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Vitamin A supplementation for the prevention of morbidity and mortality in infants one to six months of age (Review)

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Vitamin A supplementation for the prevention of morbidity and mortality in infants one to six months of age
(Review)

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[Intervention Review]

Vitamin A supplementation for the prevention of morbidity and mortality in infants one to six months of age

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ABSTRACT

Background

Vitamin A deficiency is a significant public health problem in low- and middle-income countries. Vitamin A supplementation provided to infants less than six months of age is one of the strategies to improve the nutrition of infants at high risk of vitamin A deficiency and thus potentially reduce their mortality and morbidity.

Objectives

To evaluate the effect of synthetic vitamin A supplementation in infants one to six months of age in low- and middle-income countries, irrespective of maternal antenatal or postnatal vitamin A supplementation status, on mortality, morbidity and adverse effects.

Search methods

We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 2), MEDLINE via PubMed (1966 to 5 March 2016), Embase (1980 to 5 March 2016) and CINAHL (1982 to 5 March 2016). We also searched clinical trials databases, conference proceedings and the reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials.

Selection criteria

Randomised or quasi-randomised, individually or cluster randomised trials involving synthetic vitamin A supplementation compared to placebo or no intervention provided to infants one to six months of age were eligible.

Data collection and analysis

Two review authors assessed the studies for eligibility and assessed their risk of bias and collected data on outcomes.

Main results

The review included 12 studies (reported in 22 publications). The included studies assigned 24,846 participants aged one to six months to vitamin A supplementation or control group. There was no effect of vitamin A supplementation for the primary outcome of all-cause mortality based on seven studies that included 21,339 (85%) participants (risk ratio (RR) 1.05, 95% confidence interval (CI) 0.89 to 1.25; $I^2 = 0\%$; test for heterogeneity: $P = 0.79$; quality of evidence: moderate). Also, there was no effect of vitamin A supplementation on mortality or morbidity due to diarrhoea and respiratory tract infection. There was an increased risk of bulging fontanelle within 24 to 72 hours of supplementation in the vitamin A group compared to control (RR 3.10, 95% CI 1.89 to 5.09; $I^2 = 9\%$, test for heterogeneity: $P = 0.36$; quality

Vitamin A supplementation for the prevention of morbidity and mortality in infants one to six months of age (Review)

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of evidence: high). There was no reported subsequent increased risk of death, convulsions or irritability in infants who developed bulging fontanelle after vitamin A supplementation, and it resolved in most cases within 72 hours. There was no increased risk of other adverse effects such as vomiting, irritability, diarrhoea, fever and convulsions in the vitamin A supplementation group compared to control. Vitamin A supplementation did not have any statistically significant effect on vitamin A deficiency (RR 0.86, 95% CI 0.70 to 1.06; $I^2 = 27\%$; test for heterogeneity: $P = 0.25$; quality of evidence: moderate).

Authors' conclusions

There is no convincing evidence that vitamin A supplementation for infants one to six months of age results in a reduction in infant mortality or morbidity in low- and middle-income countries. There is an increased risk of bulging fontanelle with vitamin A supplementation in this age group; however, there were no reported subsequent complications because of this adverse effect.

PLAIN LANGUAGE SUMMARY

Vitamin A supplementation for infants one to six months of age for preventing death and illnesses

Background

Vitamin A deficiency is a significant public health problem in low- and middle-income countries. Vitamin A supplementation given to children between the ages of six months and five years reduces deaths in these settings. This review focused on babies one to six months of age.

Review question

Does vitamin A supplementation in babies one to six months of age have any beneficial or harmful effects?

Study characteristics

The review authors searched the medical literature to identify relevant studies that compared the effect of vitamin A supplementation versus control on death, illnesses, and side effects in randomly selected infants aged one to six months. The literature is current to 5 March 2016. The search identified 12 studies that involved 24,846 infants. Most of the studies were well conducted and included children from Asia, Africa, and Latin America.

Key results

The results of the studies provided no convincing evidence that vitamin A supplementation reduces death or illness in infants one to six months of age (quality of evidence: moderate). Supplementation had no beneficial effects to reduce death or illness due to diarrhoea or pneumonia. Similarly, vitamin A supplementation did not reduce the proportion of children with vitamin A deficiency based on their blood levels of vitamin A (quality of evidence: moderate). Infants who were given vitamin A had an increased risk of development of bulging of soft spot at the top of the head (called bulging fontanelle) and quality of evidence for this side effect was high. However, this adverse effect did not increase subsequent risk of death or fits.

In summary, vitamin A supplementation in infants one to six months of age did not reduce death or illness; however, it increased the risk of bulging fontanelle.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Vitamin A supplementation for the prevention of morbidity and mortality in infants one to six months of age

Vitamin A supplementation for the prevention of morbidity and mortality in infants one to six months of age

Patient or population: infants 1 to 6 months of age

Setting: rural, urban/peri-urban; low- to middle-income countries

Intervention: synthetic vitamin A supplementation

Comparison: placebo or no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with young infant vitamin A supplementation				
All-cause mortality: longest follow-up, i.e. until 1 year of age	Study population		RR 1.05 (0.89 to 1.25)	21,339 (9 RCTs)	⊕⊕⊕⊙ Moderate ¹	2 studies contributed about 76% to the overall estimate (West 1995; WHO 1998). There was no substantial heterogeneity in the pooled data. Two studies were 2 x 2 factorial design trials and data were added as two data sets for each study.
	25 per 1000	26 per 1000 (22 to 31)				
Morbidity: diarrhoea: point prevalence	Study population		RR 0.99 (0.93 to 1.05)	9891 (2 RCTs)	⊕⊕⊕⊙ Moderate ¹	Even though the final quality assignment was moderate, the effect was from only 2 studies. In addition, prevalence was not as good an indicator as incidence to establish a causal association
	0 per 1000	0 per 1000 (0 to 0)				
Adverse effects: bulging fontanelle within 48 to 72 hours	Study population		RR 3.10 (1.89 to 5.09)	13,493 (9 RCTs)	⊕⊕⊕⊕ High	Consistent effect across the studies
	3 per 1000	8 per 1000 (6 to 15)				
Adverse effects: vomiting 48 to 72 hours	Study population		RR 0.95 (0.67 to 1.35)	2187 (2 RCTs)	⊕⊕⊕⊙ Low ^{2,3}	-
	49 per 1000	47 per 1000 (33 to 66)				
Adverse effects: diarrhoea	Study population		RR 1.07	2176	⊕⊕⊕⊙	-

48 to 72 hours	89 per 1000 95 per 1000 (73 to 124)	(0.82 to 1.40)	(3 RCTs)	Low ^{1,2}	
Adverse effects: fever	Study population	RR 0.94 (0.83 to 1.07)	3187 (3 RCTs)	⊕⊕⊕⊖ Low ^{1,2}	-
48 to 72 hours	194 per 1000 183 per 1000 (161 to 208)				
Vitamin A deficiency: retinol < 0.7 µmol/L	Study population	RR 0.86 (0.70 to 1.06)	1204 (4 RCTs)	⊕⊕⊕⊖ Moderate ¹	-
	221 per 1000 190 per 1000 (155 to 234)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ Downgraded one level due to serious imprecision (confidence interval for summary estimate included unity).

² Downgraded one level due to serious risk of bias.

³ Downgraded one level due to serious inconsistency (statistical heterogeneity was 94%).

BACKGROUND

Description of the condition

Vitamin A deficiency (VAD) is associated with increased risk of illness, death and blindness in young children (Wiseman 2016). The World Health Organization (WHO) estimates that about 190 million preschool children (about 33%) and 19.1 million pregnant women (about 15%) are vitamin A deficient (serum retinol less than 0.70 mmol/L) and among these about five million preschool children and nine million pregnant women had night blindness, as reported in the time period between 1995 and 2005 (WHO 2009a). More recent estimates suggest that VAD has decreased over time; however, it remains prevalent in south Asia and sub-Saharan Africa (Stevens 2015).

Infants and young children in low- and middle-income countries are at increased risk of VAD because of the following reasons: low liver stores at birth, decreased availability of vitamin A from breast milk due to maternal malnutrition or lack of adequate breastfeeding, increased demand due to rapid growth, decreased absorption and increased losses due to recurrent gastrointestinal infections (WHO 2011; Miller 2002). This leads to a sequence of reciprocal cause and effect where VAD lowers the immune system, increases the risk of gastrointestinal infection, which in turn decreases absorption of vitamin A and the cycle continues (Wiseman 2016).

Description of the intervention

Vitamin A is an essential element that cannot be produced by the human body internally by combination of raw materials, and it needs to be taken from external sources. There are two natural sources of vitamin A: provitamin A carotenoids and preformed vitamin A. Provitamin A carotenoids is found in plants, and mammals metabolise it into active vitamin A. Even though fruits and vegetables are rich sources of beta-carotene, these might not be an adequate source of vitamin A, as the conversion ratio from beta-carotene to active vitamin A is small (US IOM FNB 2000). The most active form of vitamin A, preformed vitamin A (i.e. retinol, retinal, retinoic acid and retinyl esters) is found in foods from animal sources and is most commonly used as supplementation.

Synthetic vitamin A supplementation has been associated with short-term adverse effects including vomiting and bulging fontanelle (mainly in infants) (Baqui 1995; Imdad 2010). Bulging fontanelle, the outward curving of an infant's soft spot (fontanelle), can occur in normal healthy babies when they are crying or lying down, in which case, it is self limited with no long-term consequences. Bulging fontanelle can also occur in certain pathological conditions when there is increased intracranial pressure, which can lead to potential long-term complications. Therefore, bulging fontanelle itself is not always associated with adverse outcomes unless associated with underlying serious conditions such as meningitis, encephalitis and hydrocephalus etc. (Kiesler 2003).

How the intervention might work

VAD is believed to cause an increased susceptibility to infections by impeding normal regeneration of damaged mucosal barriers and by diminishing the function of neutrophils, macrophages and natural killer cells. Vitamin A is required for adaptive immunity and plays a role in the development of T-helper (Th) cells and B-cells (Stephensen 2001). VAD also diminishes antibody-mediated

responses directed by Th2 cells, although some aspects of Th1-mediated immunity are also diminished (Stephensen 2001). These factors may account for the increased mortality seen in vitamin A-deficient infants, young children and pregnant women. Deficiency of vitamin A causes xerophthalmia and significantly increases the risk of blindness (Christian 2001; Humphrey 1992). An estimated 250,000 to 500,000 vitamin A-deficient children become blind every year, half of them dying within 12 months of losing their sight (West 2002).

