Systematic review of vitamin A supplementation in the treatment of children with severe acute malnutrition

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Abbreviations

ALRI	acute lower respiratory infection
BMI	body mass index
CI	confidence interval
CMAM	Community Management of Acute Malnutrition
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HAZ	height-for-age z-score
IU	international unit
MUAC	mid-upper arm circumference
PEM	protein-energy malnutrition
RCT	randomized controlled trial
RR	risk ratio
RUTF	ready-to-use therapeutic food
SAM	severe acute malnutrition
VA	vitamin A
VAD	vitamin A deficiency
WAZ	weight-for-age z-score
WHO	World Health Organization
WHZ	weight-for-height z-score

Measurements

cm	centimetre
dL	decilitre
g	gram
kg	kilogram
l	litre
mg	milligram
mm	millimetre
mmol	micromole
n	number
µg	microgram
µmol	micromole

Background

Severe acute malnutrition (SAM) is a significant contributor to global child mortality. While great strides have been made in recent decades towards improving the treatment of SAM *(1)*, additional investigation and analysis of new approaches and therapies are necessary in order to determine the most effective treatment. The effect of vitamin A supplementation as a possible intervention in the treatment of SAM warrants further study.

Vitamin A deficiency (VAD) is a widespread public health problem in the developing world and the leading preventable cause of blindness in children *(2)*. Vitamin A plays an important role in regulating immune function, thus VAD increases susceptibility to infection *(3)*. Preventative vitamin A supplementation in children has been shown to significantly decrease all-cause mortality as well as diarrhoea-specific mortality *(3)*. Thus, vitamin A supplementation in children with SAM may offer a way to decrease mortality.

Aim

To synthesize available evidence about the impacts of vitamin A supplementation in the care and management of SAM in children.

Review question

For children with SAM, what is the value (effectiveness and safety) of vitamin A supplementation, compared to consuming a vitamin A rich therapeutic diet?

Methodology

A search of computerized databases for all studies from 1950 to 2011 for both observational and randomized studies was conducted. Databases searched included Medline, Embase and Google Scholar. The clinical trial registries at clinicaltrials.gov, pactr.org and apps.who.int/trialsearch were also searched. Initial key words for the searches included "malnutrition", "severe malnutrition", "kwashiorkor", "marasmus", "vitamin A" and "retinol". A number of outcome measures were sought, initially including mortality, weight gain, nutritional recovery and vitamin A deficiency. Further terms were added iteratively to the search based on results obtained from the initial searches.

Searches were also conducted to identify relevant publications and study documents produced by international health organizations such as the World Health Organization (WHO), the United Nations Children's Fund (UNICEF) and Médecins sans Frontières. Included studies were limited to those published in English, French or Spanish. The titles and abstracts from these search results were scanned to identify relevant studies. The full texts of relevant studies were obtained and the list of relevant articles for inclusion was further optimized. Reference lists in relevant articles were also scanned manually and electronically (Google Scholar, Web of Science) to identify prior citations that may have been missed by the original searches. Publications that cite those previously identified articles were similarly sought.

Results

The overall quality of this evidence was rated as "Low", owing to methodological and reporting bias. See Table 1 for details of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment of the evidence.

Question: For children with SAM (with and without oedema), what is the *value (effectiveness and safety)* of high-dose vitamin A supplementation on mortality, nutritional recovery and signs of symptomatic vitamin A deficiency?

- How does *timing* of high-dose vitamin A supplementation in the treatment course of SAM affect outcomes?

Previous reviews

Review studies, to be distinguished from meta-analyses, summarize evidence in the literature around specific questions without combining and analysing the primary data. Two reviews of vitamin A supplementation strategies were identified with some relevance to this review; in both cases, the sample populations were not comprised of exclusively malnourished children *(3,4)*. The first examined efficacy of vitamin A supplementation in community-based settings around the world, finding a 25% (RR 0.75 95% CI 0.64–0.88) reduction in all-cause mortality and 30% (RR 0.70 95% CI 0.58–0.86) reduction in diarrhoea-specific mortality among children 6–59 months old *(3)*. No effect was detected for measles, meningitis or pneumonia. Investigators found a differential effect by region such that vitamin A supplementation showed more protection against morbidity and mortality in Asia than in Africa or Latin America. An earlier review examined both hospital- and community-based trials of vitamin A supplementation *(4)*. Some of the large-scale community trials showed a reduction in mortality due to vitamin A supplementation. In the hospital-based trials, severity of measles and diarrhoea infections were reduced by vitamin A supplementation, but risk of lower respiratory infection was increased *(4)*.

