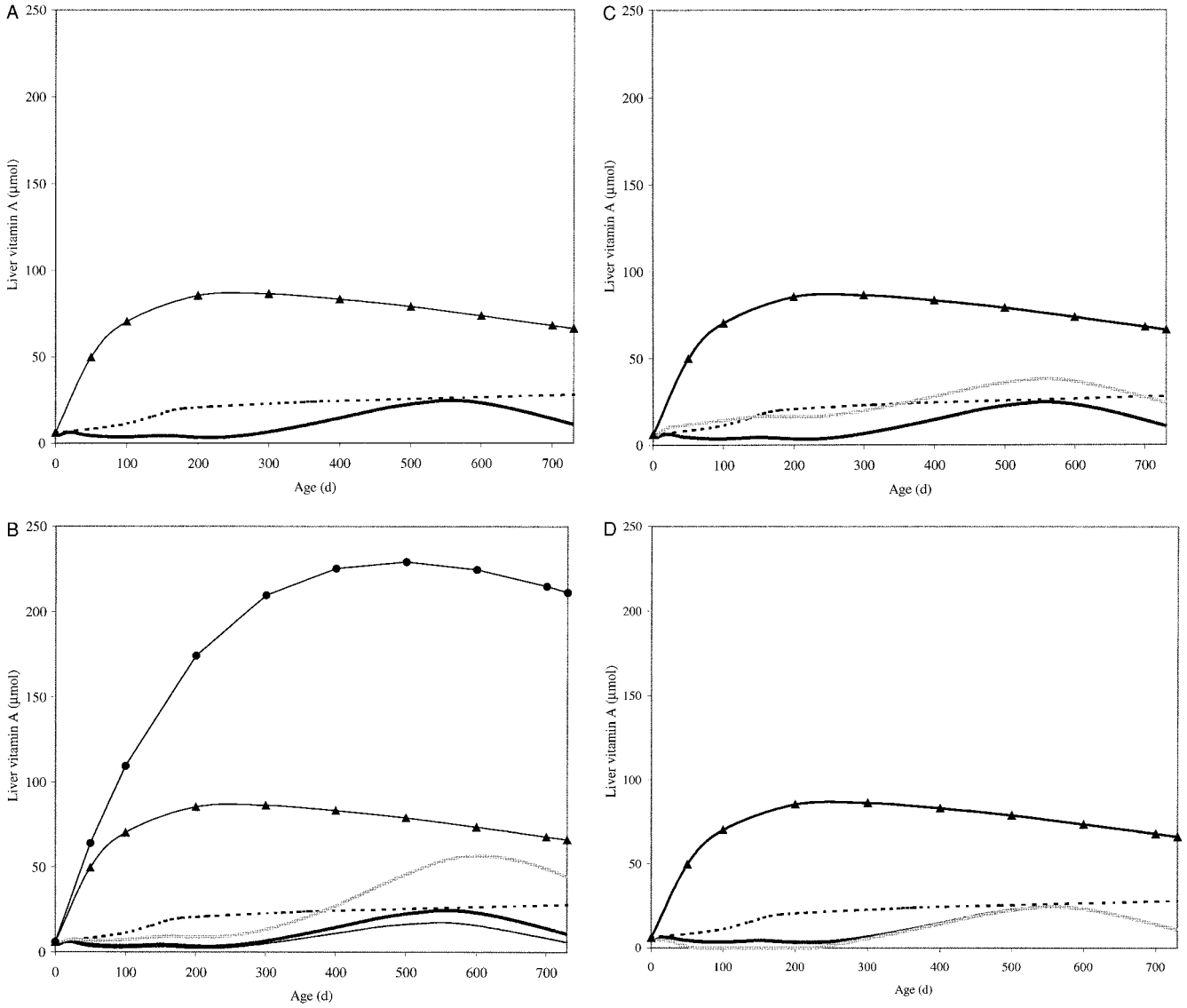

FIGURE 1 ***(a)*** Primary analysis. Estimated liver vitamin A stores in a typical developing country child by age. Input parameters: total vitamin A stores at birth [$S(0)$] = 1700 μg; basal need (U) = 180 μg of RE; catabolic rate during health ($r0$) = 1.5%/d; breast-milk intake [$b_{v0}(t)$] = volumes (dL/d) reflective of exclusive breast-feeding from birth to 6 mo, partial breast-feeding from 6 mo to 2 y, completely weaned at 2 y. Absorbable breast milk vitamin A concentration [$b_{c0}(t)$] = 50 μg of RE/dL from birth to 7 d, 30 μg of RE/dL from 30 d to 2 y. Straight-line decline days 7 to 30, 90% absorption at all time points. Absorbable non–breast-milk vitamin A intake [$f_0(t)$] = reflective of Kenyan preschoolers studied by Calloway (23). Illness prevalence [$p(t)$] = 10% over entire 2 y. Vitamin A supplementation (v_0) = none. For comparison, curves representing minimally adequate vitamin A stores (0.07 μmol/g) and estimated liver stores for a child whose dietary vitamin A intake is equivalent to that of the 50th percentile American child surveyed by NHANES III (13) assuming r_0 = 1.5%/d, $p(t)$ = 10% and v_0 = 0. ▲, NHANES III; - - -, min adequate; —-, primary analysis. ***(b)*** Sensitivity analysis of catabolic rate: estimated liver vitamin A stores in a typical developing country child by age and catabolic rate during health (r_0): 1.5%/d (primary analysis), 0.5%/d (low estimate) and 2.2%/d (high estimate). For comparison, curves representing minimally adequate vitamin A stores (0.07 μmol/g) and estimated liver stores for a child whose dietary vitamin A intake is equivalent to that of a 50th percentile American child surveyed by NHANES III (13) assuming r_0 = 1.5%/d or 0.5%/d, $p(t)$ = 10% and v_0 = 0. ●, NHANES/0.5%/d; ▲, NHANES/1.5%/d; - - -, min adequate; heavy line, primary analysis; gray line, 0.5%/d; thin line, 2.2%/d. ***(c)*** Sensitivity analysis of basal need. Estimated liver vitamin A stores in a typical developing country child by age and basal need (U): 180 μg/d (primary analysis) and 120 μg/d (sensitivity analysis). For comparison, curves representing minimally adequate vitamin A stores (0.07 μmol/g) and estimated liver stores for a child whose dietary vitamin A intake is equivalent to that of a 50th percentile American child surveyed by NHANES III (13) assuming r_0 = 1.5%/d, $p(t)$ = 10% and v_0 = 0. ▲, NHANES III; - - -, min adequate; —-, primary analysis; gray line, basal (120 μg/d). ***(d)*** Sensitivity analysis of breast milk intake. Estimated liver vitamin A stores in a typical developing country child by age and breast milk intake [$b_{v0}(t)$]: volumes reflective of exclusive breast-feeding from birth to 6 mo, partial breast-feeding 6 mo to 2 y (primary analysis), and partial breast-feeding birth to 2 y (sensitivity analysis). For comparison, curves representing minimally adequate vitamin A stores (0.07 μmol/g) and estimated liver stores for a child whose dietary vitamin A intake is equivalent to that of a 50th percentile American child surveyed by NHANES III (13) assuming r_0 = 1.5%/d, $p(t)$ = 10%, and v_0 = 0. ▲, NHANES III; - - -, min adequate; —-, primary analysis; gray line, partial breast feeding.