Why it is important to do this review

Vitamin A supplementation in children aged 6 to 59 months has been shown to reduce all-cause mortality and infection-related morbidity (Imdad 2010). This review is an update of the previous review where effectiveness of vitamin A supplementation was assessed in infants aged under six months including neonatal and maternal supplementation; however, neonatal and maternal vitamin A supplementation is assessed in separate Cochrane reviews (Haider 2011; McCauley 2015). Therefore, this review focuses on infants one to six months of age only. The period of one to six months of age is important as there is a potential platform for delivery of vitamin A along with routine vaccination, usually given at the ages of 6, 10 and 14 weeks according to WHO recommended extended programme of immunisation. Therefore, it is important to determine any beneficial or harmful effects of vitamin A when given during this age period.

OBJECTIVES

To evaluate the effect of synthetic vitamin A supplementation in infants one to six months of age in low- and middle-income countries, irrespective of maternal antenatal or postnatal vitamin A supplementation status, on mortality, morbidity and adverse reactions.

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised controlled trials (RCT) or quasi-randomised trials for inclusion. We included trials if randomisation was done at individual or cluster (such as village) level that involved synthetic vitamin A supplementation to infants one to six months of age.

Types of participants

We included trials that studied apparently healthy infants from low- and middle-income countries (as defined by World Bank), breastfed or non-breastfed, receiving vitamin A supplementation initiated between the ages of one and six months. The exact age limit was one month (more than first 28 days of life) to five months and 29 days.

We excluded trials that recruited neonates, children over six months of age or trials focusing only on maternal supplementation before pregnancy, during pregnancy or the postpartum period. We also excluded trials that included only selected subgroups of infants, such as infants who were very low birth weight (less than 1500 g), who were born to known HIV-positive mothers, or who were sick or hospitalised. Although such studies may be of clinical interest, they do not address the research question of this

review and have been the subject of previously published Cochrane reviews (Darlow 2011; Haider 2011; Imdad 2010; McCauley 2015; Oliveira 2016; Wiysonge 2011).

Types of interventions

Synthetic vitamin A supplementation compared to administration of placebo or no supplementation in breastfed or non-breastfed infants one to six months of age irrespective of maternal postpartum vitamin A supplementation status.

We considered trials providing additional interventions if the only difference between the treatment arms was vitamin A supplementation. In studies assessing different doses of vitamin A and placebo, we combined the intervention groups to create a single pair-wise comparison in order to avoid double-counting data. We excluded studies that evaluated food fortification, consumption of vitamin A-rich foods or beta-carotene supplementation.

Types of outcome measures

Primary outcomes

All-cause mortality during infancy, in the period between initiation of intervention and the last follow-up, until the age of one year.

Secondary outcomes

Cause-specific mortality (as defined by the study authors, irrespective of ascribing a single or multiple causes of death) due to:

- diarrhoea;
- acute respiratory infections;
- meningitis;
- measles.

Morbidity during infancy (as defined by the study authors, irrespective of ascribing a single or multiple causes) in the period between initiation of intervention and the last follow-up, until the age of one year:

- diarrhoea;
- acute respiratory infection or respiratory difficulty;
- fever.

Adverse effects within one week following the intervention:

- bulging fontanelle;
- vomiting;
- irritability;
- diarrhoea;
- fever.

Search methods for identification of studies

Electronic searches

For the 2016 update, we used the criteria and standard methods of Cochrane and the Cochrane Neonatal Review Group (see the Cochrane Neonatal Group [search strategy](#) for specialized register).

We conducted a comprehensive search including: the Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 2); MEDLINE via PubMed (1966 to 5 March 2016); Embase (1980 to 5

March 2016) and CINAHL (1982 to 5 March 2016) using the following search terms: (vitamin A OR retinol OR retinoid OR retinoic OR vitamin A[MeSH]), plus database-specific limiters for RCTs and neonates (see [Appendix 1](#) for the full search strategies for each database). We applied no language restrictions.

We searched clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov); the WHO International Trials Registry and Platform (www.who.int/ictpr/search/en/), and the ISRCTN Registry (www.isrctn.com/).

The previous publications of this review used the standard search strategy of the Cochrane Neonatal Review Group using CENTRAL (2010, Issue 3), MEDLINE and Embase (1966 to 15 October 2010) via PubMed and clinical trials websites (e.g. clinicaltrials.gov) using the following search terms: (Newborn OR infan* OR neonat*) AND ("vitamin A" OR retino*).

We limited the search to "humans" and "clinical trial" without language restriction. We did a lateral search using the related articles link in PubMed for the articles initially included from the search strategy.

Searching other resources

We reviewed the reference lists of identified articles and handsearched reviews, bibliographies of books and abstracts.

Data collection and analysis

Selection of studies

Two review authors (AI and ZA) independently assessed the eligibility of the trials. We first screened the titles and abstracts to select potential studies for inclusion and reviewed these studies further by reading full texts to decide about final inclusion. We resolved any potential conflicts about inclusion of studies by contacting a third review author (ZAB).

Data extraction and management

We used a data collection sheet. This included information on study characteristics such as: year of publication, location (country, urban/rural), method of recruitment, inclusion criteria, unit of analysis, risk of bias, details of intervention and comparison group, time points for collection and report of outcomes. Two review authors (AI and ZA) extracted the data independently and resolved any discrepancies by discussion. We consulted a third review author (ZAB) if we could not reach mutual agreement. For dichotomous outcomes, we extracted the total number of participants for each group and the number of participants experiencing an event. We extracted the risk ratios (RR) and 95% confidence intervals (CI) (or standard errors) of treatment effects for the outcomes.

The main analyses included the longest reported follow-up in each study. We pre-determined the order of preferences of extraction of outcomes when data were available in different formats. We used raw numbers when possible to avoid any manipulation from study authors. This means that we extracted raw values (e.g. means and standard deviations) rather than calculated effect sizes (e.g. Cohen's d). For mortality data, we gave preference to denominators in the following order: number with definite outcome known, number randomised and child-years. For other dichotomous outcomes to which both survivors and non-survivors

may have contributed data (e.g. incidence of measles), we gave preference to child-years, number with definite outcome known and number randomised.

In the case of cluster RCTs, we used adjusted estimates reported by the study authors or adjusted the sample size based on methods described in *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of risk of bias in included studies

We assessed the risk of bias according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed the included studies for their risk of bias against the following key criteria:

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting;
- other biases.

Two review authors independently evaluated and agreed the risk of bias for the individual studies. We resolved any disagreements by discussion.

Measures of treatment effect

For mortality outcomes, we used author-reported cause-specific mortality. In the case of morbidity, we combined all available data whenever possible if outcomes were measured in different ways. For example, we included all types of diarrhoea (mild, moderate and severe). In the case of pneumonia, we included lower respiratory tract infections.

Unit of analysis issues

Cluster randomised trials

When participants were randomised based on clusters rather than individuals, we followed guidelines given in the *Cochrane Handbook for Systematic Reviews of Interventions* to adjust for cluster design (Higgins 2011). We used design effect or the intra-cluster correlation (ICC) estimates as given by study authors to adjust for clustering. If design effect or ICC were not available, we used design effect as calculated previously by Beaton 1993.

Dealing with missing data

In cases of differential drop-out from studies, biased estimates of effect size may be generated. We assessed risk of bias related to attrition as described in *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). When analyses were reported for completers as well as controlling for drop-out (e.g. imputed using regression methods), we extracted the drop-outs.

Assessment of heterogeneity

We assessed statistical heterogeneity by visual inspection of forest plots, by performing the Chi² test (assessing the P value) and by calculating the I² statistic. Statistical heterogeneity was considered substantial if the P value was less than 0.10 or I² value exceeded 50%.

Assessment of reporting biases

In order to assess reporting bias from small studies, we drew funnel plots when data were available from at least 10 studies.

Data synthesis

We used Review Manager 5 software to perform the meta-analysis (RevMan 2014). We used the generic inverse-variance method of meta-analysis to pool the studies when data were available in different formats (e.g. when data were available in the form of raw numbers from one study and only summary estimate from another study). This method requires data input in the form of natural log of effect estimate (e.g. RR) and standard error, which were calculated by built in calculator in Review Manager 5 (RevMan 2014). All the analyses used fixed-effect models.

We reported the pooled results with 95% CI. We calculated RR values for dichotomous outcomes and mean differences (MD) for continuous variables.

Quality of evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes: all-cause mortality, diarrhoea, bulging fontanelle, vomiting, fever and VAD.

Two review authors independently assessed the quality of the evidence for each of the outcomes. We considered evidence from RCTs as high quality but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias. We used the GRADEpro 2014 Guideline Development Tool to create [Summary of findings for the main comparison](#) to report the quality of the evidence.

The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades:

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses

The proposed subgroup analyses for the infant mortality component in the infant supplementation analysis were:

- cumulative vitamin A dose received by the infant until the age of six months: low dose (less than 50,000 international units (IU)) versus high dose (50,000 IU or greater);
- maternal vitamin A supplementation: received versus not received;

- birth weight: less than 2500 g (low birth weight) versus 2500 g or greater (normal birth weight);
- vitamin A given with vaccination versus given independent of vaccination.

Investigation of heterogeneity

We considered heterogeneity to be substantial if the I^2 statistic exceeded 50% and visual inspection of the forest plot was indicative. We sought to explain heterogeneity in terms of sensitivity analyses, which considered the possible sources of variation as:

- cumulative dose of vitamin A supplementation;

- vitamin A status of mother;
- birth weight of neonate;
- high baseline infant mortality.

RESULTS

Description of studies

Results of the search

The search strategy identified 1110 titles. Initial screening identified 52 potentially eligible trials; of these we excluded 40 studies after reviewing full texts ([Figure 1](#)).

Figure 1. Study flow diagram: review update.

Included studies

The review included 12 studies reported in 22 publications. We treated two factorial design studies as two studies (however, counted as one overall) [([Ayah 2007](#); [Ayah 2007 \(2\)](#) one study);

([Newton 2005](#); [Newton 2005 \(2\)](#) one study)]. Five (41%) of the included studies had more than one report ([Mahalanabis 1997](#); [Newton 2010](#); [Semba 2001](#); [West 1995](#); [WHO 1998](#)). When data were available from more than one publication, we extracted relevant data from all the reports; however, we counted the study as one

overall. See [Characteristics of included studies](#) table for more details of the included studies.

All the studies contributed data to a meta-analysis for at least one of the outcomes studied in this review.

Sample size

Trials assigned 24,846 participants aged one to six months, with sample sizes ranging between 89 ([Kutukculer 2000](#)) and 10,297 ([West 1995](#)). The three largest studies contributed about 83% of the total sample size ([Daulaire 1992](#); [West 1995](#); [WHO 1998](#)). We adjusted the original sample size for two studies to account for the cluster design ([Daulaire 1992](#); [West 1995](#)).