Observational studies linking vitamin A deficiency and SAM

Several observational studies were identified in this review that demonstrate the association between SAM and vitamin A deficiency. In one study, researchers found that low serum retinol (<0.70 μmol/l) was more prevalent among hospitalized Brazilian children with SAM than those who were well nourished, after controlling for several important factors *(5)*. In a subgroup analysis, this study also found that lower serum retinol concentrations in SAM children were associated with greater diarrhoeal morbidities than those without (p=0.021). Another study of hospitalized Egyptian children with protein-energy malnutrition (PEM), kwashiorkor and marasmus assessed several biomarkers of antioxidant status; plasma vitamin A concentrations were significantly reduced in this population (p<0.05) *(6)*. The vitamin A and diarrhoea linkage in SAM was further specified in a study from Bangladesh that aimed to examine predictors and outcomes associated with shigellosis vs other forms of dysentery *(7)*. A reduction in serum retinol concentrations (0.8 μmol/l) was found to be associated with shigellosis, related disease severity and low weight-for-age z-score (WAZ). Infection with the more virulent strain, *Shigella dysenteriae* type 1, showed the lowest serum retinol concentrations.

Two other observational studies point to the link between SAM and vitamin A deficiency. In Zaire, prevalence of low serum retinol was increased in wasted children (WHZ <-2) at 38.2% when compared to non-wasted children at 17.4% (p<0.05) *(8)*. A case-control study in Bangladesh showed that diarrhoea duration (>14 days and 10–14 days) and severe PEM (<60% of reference medium) (AOR 3.8 95% CI 1.8, 8.0) were independently associated with xerophthalmia, while moderate malnutrition (6–70% WAZ) showed no association (*9*).

Vitamin A supplementation trials

WHO currently recommends that for inpatient care of children with SAM, vitamin A supplements be given on day 1 of admission – unless there is clear evidence that vitamin A was received in the last month *(10)*. Dosing guidelines are the following: 200 000 IU for children >12 months; 100 000 for children 6–12 months; and 50 000 IU for children <6 months.

Two trials in sub-Saharan Africa aimed to compare low-dose (5000 IU) vs high-dose (200 000 IU for children >1 year; 100 000 IU children <1 year) vitamin A supplementation in severely malnourished children *(11,12)*. In Senegal, hospitalized children with SAM received either the high-dose vitamin A supplement at admission or low-dose supplements daily until discharge *(11)*. Incidence and duration of respiratory infection were reduced in the low-dose group compared to the high-dose group. In a subgroup analysis, the low-dose course was protective against mortality in children with oedema (AOR 0.21, 95% CI 0.05–0.99). No differences were detected for diarrhoea morbidity or mortality. Another trial in the Democratic Republic of the Congo compared low- and high-dose courses in malnourished children *(12)*. No differences were found for mortality, acute lower respiratory infection (ALRI) or diarrhoeal morbidities. In severely malnourished children, however, the low-dose vitamin A supplementation was protective against incidence of diarrhoea (RR 0.21, 95% CI 0.07–0.62) compared to placebo. Children with no oedema had an increased risk of severe nosocomial diarrhoea associated with the high-dose supplementation compared to placebo *(12)*. These findings suggest that SAM children with oedema may benefit by a low-dose course of vitamin A supplementation during hospitalization (mortality and incidence of severe diarrhoea).

High-dose vitamin A supplementation compared to placebo alone has also produced mixed results for *infectious disease outcomes* in children with and without SAM. A trial in Tanzania supplemented children with very high doses of vitamin A – 200 000 IU at baseline and on day 2 of hospital admission, and again at four and eight months after discharge *(13)*. This resulted in a significant reduction of risk for severe watery diarrhoea (AOR 0.56, 95% CI 0.32–0.99). Among all children in the trial (normal and malnourished), the risk of cough and rapid respiratory rate increased in the vitamin A supplementation group and, for normally nourished children, the risk of acute diarrhoea also increased. An RCT in Bangladesh found that a single high-dose vitamin A (200 000 IU) treatment resulted in a significantly higher rate of clinical cure of acute shigellosis, RR 0.68 (95% CI 0.50 – 0.93) *(14)*.

