
The role of vitamin A in reducing child mortality and morbidity and improving growth

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Abstract

This is an update of knowledge on the role of the vitamin A status in determining child mortality, morbidity and growth. Recent information confirms the earlier conclusion of Beaton *et al.* that a 23% reduction in young child mortality results following improvements in the vitamin A status. Studies show that the mortality effect is primarily due to reductions in deaths due to acute gastroenteritis and measles but not acute respiratory infections (ARI) and malaria. While improvement of the vitamin A status enhances the survival of older preschool children, it remains unclear whether it benefits infants (i.e. <6 months). Vitamin A supplementation does not reduce the overall incidence and prevalence of common childhood illness; however, it reduces the incidence of more severe episodes of diarrhea. Also, vitamin A supplementation either during and/or immediately after the illness does not improve its symptomatology. Finally, contrary to earlier expectations, recently completed, placebo-controlled randomized interventions have failed to detect improvements in child growth.

Key words: vitamin A deficiency; child/ morbidity; mortality; growth

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El papel de la vitamina A
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infantiles y en la mejoría del crecimiento.
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Resumen

La presente es una revisión del conocimiento actual sobre el papel de la vitamina A en la mortalidad, morbilidad y crecimiento infantiles. Recientemente, algunas investigaciones han confirmado la conclusión de Beaton y colaboradores (1993) que indica que se puede reducir la mortalidad infantil en un 23% mejorando el estado de la vitamina A. Se ha demostrado que este efecto se debe a la reducción de la mortalidad por gastroenteritis aguda y sarampión y no por infecciones respiratorias agudas y paludismo. Queda claro que el mejoramiento del estado de la vitamina A favorece la sobrevivencia de los niños prescolares mayores; sin embargo, no se ha definido si también beneficia a los infantes (<6 meses). El suplemento de vitamina A no reduce la incidencia total ni la prevalencia de enfermedades comunes de la niñez; sin embargo, sí reduce la incidencia de episodios graves de diarrea. Asimismo, tal suplementación, ya sea durante o inmediatamente después de la enfermedad, no mejora la sintomatología. Finalmente, en contra de lo esperado, estudios recientes con asignación aleatoria a grupos que reciben vitamina A o un placebo indican que la vitamina A no mejora el crecimiento de los niños.

Palabras clave: deficiencia de vitamina A; niño/morbilidad; mortalidad; crecimiento

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Vitamin A deficiency (VAD) is a significant public health problem in much of the world (Figure 1). While clinical vitamin A deficiency, characterized by eye signs that lead to blindness, is more common in South Asia and Southeast Asia, recent data indicate that subclinical VAD (based on serum retinol values) is widespread in Latin America and Africa.¹ In the region of the Americas, VAD has been defined as a public health problem if the prevalence of serum retinol below 0.7 mmol/l is greater than 15%.² More recently, the World Health Organization (WHO) defined mild, moderate and severe levels of subclinical VAD if the prevalence of serum retinol below 0.7 mmol/l was >0-10%, 10-20% and ≥ 20% respectively.³ WHO recommends the use of at least two additional indicators, and specifies that at least one be biological (*i.e.* serum retinol, breast milk retinol). The significance of all forms of VAD is better appreciated now following extensive efforts in the last decade to assess national prevalences as well as considerable research about the role of vitamin A on child mortality, morbidity and growth.

The main objectives of this paper are to review and summarize the key findings regarding whether improvements in the vitamin A status of young children from populations with known VAD:

- Reduce mortality
- Reduce morbidity
- Improve physical growth

The majority of the studies reviewed in this paper are medium to large intervention trials that improved vitamin A status using either supplements (high dose as well as weekly RDA equivalents) or fortified products.

The comprehensive meta-analysis published by Beaton *et al.* in 1993⁴ was used as the starting point in discussing mortality and morbidity effects. Beaton *et al.*⁴ included preliminary reports that have since been published, some with additional details. Also, new studies have appeared since, especially about morbidity effects; these were identified using literature search (Medline) as well as meeting reports (*e.g.* International Vitamin A Consultative Group). Beaton *et al.*⁴ did not consider effects on physical growth and thus, the topic is reviewed more comprehensively here.