Comparisons

Eight (66%) studies compared vitamin A supplementation to placebo and the remainder compared to "no intervention".

Multiple trial arms

Four trials (33%) had multiple arms ([Ayah 2007](#); [Kutukculer 2000](#); [Newton 2005](#); [Semba 2001](#)), and three of these trials used a factorial design ([Ayah 2007](#); [Kutukculer 2000](#); [Newton 2005](#)). Two factorial design trials combined vitamin A with or without placebo between mother and infant and we used these studies as two individual studies in our review ([Ayah 2007](#); [Ayah 2007 \(2\)](#); [Newton 2005](#); [Newton 2005 \(2\)](#)). In these studies, there were individual groups where mother and infant were treated in combinations as follows: mother treated/infant untreated, mother untreated/infant treated, mother treated/infant treated and mother untreated/infant untreated. We included these analyses as follows: mother treated/infant treated versus mother treated/infant untreated and mother untreated/infant treated versus mother untreated/infant untreated. Therefore, in these two trials, the comparisons were considered in a way that mother received the same intervention in both groups and the only difference between groups was infant supplementation with vitamin A. One factorial design trial combined groups in terms of vitamin A and vitamin E ([Kutukculer 2000](#)). This study contributed data for only one outcome and reported values for only vitamin A and control group (irrespective of vitamin E), so we included the study that way. The fourth trial studied two doses of vitamin A and compared them with placebo ([Semba 2001](#)). We combined two vitamin A groups for outcomes of adverse effects as data were available separately for each vitamin A group and placebo. For morbidity outcomes, there were no data (nominators/denominators) available for each group separately but the summary estimates (relative risks) and so we included only one group (dose 25, 000 IU) to avoid double counting of control group data.

Unit of randomisation

Two studies randomised participants in clusters ([Daulaire 1992](#); [West 1995](#)). We combined these trials with individually randomised studies after adjustment for cluster design. We reduced the effective sample size as methods given in *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We used the ICC as calculated previously by [Beaton 1993](#).

Allocation ratio

Participants were evenly allocated to the intervention and control groups in almost all the studies. One study allocated 53% of

participants to the vitamin A group and the remainder to the control group ([Newton 2010](#)).

Location/setting

Trials were conducted in eight countries: eight (66%) in Asia, four of these in Bangladesh ([Baqui 1995](#); [de Francisco 1993](#); [Mahalanabis 1997](#); [Rahman 1995](#)), two in Nepal ([Daulaire 1992](#); [West 1995](#)), and one each in Indonesia ([Semba 2001](#)) and Turkey ([Kutukculer 2000](#)); three (25%) in Africa, two of them in Ghana ([Newton 2005](#); [Newton 2010](#)) and one in Kenya ([Ayah 2007](#)). There was one trial that was conducted in three countries, India, Ghana and Peru ([WHO 1998](#)), representing Asia, Africa and Latin America. Seven of the studies were conducted in rural settings ([Ayah 2007](#); [Daulaire 1992](#); [de Francisco 1993](#); [Newton 2005](#); [Newton 2010](#); [Semba 2001](#); [West 1995](#)), three in urban/peri-urban settings ([Baqui 1995](#); [Mahalanabis 1997](#); [Rahman 1995](#)), and the setting was unclear in two studies ([Kutukculer 2000](#); [WHO 1998](#)).

Age

The age range was one to six months in most of the trials. One trial included neonates and children over six months of age; however, separate data were available for ages one to five months and we included these data ([Daulaire 1992](#)). Another trial included infants less than six months of age including neonates and reported data separately for each month of age ([West 1995](#)). We included data only for infants one to five months of age from this study. In [WHO 1998](#) study, vitamin A was given at ages of 6, 10 and 14 weeks and an additional dose was given at nine months of age. Follow-up data were available for participants before nine months of age and we included them to avoid confounding by later dose of vitamin A.

Sex

Sex was reported in nine trials (75%). The majority assigned approximately equal numbers of boys and girls. One study included 58% boys ([Rahman 1995](#)). The median for boys was 51%.

Time

Most of the studies reported outcomes until six months of age. Three studies had follow-up (and/or participants) beyond six months of age; however, data for clinical outcomes were available below six months of age and we included these ([Daulaire 1992](#); [Semba 2001](#); [WHO 1998](#)).

Intervention

The dose of vitamin A ranged from 25,000 IU to 100,000 IU. The most commonly used dose regimen was 25,000 IU/dose given three times at the time of vaccination at ages 6, 10 and 14 weeks ([Baqui 1995](#); [Newton 2005](#); [Rahman 1995](#); [Semba 2001](#); [WHO 1998](#)). The second most common dose regimen was 50,000 IU/dose given three times at the time of vaccination at ages 6, 10 and 14 weeks ([de Francisco 1993](#); [Mahalanabis 1997](#); [Newton 2010](#)). One study supplemented a single dose of 100,000 IU ([Ayah 2007](#)), and two studies supplemented single doses of 50,000 IU ([Daulaire 1992](#); [West 1995](#)). The route of supplementation was oral in all studies, and vitamin A was given in liquid form.

Co-intervention

Ten of the included studies supplemented vitamin A at the time of vaccination ([Ayah 2007](#); [Baqui 1995](#); [de Francisco 1993](#); [Kutukculer 2000](#); [Mahalanabis 1997](#); [Newton 2005](#); [Newton 2010](#); [Rahman](#)

1995; Semba 2001; WHO 1998), and two studies supplemented vitamin A independent of vaccination (Daulaire 1992; West 1995). Three studies supplemented both mothers and infants (vitamin A or placebo) (Ayah 2007; Newton 2005; WHO 1998).

Excluded studies

See [Characteristics of excluded studies](#) table for the reasons for excluding 40 studies. The most common reason was that vitamin A was supplemented to neonates or to mothers only.

Risk of bias in included studies

See the 'risk of bias' table for individual included studies in the [Characteristics of included studies](#) table and [Figure 2](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ayah 2007	+	+	+	+	?	+
Ayah 2007 (2)	+	+	+	+	?	+
Baqui 1995	+	+	+	?	?	+
Daulaire 1992	+	+	-	+	?	+
de Francisco 1993	+	-	+	+	?	+
Kutukculer 2000	?	?	?	-	?	+
Mahalanabis 1997	+	+	+	+	?	-
Newton 2005	?	?	+	-	?	+
Newton 2005 (2)	?	?	+	-	?	+
Newton 2010	-	-	-	+	?	+
Rahman 1995	+	?	?	+	?	-
Semba 2001	+	+	+	+	?	+
West 1995	+	+	+	+	?	+
WHO 1998	+	+	+	+	+	+

Allocation

From a total of 12 trials, the risk of bias for sequence generation was low in nine trials (Ayah 2007; Baqui 1995; Daulaire 1992; de Francisco 1993; Mahalanabis 1997; Rahman 1995; Semba 2001; West 1995; WHO 1998), while it was unclear in two trials (Kutukculer 2000; Newton 2005). One study had high risk of sequence generation as randomisation was done based on date of birth (Newton 2010). Seven studies successfully concealed allocation, while it was at high risk of bias in two studies (de Francisco 1993; Newton 2010). Three studies provided insufficient information to make an assessment about risk of bias related to allocation concealment (Kutukculer 2000; Newton 2005; Rahman 1995).

Blinding

Eight of the included studies were at low risk of bias for blinding (Ayah 2007; Baqui 1995; de Francisco 1993; Mahalanabis 1997; Newton 2005; Semba 2001; West 1995; WHO 1998), while two were at high risk (Daulaire 1992; Newton 2010). There was insufficient information from two studies to make an assessment about risk of bias for blinding (Kutukculer 2000; Rahman 1995).

Incomplete outcome data

Nine trials reported attrition data adequately and were at low risk of bias (Ayah 2007; Daulaire 1992; de Francisco 1993; Mahalanabis 1997; Newton 2010; Rahman 1995; Semba 2001; West 1995; WHO 1998). Two studies were at high risk attrition bias (Kutukculer 2000; Newton 2005), and there was insufficient information to make an assessment in one study (Baqui 1995).

Selective reporting

Most of the studies did not have study protocols available to make an assessment about risk of bias for selective reporting.

Other potential sources of bias

Most of the included studies did not have any noticeable 'other' risk of bias except two studies that had high risk of bias. These studies recruited participants from a centre for diarrhoea treatment (Mahalanabis 1997; Rahman 1995). The primary aim of these studies was to assess adverse effects of vitamin A supplementation when it was given along with vaccination. These studies utilised a practice of giving vaccination at time of discharge at this diarrhoea treatment centre and offered vitamin A supplements to both participants and their siblings if they fell in the age range. We assumed that all the babies included in this study did not have diarrhoea because siblings were given vitamin A as well and also all the participants received two additional doses of vitamin A after the first dose when they might not have had diarrhoea.

Effects of interventions

See: [Summary of findings for the main comparison](#) Vitamin A supplementation for the prevention of morbidity and mortality in infants one to six months of age

Primary outcomes

All-cause mortality (Outcome 1.1)

Seven studies reported all-cause mortality (two of which had 2 x 2 factorial design, and data were added as 'two sets' from each study) for an overall 21,339 (85%) participants with 279 deaths in

vitamin A group and 259 deaths in comparison group (pooled effect size RR 1.05, 95% CI 0.89 to 1.25; $I^2 = 0\%$, test for heterogeneity: $P = 0.79$) (Analysis 1.1) (Ayah 2007; Ayah 2007 (2); Daulaire 1992; Mahalanabis 1997; Newton 2005; Newton 2005 (2); Newton 2010; West 1995; WHO 1998). The funnel plot drawn for this outcome was symmetrical.

Out of four 'a priori' subgroup analyses, we performed two: maternal vitamin A supplementation (Analysis 1.15) and supplementation given at the time of vaccination (Analysis 1.16). There was no differential effect of vitamin A supplementation in these subgroup analyses and overall effect and statistical significance remained almost the same. The subgroup analysis for 'dose' was not performed because all the studies of infants one to six months of age had a cumulative dose of 50,000 IU or greater. Subgroup analysis for 'low birth weight' was not performed as segregated data were not available for low birth weight infants from any of the individual studies.

Sensitivity analyses were not performed as there was no substantial statistical heterogeneity.

Secondary outcomes

Cause-specific mortality due to diarrhoea (Outcome 1.2)

One trial reported mortality due to diarrhoea with an RR of 0.59 (95% CI 0.20 to 1.70) (Analysis 1.2) (Mahalanabis 1997).

Cause-specific mortality due to acute respiratory infections (Outcome 1.3)

One trial reported cause-specific mortality due to acute respiratory infections with an RR of 2.12 (95% CI 0.40 to 11.33) (Analysis 1.3) (Mahalanabis 1997).

