

# Maternal postpartum vitamin A supplementation for the prevention of mortality and morbidity in infancy: a systematic review of randomized controlled trials

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<b>Background</b>	Maternal postpartum vitamin A supplementation (VAS) provides an opportunity to improve vitamin A nutriture of breast fed infants in developing countries and can possibly prevent infant mortality and morbidity attributable to vitamin A deficiency.
<b>Objective</b>	To evaluate the effect of maternal postpartum VAS on infant mortality, morbidity and adverse effects.
<b>Design</b>	Systematic review, meta-analysis and meta-regression of randomized controlled trials.
<b>Data sources</b>	Electronic databases and abstracts and proceedings of micronutrient conferences.
<b>Review methods</b>	Randomized or quasi-randomized, placebo-controlled trials evaluating the effect of postpartum, maternal synthetic VAS on mortality or morbidity within infancy (<1 year), or adverse effects.
<b>Results</b>	The seven included trials were from developing countries. There was no evidence of a reduced risk of mortality during infancy [relative risk (RR) 1.05, 95% confidence interval (CI) 0.92–1.20, $P=0.438$ ; $I^2=0\%$ , $P=0.940$ ]. No variable emerged as a significant predictor of mortality but data for high-risk groups (high maternal night blindness prevalence and low birth weights) was restricted. Neonatal mortality data was available from a single study, (RR 1.09, 95% CI 0.88–1.35; $P=0.422$ ). In two trials, there was no evidence of a reduced risk of cause-specific mortality. In one trial, there was no evidence of a decrease in either diarrhoea or acute respiratory infection. No adverse effects were reported in the single relevant trial.
<b>Conclusions</b>	There is no evidence of a mortality or morbidity benefit to the infant following postpartum maternal VAS. Only prevention of infant morbidity or mortality would be sufficient justification for initiating this intervention in public health programmes.
<b>Keywords</b>	Infant, postpartum, meta-analysis, vitamin A

## Introduction

Vitamin A deficiency (VAD) is a significant public health problem in developing countries, especially in Africa and Southeast Asia, most seriously affecting young children and pregnant women.<sup>1</sup> According to the present estimates, there are 127 million pre-school children with VAD (serum retinol <0.70 mmol/l or displaying abnormal impression cytology) and 4.4 million pre-school children with xerophthalmia in the developing world.<sup>1</sup> More than 7.2 million pregnant women in the developing world are vitamin A deficient (serum or breast-milk vitamin A concentrations <0.70 µmol/l) and another 13.5 million have low vitamin A status (0.70–1.05 µmol/l).<sup>1</sup> The main causes of childhood VAD in the developing world include maternal VAD resulting in low concentrations of vitamin A in breast milk, inadequate dietary intake of vitamin A during and after weaning and repeated bouts of infectious illnesses, which further decrease vitamin A levels.<sup>2</sup> Periodic vitamin A supplementation (VAS) to children >6 months old is being implemented in more than 70 countries and is considered by many international agencies to be one of the most effective public health interventions to reduce child mortality.<sup>3</sup>

Infants <6 months of age in developing countries have sub-optimal vitamin A nutriture and higher risk of mortality and morbidity when compared with older children. An improvement in their vitamin A status could possibly prevent infant mortality and morbidity. There are two approaches to supplementing vitamin A intake during the first half of infancy. First, by supplementing lactating mothers so that their infants can increase vitamin A intake through breast milk. Secondly, by providing vitamin A supplements to these infants when they come in contact with the health-care system (immediately after birth, during postnatal visits or during immunization visits). In an attempt to inform public health policy in a structured manner, this systematic review restricts itself to the first approach; it evaluates the effect of synthetic VAS in postpartum mothers on mortality, morbidity, and adverse effects in their infants until the age of 1 year.

## Methods

### Objectives

The objective of this study was to evaluate the effects and safety of prophylactic, maternal postpartum synthetic VAS irrespective of the antenatal VAS status, on mortality and morbidity in infancy (<1 year), and adverse reactions.