Vitamin A and mortality

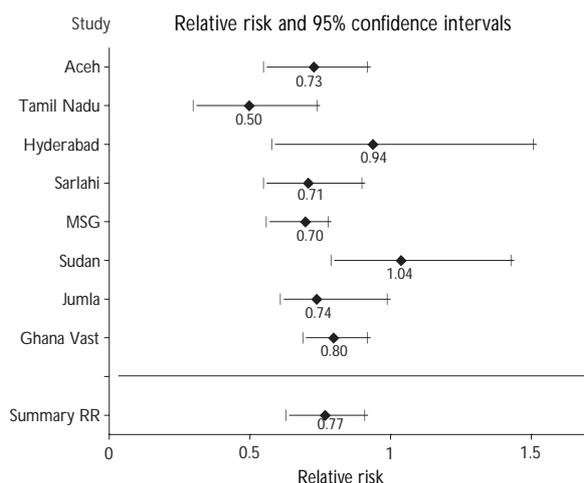
Overall mortality

Beaton *et al.*⁴ in an earlier meta-analysis of eight large community trials⁵⁻¹² concluded that improving vitamin A status in deficient populations was associated with an overall decrease of 23% in mortality rates for young children between 6 and 72 months of age (Figure 2). They also concluded that the relative effect did not vary by age, gender or mode of administration (*i.e.* dosage of supplements, fortification). Most of these

Under control
No data-problem likely
Mild
Moderate subclinical
Severe subclinical
Clinical

Source: MDIS/WHO, 1995

FIGURE 1. PREVALENCE OF VITAMIN A DEFICIENCY IN THE WORLD



Source: Beaton *et al.*⁴

FIGURE 2. IMPACT OF VITAMIN A ON MORTALITY OF YOUNG CHILDREN

studies were carried out in Asia (India, Nepal, Indonesia) where VAD is a significant public health problem and two studies were from Africa (Sudan, Ghana) where subclinical deficiency was common but clinical vitamin A deficiency was negligible. Recent analysis of the findings of the Ghana Vast Study, where overall mortality was 19% less in the vitamin A groups compared to the control group, reveals that the mortality effects did not vary by number of previous doses nor timing of dose in the season.¹³ Overall, the conclusions by Beaton *et al.*⁴ remain valid and have since been corroborated by other reviews and meta-analyses^{14,15} and later studies.¹⁶ Fawzi *et al.*¹⁷ reported a strong association in Sudan between dietary vitamin A intake and mortality, even after controlling for socioeconomic status. It is not clear why this should be so since vitamin A supplementation was found not to affect mortality in the same study.¹¹

Cause-specific mortality

There is unequivocal evidence that vitamin A supplementation reduces mortality in children with measles.¹⁸⁻¹⁹ Analysis of cause-specific mortality from the Ghana Vast Study showed that while the mortality due to acute gastroenteritis was significantly lower in the vitamin A group, there were no differences in mortality due to acute respiratory infections (ARI) and malaria.^{13,20} In summary, earlier findings that vitamin A reduces measles and diarrheal mortality but not death attributed to ARI have been confirmed.

Mortality in early infancy (< 6 mo of age)

The benefits of improving vitamin A status in young infants remains a controversial topic. West *et al.*²¹ found that vitamin A supplementation did not reduce early infant mortality (< 6 months of age) although mortality was reduced among older infants and preschool children in the same population.⁹ The authors suggest that the lack of benefit in the very young may have been due to the protective effect of breast-feeding. In contrast, Humphrey *et al.*²² reported a lower risk of dying during the first year of life for the vitamin A group (RR= 0.36, CI 0.16 - 0.87) in a randomized controlled trial (RCT) where newborns received 50 000 IU of vitamin A within 24 hours of birth. Interestingly, although there were no significant differences in morbidity, a higher proportion of infants in the control group were brought for medical care, specifically treatment of cough and fever, substantiating the effect of vitamin A on severity of illness that has been shown in older children (see "Vitamin A and morbidity"). A study from Bangladesh²³ also reported reduced infant mortality following supplementation of breast-feeding mothers with 300 000 IU post partum. Unfortunately, these findings are difficult to interpret since full details of the study have not been published. A major concern with providing high dose vitamin A supplements to infants below 6 months of age is the potential for toxicity and side effects. There have been reports of bulging fontanelle at doses of both 25 000 IU²⁴ and 50 000 IU.²⁵ Although the significance of this phenomenon is unclear, one follow-up study revealed no evidence of long term consequences.²⁶ The appropriate and safe dose for infants has still not been resolved, and the results of a WHO sponsored multi-country (India, Peru, Ghana) RCT where Vitamin A supplements are given with immunization are awaited.* However, it is worth noting that these risks are not there by providing vitamin A supplements to lactating women which can benefit the mother as well as improve breast-milk retinol.²⁷