Cause-specific mortality due to meningitis (Outcome 1.4)

One trial contributed data for cause-specific mortality due to meningitis with an RR of 0.35 (95% CI 0.01 to 8.58) (Analysis 1.4) (Mahalanabis 1997).

Morbidity due to diarrhoea (Outcome 1.5)

Two trials provided data for morbidity due to diarrhoea (Semba 2001; WHO 1998). The pooled RR was 0.99 (95% CI 0.93 to 1.05; $I^2 = 0\%$, test for heterogeneity: $P = 0.49$) (Analysis 1.5).

Morbidity due to acute respiratory tract infection (Outcome 1.6)

One trial reported morbidity due to acute respiratory tract infection with an effect size of 0.98 (95% CI 0.81 to 1.19) (Analysis 1.6) (WHO 1998).

Morbidity due to fever (Outcome 1.7)

One study contributed data for morbidity due to fever with an RR of 0.69 (95% CI 0.56 to 0.85) (Analysis 1.7) (Semba 2001).

Adverse effects: bulging fontanelle (Outcome 1.8)

Nine trials reported bulging fontanelle (Baqui 1995; de Francisco 1993; Kutukculer 2000; Mahalanabis 1997; Newton 2010; Rahman 1995; Semba 2001; West 1995; WHO 1998). The pooled RR was 3.10 (95% CI 1.89 to 5.09; $I^2 = 9\%$, test for heterogeneity: $P = 0.36$) (Analysis 1.8). Subgroup analysis for maternal supplementation showed no statistically significant difference when vitamin A

was given to both mothers and infants compared to infants only ([Analysis 1.17](#)). All the included studies in this analysis supplemented vitamin A at the time of vaccination, so no subgroup analyses were performed for this aspect of the intervention.

Adverse effects: vomiting (Outcome 1.9)

Two trials provided data on vomiting with a pooled RR of 0.95 (95% CI 0.67 to 1.35; $I^2 = 94\%$, test for heterogeneity: $P < 0.0001$) ([Analysis 1.9](#)) ([Semba 2001](#); [West 1995](#)).

Adverse effects: irritability (Outcome 1.10)

Four trials provided data on irritability with a pooled RR of 0.88 (95% CI 0.65 to 1.20; $I^2 = 0\%$, test for heterogeneity: $P = 0.63$) ([Analysis 1.10](#)) ([Mahalanabis 1997](#); [Newton 2010](#); [Rahman 1995](#); [West 1995](#)).

Adverse effects: diarrhoea (Outcome 1.11)

Three trials provided data on diarrhoea with a pooled RR of 1.07 (95% CI 0.82 to 1.40; $I^2 = 0\%$, test for heterogeneity: $P = 0.39$) ([Analysis 1.11](#)) ([Mahalanabis 1997](#); [Rahman 1995](#); [West 1995](#)).

Adverse effects: fever (Outcome 1.12)

Three trials provided data on fever with a pooled RR of 0.94 (95% CI 0.83 to 1.07; $I^2 = 83\%$, test for heterogeneity: $P = 0.003$) ([Analysis 1.12](#)) ([Newton 2010](#); [Semba 2001](#); [West 1995](#)).

Convulsions (Outcome 1.13)

One study contributed data for convulsions with an RR of 0.19 (95% CI 0.01 to 3.85) ([Analysis 1.13](#)) ([Newton 2010](#)).

Vitamin A deficiency (Outcome 1.14)

Three trials reported VAD with a pooled RR of 0.86 (95% CI 0.70 to 1.06; $I^2 = 27\%$, test for heterogeneity: $P = 0.25$) ([Analysis 1.14](#)) ([Ayah 2007](#); [Mahalanabis 1997](#); [WHO 1998](#)).

DISCUSSION

Summary of main results

Vitamin A supplementation for infants one to six months of age showed no effect on all-cause mortality during infancy. The pooled effect size suggested an increased risk of 5%; however, results were not statistically significant (RR 1.05, 95% CI 0.89 to 1.25). There were no significant effects on mortality or morbidity due to diarrhoea or respiratory tract infection. There was a three times increased risk of bulging fontanelle in the vitamin A supplemented group compared to control (RR 3.10, 95% CI 1.89 to 5.09). There was no increased risk of other adverse effects such as vomiting, irritability, diarrhoea, fever and convulsions. Vitamin A supplementation did not decrease VAD in the intervention group compared to control.

Overall completeness and applicability of evidence

This review used comprehensive methods to evaluate risks and benefits associated with vitamin A supplementation in infants one to six months of age. The 12 included studies contributed 24,846 participants and were conducted in low- and middle-income countries. Most studies contributed data for at least two outcomes (i.e. all-cause mortality and adverse effect of bulging fontanelle); results were consistent among all the studies with no substantial statistical heterogeneity.

Does vitamin A supplementation have 'any' benefit in terms of protection against mortality or morbidity when given between ages one and six months? Based on the findings of this review, the most likely answer is 'no'. There were no beneficial effects on all-cause or cause-specific mortality and morbidity. The primary analysis for all-cause mortality included seven trials and 21,877 (88%) participants and had no statistical heterogeneity in the pooled data. The number of studies in cause-specific mortality and morbidity were small, and no solid conclusion can be made from them except that current evidence does not support any beneficial effect of vitamin A supplementation in this age group.

Is there any risk or harmful effects associated with vitamin A supplementation in infants one to six months of age? The most important finding of this review was that the incidence of bulging fontanelle was three times higher in vitamin A group compared to control in the first 24 to 72 hours post supplementation. Almost all the studies that reported this outcome also reported that it was self resolved in all the cases, and there was no increased risk of mortality, convulsions or irritability. It is not clear if there was a dose-response relationship for this outcome as two small studies reported higher incidence with subsequent doses ([Baqui 1995](#); [de Francisco 1993](#)); however, a subsequent larger study did not reproduce these results ([WHO 1998](#)).

Does vitamin A supplementation at the time of vaccination have any beneficial or harmful effects for response to vaccines? Ten of the included studies supplemented vitamin A at the time of vaccination mostly at ages of 6, 10 and 14 weeks. Five of these studies reported serum levels of antibodies to different vaccines and there was no differential effect of vitamin A in favour or against the antibody response to tetanus toxoid, polio, measles, hepatitis B and influenza vaccines ([Table 1](#)).

Quality of the evidence

[Summary of findings for the main comparison](#) shows overall quality assessment of pooled estimates. We graded most of the outcomes as moderate or low quality. These assessments considered type of studies, risk of bias, consistency, indirectness, imprecision and strength of association and publication bias, etc. ([Balslem 2011](#)). Most of the assessments for outcomes of this review were influenced by imprecision of summary estimate and risk of bias in included studies. In terms of risk of bias, the study by [Newton 2010](#) was at high risk of bias for sequence generation because randomisation was done based on date of birth. Also blinding was not done in this study. Two studies were at high risk of 'other' bias because the participants were recruited at time of discharge from a centre that treated children with diarrhoea ([Mahalanabis 1997](#); [Rahman 1995](#)). We assumed that most of these infants had recovered from diarrhoea before receiving the first dose of vitamin A supplementation, and these infants were given two subsequent doses when they did not have diarrhoea. Therefore, it is less likely that all of these infants were having diarrhoea at the time of vitamin A supplementation, and they received at least two doses when they were diarrhoea-free.

Potential biases in the review process

This review applied standard Cochrane guidelines for clearly defined inclusion/exclusion criteria, and a comprehensive search strategy for identification of relevant studies. We combined cluster randomised trials with individual randomised trials for meta-

analyses and applied an appropriate adjustment to reduce their effective sample size.

The comprehensive search strategy aimed to identify all published and unpublished studies, though none of the included studies were unpublished. It is more likely that a study with positive results will be published compared to a study that had negative results; however, the funnel plot for the primary outcome was symmetrical (data not shown).

Most of the studies that reported the primary outcome did not report secondary outcomes that might lead to selective outcome reporting bias.

Agreements and disagreements with other studies or reviews

The findings of lack of effect of vitamin A supplementation for infants one to six months of age for all-cause mortality are in agreement with a previous review done by our team ([Imdad 2011](#)). The previous review by our team mainly focused on mortality outcome as part of an exercise to develop summary estimates for the Lives Saved Tool ([LiST 2014](#); [Imdad 2011](#)). The current review not only assessed mortality outcomes but also those of morbidity and adverse effects. A previous version of this review included infants under six months of age, including neonates. A subgroup analysis for all-cause mortality for infants one to six months of age in that review showed similar results for all-cause mortality (RR 1.05, 95% CI 0.84 to 1.32) ([Gogia 2011](#)).

It is surprising to note that there is strong evidence that vitamin A supplementation reduces morbidity and mortality in children 6 to 59 months of age ([Imdad 2010](#)) and not in infants one to six months of age. Vitamin A is thought to work by reducing mortality and morbidity related to infectious diseases, mainly diarrhoea and measles. There were not enough studies that reported cause-specific mortality or morbidity in this review; therefore, it is difficult to make a statement if vitamin A had any differential effect on these infectious causes.

Recently published literature has described the development of human gastrointestinal microbiota over time and how it can determine risk for certain diseases ([Blanton 2016](#); [Cho 2012](#)). It was shown that human gastrointestinal microbiota changes significantly in the first two years of life and younger children had certain bacteria that are essential for growth ([Blanton 2016](#)). Is it

that fecal microbiota of younger infants is not mature enough to have detrimental effect from vitamin A supplementation? Future research might provide further insight into this question.

AUTHORS' CONCLUSIONS

Implications for practice

There is no protective effect of vitamin A supplementation in infants one to six months of age against mortality or morbidity. Vitamin A supplementation in this age group increases the risk of bulging fontanelle; however, there was no evidence of subsequent complication from this adverse effect. There was no demonstrable effect of vitamin A supplementation on immune response to vaccination.