Two more trials examined high-dose vitamin A treatment on non-measles pneumonia *(15,16)*. The trial in Mozambique, which supplemented vitamin A (200 000 IU) on admission, found improved indicators of recovery associated with treatment, a significant increase in rate of clinical discharge and a non-significant reduction in inpatient days *(15)*. The Brazilian trial supplemented children at very high doses 200 000 IU (100 000 IU for infants) on day 1 and another 200 000 IU (100 000 IU for infants) on day 2 of admission. Pneumonia outcomes were similar in the placebo and vitamin A groups, but children receiving vitamin A were less likely to have fever by day 3 and to fail to respond to first line antibiotic (p=0.05) *(16)*.

Other trials have found adverse or neutral effects associated with high-dose vitamin A supplementation. In Peru, children receiving 200 000 IU on day 1 (100 000 ≤1 year) and 100 000 on day 2 (50 000 IU ≤1 year) showed decreased blood oxygen saturation, increased prevalence of retractions, auscultatory evidence of consolidation and supplemental oxygen needed ($p<0.05$) when compared to placebo-treated children *(17)*. High-dose vitamin A was also examined as adjuvant treatment for ALRI in Guatemala with no significant differences detected on rate of normalization in respiratory rate, oxygen saturation SpO_2, temperature or clinical score *(18)*. Severely malnourished children (<70% WHZ NCHS) were excluded in this trial, and the lack of a biomarker response for serum retinol concentrations also suggests low levels of vitamin A deficiency at baseline. A community-based trial in Indonesia also demonstrated increased risk of acute respiratory infection 8%

and ARLI by 39% in the vitamin A treated group *(19)*. Another community-based trial in Nepal applying a similar vitamin A dosage found a protective effect associated with vitamin A supplementation for mortality, though confounding factors were not accounted for in this cluster design *(20)*. In another study, Vietnamese children hospitalized for pneumonia showed no significantly improved outcomes with high-dose vitamin A *(21)*.

Two RCTs with factorial design tested the effect of vitamin A and zinc supplementation as treatment for respiratory and diarrhoeal infectious morbidities *(22,23)*. In India, children hospitalized for severe ARLI were randomized to one of four groups: vitamin A (10 000 μg RE 2x/day for four days); zinc (10 mg 2x/day for five days); vitamin A + zinc; and placebo. No differences in resolution of ill status, fever, tachypnea and feeding difficulties were observed for the vitamin A groups *(22)*. In the other RCT, also conducted in India, using a similar factorial design but different dosages, there were effects observed for zinc supplementation on prolonged diarrhoea, but no effects for vitamin A *(23)*.

While the association between measles and vitamin A deficiency is established, minimal evidence exists for the efficacy of vitamin A supplementation in malnourished children with measles. Two studies conducted in South Africa, with only a portion of the sample malnourished, demonstrated positive health outcomes (pneumonia recovery among others) due to vitamin A supplementation in children with measles *(24,25)*. In one of the trials, weight gain over a six-week period was found to be significantly greater in the vitamin A supplemented group compared to placebo (p=0.04) *(24)*. Only one other trial was identified that looked explicitly at vitamin A supplementation and growth *(26)*. This trial compared high-dose vitamin A supplementation, Mebendazole antiparasitic and placebo in discharged, moderately malnourished children. At the 12-month follow-up visit, those in the vitamin A supplemented group had significantly greater weight and mid-upper arm circumference (MUAC) gain than the placebo group. When stratified by sex, however, this effect was only significant for boys *(26)*.

No direct evidence is available on how the timing of high-dose vitamin A supplementation in the treatment course of SAM affects nutritional recovery, mortality, weight gain and signs of symptomatic vitamin A deficiency or biological indicators of vitamin A status. Subgroup analyses from the two studies comparing high-dose and low-dose vitamin A supplementation treatment courses give some indication that low-dose vitamin A is protective for severely malnourished children against diarrhoea incidence (*12*), and for mortality among children with oedema at baseline (*11*). Other trials examined different high-dose vitamin A supplementation treatment courses in relation to placebo. Several trials supplemented children once at enrolment (*15,16,18–20*), and two tested the effect of high-dose supplementation over multiple days (*13,17*). Due to heterogeneity in these studies, conclusions regarding the timing of high-dose supplementation are not possible. Further, the studies were not exclusive for children with SAM.