Vitamin A and morbidity

Overall morbidity

A summary of the intervention studies,^{7-9,28-38,†} that have examined the effect of vitamin A on morbidity is shown

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† Kothari GA, Naik EG. The effect of vitamin A prophylaxis on morbidity and mortality among children in urban slums in Bombay. Unpublished draft.

in Table I (adapted from Beaton *et al.*)⁴ Studies published since the 1993 review by Beaton *et al.*⁴ support the original conclusion that improvements in vitamin A status do not reduce the overall incidence and prevalence of common childhood illness such as diarrhea and respiratory illness.^{36,38} Although Fawzi *et al.*³⁹ reported evidence of a dose response relationship between quintiles of dietary vitamin A intake and risk of measles, diarrhea and cough with fever in the Sudan, it should be noted that the intervention (vitamin A supplementation) had no effect. Also, it is possible that nutrients associated with vitamin A intake may be responsible for the association observed.

Of greater significance is the growing evidence^{35, 40-41} in support of the severity hypothesis that had been proposed *i.e.* vitamin A supplementation reduces the incidence of more severe episodes of diarrhea compared to the placebo treated children. In Brazil, Barreto *et al.*³⁶ found a 20% reduction in the incidence of severe episodes of diarrhea (defined as an episode of 3 or more days duration and mean of 5 or more liquid or semi solid stools per 24 hours). Furthermore, there was also evidence of a dose response with degree of severity. The Ghana Vast study also found significant differences in severity as well as in

clinic attendances and hospital admissions.¹³ In contrast, improving vitamin A status did not reduce the incidence or severity of ARI.⁴²

Following an episode of illness

Infections can increase vitamin A requirements due to increased losses and/or impaired transport. Recent studies have shown that about 1-2 RDA equivalents of vitamin A can be lost in the urine during an infection.^{43,44} Therefore, one might expect that improving vitamin A status either during and/or immediately after an episode of illness such as diarrhea, respiratory illness or measles, may be beneficial.

Several well designed RCT^{19,20,45,46} have demonstrated conclusively that improvements in vitamin A status following an episode of measles significantly reduce both case fatality rates as well as subsequent morbidity and complications. These findings have been translated into practice by a WHO recommendation whereby all cases of measles should receive vitamin A supplements.⁴⁷

Treatment of children with bronchopulmonary dysplasia with vitamin A was found to reduce complications in the United States.⁴⁸ In contrast, Quinlan

Table I
REPORTED EFFECTS OF VITAMIN A SUPPLEMENTATION ON THE INCIDENCE AND DURATION OF DIARRHEA AND RESPIRATORY INFECTIONS IN NON-HOSPITALIZED CHILDREN*

Authors (year)	Study site	Effects on diarrhea	Effects on respiratory infections
Best studies			
Ghana Vast (1993) ¹²	Ghana	None	None
Barreto <i>et al.</i> (1994) ³⁶	Brazil	6% decrease	None
Rahamtullah <i>et al.</i> (1991) ²⁸	South India	None	None
Dibley <i>et al.</i> (1996) ³⁷	Indonesia	None	ALRI increased
Large studies			
Abdeljaber <i>et al.</i> (1991) ²⁹	Indonesia	None	None
Stansfield <i>et al.</i> (1992) ³⁰	Haiti	11% increase	15% increase
Vijayaraghavan <i>et al.</i> (1990) ⁷	India	None	None
West <i>et al.</i> (1991) ⁸	Nepal	None overall; 11% decrease in dysentery	None
Smaller studies			
Bloem <i>et al.</i> (1990) ³²	Thailand	None	60% reduction only in 1-2 yr old after 4 months
Ndossi <i>et al.</i> (1992) ³⁴	Tanzania	None	None
Ramakrishnan <i>et al.</i> (1995) ³⁸	India	None	None
Bakshi and Gopaldas (1988) ³¹	India	None	possible reduction
Lie <i>et al.</i> (1993) ³³	China	60% reduction	70% reduction
Sinha <i>et al.</i> (1976) ³⁵	India	None	None