Implications for research

Considerable research has already been conducted to evaluate the effect of vitamin A supplementation in the first six months of life on infant outcomes. Most of the studies included in this review were conducted in the mid-1990s and early 2000s, and it is not clear if there would be any beneficial effect related to vitamin A supplementation when the overall prevalence of vitamin A deficiency is decreasing ([Stevens 2015](#)). It will be interesting to know if vitamin A supplementation during infancy enhances the effect of vitamin A given later in life. One study addressed this question in the past when a post-hoc analysis was done for participants who were given vitamin A during the neonatal period and mortality was assessed during one to three years of life ([Fisker 2011](#)). This study showed that mortality was lower for children who received vitamin A as neonates and received subsequent routine vitamin A according to the World Health Organization guideline ([Fisker 2011](#)). However, this study was not powered to assess this outcome (post-hoc analysis) and vitamin A was given during the neonatal period. It is not clear if a similar effect can be shown for vitamin A when given during one to six months of life.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ayah 2007

Methods	Randomised, placebo-controlled, double-blind, 2 x 2 factorial trial Data collection: July 1999 to November 2001
Participants	n = 564 Inclusion criteria: recently delivered women with live singleton neonates Exclusion criteria: none 51% boys
Interventions	2 x 2 factorial design Aa group: maternal vitamin A, infant vitamin A (mother received 400,000 IU vitamin A within 24 hours of delivery; infant received 100,000 IU vitamin A at 14 weeks of age with DPT and OPV vaccines; n = 142) Pa group: maternal placebo, infant vitamin A (mother received placebo within 24 hours of delivery; infant received 100,000 IU vitamin A at 14 weeks of age with DPT and OPV vaccines; n = 143) Ap group: maternal vitamin A, infant placebo (mother received 400,000 IU vitamin A within 24 hours of delivery; infant received placebo at 14 weeks of age with DPT and OPV vaccines; n = 140) Pp group: maternal placebo, infant placebo (mother received placebo within 24 hours of delivery; infant received placebo at 14 weeks of age with DPT and OPV vaccines; n = 139) All pregnant women received presumptive malarial treatment in their second and third trimesters In Ayah 2007 , we included data for Aa vs. Ap, and in Ayah 2007 (2) we included data for Pa vs. Pp groups
Outcomes	Infant supplementation: all-cause mortality, bulging fontanelle
Notes	Location: Bondo District, rural western Kenya (Africa) HIV status: earlier HIV prevalence reported as 28% among antenatal clinic attendees; however, the trial was conducted before to the availability of HIV testing and antiretroviral prophylaxis for antenatal women in public sector facilities in western Kenya Mortality outcome data were taken from figure 1 (trial profile). We included raw numbers after mother-infant pair was randomised. We treated the trial as 2 studies and included data in a way that mother

Ayah 2007 (Continued)

received the same supplementation between the groups and only difference was infant vitamin A supplementation i.e. Aa vs. Ap and Pa vs. Pp

Adverse effect of bulging fontanelle was recorded as a comparison of infants receiving vitamin A or placebo irrespective of maternal vitamin A supplementation. We included the data as 1 group for this comparison

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"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"
Allocation concealment (selection bias)	Low risk	"The randomization codes were concealed for the entire trial duration and only revealed after completion of data analysis"
Blinding (performance bias and detection bias) All outcomes	Low risk	"...prepared and supplied the vitamin A and identical-looking placebo supplements as oily capsules in brown bottles coded as X or Y"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition of 8% at 14 weeks' follow-up and that of 22% at 26 weeks. The reasons for attrition were described for each group and comparable among groups. All analyses were by intention to treat
Selective reporting (reporting bias)	Unclear risk	No protocol was not available to make an assessment
Other bias	Low risk	The study seemed to be free of other bias

Ayah 2007 (2)

Methods	See Ayah 2007 above
Participants	See Ayah 2007 above
Interventions	<p>2 x 2 factorial design</p> <p>Aa group: maternal vitamin A, infant vitamin A (mother received 400,000 IU vitamin A within 24 hours of delivery; infant received 100,000 IU vitamin A at 14 weeks of age with DPT and OPV vaccines; n = 142)</p> <p>Pa group: maternal placebo, infant vitamin A (mother received placebo within 24 hours of delivery; infant received 100,000 IU vitamin A at 14 weeks of age with DPT and OPV vaccines; n = 143)</p> <p>Ap group: maternal vitamin A, infant placebo (mother received 400,000 IU vitamin A within 24 hours of delivery; infant received placebo at 14 weeks of age with DPT and OPV vaccines; n = 140)</p> <p>Pp group: maternal placebo, infant placebo (mother received placebo within 24 hours of delivery; infant received placebo at 14 weeks of age with DPT and OPV vaccines; n = 139)</p> <p>All pregnant women received presumptive malarial treatment in their second and third trimesters</p> <p>In Ayah 2007, we included data for Aa vs. Ap, and in Ayah 2007 (2), we included data for Pa vs. Pp groups</p>
Outcomes	See Ayah 2007 above

Ayah 2007 (2) (Continued)

Notes See [Ayah 2007](#) above

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Ayah 2007 above
Allocation concealment (selection bias)	Low risk	See Ayah 2007 above
Blinding (performance bias and detection bias) All outcomes	Low risk	See Ayah 2007 above
Incomplete outcome data (attrition bias) All outcomes	Low risk	See Ayah 2007 above
Selective reporting (reporting bias)	Unclear risk	See Ayah 2007 above
Other bias	Low risk	See Ayah 2007 above

Baqui 1995

Methods	Randomised, double-blind, placebo-controlled trial Data collection: 1993
Participants	n = 167 Inclusion criteria: infants registered in local demographic surveillance system aged 6 to 7 weeks Exclusion criteria: severe malnutrition (defined as weight/age < 60% of the National Center for Health Statistics reference median); clinical vitamin A deficiency (any signs or symptoms) 41% boys
Interventions	Intervention: vitamin A 25,000 IU palmitate in peanut oil and transport media, given at 6, 10 and 14 weeks of age (n = 86) Control: soybean oil and the same transport media given at 6, 10 and 14 weeks of age (n = 81)
Outcomes	Mortality: not recorded Morbidity: not recorded Adverse effects: bulging fontanelle Follow-up on days 1, 2, 3 and 8
Notes	Location: slum population, Dhaka city, Bangladesh (Asia). The study was carried out in the Urban Surveillance System (USS) area of the Urban Health Extension Project (UHEP) of the International Centre for Diarrhoeal Disease Research, Bangladesh

Baqui 1995 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"5 different numbers between 1 to 10 were randomly assigned to bottle A and rest 5 were assigned to bottle B. The last digit of the serial number assigned to the infant determined the bottle from which the infant received the supplement, each infant received all doses from bottle with the same code"
Allocation concealment (selection bias)	Low risk	"The randomization code was supplied in a sealed envelope to a committee of two paediatricians and a statistician who were not involved in the study. The code was made available after data analysis was completed"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Vitamin A and placebo were supplied by a local pharmaceutical company as 1 ml of fluid in small, dark bottles, which were marked "A" or "B" "
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9.7% of infants lost to follow-up and not accounted for in the analysis. Reason for attrition were not given
Selective reporting (reporting bias)	Unclear risk	Protocol was not available to make an assessment
Other bias	Low risk	Study seemed to be free of other bias

Daulaire 1992

Methods	Cluster randomised, non-placebo controlled trial conducted in Jumla district, Nepal, Asia
Participants	<p>n = 7197 aged 1 to 59 months; 1058 aged 1 to 5 months</p> <p>Inclusion criteria: children 1 to 59 months of age</p> <p>Exclusion criteria: infants < 1 month of age</p> <p>16 clusters were randomly assigned either to vitamin A or control group. These included 7197 children in which 3786 children were in vitamin A group and 3411 in control group. There were 547 infants in vitamin A group and 511 in placebo group who were aged 1 to 5 months</p> <p>51% boys</p>
Interventions	<p>Intervention: vitamin A 50,000 IU for infants < 6 months old (n = 547)</p> <p>Control: no intervention (n = 511)</p> <p>Following doses of vitamin A were used for older children: 100,000 IU for infants 6 to 12 months of age and 200,000 IU for children aged 12 to 59 months</p>
Outcomes	<p>Mortality: given</p> <p>Morbidity: not given</p> <p>Adverse effects: not given</p>
Notes	Location: remote mountainous region of north-western Nepal with a total population of about 80,000, with 12,000 children < 5 years of age. This area was considered as 1 of the poorest and most medically underserved areas of the country. Infant mortality rate was 189 deaths per 1000 live births and child (1

Daulaire 1992 (Continued)

to 4 years of age) mortality rate was 52 per 1000 per year. Malnutrition was prevalent in the study area, and 26% of children aged 1 to 4 years were had substantial malnutrition. A survey of 3651 children in children under 5 years showed active xerophthalmia in 1.3% to 2% of population and 1% to 5% among infants, which is high for this age group. Disaggregated data on mortality were available according to different age groups

We included data for infants 1 to 5 months of age only according to the objectives of our review

Cluster design; however, the design effect was not given. We adjusted for cluster design by decreasing the effective sample size using methods given in *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We used a design effect of 1.92 as calculated previously by Beaton 1993

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"We randomly selected by card eight of the 16 sub-districts for vitamin A supplementation" Probably done
Allocation concealment (selection bias)	Low risk	Allocation concealment is usually not a major issue in a cluster randomised trial as sequence generation is done at once for all clusters
Blinding (performance bias and detection bias) All outcomes	High risk	Control group was open so essentially no masking was done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Low risk	This study appeared to be free of other bias

de Francisco 1993

Methods	Randomised, double-blind, placebo-controlled trial
Participants	n = 191 Inclusion criteria: infants Exclusion criteria: severe malnutrition defined as weight < 60% of National Center for Health Statistics
Interventions	Intervention: vitamin A 50,000 IU (palmitate in peanut oil and transport media) at 1.5, 2.5 and 3.5 months of age (n = 96) Control: soybean oil and the same transport media as above at 1.5, 2.5 and 3.5 months of age (n = 95) Infants were examined on days 1, 2, 3 and 8 after supplementation
Outcomes	Mortality: not recorded Morbidity: not recorded Adverse effects: bulging fontanelle

Vitamin A supplementation for the prevention of morbidity and mortality in infants one to six months of age (Review)

de Francisco 1993 (Continued)

Follow-up on days 1, 2, 3 and 8

Notes	<p>Location: rural Bangladesh (Asia). "The trial was conducted in the Matlab Maternal and child health-family planning (MCH-FP) programme intervention area. This part of Bangladesh has an agricultural subsistence economy, poor infrastructure and communications, and high poverty and illiteracy rates. Bangladesh is classified as a country where vitamin A deficiency has reached public health significance".</p> <p>Study funded by the USUSAID under grant No. DPE-5986-A-00-1009-00 with the International Centre for Diarrhoeal Disease Research, Bangladesh</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computerised randomization procedure had been used to assign a bottle code to each infant"
Allocation concealment (selection bias)	High risk	"The randomization code was supplied to a committee of two paediatricians and a statistician, who were able to stop the trial"
Blinding (performance bias and detection bias) All outcomes	Low risk	<p>"Vitamin A (50,000 IU palmitate in peanut oil and transport media) and a placebo (soybean oil and the same transport media) were supplied as 1 mL liquid in dark small, bottles, which were marked A or B"</p> <p>Outcome assessors were unaware of the bottle code</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Losses of follow-up were minimal and equally distributed in the vitamin A and placebo groups"
Selective reporting (reporting bias)	Unclear risk	The protocol was not available to make an assessment
Other bias	Low risk	This study seemed to be free of other bias