The pre-specified sub-group analyses for the infant mortality component in the maternal postpartum supplementation review were:

- (i) cumulative vitamin A dose received by the mother during the intervention phase, low

- dose ( $\leq 200\,000$  IU) vs high dose ( $>200\,000$  IU) (as per WHO recommendations);
- (ii) number of vitamin A doses received, single vs multiple (two or more) doses;
- (iii) baseline maternal vitamin A status, maternal night blindness prevalence of  $\leq 5\%$  (low) vs  $>5\%$  (high), and mean maternal antenatal or postpartum serum retinol levels of  $>1.1$  µmol/l (low) vs  $\leq 1.1$  µmol/l (high);
- (iv) birth weight of the offspring,  $<2500$  g low birth weight (LBW) vs  $\geq 2500$  g (not LBW);
- (v) infant mortality rate in the placebo group, lower half of infant mortality rate from the included trials (below median) vs upper half of infant mortality rate from the included trials (above median);
- (vi) follow-up age,  $\leq 6$  months vs  $>6$  months;
- (vii) development status of the trial area, developing vs developed countries (as defined by the Human Development Report).<sup>4</sup>

### Inclusion criteria

#### Types of trials

Randomized (including cluster-randomized) or quasi-randomized placebo controlled trials were included, irrespective of publication status and language.

#### Types of participants

Participants comprised apparently healthy mothers receiving prophylactic, synthetic VAS initiated within 6 weeks of delivery. Trials conducted on selected sub-groups of infants, such as those who were very low birth weight (<1500 g), HIV positive, born to known HIV-positive mothers, or sick or hospitalized, were excluded. Although such trials may be of clinical interest, they do not address the research question of this review and have been the subject of earlier systematic reviews.<sup>5,6,7</sup>

#### Types of intervention

Synthetic oral VAS initiated in the postpartum mother within 6 weeks of delivery, irrespective of the antenatal VAS status, was compared against a placebo. Infants in intervention and placebo groups should not have been supplemented with vitamin A but could have received placebo. Trials providing additional interventions were included if the only difference between the treatment arms was postpartum maternal synthetic oral VAS. Trials involving supplementation with vitamin-A-rich foods or  $\beta$ -carotene were excluded.

#### Types of outcome measures

*Primary.* (i) Infant mortality rate (in the period between initiation of intervention and the last follow-up within the age of 1 year); and (ii) neonatal mortality rate (in the period between initiation of intervention and the last follow-up within the age of 1 month).

*Secondary.* (i) Cause-specific mortality due to diarrhoea, acute respiratory infections and causes other than these (as defined by the authors, irrespective of ascribing a single or multiple causes of death), in the period between initiation of intervention and the last follow-up within the age of 1 year; (ii) prevalence or incidence of morbidities due to diarrhoea, acute respiratory infection or respiratory difficulty, cough or running nose, ear infection, fever and vomiting (as defined by the authors), in the period between initiation of intervention and the last follow-up within the age of 1 year; (iii) severity of morbidities as assessed by clinic or hospital visits and hospitalizations (as defined by the authors), in the period between initiation of intervention and the last follow-up within the age of 1 year; and (iv) adverse effects including bulging fontanel, vomiting, irritability, diarrhoea and fever (as defined by the authors).

### Search strategy

We searched computerized bibliographic medical databases, including MEDLINE, CENTRAL, EMBASE, IBIDS, CINAHL and HealthSTAR and clinical trials website (<http://www.clinicaltrials.gov>) until 5 March 2009 with no language restrictions. The broad search strategy employed for MEDLINE was: (“Vitamin A”[All Fields] OR (“vitamin a”[MeSH Terms] OR “vitamin a”[All Fields] OR “retinol”[All Fields])) AND “infant”[MeSH Terms]. A similar strategy was used for other databases. A lateral search using the reference lists of identified articles and ‘related articles’ link in PubMed was done for articles initially selected from the search strategy. We also reviewed the reference lists of identified articles and hand-searched reviews, bibliographies of books and abstracts and proceedings of international conferences or meetings. Experts in the field were contacted to identify any additional or ongoing trials. The title and abstract of the trials identified in the computerized search were scanned to exclude trials that were obviously irrelevant. Full texts of the identified trials that fulfilled the inclusion criteria were reviewed. We attempted to include published and unpublished trials, irrespective of language.