* This table is an adapted version of Table 4.4 from Beaton *et al.* (1993).⁴ Best studies are those with double blind, placebo controlled designs, large sample sizes and data collected prospectively at least weekly. Large and small studies are those with sample sizes above and below a thousand respectively

*et al.*⁴⁹ found no beneficial effects of administering 100 000 IU vitamin A on measures such as severity, hospitalization, intensive care or need for oxygen in a RCT of young children infected with respiratory syncytial virus in the USA. Several RCT conducted among cases admitted for ARI in hospital settings in developing countries (Guatemala, Peru, Tanzania) have also failed to show any benefits of vitamin A supplementation,⁵⁰⁻⁵² in spite of using a variety of objective measures, such as ventilation rates, oxygen saturation, respiratory rates, heart rates and temperatures. In fact, the vitamin A supplemented group sometimes fared worse than the control group.⁴⁹⁻⁵⁰ Nevertheless, these findings are concordant with earlier community-based studies that failed to show reductions in incidence or duration of ARI (Table I).

Bhandari *et al.*⁴¹ conducted a randomized trial of children with diarrhea and found, 90 days after vitamin A administration that the incidence of measles but not other morbidity, was reduced in treated children below 23 months of age. The prevalence of diarrhea associated with fever was also reduced but only among older children (24-60 mo). In the same study, the authors⁵³ also found that vitamin A supplementation reduced both the severity and risk of persistent diarrhea for that episode, but only among non breast-fed children. These findings are consistent with earlier reports that observed a protective effect of breast feeding against severe VAD, even after the first year of life.^{54,55} Dewan *et al.*⁵⁶ in a RCT of children admitted with acute diarrhea of less than 3 days also found that vitamin A supplementation reduced the duration and severity of that episode, but only among children with clinical or subclinical VAD based on conjunctival impression cytology >3/5. Walser *et al.*⁵⁷ also reported reductions of about 3 days in the duration of a diarrheal episode among children who were "historically at risk of persistent diarrhea," in a study in Brazil using a pre-post design (3 months before and after administration of vitamin A). In an earlier study in Bangladesh however, no benefit was observed among children hospitalized for diarrhea.⁵⁸

AIDS and HIV infection

The role of vitamin A in the transmission of HIV infection and on its progression to AIDS is an important emerging area of research. Like measles, HIV infection depresses serum retinol and retinol binding protein.^{59,60} A U-shaped relationship has been shown between vitamin A intake and the progression of HIV infection to AIDS in men, where the top and lowest quartiles of intake were associated with fastest rates.⁶¹ These re-

lationships pose new challenges to many developing countries where VAD is common and the prevalence of HIV infection is increasing dramatically.^{62,63}

In a study conducted in Malawi,⁶⁴ poor vitamin A status (based on serum retinol) in pregnant women was associated with increased risk of vertical transmission of HIV infection from mother to children. Based on these findings, several controlled trials are currently under way in Africa (Zaire, Malawi) to determine whether vitamin A supplementation can reduce vertical transmission of HIV infection.

Another area of interest is the role of vitamin A in improving the quality of life of children infected with HIV. A recent study of children born to HIV infected women from South Africa,⁶⁵ found that although there was no reduction in overall morbidity, the incidence of all diarrheas was reduced by 29% in the vitamin A group. This effect was greater for more severe cases, defined by duration >7 days and hospital admission. Similar differences were also seen among the HIV infected children. Preliminary results from another RCT (n= 77) in South Africa⁶⁶ also support the use of vitamin A in the standard case management of young children with AIDS. Vitamin A supplementation (200 000 IU on 2 consecutive days) was associated with improved vitamin A status and immune function four weeks later (increased lymphocyte numbers, CD4, CD52 and CD29 counts) compared to the placebo. These studies strongly suggest the importance of vitamin A status in HIV infection.