contains 1.05 μmol/L (30 μg/dL), is fed a diet similar to the Kenyan children studied in the NCRSP study and is ill about 10% of the time. The liver vitamin A stores for this typical child are plotted in **Figure 1**a. For comparison, we drew a line representing "minimally adequate" vitamin A stores, 0.07 μmol/g (20 μg/g). We also calculated and included lines representing the liver stores for a child whose dietary vitamin A intake is equivalent to that of the 50th percentile American child surveyed by NHANES III (13), assuming that child also has a catabolic rate of 1.5%/d, is sick 10% of the time and did not take any vitamin A supplements.

During the first 3 wk, our primary analysis child is able to maintain the meager stores he or she is born with (6 μmol). But, as the mother's milk matures and the vitamin A content

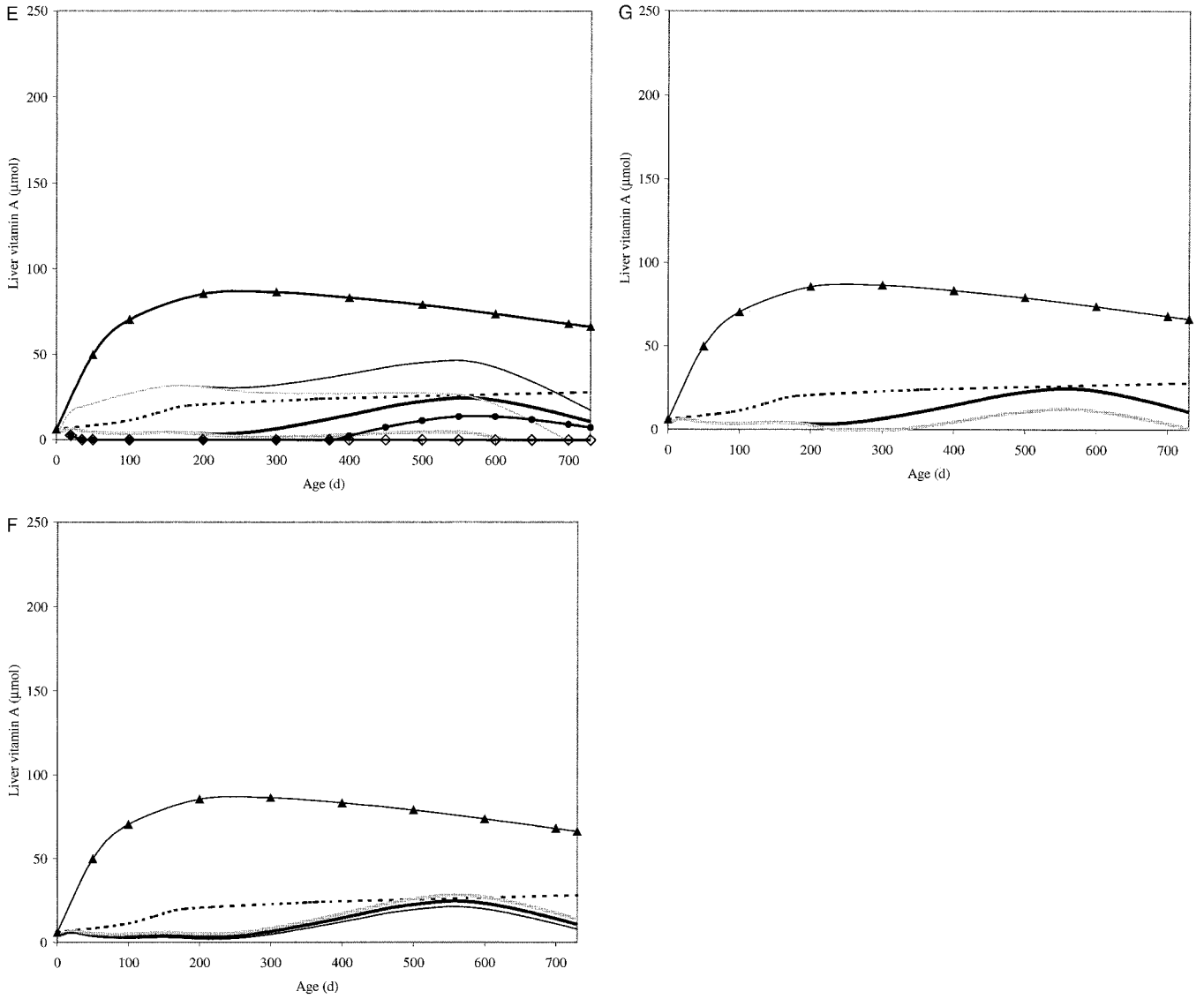

FIGURE 1 Continued ***(e)*** Sensitivity analysis of vitamin A intake. Estimated liver vitamin A stores in a typical developing country child by age, breast milk vitamin A concentration, $b_{c0}(t)$, and weaning diet, $f_0(t)$. Absorbable breast milk vitamin A concentration from birth to 7 d and from 30 d to 2 y, respectively, is 50 and 30 μg/dL (primary analysis), 90 and 50 μg/dL (sensitivity analysis for adequate concentration) and 35 and 20 μg/dL (sensitivity analysis for very low concentration), with a straight-line decline in vitamin A concentration from days 7 to 30. Absorbable nonbreast milk vitamin A intake is reflective of Kenyan preschoolers studied by Calloway (23) (primary analysis) and Indian preschoolers studied by Ramakrishnan et al. (24) (sensitivity analysis). For comparison, the curves representing minimally adequate vitamin A stores (0.07 μmol/g) and estimated liver stores for a child whose dietary vitamin A intake is equivalent to that of a 50th percentile American child surveyed by NHANES III (13) assuming r_0 = 1.5%/d, $p(t)$ = 10% and v_0 = 0. ▲, NHANES III; - - -, min adequate; heavy line, primary analysis; thin line, "adequate"/Kenya; hairline, "adequate"/India; gray line, "low"/India; ●, "very low"/Kenya; ◇, "very low"/India. ***(f)*** Sensitivity analysis of illness prevalence: estimated liver vitamin A stores in a typical developing country child by age and probability of illness [$p(t)$]: 10% over entire 2 y (primary analysis), 20% over entire 2 y (sensitivity analysis), and never sick (sensitivity analysis). For comparison, curves representing minimally adequate vitamin A stores (0.07 μmol/g) and estimated liver stores for a child whose dietary vitamin A intake is equivalent to that of a 50th percentile American child surveyed by NHANES III (13) assuming r_0 = 1.5%/d, $p(t)$ = 10%, and v_0 = 0. ▲, NHANES III; - - -, min adequate; heavy line, primary analysis; gray line, no illness; thin line, 20% prevalence. ***(g)*** Sensitivity analysis of helminth infection: estimated liver vitamin A stores in a typical developing country child by age and helminth infection: uninfected (primary analysis) and infected at 6 mo of age and onward (sensitivity analysis). For comparison, curves representing minimally adequate vitamin A stores (0.07 μmol/g) and estimated liver stores for a child whose dietary vitamin A intake is equivalent to that of a 50th percentile American child surveyed by NHANES III (13) assuming r_0 = 1.5%/d, $p(t)$ = 10% and v_0 = 0. ▲, NHANES III; - - -, min adequate; —-, primary analysis; gray line, helminth infection.

falls, the daily absorbable intake is not much more than the child's basal requirement and, with catabolic losses, is not enough for the child to amass liver vitamin A stores. By 3 mo of age, stores have declined to about 4 μmol. The child begins to consume greater quantities of breast milk and is able to maintain, but not build, liver stores over the next 5 mo. Beginning at ~8 mo, increased weaning food consumption together with continued breast-feeding allows this child to accumulate vitamin A, and liver stores grow to 25 μmol by 18 mo of age. Thus, at 18 mo this child approaches, but never attains, a minimally adequate liver vitamin A concentration (20 μmol/g). However, over the next 6 mo, the child's breast-milk intake falls, needs and losses exceed intake and total stores fall. By 2 y of age, liver stores have fallen to 11 μmol and, if the child continues in this pattern, stores will soon be depleted. Peak liver vitamin A concentration briefly achieved at 18 mo is still less than half that of the average American child.

Sensitivity analysis

Catabolic rate. Substituting the slower adult rate of catabolism (0.5%/d), a very conservative estimate for growing infants, the developing country child's liver stores remain less than the minimally adequate concentration for the entire first y of life (Fig. 1b). Liver stores then increase between 12 and 20 mo, when they peak at ~60 μmol. However, as the child is weaned from the breast and breast-milk intake declines, stores decrease quickly. It is interesting to note that, although stores are adequate during the entire 2nd y of life, they remain, on average, about one-fourth that of the NHANES III child, assuming the same catabolic rate.

Substituting the higher catabolic rate of 2.2%, measured in Peruvian preschool children (44,64), total stores remain at about the level the child was born with (6 μmol) until about 10 mo of age. The child is then in slightly positive vitamin A balance and stores peak at ~18 μmol at 18 mo of age. As breast milk volume decreases after 18 mo, the child is in negative balance and completely depletes stores shortly after 2 y.

Basal requirement. Substituting 120 μg/d for *U*, basal requirement, this child's intake of vitamin A is sufficient to build stores that more closely approximate and, by 1 y of age, even surpass minimally adequate levels (Fig. 1c). But, as the child consumes less breast milk, the weaning diet does not contribute enough vitamin A to meet the reduced basal needs and maintain the current level of stores, and liver vitamin A falls below 0.07 μmol/g before 2 y of age.

Exclusivity of breast-feeding during early infancy. If the child is only partially breast-fed (as most babies in the world are by 3 mo of age), volume intake is about 15% lower (17), and the child completely depletes liver stores at ~3 mo (Fig. 1d).

Vitamin A intake. Still assuming the low vitamin A breast-milk concentrations considered in the primary analysis [colostrum = 1.75 μmol/L (50 μg/dL), mature milk = 1.05 μmol/L (30 μg/dL)], but substituting the diet lower in vitamin A consumed by the Indian children studied by Ramakrishnan et al. (24), the combined vitamin A intake from breast milk and weaning foods is not enough to accumulate any vitamin A stores, and the child's liver is depleted by 21 mo of age (Fig. 1e).

Substituting a breast milk vitamin A concentration considered to be adequate [colostrum = 3.1 μmol/L (90 μg/dL) and 1.75 μmol/L (50 μg/dL)] and still assuming the Kenyan weaning diet, the child's liver stores grow and quickly exceed minimally adequate levels. However, as breast milk volume declines after 18 mo, liver stores decrease and, by 2 y, fall below adequate levels (Fig. 1e). If the child is weaned onto a diet similar to that consumed by the Indian children studied by Ramakrishnan et al. (24), liver stores fall below minimally adequate at 18 mo and are depleted at 23 mo of age.

Substituting a very low breast milk vitamin A concentration [colostrum = 1.2 μmol/L (35 μg/dL), mature milk = 0.70 μmol/L (20 μg/dL)] and assuming the Kenyan diet, the child's liver stores are completely depleted by 1 mo of age and remain so throughout the entire first y of life (Fig. 1e). When the quantity of non–breast-milk dietary sources consumed increases in the 2nd y of life, the child briefly accumulates liver stores during a period between 12 and 18 mo, but stores peak at only 10 μmol, from which point they decrease. Substitute both the very low breast-milk vitamin A concentration and the Indian diet, and the child's liver vitamin A stores are not only depleted by 1 mo of age but remain depleted over the entire first 2 y of life. An important observation here is that, with the assumptions we have used, once breast-milk vitamin A concentration falls much below 1.05 μmol/L (30 μg/dL), babies are in negative vitamin A balance, even if they are exclusively breast-feeding.