### Data abstraction and statistical analysis

Both authors extracted data separately, which were then compared and differences resolved with mutual agreement. Requests to the original investigators for additional data and information regarding definitions of outcomes, and other clarifications, were made where required. For cluster-randomized trials, the stated cluster adjusted relative risk (RR) and 95% confidence interval (CI) were used, irrespective of the method employed. In the absence of this information, raw data were to be sought from authors to calculate the design effect. In case of non-availability of raw data, it was proposed to recalculate the RRs for sensitivity analysis using a design effect inflation of

standard error (SE) by the pooled estimate based on other cluster-randomized trials.<sup>8</sup>

Meta-analysis and meta-regression were performed with user-written programs on STATA (version 9.2) software.<sup>9,10</sup> The presence of bias in the extracted data was evaluated quasi-statistically using the funnel plot. Formal statistical tests for funnel plot asymmetry, namely the Begg’s and Egger’s methods were also conducted with the user-written ‘metabias’ command in the STATA (version 9.2) software.<sup>11,12</sup> Pooled estimates (RR with 95% CI) of the evaluated outcome measures were calculated by the generic inverse variance method by the user-written ‘metan’ command in STATA (version 9.2) software using both random- and fixed-effect models. This program also computes the formal tests of heterogeneity, namely, the statistic Cochran  $Q$  and  $I^2$  (variation in pooled estimate attributable to heterogeneity).<sup>13</sup>

Sensitivity and sub-group analyses (specified above) were conducted for the primary outcome (all-cause mortality during infancy) by disaggregating results with the user-written ‘metan’ command (‘by option’) in STATA (version 9.2) software.<sup>14</sup> The contribution of these variables to heterogeneity was also explored by meta-regression using the ‘metareg’ command in STATA (version 9.2) software with the restricted maximum likelihood option.<sup>15</sup>

## Results

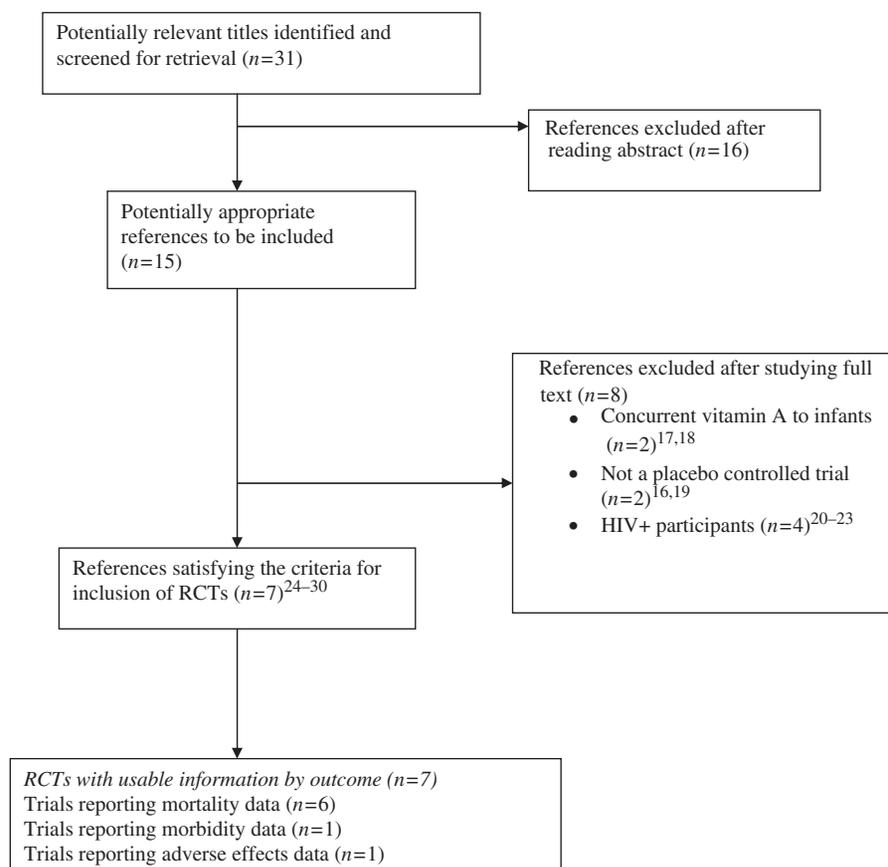
### Trial flow

Fifteen potentially eligible references were identified.<sup>16–30</sup> Amongst these, eight references were excluded<sup>16–23</sup> for the reasons identified in Figure 1. The remaining seven references provided data on seven trials satisfying the inclusion criteria; six trials provided mortality data, one trial had relevant morbidity data and three trials provided adverse effects data.