In summary, findings to date indicate that improvements in Vitamin A status can reduce the severity of diarrhea and post-measles morbidity and perhaps HIV infection. However, one cannot expect any benefits for ARI, one of the leading early childhood illnesses.

Child growth

Vitamin A was first identified as the growth promoting factor 'A'. Studies in the 1920's-30's demonstrated arrested growth, especially weight gain in rats, following acute vitamin A depletion.⁶⁷⁻⁷¹ However, even today effects on linear growth, bone formation and body composition in animals are less clear.¹⁶ The following section examines the evidence among humans, especially preschool age children.

Observational studies

Several studies have reported an association between vitamin A status and child growth, especially in malnourished populations.⁷²⁻⁷⁷ Night blindness and/or con-

junctival signs of vitamin A deficiency have been associated more commonly with stunting.⁷⁴⁻⁷⁶ However, most of these studies were cross sectional and did not adequately control for confounding variables that are commonly associated with vitamin A deficiency (e.g. poverty, poor sanitation).

Intervention trials

Although vitamin A deficiency has been shown to impair growth in the animal model, and the more recently completed placebo-controlled, randomized intervention trials,^{29,34,78,79,*} however, have failed to detect improvements in child growth. A brief description of the intervention studies on vitamin A and growth of young children is presented in Table II.

Based on the significant impact of vitamin A supplementation in reducing child mortality, the widely held assumption in the late 1980's was that this effect was due to vitamin A reducing both the incidence and severity of common killing diseases, notably diarrhea and respiratory infections, and would thereby improve growth (Figure 3).⁸⁰ Surprisingly, many of the studies that failed to show improvements in growth were the same that demonstrated significant mortality reductions as well as improvements in vitamin A status in the treatment group. More importantly, all these studies included young children below 3 years of age who have been shown to be most susceptible to growth fal-

tering and therefore most likely to respond to supplementation.^{81,82} Inadequate follow-up period is not an issue either. Other studies using the same follow-up period, *i.e.* one year, have demonstrated effects on growth following intervention such as supplementary feeding, iron supplementation and improved sanitation and hygiene.⁸³⁻⁸⁵ However, there were also no reductions in overall morbidity in most of these studies either, which may explain the lack of impact on growth.⁴ Only one study from China reported reductions in morbidity, but there were no improvements in growth.³⁴ It is noteworthy that no placebo was used for the control group in the two earlier intervention trials^{10,86} that did report positive effects on growth.

In a recent review, Sommer and West¹⁵ suggest that vitamin A is only likely to impact growth in children who are extremely vitamin A deficient, based on recent findings from Nepal.⁸⁷ Although significant 16 month gains in weight, height, arm circumference and subscapular skinfolds were seen among xerophthalmic cases compared to similarly wasted non-xerophthalmic children. This group constituted only <2% of the total sample and were not part of the randomized design. More importantly, this study also failed to detect improvements in weight or length gain among non-xerophthalmic children who received vitamin A supplements when compared to the controls.

Of interest, however, is the recent evidence on seasonal differences in the response to supplementation^{88,89} and effects on body composition among children with subclinical vitamin A deficiency. In the only study which included measures of fat, West *et al.*⁸⁷ found that the vitamin A supplemented children had a 0.22 cm² increase in muscle area compared to the control group, although weight gain was similar. Recent-

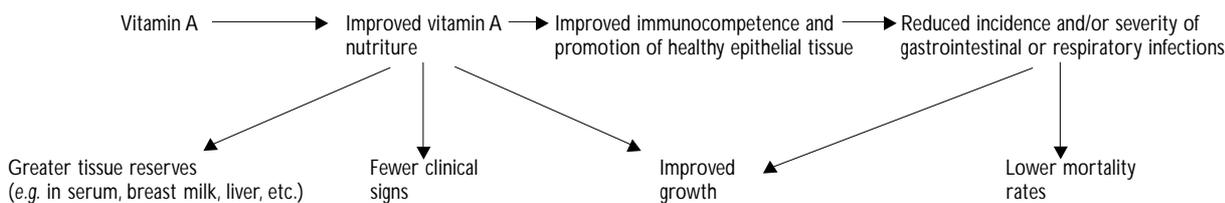
* Kothari GA, Naik EG. The effect of vitamin A prophylaxis on morbidity and mortality among children in urban slums in Bombay. Unpublished draft.