Kutukculer 2000

Methods	Randomised control trial
Participants	<p>n = 89</p> <p>Inclusion criteria: healthy infants aged 2 months</p> <p>Exclusion criteria: infants who have prematurity, low birthweight (< 10%), congenital anomalies, systemic diseases, intrauterine infections. In addition, infants born to once or twice-immunised mothers against tetanus during pregnancy not included</p>
Interventions	<p>Group A: vitamin A 30,000 IU orally (retinol palmitate 30,000 IU) for 3 days just after all 3 doses of primary vaccination (n = 24)</p> <p>Group E: vitamin E 100 IU oral for only 1 day after the injections for primary immunisation (n = 21)</p> <p>Group AE: vitamin A 30,000 IU + vitamin E 100 IU as a single dose (n = 21)</p> <p>Group C: control with no vitamin supplementation after DPT immunisation (n = 23)</p>

Kutukculer 2000 (Continued)

Outcomes	The geometric mean titers of serum tetanus antitoxin were measured in response to vitamin A supplementation at 2, 5, and 6 to 18 months. Adverse effects were also reported at 24 and 48 hours after vitamin supplementation
Notes	<p>Conducted in Turkey</p> <p>All the infants received vitamin D 400 IU daily for 1 year. All infants breastfed until 4 to 6 months of age. Then, fed with a standard feeding schedule in order to minimise the effects of feeding on the development of the immune system</p> <p>This study contributed data for only one outcome, i.e. bulging fontanelle and data were given and included only for vitamin A alone (group A) and control (group C)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient data make an assessment
Allocation concealment (selection bias)	Unclear risk	Insufficient data make an assessment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient data make an assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	All participants enrolled were not accounted for in the analysis. During follow-up, some of the infants who had pulmonary infections or diarrhoea lasting > 1 week and infants who did not receive vitamins regularly and who were not vaccinated on time were excluded from the study. As a result, 70 infants were evaluated at 5 months and 40 at 16 to 18 months. It was not further described if there was a differential attrition among groups
Selective reporting (reporting bias)	Unclear risk	Study protocol was not available to make an assessment
Other bias	Low risk	This study seemed to be free of other bias

Mahalanabis 1997

Methods	Randomised, double blind, clinical trial
Participants	<p>n = 210</p> <p>Infants aged 6 to 17 weeks attending immunisation clinics for first dose of DPT and OPV</p>
Interventions	<p>Intervention: vitamin A 50,000 IU in peanut oil given with immunisation contact (n = 97)</p> <p>Control: soybean oil given at each immunisation contact (n = 103)</p> <p>3 doses were given at 1, 4 and 8 weeks along with immunisation. Follow-up at 1, 3 and 6 months after the third dose</p>
Outcomes	<p>Mortality: given</p> <p>Adverse effects: given</p>

Mahalanabis 1997 (Continued)

Notes	<p>Location: urban area in Dhaka, Bangladesh</p> <p>Participants were recruited from diarrhoea treatment centre of International Centre for Diarrhoeal Disease Research, Bangladesh and it was not clear if participants actually had diarrhoea at enrolment. We included this study as children were given vitamin A beyond hospitalisation and we assumed that at least 2nd and 3rd dose was given when child was free of diarrhoea</p> <p>Morbidity outcomes were given in a separate publication and numbers were reported per child year. The exact denominator was not given so data were not pooled</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A randomization table was prepared by a person not directly involved with the conduct of the study using permuted blocks of random numbers"
Allocation concealment (selection bias)	Low risk	"Sets of three bottles containing either vitamin A or placebo for each patient were serially numbered according to the randomization chart and corresponding to the study serial numbers"
Blinding (performance bias and detection bias) All outcomes	Low risk	<p>"Vitamin A palmitate 50,000 IU in peanut oil made up into a liquid formulation and a placebo made from soybean oil in a liquid formulation were provided as individual doses in screw-capped dark bottles by a pharmaceutical company"</p> <p>Probably done</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition was given in table 1 of the study
Selective reporting (reporting bias)	Unclear risk	Insufficient data to permit judgement
Other bias	High risk	Study participants were recruited from diarrhoea treatment centre of International Centre for Diarrhoeal Disease Research, Bangladesh and it was not clear if participants actually had diarrhoea at the of enrolment. Therefore, it is not clear if the study participants were representative of otherwise healthy children from the community

Newton 2005

Methods	<p>Randomised, placebo-controlled, 2 x 2 factorial design trial</p> <p>Data collection: November 1996 to January 1999</p>
Participants	<p>n = 1085, mother-infant pair</p> <p>Inclusion criteria: newly delivered mother and her infant recruited 3 to 4 weeks' postpartum</p> <p>Exclusion criteria: families intending to move out of the study area</p>
Interventions	<p>2 x 2 factorial design</p> <p>Aa group: maternal vitamin A, infant vitamin A (mother received vitamin A 200,000 IU at 3 to 4 weeks' postpartum; infant received vitamin A 25,000 IU at 6, 10 and 14 weeks of age with DPT and OPV vaccines; n = 274)</p>

Newton 2005 (Continued)

Pa group: maternal placebo, infant vitamin A (mother received placebo within 24 hours of delivery; infant received vitamin A 25,000 IU at 6, 10 and 14 weeks of age with DPT and OPV vaccines; n = 265)

Ap group: maternal vitamin A, infant placebo (mother received vitamin A 200,000 IU within 24 hours of delivery; infant received placebo at 6, 10 and 14 weeks of age with DPT and OPV vaccines; n = 269)

Pp group: maternal placebo, infant placebo (n = 277)

In [Newton 2005](#), we included data for Aa vs. Ap, and in [Newton 2005 \(2\)](#), we included data for Pa vs. Pp

Outcomes	Mortality Morbidity: not recorded Adverse effects: not recorded Follow-up at 6 months
Notes	Location: Kintampo, Ghana (Africa) Breastfeeding rate almost 100% and 51% of children aged < 5 years in the area had serum retinol concentrations < 0.70 µmol/L 3 vitamin A supplementation strategies were investigated: supplementation of breastfeeding mothers with RE vitamin A 200,000 IU within 4 weeks of delivery; Expanded Program on Immunization-linked supplementation of infants with RE vitamin A 25,000 IU at 6, 10 and 14 weeks and combined mother and child supplementations. A fourth group in which mother and child were given placebos served as controls

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Mothers and infants were allocated to 1 of 4 treatment groups, using a blocked randomization scheme" No further details were available to make an assessment
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make an assessment
Blinding (performance bias and detection bias) All outcomes	Low risk	"The test and placebo capsules were identical in size colour and shape"
Incomplete outcome data (attrition bias) All outcomes	High risk	Only infants of mothers for which blood sample was obtained in the end of the study were included in the analysis; attrition was 34.6%
Selective reporting (reporting bias)	Unclear risk	Study protocol was not available to make an assessment
Other bias	Low risk	Enrolment of participants was extended due to higher than planned loss to follow-up; sample size calculation provided, but unclear whether a protocol was published a priori Supported by a grant from the Wellcome Trust

Newton 2005 (2)

Methods	See Newton 2005 above
Participants	See Newton 2005 above
Interventions	<p>2 x 2 factorial design</p> <p>Aa group: maternal vitamin A, infant vitamin A (mother received vitamin A 200,000 IU at 3 to 4 weeks' postpartum; infant received vitamin A 25,000 IU at 6, 10 and 14 weeks of age with DPT and OPV vaccines; n = 274)</p> <p>Pa group: maternal placebo, infant vitamin A (mother received placebo within 24 hours of delivery; infant received vitamin A 25,000 IU at 6, 10 and 14 weeks of age with DPT and OPV vaccines; n = 265)</p> <p>Ap group: maternal vitamin A, infant placebo (mother received vitamin A 200,000 IU within 24 hours of delivery; infant received placebo at 6, 10 and 14 weeks of age with DPT and OPV vaccines; n = 269)</p> <p>Pp group: maternal placebo, infant placebo (n = 277)</p> <p>In Newton 2005, we included data for Aa vs. Ap, and in Newton 2005 (2), we included data for Pa vs. Pp</p>
Outcomes	See Newton 2005 above
Notes	See Newton 2005 above

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Newton 2005 above
Allocation concealment (selection bias)	Unclear risk	See Newton 2005 above
Blinding (performance bias and detection bias) All outcomes	Low risk	See Newton 2005 above
Incomplete outcome data (attrition bias) All outcomes	High risk	See Newton 2005 above
Selective reporting (reporting bias)	Unclear risk	See Newton 2005 above
Other bias	Low risk	See Newton 2005 above

Newton 2010

Methods	Open label, quasi-randomised, controlled trial
Participants	<p>n = 1095</p> <p>Infants aged 6 to 14 weeks</p>
Interventions	Intervention: vitamin A 50,000 IU orally with vaccines at each visit at 6, 10 and 14 weeks of age (n = 559)

Newton 2010 (Continued)

Control: no placebo given (n = 518)

At the end of the trial, at 18 weeks of age, all infants were given vitamin A 100,000 IU. Mothers of infants in both groups had received vitamin A 400,000 IU as retinol palmitate, post delivery

Outcomes	Mortality: not reported Morbidity: not reported Adverse effects: reported
Notes	Location: 3 towns in the Ashanti region of Ghana Results reported in 3 different publications

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Infants were assigned to intervention or control group based on date of birth
Allocation concealment (selection bias)	High risk	Inadequate randomisation methods and open-label trial. Probably not done
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not done due to cost and logistical constraint
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition of about 18% that was balanced between the 2 groups
Selective reporting (reporting bias)	Unclear risk	Insufficient data to assess
Other bias	Low risk	This study seemed to be free of other bias

Rahman 1995

Methods	Individual, randomised controlled trial
Participants	n = 199 Inclusion criteria: infants aged 6 to 17 weeks Exclusion criteria: any infant with serious illness
Interventions	Intervention: vitamin A 25,000 IU given for 3 doses (n = 101) Control: soya bean oil (n = 98) Vitamin A was given with vaccination
Outcomes	Adverse effects
Notes	Location: Bangladesh

Rahman 1995 (Continued)

Participants were recruited from a centre where infants were treated for diarrhoea; however, not all the children had diarrhoea at the time of vitamin A supplementation

Data for vomiting unclear so not included in analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A randomization list was prepared by senior staff..." Most likely done
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make an assessment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information to make an assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Study protocol was not available to make an assessment
Other bias	High risk	Participants were recruited from a centre where infants were treated for diarrhoea; however, not all the children had diarrhoea at the time of vitamin A supplementation