Table 1 summarizes the baseline characteristics of the included trials. Breast feeding rates were documented in three studies<sup>24,26,27</sup> and approached 100%. The quality of studies was assessed using risk of bias table incorporating adequacy of sequence generation, allocation concealment, blinding and attrition (Table 2).

### Primary outcomes (mortality)

All six trials<sup>24–29</sup> reporting mortality were conducted in developing countries (three in Asia and three in Africa). Only two trials<sup>25,29</sup> were cluster-randomized, and in both the cluster design-adjusted results were available. Allocation concealment, blinding of subjects and blinding of outcome assessors were considered adequate in five studies, and loss to follow-up was <10% in two trials. Antenatal VAS had also been given in two studies. The cumulative vitamin A dose received by the postpartum mother was  $\leq 200\,000$  IU in one trial and  $>200\,000$  IU in five



**Figure 1** Trial flow for selection of randomized controlled trials (RCTs) to be included in meta-analysis

studies. The intervention had been given as a single dose in four studies and as multiple doses in two trials. Information on prevalence of maternal night blindness was available in only two studies (>5% in one and ≤5% in the other). Mean maternal (antenatal or postnatal) serum retinol levels (μmol/l) in the placebo group were documented in four trials, and were ≤1.1 in two and >1.1 in the other two. Information on mean birth weight was available in three studies and was >2500 g in two of them. The infants' follow-up age was ≤6 months in four trials and >6 months in two studies.

#### **Mortality during infancy**

Relevant data for evaluating the pooled RR of all-cause mortality during infancy was available from six trials (supplementary Table 1 available as supplementary data at *IJE* online). The funnel plot (supplementary Figure 1 available as supplementary data at *IJE* online) was symmetrical, suggesting the absence of publication bias, Egger's  $P=0.735$ . There was no evidence of a reduced risk of mortality during infancy (Table 3). The pooled RR for mortality was 1.05 (95% CI 0.92–1.20,  $P=0.438$ ; test for heterogeneity: Cochran  $Q=1.28$ ,  $I^2=0\%$ ,  $P=0.940$ ) by random effects model (Figure 2).

Identical estimates were derived from the fixed-effects model. On conducting pre-specified sub-group and sensitivity analyses (Table 3), no significant difference was identified between the strata of any variable. However, information on maternal night blindness and maternal serum retinol was available in only two and four trials, respectively. On univariable metaregression also, none of these variables achieved significance (supplementary Table 4 available as supplementary data at *IJE* online).

#### **Mortality during neonatal period**

Relevant data were available from only one trial,<sup>25</sup> which documented an RR of 1.09 (95% CI 0.88–1.35;  $P=0.422$ ).

#### **Secondary outcomes**

##### **Cause-specific mortality**

Only two trials documented information on the cause of death, which was ascertained by verbal autopsy or lay reporting. With the random-effects model, there was no evidence of a reduced risk of deaths due to respiratory causes (RR 1.59, 95% CI 0.84–2.99,  $P=0.154$ ;  $I^2=0\%$ ,  $P=0.321$ ), diarrhoeal etiology (RR 2.57, 95% CI 0.72–9.12,  $P=0.145$ ;  $I^2=11.8\%$ ,