Table II
INTERVENTION STUDIES OF VITAMIN A AND GROWTH OF PRESCHOOL CHILDREN

Authors (year)	Study site	Study subjects	Intervention*	Results	
				Weight gain	Length gain
Muhilal <i>et al.</i> (1988) ⁹	Indonesia	< 3 y, all	Vit A fortified MSG	NS	+
West <i>et al.</i> (1988) ⁸⁶	Indonesia	< 3 y, all	Biannual high dose	+ [†]	NS
Rahamtullah <i>et al.</i> (1991) ²⁸	South India	< 3 y, all	RDA equivalent	NS	NS
Lie <i>et al.</i> (1993) ³³	China	< 3 y, all	Biannual high dose	NS	NS
Ndossi <i>et al.</i> (1992) ³⁴	Tanzania	< 3 y, all	4 monthly high dose	NS	NS
Ramakrishnan <i>et al.</i> (1995) ³⁸	India	< 3 y, all	4 monthly high dose	NS	NS
Kirkwood <i>et al.</i> (1996) ⁷⁹	Ghana	< 3 y, all	4 monthly high dose	NS	NS
West <i>et al.</i> (1997) ⁸⁷	Nepal	< 3 y, all	4 monthly high dose	NS	NS
Bahl <i>et al.</i> (1997) ⁸⁸	India	< 3 y, all	4 monthly high dose	NS	NS

* All these studies were double blind placebo controlled randomized trials except no placebo was used by West *et al.*⁸⁶ and Muhilal *et al.*⁹

[†] Males only



Source: NRC, 1987⁹⁰

FIGURE 3. POTENTIAL EFFECTS OF IMPROVING VITAMIN A STATUS IN YOUNG CHILDREN

ly, Bahl *et al.*⁸⁸ found that children supplemented with vitamin A during the summer gained 140 g more than those who received the placebo during the 90 day follow-up period. These children had been admitted for diarrhea of ≤ 7 days at enrollment. Although these findings are plausible based on our knowledge on the effect of season on the availability and intakes of vitamin A rich foods especially in South Asia,^{89,90} they need to be replicated and examined by different levels of vitamin A status.

In conclusion, findings to date indicate that vitamin A supplementation is unlikely to improve the growth of young children who are only mildly to moderately vitamin A deficient.

Summary

The major conclusions from this review on the role of vitamin A on young child mortality, morbidity and growth in populations where VAD is a significant public health problem are summarized below.

Improvements in the Vitamin A status of young children reduce:

- Mortality by 23% except in very young infants (<6 mo)
- Severity of diarrhea and measles
- Post measles complications

But have no impact on:

- Incidence of common childhood illness
- Acute respiratory infections
- Child growth

The policy implications of these findings, especially for populations with no clinical VAD have become clearer. This is especially relevant for Latin America, a major part of the developing world where clinical VAD is almost absent, but subclinical VAD persists.

Although there are no studies to date demonstrating the effect of vitamin A on mortality from Latin America, one would expect similar benefits, since the extent of the subclinical VAD is similar to the Ghana study. Although subclinical VAD is not severe in some Latin American countries (*i.e.* Costa Rica, Bolivia, Panama), the prevalence of serum retinol <0.7 mmol/l is high (26-55%) in countries such as Guatemala, Mexico, Nicaragua and Brazil. The prevalence of low serum retinol values (<0.7 mmol/l) was 57% in the Ghana study.

In contrast to the mortality trials, quite a few of the studies examining morbidity as an outcome were carried out in Latin America. One of the earliest studies suggesting a role for vitamin A was the observational study by Arroyave *et al.*⁷⁶ in Guatemala. More recently, the significant finding that vitamin A reduces the severity of diarrhea was based on a study of children with subclinical deficiency in North East Brazil.³⁶ Similarly, the studies that showed that vitamin A has no impact on ARI were also from Latin America (Peru, Guatemala).^{51,52} These studies have provided valuable insights on the mechanism by which vitamin A can reduce mortality and also suggest potential benefits for Latin America. Finally, we do not expect any benefits in child growth, since most of the studies clearly showed no improvements in children with subclinical deficiency.

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