Semba 2001

Methods	Randomised, double-blind, placebo-controlled clinical trial
Participants	n = 467 Inclusion criteria: infants < 6 weeks of age Exclusion criteria: none
Interventions	Group 1: vitamin A 25,000 IU at 6, 10 and 14 weeks of life (n = 156) Group 2: vitamin A 50,000 IU at 6, 10 and 14 weeks of life (n = 155) Control: placebo (n = 156) Co-intervention with OPV and DPT vaccine at each visit
Outcomes	Mortality: not recorded Morbidity Adverse effects Follow-up within 24 hours of first visit at 6 weeks in 293 infants; follow-up at 10 and 14 weeks and at 9, 10 and 15 months

Semba 2001 (Continued)

Notes

Location: Indonesia (Asia). Supported by grants from the National Institutes of Health (AI35143, HD30042); the Thrasher Research Fund; the WHO Expanded Programme on Immunization and the Office of Nutrition, Bureau for Science and Technology, USAID (Cooperative Agreement DAN-0045-A-5094-00)

Protocol mentioned but no details given

For morbidity outcomes of diarrhoea and fever, we included data for only 1 group (25,000 IU) to avoid counting the placebo data twice as the individual level data were not available

For adverse effects, we combined both vitamin A groups as the data were given for each group separately

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomly allocated by number table in blocks of ten"
Allocation concealment (selection bias)	Low risk	"Infants received identification numbers as they were enrolled into the study, and each identification number had an envelope with an identical capsule containing either vitamin A or placebo. At the time of treatment allocation, both paediatrician and study nurse were required to verify the identification number of the infant"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Identical capsules containing either vitamin A or placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions and attrition was 8.4%; reasons for attrition and exclusions not reported
Selective reporting (reporting bias)	Unclear risk	Study protocol was not available to make an assessment
Other bias	Low risk	This study seemed to be free of other bias

West 1995

Methods	Cluster-randomised, double-masked, placebo-controlled trial Data collection: September 1989 to December 1991
Participants	All ages: n = 11,918; 1 to 5 months of age: n = 10,297 Inclusion criteria: infants aged ≤ 6 months Exclusion criteria: none
Interventions	Intervention: vitamin A 50,000 IU 1 oral dose (3 drops of oil) for neonates, 100,000 IU (6 drops of oil) for infants 1 to 5 months of age; n = 5256 aged 1 to 5 months) Control: 1 oral dose of placebo, 75 RE (250 IU) for neonates or 150 RE (500 IU) for infants 1 to 5 months of age; n = 5041 aged 1 to 5 months)

West 1995 (Continued)

All supplements also contained vitamin E ~ 3.3 IU/drop, added as an antioxidant

Outcomes	Mortality Morbidity: not recorded Adverse effects Follow-up 4 monthly until 6 months of age
Notes	Location: Sarlahi, Nepal (Asia) Setting: community trial (261 wards in 29 village development areas (33,000 households)) We included only data for infants 1 to 5 months of age Cluster adjustment: we decreased the effective sample size using methods giving in <i>Cochrane Handbook for Systematic Reviews of Interventions</i> and using a design effect of 1.22 as calculated previously by Beaton 1993 Supported by a grant from Johns Hopkins University and assistance from Hoffmann-La Roche industry (Basel, Switzerland) A protocol was described but no details were provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>"Two hundred sixty-one wards in 29 contiguous village development areas (VDAs) in the District of Sanlahi were mapped and 33,000 households were numbered. After a random start, wards were systematically assigned, blocked on VDAs, for infants to receive an oral dose of vitamin A"</p> <p>Most likely done</p>
Allocation concealment (selection bias)	Low risk	Allocation concealment is usually not a major concern in cluster trial as sequence is generated all at once
Blinding (performance bias and detection bias) All outcomes	Low risk	"The supplements were given as single-dose gelatin capsules of identical taste and appearance." "Capsule codes were broken" after the study was over
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All analyses were performed on an intention-to-treat basis, that is, by randomized treatment group irrespective of individual compliance to the dosing regimen"
Selective reporting (reporting bias)	Unclear risk	In the absence of trial protocol, it is unclear if all prespecified outcomes were reported
Other bias	Low risk	This study seemed to be free of other bias

WHO 1998

Methods	Randomised, double-blind, multicentre trial
Participants	n = 9424 Inclusion criteria: pregnant women and women with newborn babies

Vitamin A supplementation for the prevention of morbidity and mortality in infants one to six months of age (Review)

WHO 1998 (Continued)

Exclusion criteria: families intending to leave study site

Interventions	<p>Intervention: vitamin A (mothers 21 to 42 days' postpartum in Ghana and 18 to 28 days' postpartum in India and Peru received vitamin A 200,000 IU at enrolment; infants received 25,000 IU at 6, 10 and 14 weeks in India and Ghana and at 2, 3 and 4 months in Peru) (n = 4716)</p> <p>Control: placebo to both mothers and infants at the same time as the vitamin A group (n = 4708)</p> <p>At 9 months, with measles immunisation, infants in the vitamin A group were given vitamin A 25,000 IU, whereas those in control group received vitamin A 100,000 IU. Vitamin A was provided as retinol palmitate with minute amounts of vitamin E; placebo was soy bean oil</p>
Outcomes	<p>Mortality</p> <p>Morbidity</p> <p>Adverse effects</p> <p>Follow-up: 4 weekly until 12 months of age</p>
Notes	<p>Location: "The trial was implemented in three countries that have clinical (Ghana and India) or severe subclinical (Peru) vitamin A deficiency. The sites were the Brong Ahafo region of Ghana (Kintampo), New Delhi, India (Dakshinपुरी and Tigrī), and Lima, Peru (Canto Grande). Available data from the sites indicated these regions to be areas of severe subclinical vitamin A deficiency, according to WHO's criteria. The proportion of children younger than 5 years with serum retinol equal or below 0.70 mmol/L exceeded 20% in the three sites - values range from 44% in New Delhi to 51% in Kintampo"</p> <p>We included mortality, morbidity and adverse effect data for follow-up until 9 months of age as children got additional vitamin A at 9 months at the time of measles vaccination. We used the raw numbers where possible as per protocol for this review</p> <p>For outcomes of bulging fontanelle outcomes, we included data for first dose as most of other pooled studies reported data for first dose</p> <p>Supported by Child Health and Development Division, WHO (Geneva), Indian Council of Medical Research and Johns Hopkins Family Health and Child Survival Co-operative agreement with USAID</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Identification numbers were generated by computer at the data management centre at John Hopkins University in Baltimore, and assigned as random permuted blocks of size eight"
Allocation concealment (selection bias)	Low risk	"Three sealed copies of study codes were prepared and kept at WHO in Geneva, with the ethics committee of the All India Institute of Medical Sciences in New Delhi, and at the data management centre in Baltimore. Access was limited to one data manager, who had no direct involvement in the data analysis, and who prepared information requested by the treatment effects monitoring committee"
Blinding (performance bias and detection bias) All outcomes	Low risk	"The supplements and placebo, in identical opaque gelatin capsules, were packaged in individually coded blister packs in Baltimore"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All analyses were intention to treat; reasons and distributions in the 2 groups were provided

WHO 1998 (Continued)

Selective reporting (reporting bias)	Low risk	All clinically relevant outcomes reported
Other bias	Low risk	Sample size calculation reported; protocol and study standard operating procedure available in the WHO, Geneva on request

DPT: diphtheria, pertussis (whooping cough) and tetanus; HIV: human immunodeficiency virus; IU: international units; n: number of participants; OPV: oral polio vaccine; RE: retinol equivalent; USAID: US Agency for International Development; WHO: World Health Organization.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ahmad 2014	Vitamin A supplemented during neonatal period
Basu 2003	Not placebo controlled
Benn 2000	Vitamin A supplemented after 6 months of age
Benn 2008	Vitamin A supplemented during neonatal period
Benn 2010	Vitamin A supplemented during neonatal period
Benn 2014	Vitamin A given during neonatal period
Bhaskaram 1997	Vitamin A given at 9 months of age
Bhaskaram 1998	Supplementation given to mothers only
Biering-Sørensen 2013	Vitamin A supplemented during neonatal period
Coles 2001	Vitamin A given during neonatal period
Coles 2011	Vitamin A given during neonatal period
Coutsoudis 1999	Trial conducted on HIV-positive women
Darboe 2007	Both treatment groups received vitamin A and it was not possible to study isolated effect of vitamin A supplementation
Delvin 2000	Supplementation given during neonatal period
Dimenstein 2007	Vitamin A given to mothers only
Fahmida 2007	Even though 1 of the group was supplemented with vitamin A (iron + zinc + vitamin A), all the children in study received therapeutic dose of vitamin A, i.e. 100,000 IU. So it was not possible to determine independent effect of vitamin A. Also supplementation started in infants < 6 months of age and continued for 6 months after start of supplementation
Fawzi 2002	Trial conducted on HIV-positive women
Fernandes 2012	Vitamin A given to mothers only
Fisker 2011	Follow-up study of a neonatal randomised trial

Study	Reason for exclusion
Garcia 2011	Vitamin A given to neonates only
Humphrey 1996	Vitamin A supplemented during neonatal period only
Humphrey 2006	Reports data only on HIV-positive women
Katz 2000	Vitamin A supplemented to mother only
Kiraly 2013	Vitamin A supplemented during neonatal period
Kirkwood 2010	Vitamin A given to women of reproductive age only
Klemm 2008	Vitamin A supplemented during neonatal period
Kumwenda 2002	Trial conducted on HIV-positive women
Lund 2014	Vitamin A supplemented during neonatal period
Malaba 2005	Vitamin A supplemented to mothers and neonates only
McDonald 2014	Study protocol. Vitamin A supplemented during neonatal period
Miller 2006	Trial predominantly (81.1%) on infants born to HIV-positive mothers
Nankabirwa 2011	Half of the children were > 6 months of age
Rahmathullah 2003	Vitamin A supplemented during neonatal period
Rice 1999	Maternal supplementation only
Roy 1997	Not placebo controlled
Schmidt 2002	Maternal supplementation only in the antenatal period
Stabell 1995	Most of the participants > 6 months of age. Study was included in review of vitamin A supplementation in children 6 to 59 months of age
Stoltzfus 1993	Maternal supplementation only
Venkatarao 1996	Supplementation given at 6 months of age. Study was included in review on vitamin A supplementation in children 6 to 59 months of age
Vinutha 2000	Not placebo controlled

IU: international unit.