**Table 1** Characteristics of trials included in the review

Author	Participants	Intervention	Follow-up	Outcomes
Venkatarao <i>et al.</i> <sup>24</sup>	Location—India (Asia) Inclusion criteria—mother and neonate Exclusion criteria—none	Intervention group ( <i>n</i> = 301)— vitamin A 300 000 IU to the mother— one dose, 7–14 days postpartum Control group ( <i>n</i> = 297)—placebo Breastfeeding ~100%	Follow-up at least fort- nightly for 6 months	Mortality Morbidity Adverse effects
Bhaskaram and Balakrishna <sup>30</sup>	Location—India (Asia) Inclusion criteria—mother and neonate Exclusion criteria—none	Intervention group—mothers received 200 000 IU vitamin A within 24 h of delivery Control group—placebo	Follow-up for first 5 days of life	Mortality—NR Morbidity—NR Adverse effects
Katz <i>et al.</i> <sup>25</sup>	Location—Nepal (Asia) Inclusion criteria—women of child bearing age Exclusion criteria—families moving into the study area	Intervention group ( <i>n</i> = 583)—23 300 IU vitamin A weekly until 24 weeks post- partum Control group ( <i>n</i> = 5202)—placebo to mother	Follow-up at 3 and 6 months postpartum	Mortality Morbidity—NR Adverse effects—NR
Malaba <i>et al.</i> <sup>26</sup>	Location—Zimbabwe (Africa) Inclusion criteria—mother and neonate Exclusion criteria—Birth weight <1500 g, life threatening illness, families intending to move out of study area	Intervention group ( <i>n</i> = 2330)— vitamin A 400 000 IU to the mother— one dose, within 96 h of delivery Control group ( <i>n</i> = 2309)—placebo to mother Breastfeeding ~100%	Follow-up at 6 weeks, 3 months and then 3 monthly until 1 year	Mortality Morbidity—NR Adverse effects—NR
Newton <i>et al.</i> <sup>27</sup>	Location—Ghana (Africa) Inclusion criteria—mother and neonate Exclusion criteria—families intending to move out of the study area	Intervention group ( <i>n</i> = 269)— vitamin A 200 000 IU to the mother— one dose, 3–4 weeks postpartum Control group ( <i>n</i> = 201)—placebo to mother Breastfeeding ~100%	Follow-up at 6 months	Mortality Morbidity—NR Adverse effects—NR
Ayah <i>et al.</i> <sup>28</sup>	Location—Kenya (Africa) Inclusion criteria—mother and singleton neonate Exclusion criteria—none	Intervention group ( <i>n</i> = 282)—mother received 400 000 IU vitamin A within 24 h of delivery Control group ( <i>n</i> = 282)—placebo	Follow-up at 14 weeks	Mortality Morbidity—NR Adverse effects
Klemm <i>et al.</i> <sup>29</sup>	Location—Bangladesh (Asia) Inclusion criteria—mother and neonate Exclusion criteria—infants who died before supplementation, who were born outside of the study area, infants who were not supplemented after repeated staff visits during the first 30 days following birth	Intervention group ( <i>n</i> = 2717)—vitamin A 23 300 IU weekly during pregnancy until 12 weeks postpartum Control group ( <i>n</i> = 2632)—placebo	Follow-up weekly at home for the first 12 weeks of life and then again at 24 weeks of age	Mortality Morbidity—NR Adverse effects—NR

NR: not reported.

Table 2 Risk of bias in included studies

Study	Adequate sequence generation?	Allocation concealment?	Blinding?	Attrition, %
Venkatarao <i>et al.</i> <sup>24</sup>	Quote: '...were randomly allocated' Comment: probably inadequate Judgement: unclear	Quote: '...administered the appropriate capsules to the mother from the sealed envelope supplied by the Statistical Section at the Camp Office.' Comment: adequate Judgement: yes	Quote: '...capsules that were similar in color.' Comment: adequate Judgement: yes	23
Katz <i>et al.</i> <sup>25</sup>	Quote: '30 sub-district areas (village development communities), each composed of 9 wards, were enrolled in the study. Within each sub-district, each of the 9 wards were randomly assigned to receive 1 of the 3 treatments, resulting in 90 wards assigned to each treatment group.' Comment: probably done, since earlier reports from the same investigators clearly describe use of random sequences Judgement: yes	Quote: 'All capsules ... were shipped to Nepal in opaque plastic bottles labeled with 1 of 3 masked, numeric codes. The bottles were re-labeled with individual ward numbers that had been assigned to the specific codes.' Comment: adequate Judgement: yes	Quote: '...gelatin capsules of identical appearance' Comment: adequate Judgement: yes	8.1
Malaba <i>et al.</i> <sup>26</sup>	Quote: 'Study identification numbers were randomly allocated to the treatment groups by computer in blocks of 12. The numbers were printed on adhesive labels and affixed to amber-colored zip-lock plastic bags that were packed with the assigned capsules.' Comment: adequate Judgement: yes	Quote: 'A separate team at Johns Hopkins University prepared the study capsule packets. Lists linking the study number to the treatment were kept in sealed envelopes and encrypted computer files.' Comment: adequate Judgement: yes	Quote: 'Treatment and placebo capsules appeared identical.' Comment: adequate Judgement: yes	11.5
Newton <i>et al.</i> <sup>27</sup>	Quote: 'Mothers and infants were allocated to 1 of 4 treatment groups, using a blocked randomization scheme.' Comment: probably adequate Judgement: yes	Not reported. Comment: not reported Judgement: unclear	Quote: 'The test and placebo capsules were identical in size color and shape.' Comment: adequate Judgement: yes	34.6
Ayah <i>et al.</i> <sup>28</sup>	Quote: 'Two random sequences of X and Y were prepared, one for the mothers and one for the infants. Identification numbers from 1 to 700 were assigned consecutively to each of the two lists and mother-infant pairs of capsules were packaged in zip-lock bags numbered from 1 to 700 and kept in batches of ten.' Comment: adequate Judgement: yes	Quote: 'The randomisation codes were concealed for the entire trial duration and only revealed after completion of data analysis.' Comment: adequate Judgement: yes	Quote: '...prepared and supplied the vitamin A and identical-looking placebo supplements as oily capsules in brown bottles coded as X or Y.' Comment: adequate Judgement: yes	13.65
Klemm <i>et al.</i> <sup>29</sup>	Quote: 'Sectors were listed in geographically contiguous order and were randomized in blocks of 4 within each of 3 previously randomized maternal supplementation trial treatment arms ...' Comment: probably done, since earlier reports from the same investigators clearly describe use of random sequences Judgement: yes	Quote: '...administered a sector-coded supplement containing either 50 000 IU of vitamin A or placebo.' Comment: adequate Judgement: yes	Quote: 'The supplements for both groups were opaque gelatinous capsules identical in shape, size, and color containing edible oil.' Comment: adequate Judgement: yes	0.01