Sickness. If we assume this child never gets sick, liver vitamin A stores exceed minimally adequate levels at 17 mo but only for a brief time before stores again fall below adequacy (Fig. 1f). Substitute a 20% probability of illness while maintaining all other assumptions in the primary analysis, and liver stores peak at only 21 μmol and are depleted shortly after 2 y.

Finally, helminths infect 20% of children worldwide (68) and, in some populations such as that of coastal eastern Africa (69), nearly all children are infected with helminths. We estimated liver vitamin A stores assuming the child was infected with helminths at 6 mo of age and older (Fig. 1g) and assuming that infection reduces the absorption of vitamin A from breast milk and food by 20% (70). With helminth infection, liver stores are decreased by about half and become negligible by 2 y.

Thus, regardless of what we assume about the probability of illness, inadequate vitamin A intake (from breast milk and from food) is the predominant cause of vitamin A deficiency in children. Helminth infection has a larger impact on vitamin A stores than such acute illnesses as diarrhea and respiratory infection, because it is a chronic infection that reduces absorbable intake of both breast milk and food over long periods of time. Although illness plays a less important role in determining vitamin A status than intake on a population basis, the probability of illness increases with vitamin A deficiency. Thus, the very children already consuming the least vitamin A are the ones most vulnerable to the further negative effects of illness, even if those effects are modest.

Can a child in a developing country attain minimally adequate vitamin A stores by 2 y of age with diet alone?

During the second y of life (12–23 mo), complementary food diets can be more varied and substantial because children have teeth and the motor skills necessary to consume more fruits, vegetables and other solid foods. Therefore, we need to consider whether, with an aggressive dietary education intervention, children with marginal or absent vitamin A stores at age 12 mo would be able to consume a sufficient quantity of locally available vitamin A-rich foods over the 2nd y of life to succeed in building minimally adequate liver stores of vitamin A. Using eq. 11, we calculate the amount of vitamin A the child would need to consume from nonbreast milk foods to

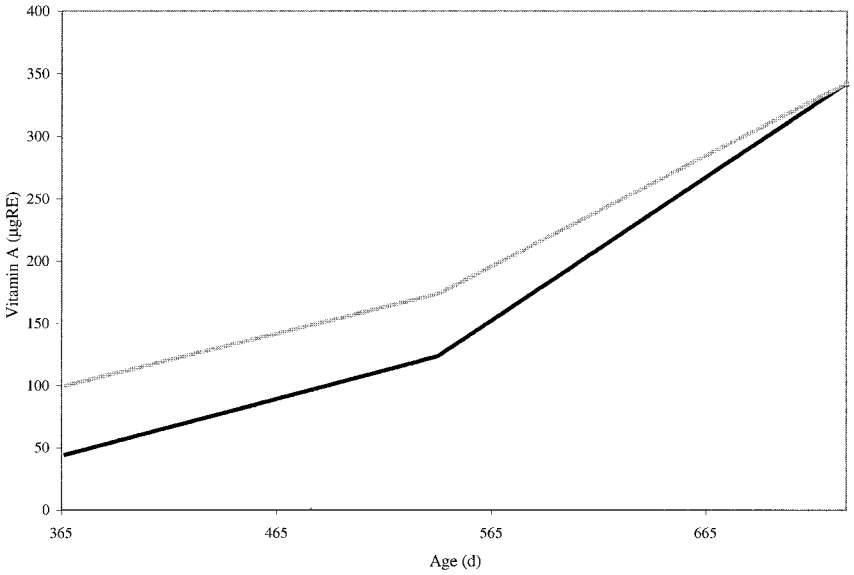

FIGURE 2 Estimated amount of non–breast-milk dietary vitamin A that must be consumed by a typical developing country child evaluated in the primary analysis (Fig. 1a) and in the sensitivity analysis when breast-milk vitamin A concentration = 20 μg/dL (very low; see Fig. 1d) to build minimally adequate liver vitamin A stores (0.07 μmol/g) between 1 and 2 y. —, primary analysis; gray line, very low.

build minimally adequate vitamin A liver stores (0.07 μmol/g × 400 g = 28 μmol, or 8000 μg) by age 24 mo (730 d). Thus, if S (365) = 0 and S (730) = 8000, **Figure 2** shows how much vitamin A the child would need to consume each day from 1 to 2 y of age from nonbreast milk food. On average, he or she must consume 160 μg/d if breast milk containing 1.05 μmol/L (30 μg/dL) is also being consumed and 200 μg/d if breast milk containing 0.7 μmol/L (20 μg/dL) is also being consumed.

How much non–breast-milk food must this child eat to meet the vitamin A need?

If we estimate that spinach has 4000 μg of β-carotene per 100 g and that 1 μg of retinol is equivalent to 26 μg of β-carotene, this child would need to eat about 105 and 130 g of spinach each day to get 160 and 200 μg of RAE, respectively (**Table 5**). In a study of vulnerable preschool Indonesian children, the usual portion size of spinach and other dark-green leafy vegetables, such as cassava leaves and swamp cabbage, was 15 g/d (71)—or ~1/10th of what they need.

Mangoes are popular among young children, grow freely in family gardens, and are rich in provitamin A carotenoids, which are more bioavailable than the carotenoids in dark-green leafy vegetables. Unfortunately, mangoes are seasonal and generally are available for only about 2 mo of the year. Is it possible for this child to eat enough mangoes while they are in season to meet the vitamin A requirement for a whole 2nd y of life? If we estimate that a mango has 3000 μg of β-carotene per 100 g, and we use the 1:12 conversion factor for μg of RAE:μg of β-carotene, on each of the 60 d mangoes are available each year, the child would need to eat 390 g (about six mangoes) or 490 g (about seven mangoes) each day of mango season to receive the needed 160 or 200 μg of RAE, respectively. Again, the usual portion size consumed by children in the Indonesian study (55 g) is only about 1/10th of what is needed.