DATA AND ANALYSES

Comparison 1. Young infant vitamin A supplementation versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality: longest follow-up	9	21339	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.89, 1.25]
2 Diarrhoea-specific mortality at longest follow-up	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.20, 1.70]
3 Acute respiratory infection-specific mortality at longest follow-up	1	200	Risk Ratio (M-H, Fixed, 95% CI)	2.12 [0.40, 11.33]
4 Meningitis-specific mortality	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.58]
5 Morbidity: diarrhoea: point prevalence	2		Risk Ratio (Fixed, 95% CI)	0.99 [0.93, 1.05]
6 Morbidity: lower respiratory tract infection: period prevalence	1		Risk Ratio (Fixed, 95% CI)	0.98 [0.81, 1.19]
7 Morbidity: fever: period prevalence	1		Risk Ratio (Fixed, 95% CI)	0.69 [0.56, 0.85]
8 Adverse effects: bulging fontanelle	9	13493	Risk Ratio (M-H, Fixed, 95% CI)	3.10 [1.89, 5.09]
9 Adverse effects: vomiting	2	2187	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.67, 1.35]
10 Adverse effects: irritability	4	3416	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.65, 1.20]
11 Adverse effects: diarrhoea	3	2176	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.82, 1.40]
12 Adverse effects: fever	3	3187	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.83, 1.07]
13 Adverse effects: convulsions	1	1077	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.85]
14 Vitamin A deficiency: retinol < 0.7 µmol/L	4	1204	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.70, 1.06]
15 Subgroup analysis: all-cause mortality: co-supplementation with vaccination	9	21339	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.89, 1.25]
15.1 Supplementation at the time of vaccination	7	12350	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.82, 1.28]
15.2 Supplementation independent of vaccination	2	8989	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.86, 1.40]
16 Subgroup analysis: all-cause mortality: maternal vitamin A supplementation	9	21339	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.89, 1.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Maternal vitamin A supplementation	3	10249	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.79, 1.32]
16.2 No maternal vitamin A supplementation	6	11090	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.87, 1.34]
17 Subgroup analysis: adverse effects: bulging fontanelle: supplementation at the time of vaccination	9	13493	Risk Ratio (M-H, Fixed, 95% CI)	3.10 [1.89, 5.09]
17.1 Supplementation at the time of vaccination	8	11352	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [1.81, 5.30]
17.2 Supplementation independent of vaccination	1	2141	Risk Ratio (M-H, Fixed, 95% CI)	3.13 [0.86, 11.32]

Analysis 1.1. Comparison 1 Young infant vitamin A supplementation versus placebo, Outcome 1 All-cause mortality: longest follow-up.

Analysis 1.2. Comparison 1 Young infant vitamin A supplementation versus placebo, Outcome 2 Diarrhoea-specific mortality at longest follow-up.

Study or subgroup	Vitamin A n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: $Z=0.98(P=0.33)$					
Favours vitamin A 0.01 0.1 1 10 100 Favours control					

Analysis 1.3. Comparison 1 Young infant vitamin A supplementation versus placebo, Outcome 3 Acute respiratory infection-specific mortality at longest follow-up.

Study or subgroup	Vitamin A n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mahalanabis 1997	4/97	2/103		100%	2.12[0.4,11.33]
Total (95% CI)	97	103		100%	2.12[0.4,11.33]
Total events: 4 (Vitamin A), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=0.88(P=0.38)$					
Favours vitamin A 0.01 0.1 1 10 100 Favours control					

Analysis 1.4. Comparison 1 Young infant vitamin A supplementation versus placebo, Outcome 4 Meningitis-specific mortality.

Study or subgroup	Vitamin A n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mahalanabis 1997	0/97	1/103		100%	0.35[0.01,8.58]
Total (95% CI)	97	103		100%	0.35[0.01,8.58]
Total events: 0 (Vitamin A), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=0.64(P=0.52)$					
Favours vitamin A 0.01 0.1 1 10 100 Favours control					

Analysis 1.5. Comparison 1 Young infant vitamin A supplementation versus placebo, Outcome 5 Morbidity: diarrhoea: point prevalence.

Study or subgroup	Vitamin A	Placebo	log[Risk Ratio]	Risk Ratio	Weight	Risk Ratio
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
Semba 2001	0	0	-0.2 (0.273)		1.35%	0.82[0.48,1.4]
WHO 1998	0	0	-0 (0.032)		98.65%	0.99[0.93,1.05]
Total (95% CI)					100%	0.99[0.93,1.05]
Heterogeneity: Tau²=0; Chi²=0.47, df=1(P=0.49); I²=0%						
Test for overall effect: Z=0.4(P=0.69)						
<div><div></div><div>Favours vitamin A</div><div>0.010.1110100</div><div>Favours control</div></div>						

Analysis 1.6. Comparison 1 Young infant vitamin A supplementation versus placebo, Outcome 6 Morbidity: lower respiratory tract infection: period prevalence.

Analysis 1.7. Comparison 1 Young infant vitamin A supplementation versus placebo, Outcome 7 Morbidity: fever: period prevalence.

Analysis 1.8. Comparison 1 Young infant vitamin A supplementation versus placebo, Outcome 8 Adverse effects: bulging fontanelle.

Analysis 1.9. Comparison 1 Young infant vitamin A supplementation versus placebo, Outcome 9 Adverse effects: vomiting.

Analysis 1.10. Comparison 1 Young infant vitamin A supplementation versus placebo, Outcome 10 Adverse effects: irritability.

Analysis 1.11. Comparison 1 Young infant vitamin A supplementation versus placebo, Outcome 11 Adverse effects: diarrhoea.

Analysis 1.12. Comparison 1 Young infant vitamin A supplementation versus placebo, Outcome 12 Adverse effects: fever.

Analysis 1.13. Comparison 1 Young infant vitamin A supplementation versus placebo, Outcome 13 Adverse effects: convulsions.

Analysis 1.14. Comparison 1 Young infant vitamin A supplementation versus placebo, Outcome 14 Vitamin A deficiency: retinol < 0.7 $\mu\text{mol/L}$.

**Analysis 1.15. Comparison 1 Young infant vitamin A supplementation versus placebo,
Outcome 15 Subgroup analysis: all-cause mortality: co-supplementation with vaccination.** **Analysis 1.16. Comparison 1 Young infant vitamin A supplementation versus placebo,
Outcome 16 Subgroup analysis: all-cause mortality: maternal vitamin A supplementation.**

Analysis 1.17. Comparison 1 Young infant vitamin A supplementation versus placebo, Outcome 17 Subgroup analysis: adverse effects: bulging fontanelle: supplementation at the time of vaccination.

ADDITIONAL TABLES

Table 1. Effect of vitamin A supplementation on response to vaccination in first six months of life

Study ID	Intervention	Type of vaccination	Response to vaccine
Kutukculer 2000	Vitamin A dose and frequency: vitamin A 30,000 IU for 3 days just after each 3 doses of DPT Control: no vitamin A supplementation	DPT	Vitamin A administered orally for 3 consecutive days after each 3 doses of DPT for primary immunisation did not affect the specific antibody response against tetanus toxoid
Newton 2005	Vitamin A dose and frequency: vitamin A 25,000 IU RE at 6, 10 and 14 weeks Control: placebo	DPT/OPV	Vitamin A supplementation does not affect infants' antibody responses to tetanus toxoid or OPV delivered at EPI contacts
Newton 2010	Vitamin A dose and frequency: vitamin A 50,000 IU at 6, 10 and 14 weeks Control: no vitamin A supplementation	Hib + Hep	No significant difference ($P = 0.93$) in the geometric mean concentration of <i>Haemophilus influenzae</i> type b antibodies in the intervention (2.45) and in the control group (2.51); ratio of geometric mean concentration 0.98 (95% CI 0.59 to 1.62). Similarly, no significant difference ($P = 0.29$) in the geometric mean concentration of hepatitis B antibodies in the intervention (1.28) and in the control group (1.71); ratio of geometric mean concentration 0.74 (95% CI 0.43 to 1.28)
Semba 2001	Vitamin A dose and frequency: vitamin A 25,000 RE; vitamin A 50,000 IU at 6, 10 and 14 week of age; vitamin A 100 000 IU at 9 months of age Placebo	DPT/OPV and measles	There was no differential effect of vitamin A supplementation in favour or against measles vaccination
WHO 1998	Vitamin A dose and frequency: vitamin A 25,000 IU with the first, second and third doses of DPT/OPV at 6, 10 and 14 weeks in India and Ghana and at 2, 3 and 4 months in Peru; vitamin A 25,000 IU at 9 months Placebo: soybean oil. Received vitamin A 100,000 IU at 9 months	DPT/OPV and measles	"Vitamin A given to the mothers in the postpartum period and their infants with OPV did not interfere with the antibody response to any of the three polioviruses and enhanced the response to poliovirus type 1" (Data from Indian site only)

DPT: diphtheria, pertussis (whooping cough) and tetanus; EPI: extended programme of immunisation; Hep: hepatitis; Hib: *Haemophilus influenzae* type b; IU: international unit; OPV: oral polio vaccine; RE: retinol equivalent.

APPENDICES

Appendix 1. Standard search methodology

Search Strategy 2010:

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR Clinical Trial[ptyp] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh]))

Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Cochrane Library: (infant or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW)

Updated Search Date: March 5, 2016

Search Terms: (vitamin A OR retinol OR retinoid OR retinoic OR vitamin A[MeSH])

Plus the following database-specific terms:

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR Clinical Trial[ptyp] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh]))

Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Cochrane Library: (infant or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW)

WHAT'S NEW

Date	Event	Description
6 February 2017	Amended	Added external source of support

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 10, 2011

Date	Event	Description
29 August 2016	New citation required but conclusions have not changed	While the age range of the included participants has changed, the results have not changed.
29 August 2016	New search has been performed	This is an update of the previous review. This update included infants 1 to 6 months of age only, compared to previous review where neonatal and maternal supplementation were also included (Gogia 2011).

CONTRIBUTIONS OF AUTHORS

AI and ZA screened the titles, extracted the data and contributed to characteristics of included studies table.

AI conducted the analysis and wrote the manuscript.

ZAB supervised each aspect of this review, helped interpretation of the analyses and contributed to manuscript writing.

DECLARATIONS OF INTEREST

None known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This update included infants one to six months of age only, compared to the previous review, which also included neonates ([Gogia 2011](#)).

INDEX TERMS

Medical Subject Headings (MeSH)

*Developing Countries; *Dietary Supplements [adverse effects]; *Infant Mortality; Breast Feeding; Cause of Death; Diarrhea [epidemiology]; Lactation; Milk, Human [chemistry]; Postpartum Period; Randomized Controlled Trials as Topic; Respiratory Tract Infections [epidemiology]; Vitamin A [*administration & dosage] [adverse effects] [physiology]; Vitamin A Deficiency [mortality] [*therapy]; Vitamins [*administration & dosage] [adverse effects]

MeSH check words

Female; Humans; Infant; Infant, Newborn