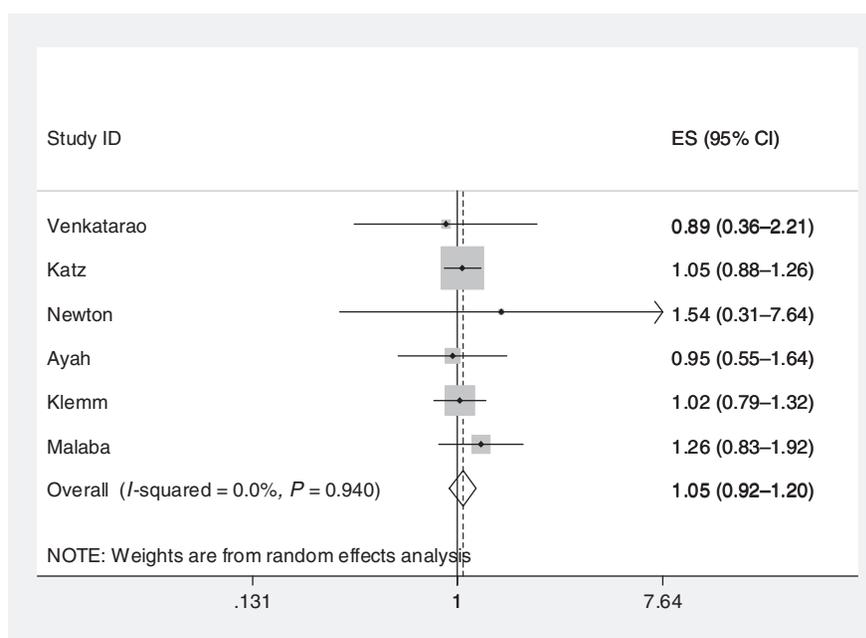
**Table 3** Sensitivity and sub-group analyses for RR of all-cause mortality during infancy