If we consider the equivalent in animal products, assuming 90% of preformed vitamin is absorbed (40), the child would have to consume ~2.5 eggs or 0.360 L of cow's milk per day or 9 g of chicken liver per week. More realistically, the child's daily vitamin A intake should come from a combination of

TABLE 5

Amount of food needed to provide 160 μg of RAE if 0%, 25% and 75% come from preformed vitamin A

		0% preformed	25% preformed	75% preformed	
Food	Vitamin A content per 100 g of food	Amount to provide 160 μg of RAE (g)	Amount to provide 120 μg of RAE (g)	Amount to provide 40 μg of RAE (g)	Usual portion size (g) [3]
Spinach[1]	4000 μg of β-carotene	105	80	25	15
Swamp cabbage	1800 μg of β-carotene	230	170	60	15
Mustard greens	3200 μg of β-carotene	130	100	30	20
Mango[2] (60 d/y)	3000 μg of β-carotene	390	290	100	55
			40 μg of retinol	120 μg of retinol	
Eggs[4]	80 μg of RE per egg		½ egg/d	2 eggs/d	35 g
Cow's milk	100 μg of RE/200 mL		90 mL/d	270 mL/d	40 g
Chicken liver	13,700 μg of RE/100 g		2½ g/wk	7 g/wk	15 g

[1] 1 μg of RAE = 26 μg of β-carotene for dark-green leafy vegetables.
[2] 1 μg of RAE = 12 μg of β-carotene for mango.
[3] Usual portion sizes consumed by Indonesian children 1 y of age (71).
[4] 90% of preformed vitamin A in animal products is absorbed.

different vitamin A-containing foods. Table 5 shows how much fruits and vegetables a child would have to consume if 25 and 75% of the vitamin A in the diet is preformed vitamin A. These amounts are still greater than the amounts likely to be consumed by children.

What are the liver vitamin A stores if the reference child also receives the newly revised WHO vitamin A supplementation regimen or a 6-mo regimen beginning at 6 mo of age?

The resulting liver vitamin A stores for the primary analysis child who also receives the full newly revised WHO supplementation regimen are shown in **Figure 3**a. During the first 6 mo, liver vitamin A stores approximate those of the NHANES III 50th percentile child. As breast milk consumption decreases and all the maternal dose has been transferred through breast milk by 9 mo of age, liver stores fluctuate greatly with administration of each high-dose supplement. Before the first 200,000-IU dose is given at 12 mo, stores dip below minimally adequate levels (0.07 μmol/g). For about 1 mo after each dose at 12 and 18 mo, vitamin A stores exceed that of the NHANES III child. Because breast milk volume steadily decreases between 18 and 24 mo, liver vitamin A stores fall below minimally adequate levels before the dose is received at 2 y. However, this child, who receives every dose of the regimen, is able to maintain a minimally adequate liver vitamin A concentration most of the time over the first 2 y of life. It is interesting to note that, even though the child receives every recommended supplement of vitamin A, liver stores only briefly (at 12, 18 and 24 mo) exceed the liver stores achieved by the 50th percentile American child from diet alone (NHANES III) and are still well below the proposed cut-off of 1.05 μmol (300 μg) per gram of liver for vitamin A toxicity (61).

If the primary analysis child does not receive any supplementation during the first 6 mo but instead receives 6-mo high-dose supplements beginning at 6 mo (as is now being done in many countries) the 100,000-IU dose given at 6 mo will raise stores into the adequate range, but the peak is not as high or maintained as long as it would be if the child were building on the multiple doses of early infancy (Fig. 3b). From 12 mo onward, the child will achieve stores equivalent to that of the child receiving the newly revised WHO regimen.

Young children become vitamin A deficient primarily because their mothers are vitamin A deficient and produce breast milk that is low in vitamin A, and their diets contain too little available vitamin A. A third contributing factor, especially for the most vulnerable children, is frequent illness. Exclusive breast-feeding cannot maintain adequate liver vitamin A stores in babies once the vitamin A content of their mothers' milk falls below 1.05 μmol/L (30 μg/dL). To overcome vitamin A deficiency with fruits and vegetables alone, children need to increase current portion sizes about 10-fold.

Vitamin A supplementation programs are the most important and effective intervention currently available. The supplementation regimen recently proposed by WHO will meet the needs of most children but for some, just barely, especially if their mothers are extremely vitamin A deficient, their diets contain very little vitamin A, and they are sick more than average (estimated as 10% of the time). Therefore, supporting realistic dietary changes—for example, encouraging mothers to add even modest amounts of animal sources of vitamin A to their children's diets; fortifying weaning foods, condiments and staples; and solar-drying mangoes to make them available more often during the year—continues to have a role in meaningfully improving the vitamin A status of children who