Table 1

Question: Should high-dose vitamin A supplementation vs low-dose vitamin A supplements be used in children with severe acute malnutrition?
Settings: hospital
Bibliography:

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**High-dose vitamin A supplementation**	**Low-dose vitamin A supplements**	**Relative (95% CI)**	**Absolute**		
Mortality												
3	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness[1]	Serious[1]	None	86/1034 (8.3%)	92/1038 (8.9%)	RR 1.11 (0.84 to 1.47)	10 more per 1000 (from 14 fewer to 42 more)	⊕⊕OO LOW	CRITICAL
Diarrhoea (duration in days)												
3	Randomized trials	Serious[2,3]	No serious inconsistency	Serious[1,2,3]	Serious[1,3]	None	-	-	Not pooled	Not pooled	⊕OOO VERY LOW	CRITICAL
Incidence of lower respiratory infections – not reported												
2	-	-[4]	-	-[5]	-[6]	None	-	-	-	-	⊕OOO VERY LOW	CRITICAL

[1] Different criteria were used to define degree of malnutrition in the study populations and different duration of vitamin A supplementation were used in the trials.
[2] Only two investigators have contributed data.
[3] The authors used different classifications of type of diarrhoea and did not provide data according to a pre-specified definition. Details of the use of reported data is described in the narrative.
[4] Only one investigator contributed data (two trials) to this outcome.
[5] The author used different definitions of lower respiratory infections outcomes in the two studies.
[6] Number of cases is not reported. Authors simply state in the articles that there are non-significant differences between the groups.

Conclusions

Globally, 100–140 million children are vitamin A deficient, 4.4 million of whom have xerophthalmia *(27,28)*. Vitamin A is crucial to immunity through maintenance of mucosal barriers and other humoral and cellular immune pathways. However, evidence from trials of vitamin A supplementation has not consistently produced positive health outcomes. Vitamin A toxicity and adverse health outcomes can result under certain conditions. We reviewed 37 studies for evidence of vitamin A and SAM, 21 of which met the GRADE criteria at medium quality or above.

Observational studies confirmed the links between poor vitamin A status and SAM *(5–9)*. Diarrhoeal morbidities appeared to mediate this relationship, though not entirely as revealed by independent associations between diarrhoea, low WAZ and vitamin A *(9)*. Shigellosis, in particular increases the risk of vitamin A deficiency *(7)*.

Findings from previous reviews and RCTs showed mixed results on the efficacy and safety of vitamin A supplementation in the treatment of severely malnourished children. One recurring problem with the interpretation of these studies was the GRADE criteria of indirectness. Many examined vitamin A supplementation in populations with both well-nourished and malnourished children and, therefore, could draw conclusions about vitamin A efficacy and SAM only through subgroup analyses. Two review studies with both well-nourished and malnourished children found reductions in mortality across large-scale community-based trials; the effect was observed more frequently in Asia and for diarrhoea-related mortality in particular *(3,4)*. One of the review studies also included hospital-based trials of vitamin A supplementation and found that severity of measles and diarrhoea disease was reduced, but ALRI risk was increased with supplementation *(4)*.

Evidence from RCTs examined in this review point to some conclusions regarding vitamin A and SAM. First, studies suggested that low-dose vitamin A supplementation (5000 IU) daily until discharge from the hospital is more effective for reducing mortality for children with oedema, incidence of severe diarrhoea and incidence and duration of respiratory infection than a single high-dose vitamin A supplementation (200 000 IU >12 months; 100 000 IU ≤12 months) on day 1 of hospital admission *(11,12)*.

Second, high-dose vitamin A supplementation may be beneficial for treating severely malnourished children in cases of severe diarrhoea or shigellosis *(13,14)*. There was no evidence, however, for the efficacy and safety of vitamin A supplementation in severely malnourished children presenting with non-measles pneumonia and other ALRI. Some trials demonstrated positive outcomes *(15,16)*, while others showed adverse events or no significant findings associated with vitamin A supplementation *(17–23)*. High-dose vitamin A supplementation for measles-specific respiratory illness, however, was effective treatment for severely malnourished children *(24,25)*.

No evidence was identified that directly examined outcomes associated with the timing of high-dose vitamin A supplementation among children with SAM.

Finally, the review did find some evidence for positive growth outcomes associated with vitamin A supplementation after hospital discharge in severely malnourished children *(12,24)*. In both trials, vitamin A supplementation at discharge was associated with weight gain in the follow-up period. This evidence is relatively dated and limited, and should be studied further, potentially with use of ready-to-use therapeutic foods (RUTF) and CMAM as well as vitamin A supplementation.

Further research

- Studies are needed to replicate findings for the efficacy of low-dose vitamin A supplementation in the treatment of severely malnourished children with oedema and severely malnourished children presenting with severe diarrhoea or shigellosis.

- More research is needed to examine the efficacy and effectiveness of various strategies to improve vitamin A nutrition (supplementation, RUTF and other food supplements, improved diet) after hospital discharge of children treated for SAM.

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