Stratification variable <sup>a</sup>	No. of trials	Random effects model RR (95% CI); <i>P</i> -value	Tests for heterogeneity <i>I</i> <sup>2</sup> (%); <i>Q</i> ( <i>P</i> -value)	<i>P</i> -value for heterogeneity in sub-groups
Overall	6	1.05 (0.92–1.21); 0.439	0.0; 1.28 (0.937)	
<b>Allocation concealment</b>				
Adequate	4	1.06 (0.92–1.21); 0.437	0.0; 0.93 (0.817)	
Others	2	1.02 (0.46–2.24); 0.964	0.0; 0.33 (0.563)	0.930
<b>Attrition</b>				
<10%	2	1.04 (0.90–1.21); 0.606	0.0; 0.03 (0.854)	
≥10%	4	1.12 (0.82–1.52); 0.478	0.0; 1.07 (0.784)	0.679
<b>Follow-up age (months)</b>				
≤6	4	1.04 (0.90–1.20); 0.623	0.0; 0.37 (0.946)	
>6	2	1.19 (0.81–1.74); 0.372	0.0; 0.47 (0.495)	0.508
<b>Total vitamin A dose (units) received by mother</b>				
≤200 000	1	1.54 (0.31–7.63); 0.599	Not applicable	
>200 000	5	1.05 (0.92–1.20); 0.464	0.0; 1.06 (0.900)	0.643
<b>Number of vitamin A doses received</b>				
Single	4	1.12 (0.82–1.52); 0.478	0.0; 1.07 (0.784)	
Multiple	2	1.04 (0.90–1.21); 0.606	0.0; 0.03 (0.854)	0.679
<b>Maternal night blindness</b>				
≤5 %	1	1.26 (0.83–1.92); 0.273	Not applicable	
>5 %	1	1.02 (0.79–1.32); 0.886	Not applicable	0.392
<b>Mean maternal serum retinol in placebo group<sup>b</sup> (μmol/l)</b>				
≤1.1	2	1.08 (0.87–1.35); 0.483	0.0; 0.73 (0.392)	
>1.1	2	1.04 (0.88–1.23); 0.660	0.0; 0.12 (0.727)	0.777

<sup>a</sup>Not done for blinding and trial site as all trials were assessed to be double blind, and were from developing countries. Separate data were not available according to birth weight (low birth weight and normal birth weight).

<sup>b</sup>Includes ante-partum or postpartum estimations in sub-samples in the placebo group.

Estimates from random and fixed-effect models were identical for all variables.

**Figure 2** Forest plots for RR of infant mortality following maternal postpartum VAS (trials = 6); ES = Effect size (RR)

$P=0.287$ ), or causes other than respiratory or diarrhoeal morbidities (RR 0.62, 95% CI 0.09–4.09,  $P=0.618$ ;  $I^2=64.5\%$ ,  $P=0.093$ ) (supplementary Table 2 available as supplementary data at *IJE* online). Similar results were obtained with the fixed-effects model.

### Morbidities

Morbidity details were available only in one study for diarrhoea and acute respiratory infections.<sup>24</sup> In relation to infant follow-up from birth to 6 months of age, the two intervention arms (only maternal supplementation and both maternal and child supplementation) were combined as the child supplementation had been done at 6 months of age, and compared with the placebo group. There was no evidence of a decrease in either of the recorded morbidity (RR; 95% CI), namely, diarrhoea (1.08; 0.94–1.24) or acute respiratory infection (1.08; 0.98–1.19). The morbidity comparison between 6 and 12 months of age was in relation to only maternal supplementation and placebo groups. In this age group also, there was no evidence of a decrease in either diarrhoea (1.10; 0.99–1.23) or acute respiratory infection (0.96; 0.85–1.08).

### Severity of morbidities

Information on severity of morbidities, as assessed by clinic visits and hospitalization, was not available in any trial.

### Adverse effects

Relevant information was reported in one study,<sup>30</sup> but no adverse effects were documented in either group during the follow-up.

## Discussion

Public health programmes in developing countries can adopt postpartum VAS for benefiting mothers and/or infants. This review evaluated only the biological benefits and safety of this intervention in relation to infants. We found no evidence of a reduced risk of all-cause mortality during infancy. Limited data from one to two trials did not indicate a reduced risk of mortality during neonatal period, cause-specific mortality and morbidities. However, data for important risk groups (high prevalence of maternal night blindness and low birth weight) were quite limited. No adverse effects were reported in the single relevant trial.

### Strengths and limitations of analyses

The main conclusion regarding all-cause mortality remained stable over a large spectrum of sensitivity and stratified analyses performed, and there was no evidence of heterogeneity. Both random and fixed-effects models were used for pooling the data and the results

were invariably synchronous. Analysis of six trials, though admittedly not robust proof, indicated no formal evidence of publication bias. Cluster and individually randomized trials were appropriately combined by design effect correction for the primary outcome.