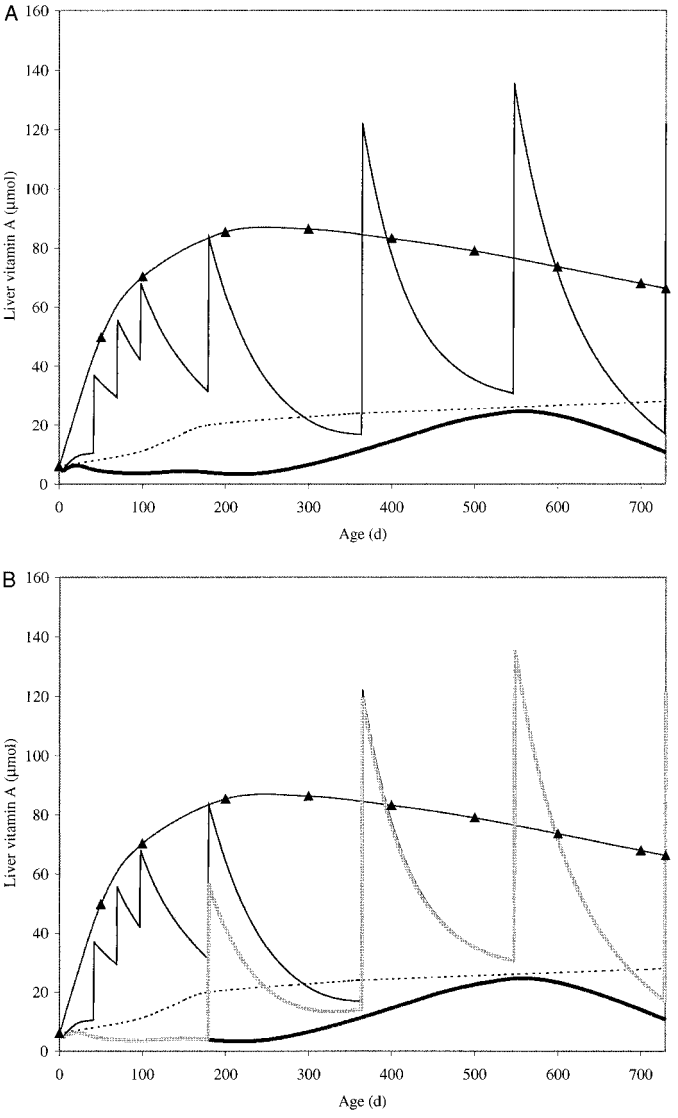

FIGURE 3 ***(a)*** Sensitivity analysis of newly recommended vitamin A supplementation regimen. Estimated liver vitamin A stores in a typical developing country child by age without supplementation (primary analysis) or receiving the newly recommended WHO regimen. Mother: two doses; 200,000 IU within 8 wk of delivery. Infant: 50,000 IU at 42, 70 and 98 d; 100,000 IU at 180 d; and 200,000 IU at 365, 548 and 730 d (sensitivity analysis). For comparison, curves representing minimally adequate vitamin A stores (0.07 μmol/g) and estimated liver stores for a child whose dietary vitamin A intake is equivalent to that of a 50th percentile American child surveyed by NHANES III (13) assuming r_0 = 1.5%/d, $p(t)$ = 10% and v_0 = 0. ▲, NHANES III; - - -, min adequate; heavy line, primary analysis; thin line, WHO supplement. ***(b)*** Sensitivity analysis of 6-mo vitamin A supplementation regimen beginning at 6 mo. Estimated liver vitamin A stores in a typical developing country child by age and vitamin A supplementation regimen: none (primary analysis), the newly recommended WHO regimen [mother: two doses, 200,000 IU within 8 wk of delivery; infant: 50,000 IU at 42, 70 and 98 d; 100,000 IU at 180 d; and 200,000 IU at 365, 548 and 730 d (sensitivity analysis)], or 6-mo supplementation [mother, none; infant, 100,000 IU at 180 d; 200,000 IU at 365, 548 and 730 d (sensitivity analysis)]. For comparison, curves representing minimally adequate vitamin A stores (0.07 μmol/g) and estimated liver stores for a child whose dietary vitamin A intake is equivalent to that of a 50th percentile American child surveyed by NHANES III (13) assuming r_0 = 1.5%/d, $p(t)$ = 10% and v_0 = 0. ▲, NHANES III; - - -, min adequate; heavy line, primary analysis; thin line, WHO supplement; gray line, 6-mo supplement.

eat a traditional developing country diet. However, even these interventions rarely result in sufficient intake in the absence of supplementation.

Editor's note. These estimates and conclusions are based on data currently available. Future data, and more refined analytic techniques, are desirable and welcomed but, in the opinion of the authors and outside reviewers, are unlikely to alter the conclusions reached.

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LITERATURE CITED

1. West, K. P. (2002) Extent of vitamin A deficiency among preschool children and women of reproductive age. J. Nutr. 132: 2857S–2866S.
2. Humphrey, J. H., West, K. P., Jr. & Sommer, A. (1992) Vitamin A deficiency and attributable mortality among under-5-year-olds. Bull. W.H.O. 70: 225–232.
3. Beaton, G. H., Martorell, R., Aronson, K. J., Edmonston, B., McCabe, G., Ross, A. C. & Harvey, B. (1993) Effectiveness of vitamin A supplementation in the control of young child morbidity and mortality in developing countries. Nutrition Policy Discussion Paper 13: Administrative Committee on Coordination—Subcommittee on Nutrition, WHO, Geneva.
4. De Benoist, B., Martines, J. & Goodman, T. (2001) Vitamin A supplementation and the control of vitamin A deficiency: Conclusions. Food Nutr. Bull. (Special Issue on Vitamin A Supplementation and the Control of Vitamin A Deficiency) 22: 335–337.
5. Katz, J., Khatry, S. K., West, K. P., Jr., Humphrey, J. H., Leclerq, S. C., Pradhan, E. K., Pohkrel, R. P. & Sommer, A. (1995) Night blindness is prevalent during pregnancy and lactation in rural Nepal. J. Nutr. 125: 2122–2127.
6. Starbuck, E. (1993) Night blindness during pregnancy as a risk marker for early infant death in Jumla, Nepal. Doctoral thesis, Johns Hopkins University, Baltimore, MD.
7. Christian, P., West, K. P., Khatry, S. K., LeClerq, S. C., Kimbrough-Pradhan, E., Katz, J. & Shrestha, S. R. (2001) Maternal night blindness increases risk of mortality in the first 6 months of life among infants in Nepal. J. Nutr. 131: 1510–1512.
8. Christian, P., West, K. P., Jr., Khatry, S. K., Pradhan, E. K., LeClerq, S. C., Katz, J., Shrestha, S. R., Dali, S. M. & Sommer, A. (2000) Night blindness during pregnancy and subsequent mortality among women in Nepal: effects of vitamin A and β-carotene supplementation. Am. J. Epidemiol. 152: 542–547.
9. West, K. P., Katz, J., Khatry, S. K., LeClerq, S. C., Pradhan, E. K., Shrestha, S. R., Connor, P. B., Dali, S. M., Christian, P., Pokhrel, R. P. & Sommer, A. (1999) Double blind, cluster randomised trial of low dose supplementation with vitamin A or beta carotene on mortality related to pregnancy in Nepal. The NNIPS-2 Study Group. Br. Med. J. 318: 570–575.
10. Christian, P., West, K. P., Jr., Khatry, S. K., Katz, J. K., Shrestha, S. R., Pradhan, E. K., LeClerq, S. C. & Pokhrel, R. P. (1998) Night blindness of pregnancy in rural Nepal—nutritional and health risks. Int. J. Epidemiol. 27: 231–237.
11. Newman, V. (1993) Vitamin A and breastfeeding: A comparison of data from developed and developing countries. Wellstart International, San Diego, CA.
12. IOM. (2001) Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc, pp. 4–22. National Academy Press, Washington, DC.
13. NHANES III 1988–1994. (2000) ENVIRON International Corporation and Iowa State University Department of Statistics, Hyattsville, MD.
14. Balluz, L. S., Kieszak, S. M., Philen, R. M. & Mulinare, J. (2000) Vitamin and mineral supplement use in the United States. Arch. Fam. Med. 9: 258–262.
15. Zeitlin, M. F., Megawangi, R., Mara Kramer, E. & Armstrong, H. C. (1992) Mothers' and children's intakes of vitamin A in rural Bangladesh. Am. J. Clin. Nutr. 56: 136–147.
16. UNICEF. (2000) State of the World's Children 2000. www.unicef.org/sowc00. UNICEF, New York, NY.
17. WHO. (1998) Complementary Feeding of Young Children in Developing Countries: a review of current scientific knowledge. WHO, Geneva, Switzerland. Pub no. WS 130 98 CO.
18. Wallingford, J. C. & Underwood, B. A. (1986) Vitamin A deficiency in pregnancy, lactation, and the nursing child. In: Vitamin A Deficiency and Its Control (Bauernfeind, J., ed.), pp. 101–152. Academic Press, New York, NY.
19. Chappell, J. E., Francis, T. & Clandinin, M. T. (1985) Vitamin A and E content of human milk at early stages of lactation. Early Hum. Dev. 11: 157–167.
20. Fomon, S. J. (1993) Human milk and breast feeding. In: Nutrition of Normal Infants (Craven, L., ed.), pp. 409–422. Mosby-Year Book, St. Louis, MO.
21. FAO/WHO Expert Consultation. (1988) Requirements of vitamin A, iron, folate and vitamin B12. FAO Food Nutr. Ser. 23: 16–32.
22. West, C. E., Eilander, A. & van Lieshout, M. (2002) Consequences of revised estimates of carotenoid bioefficacy for dietary control of vitamin A deficiency in developing countries. J. Nutr. 132: 2920S–2926S.
23. Calloway, D. H., Murphy, S. P., Beaton, G. H. & Lein, D. (1993) Estimated vitamin intakes of toddlers: predicted prevalence of inadequacy in village populations in Egypt, Kenya, and Mexico. Am. J. Clin. Nutr. 58: 376–384.
24. Ramakrishnan, U., Martorell, R., Latham, M. C. & Abel, R. (1999) Dietary vitamin A intakes of preschool-age children in South India. J. Nutr. 129: 2021–2027.
25. de Pee, S., West, C. E., Permaesih, D., Martuti, S., Muhilal, & Hautvast, J. G. (1998) Orange fruit is more effective than dark-green, leafy vegetables in increasing serum concentrations of retinol and beta-carotene in schoolchildren in Indonesia. Am. J. Clin. Nutr. 68: 1058–1067.