It would be prudent to consider the following limitations of the systematic review before drawing any inferences for revising policy. First, all the trials were conducted in developing countries, which limits the generalization of the findings to developed countries. However, the policy of adopting prophylactic, synthetic VAS programmes is likely to be relevant only in the context of developing countries. Secondly, there were only a few studies providing information on high-risk groups (maternal night blindness prevalence >5% or low maternal serum retinol levels, and low birth weight infants), which limited the statistical power to detect differences in mortality risk in such subjects. Thirdly, the initiation of intervention and the follow-up duration was variable, which precluded constitution of a uniform measure across the studies to explore the possibility of a lower RR of mortality in settings with high baseline mortality. Finally, we did multiple subgroup and meta-regression analyses for important pre-specified variables, which increased the possibility of false positive results.

### Inclusion and exclusion criteria

A few decisions in relation to methodology deserve explanation. (i) Exclusion of non-placebo but controlled trials to obviate the possibility of bias due to 'Hawthorne effect', which has been a contentious issue in relation to defining the child survival effect of VAS.<sup>31–34</sup> Only two trials were excluded due to this reason,<sup>16,19</sup> and in none of these was information on all-cause mortality available. However, these two studies of maternal postpartum VAS did depict morbidity data. On including these two trials, there was no evidence of decreased risk of diarrhoea (RR 0.43, 95% CI 0.11–1.62) or acute respiratory infection (RR 0.51, 95% CI 0.20–1.32). (ii) For evaluating cause-specific mortality, it was decided to pool data from studies reporting a single or multiple reasons of death, with the underlying philosophy that the assessed cause had contributed to mortality either partially or wholly. (iii) We excluded trials in which participants were HIV-positive to factor for potential effect modification by an immunosuppressive condition. In some settings, however, it would be impossible to distinguish such participants from HIV-negative participants. However, there was no evidence of a reduced risk of mortality during infancy on including trials from HIV-positive mothers also (RR 1.09, 95% CI 0.99–1.20;  $P=0.080$ ;  $I^2=0\%$ ) (supplementary Figure 2 available as supplementary data at *IJE* online). (iv) Breastfeeding is the sole link in transferring vitamin A to the neonate. Breastfeeding rates could be documented only in three trials

reporting mortality and were ~100%. The authors of the three other trials were contacted for the relevant data but the data were not made available. The latter three trials were also conducted in countries with a high traditional rate of breastfeeding and there is no reason to believe that the breastfeeding rates in these studies would be any different.<sup>35</sup>

### Comparison with earlier reviews

Our findings are in consonance with a recent systematic review of trials of prenatal and postnatal VAS of HIV-infected women.<sup>7</sup> Similarly, another systematic review could document no convincing evidence of a reduced risk of mortality and possibly morbidity after neonatal supplementation with vitamin A.<sup>36</sup> The biological rationale for both the interventions (maternal and neonatal VAS) is similar, at least in relation to prevention of infant mortality. Maternal VAS aims to improve the vitamin A nutriture of the neonate by increasing the amount of vitamin A transferred through breast milk (with slight contribution from the augmentation of placental transfer of vitamin A), whereas neonatal VAS improves vitamin A status directly.

### Implications for policy

Public health programmes in developing countries can opt for adopting postpartum VAS for maternal and/or infant benefits (improving vitamin A nutriture, or reducing morbidity or mortality). As there is no evidence of a mortality or morbidity benefit to the infant, these considerations would not alone be sufficient justification for initiating this intervention in public health programmes. However, policy formulation would be based on deliberation of additional consequences, including improvement of maternal and infant vitamin A status, maternal benefits (morbidity or mortality), maternal safety and cost-effectiveness.

### Implications for future research

Considerable research has already been conducted for evaluating the mortality and morbidity benefits of maternal VAS, and heterogeneity amongst the trials was unusual. The need for conducting further studies designed solely to evaluate these outcomes is therefore uncertain. However, there are some information gaps, which must be addressed if any future trials are contemplated: (i) population-based studies examining the role of VAS in specific high-risk conditions like high prevalence of maternal night blindness and low birth weight infants; (ii) effect on severity of morbidities; and (iii) adverse reactions.

### Contributors

SG prepared the protocol, applied the search strategy, retrieved the articles, extracted data and did the statistical analysis. HSS developed the idea for review,

finalized the protocol and search strategy, extracted data, and did the statistical analysis. Both authors contributed to the drafting of the final version of the paper, and will act as joint guarantors.

## Supplementary Data

Supplementary data are available at *IJE* online.

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