26. de Pee, S., West, C. E., Muhilal, Karyadi, D. & Hautvast, J. G. (1995) Lack of improvement in vitamin A status with increased consumption of dark-green leafy vegetables. Lancet 346: 75–81.
27. Torronen, R., Lehmusaho, M., Hakkinen, S., Hanninen, O. & Mykkanen, H. (1996) Serum β-carotene response to supplementation with raw carrots, carrot juice or purified β-carotene in healthy non-smoking women. Nutr. Res. 16: 565–575.
28. Micozzi, M. S., Brown, E. D., Edwards, B. K., Bieri, J. G., Taylor, P. R., Khachik, F., Beecher, G. R. & Smith, J. C. (1992) Plasma carotenoid response to chronic intake of selected foods and β-carotene supplements in men. Am. J. Clin. Nutr. 55: 1120–1125.
29. Van het Hof, K. H., Brouwer, J. A., West, C. E., Haddeman, E., Steegers-Theunissen, R. P., van Dusseldorp, M., Weststrate, J. A., Ekes, T. K. & Hautvast, J. G. (1999) Bioavailability of lutein from vegetables is five times higher than that of β-carotene. Am. J. Clin. Nutr. 70: 261–268.
30. Castenmiller, J. J., West, C. E., Linssen, J. P., van het Hof, K. H. & Voragen, A. G. (1999) The food matrix of spinach is a limiting factor in determining the bioavailability of beta-carotene and to a lesser extent of lutein in humans. J. Nutr. 129: 349–355.
31. Tomkins, A. (1981) Nutritional status and severity of diarrhoea among pre-school children in rural Nigeria. Lancet i: 860–862.
32. Molbak, K., Wested, N., Hojlyng, N., Scheutz, F., Gottschau, A., Aaby, P. & da Silva A.P. (1994) The etiology of early childhood diarrhea: a community study from Guinea-Bissau. J. Infect. Dis. 169: 581–587.
33. Rowland, M. G. M., Goh Rowland, S. G. J. & Cole, T. J. (1988) Impact of infection on the growth of children from 0 to 2 years in an urban West African community. Am. J. Clin. Nutr. 47: 134–138.
34. Black, R. E., Brown, K. H., Becker, S. & Yunus, M. (1982) Longitudinal studies of infectious diseases and physical growth of children in rural Bangladesh. Am. J. Epidemiol. 115: 305–314.
35. Bentley, M. E., Stallings, R. Y., Fukumoto, M. & Elder, J. A. (1991) Maternal feeding behavior and child acceptance of food during diarrhea, convalescence, and health in the central sierra of Peru. Am. J. Public Health 81: 43–47.
36. Brown, K. H., Black, R. E., Robertson, A. D. & Becker, S. (1985) Effects of season and illness on the dietary intake of weanlings during longitudinal studies in rural Bangladesh. Am. J. Clin. Nutr. 41: 343–355.
37. Esrey, S. A., Creed, H., Brown, K. H., Bentley, M. E. & Lopez de Romana, G. (1988) Energy intake during diarrhea, convalescence, and health by rural Peruvian children. FASEB J. 2: 1194 (abstr).
38. Brown, K. H., Stallings, R. Y., Creed de Kanashiro, H., Lopez de Romana, G. & Black, R. E. (1990) Effects of common illnesses on infants' energy intakes from breast milk and other foods during longitudinal community-based studies in Huascar (Lima) Peru. Am. J. Clin. Nutr. 52: 1005–1013.
39. Martorell, R., Yarbrough, C., Yarbrough, S. & Klein, R. E. (1980) The impact of ordinary illnesses on the dietary intake of malnourished children. Am. J. Clin. Nutr. 33: 345–350.
40. Sivakumar, B. & Reddy, V. (1972) Absorption of labelled vitamin A in children during infection. Br. J. Nutr. 27: 299–304.
41. Reddy, V., Raghuramulu, N., Arunjyoti, Shivaprakash, M. & Underwood, B. (1986) Absorption of vitamin A by children with diarrhea during treatment with oral rehydration salt solution. Bull. W.H.O. 64: 721–724.
42. Beisel, W. R. (1972) Nutrient wastage during infection. In: Proceedings of the 9th International Congress on Nutrition, Mexico (Chaves, A., Bourges, H., Basta, S., eds), pp. 160–167. Karger, Basel, Switzerland.
43. Sauberlich, H. E., Hodges, H. E., Wallace, D. L., Kolder, H., Canham, J. E., Hood, J., Raica, N. & Lowry, L. K. (1974) Vitamin A metabolism and requirements in the human studied with the use of labeled retinol. Vitam. Horm. 32: 251–275.
44. Haskell, M. J., Lembche, J. L., Salazar, M., Peerson, J. H., Green, M. H. & Brown, K. H. (1999) Plasma retinol and estimated vitamin A pool size in a population of pre-school aged Peruvian children. FASEB J. 13: A897 (abs.).
45. Green, M. H., Green, J. B. & Lewis, K. C. (1987) Variation in retinol utilization rate with vitamin A status in the rat. J. Nutr. 117: 694–703.
46. Lawrie, N. R., Moore, T. & Rajagopal, K. R. (1941) The excretion of vitamin A in urine. Biochem J. 35: 825–837.
47. Stephensen, C. B., Alvarez, J. O., Kohatsu, J., Hardmeier, R., Kennedy, J. I., Jr., & Gammon, R. B., Jr. (1994) Vitamin A is excreted in the urine during acute infection. Am. J. Clin. Nutr. 60: 388–392.
48. Alvarez, J., Salazar-Lindo, E., Kohatsu, J., Miranda, P. & Stephensen, C. B. (1995) Urinary excretion of vitamin A in children with acute diarrhea. Am. J. Clin. Nutr. 61: 1273–1276.
49. Mitra, A. K., Alvarez, J. O. & Stephensen, C. B. (1998) Increased urinary retinol loss in children with severe infections. Lancet 351: 1033–1034.
50. Campos, F. & Flores, H., Underwood, B. (1987) Effect of an infection

on vitamin A status of children as measured by the relative dose response (RDR). Am. J. Clin. Nutr. 46: 91–94.

51. Reddy, V., Bhaskaram, P., Raghuramulu, N., Milton, R. C., Rao, V., Madhusudan, J. & Krishna, K. V. (1986) Relationship between measles, malnutrition, and blindness: a prospective study in Indian children. Am. J. Clin. Nutr. 44: 924–930.

52. Voorhoeve, H. W. A. (1966) Xerophthalmia in the presence of kwashiorkor in Nigeria. Trop. Geogr. Med. 18: 15–19.

53. Foster, A. & Sommer, A. (1987) Corneal ulceration, measles, and childhood blindness in Tanzania. Br. J. Ophthalmol. 71: 331–343.

54. Barclay, A. J., Foster, A. & Sommer, A. (1987) Vitamin A supplements and mortality related to measles: a randomized clinical trial. Br. Med. J. Clin. Res. Ed. 294: 294–296.

55. Hussey, G. D. & Klein, M. (1990) A randomized, controlled trial of vitamin A in children with severe measles. N. Engl. J. Med. 323: 160–164.

56. WHO/UNICEF/IVACG. (1997) Vitamin A Supplements: A Guide to their Use in the Treatment and Prevention of Vitamin A Deficiency and Xerophthalmia, 2nd ed. WHO, Geneva, Switzerland. Pub no. QU 167 97 VI.

57. Olson, J. A. (1996) Vitamin A. In: Present Knowledge in Nutrition (Ziegler, E., and Filer, L. J., Jr., eds), pp. 109–119. International Life Sciences Institute Press, Washington, DC.

58. Altman, P. L. & Dittmer, D. S., Eds. (1962) Growth including reproduction and morphological development, pp. 346. Federation of American Societies for Experimental Biology, Washington, DC.

59. Humphrey, J. H. & Rice, A. L. (2000) Vitamin A supplementation of young infants. Lancet 356: 422–424.

60. Olson, J. A. (1987) Recommended dietary intake (RDI) of vitamin A in humans. Am. J. Clin. Nutr. 45: 704–716.

61. Olson, J. A., Gunning, D. B. & Tilton, R. A. (1984) Liver concentrations of vitamin A and carotenoids, as a function of age and other parameters, of American children who died of various causes. Am. J. Clin. Nutr. 39: 903–910.

62. Olson, J. A. (1979) Liver vitamin A reserves of neonates, preschool children and adults dying of various causes in Salvador, Brazil. Arch. Latinoam. Nutr. 29: 521–545.

63. Sommer, A. & West, K. (1996) Vitamin A Deficiency: Health, Survival, and Vision. Oxford University Press, New York, NY.

64. Allen, L. & Haskell, M. (2001) Vitamin A requirements of infants under 6 months of age. Food Nutr. Bull. 22: 214–234.

65. Neville, P. (1988) Studies in human lactation: milk volumes in lactating women during the onset of lactation and full lactation. Am. J. Clin. Nutr. 48: 1375–1386.

66. Stoltzfus, R. J., Hakimi, M., Miller, K. W., Rasmussen, K. M., Dawiesah, S., Habicht, J. P. & Dibley, M. J. (1993) High dose vitamin A supplementation of breast-feeding Indonesian mothers: effects on the vitamin A status of mother and infant. J. Nutr. 123: 666–675.

67. Bausch, J. & Rietz, P. (1977) Method for the assessment of vitamin A liver stores. Acta Vitaminol. Enzymol. 31: 99–112.

68. Warren, K. S., Bundy, D. A. P., Anderson, R. M., Davis, A. R., Henderson, D. A., Jamison, D. T., Prescott, N. & Senft, A. (1933) Helminth infections. In: Disease Control Priorities in Developing Countries (Jamison, D. T., Mosley, W. H., Measham, A. R., Bobadilla, J. L., eds.), pp. 131–160. World Bank, Oxford Medical Publications, New York, NY.

69. Stoltzfus, R. J., Chwaya, H. M., Montresor, A., Albonico, M., Savioli, L. & Tielsch, J. M. (2000) Malaria, hookworms, and recent fever are related to anemia and iron status indicators in Zanzibari children 0–5 years and these relations change with age. J. Nutr. 130: 1724–1733.

70. Sivakumar, B. & Reddy, V. (1975) Absorption of vitamin A in children with ascariasis. J. Trop. Med. Hyg. 78: 114–115.

71. Humphrey, J., Friedman, D., Natadisastra, G. & Muhilal. (2000) 24-Hour history is more closely associated with vitamin A status and provides a better estimate of dietary vitamin A intake of deficient Indonesian preschool children than a food frequency method. J. Am. Diet. Assoc. 100: 1501–1507.