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

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[Intervention Review]

Vitamin A supplementation for the prevention of morbidity and mortality in infants six months of age or less

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ABSTRACT

Background

Vitamin A deficiency is a significant public health problem in low and middle income countries. Vitamin A supplementation (VAS) provided to lactating postpartum mothers or to infants less than six months of age are two possible 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:

1. VAS in postpartum breast feeding mothers in low and middle income countries, irrespective of antenatal VAS status, on mortality, morbidity and adverse effects in their infants up until the age of one year.

2. VAS initiated in the first half of infancy (≤ 6 months of age) in low and middle income countries, irrespective of maternal antenatal or postnatal VAS status, on mortality, morbidity and adverse effects up until the age of one year.

Search strategy

The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), EMBASE, MEDLINE, clinical trials websites, conference proceedings, donor agencies, 'experts' and researchers (up to October 15, 2010).

Selection criteria

Randomized or quasi-randomised, individually or cluster randomised, placebo controlled trials involving synthetic VAS provided to the postpartum mothers or their infants up to the age of six months were eligible.

Data collection and analysis

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

Main results

Of the 18 included studies, eight provided information on maternal VAS and 15 on infant VAS.

For maternal VAS, there was no evidence of a reduced risk of mortality of their babies during infancy (96,203 participants, seven studies, high quality evidence; random-effects model RR 1.00, 95% CI 0.94 to 1.06, P = 0.9; test of heterogeneity I^2 = 0%, P = 0.9) or in the neonatal period (moderate quality evidence); nor of morbidities (very low quality evidence).

For infant VAS, there was no evidence of a reduced risk of mortality during infancy (59,402 participants, nine studies, moderate quality evidence; random-effects model RR 0.97, 0.83 to 1.12, P = 0.65; test of heterogeneity I^2 = 49%, P = 0.05) or in the neonatal period, nor morbidities (low quality evidence), but an increased risk of bulging fontanelle (32,978 participants, 10 studies, low quality evidence; random-effects model RR 1.55, 1.05 to 2.28, P = 0.03; test of heterogeneity I^2 = 68%, P = 0.0009).

Authors' conclusions

There is no convincing evidence that either maternal postpartum or infant vitamin A supplementation results in a reduction in infant mortality or morbidity in low and middle income countries.

PLAIN LANGUAGE SUMMARY

Vitamin A supplementation given to mothers of newborn children or infants below six months of age for preventing death and illnesses in the first year of life

Vitamin A deficiency is a significant public health problem in low and middle income countries. Vitamin A supplementation (VAS) given to children between the age of six months and five years has been shown to reduce deaths in these settings. Infants below one year of age are at higher risk of developing vitamin A deficiency. There are two possible ways to enhance the vitamin A status of these infants. Firstly, VAS can be given to lactating mothers to increase the vitamin A content of their breast milk, and secondly, VAS can be given direct to young infants below six months of life. Researchers have examined the potential role of these two strategies in preventing death and illness in the first year of life.

The review authors searched the medical literature for these two strategies to identify relevant studies that had compared the effect of VAS and placebo on death, illnesses and side effects in randomly selected infants.

The results of the studies provided no convincing evidence that maternal VAS reduced the risk of death within the first year of life (96,203 infants, seven studies) or within the first month of life; nor illnesses. There was also no convincing evidence that VAS of infants below six months of age reduced the risk of death within the first year of life (59,402 infants, nine studies) or within the first month of life; nor did it reduce illnesses. However, this intervention may increase the possibility of developing the side effect of bulging fontanelle, which results from increased pressure of the fluid that bathes the brain (32,978 infants, 10 studies). The quality of evidence for the risk of death within the first year of life was moderate to high, but it was poor for illnesses and side effects.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Maternal Vitamin A Supplementation compared to Placebo for the prevention of morbidity and mortality in infants up to six weeks of age

Patient or population: patients with the prevention of morbidity and mortality in infants up to six weeks of age
Settings: Low and middle income countries
Intervention: Maternal Vitamin A Supplementation
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Maternal Vitamin A Supplementation				
All-cause mortality in the first year of life Follow-up: 6-12 months	**Low risk population**[1]		**RR 1** (0.94 to 1.06)	96203 (7 studies)	⊕⊕⊕⊕ **high**[2]	Trials gave vitamin A to mothers in developing countries, reflecting the main question of the review. CER from external sources.
	41 per 1000	**41 per 1000** (39 to 43)				
	Medium risk population[1]					
	62 per 1000	**62 per 1000** (58 to 66)				
	High risk population[1]					
	81 per 1000	**81 per 1000** (76 to 86)				
All-cause mortality at 1 month Follow-up: 1 months	**Medium risk population**[3]		**RR 0.98** (0.87 to 1.11)	84537 (2 studies)	⊕⊕⊕◯ **moderate**[4]	Data analysed as risk ratios. Cumulative risk and incidence ratios from studies were combined to generate a pooled risk

						ratio. CER from external sources.
	30 per 1000	**29 per 1000** (26 to 33)				
ARI-related mortality in the first year of life verbal autopsy or lay reporting Follow-up: 12 months	**Low risk population**[5]		**RR 1.59** (0.84 to 2.99)	5207 (2 studies)	⊕○○○ **very low**[6,7,8]	The studies reported risk ratios and 95% confidence intervals. In the absence of dichotomous data CERs were calculated based on external data.
	9 per 1000	**15 per 1000** (8 to 28)				
	High risk population[5]					
	11 per 1000	**18 per 1000** (9 to 33)				
Diarrhoea-related mortality in the first year of life verbal autopsy or lay reporting Follow-up: 12 months	**Low risk population**[9]		**RR 2.57** (0.72 to 9.12)	5207 (2 studies)	⊕○○○ **very low**[6,8,10]	The studies reported risk ratios and 95% confidence intervals. In the absence of dichotomous data CERs were calculated based on external data.
	8 per 1000	**20 per 1000** (6 to 71)				
	High risk population[9]					
	9 per 1000	**24 per 1000** (7 to 85)				
Morbidity due to acute respiratory infections[11] Follow-up: mean 12 months	**Study population**		**Rate ratio 0.96** (0.85 to 1.08)	598 (1 study)	⊕○○○ **very low**[11,12]	Data were analysed as ratios of rates. No estimates of cumulative risk available. Estimates of morbidity not available from external sources.
	See comment	See comment				
	Medium risk population					

Morbidity due to diarrhoea[11] Follow-up: mean 12 months	**Study population**	**RR 1.10** (0.99 to 1.23)	598 (1 study)	⊕○○○ **very low**[11,12]	Data were analysed as ratios of rates. No estimates of cumulative risk available. Estimates of morbidity not available from external sources.
	See comment See comment				
	Medium risk population				
Adverse effects	**Study population**	**RR 0** (0 to 0)	700 (2 studies)	See comment	No adverse events were reported in two trials providing this information (Bhaskaram 1998, Venkatarao 1996).
	See comment See comment				
	Medium risk population				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Control group risk taken from the World Health Statistics 2010 (http://www.who.int/whosis/whostat/2010/en/index.html) for mortality before 1 year of age recorded in 2008 in the countries where included studies were conducted (Bangladesh, Ghana, India, Kenya, Nepal, Zimbabwe). The lowest, medium and highest mortality rates were entered for these countries.

[2] Trial design was adequately reported in all but three trials that accounted for 6.6% of the weight in the pooled analysis (Klemm 2008, Newton 2005, Venkatarao 1996). Three trials were cluster randomised with adjustment for the design effect (Katz 2000, Kirkwood 2010, Klemm 2008). The cumulative vitamin A dose received by the postpartum mothers was similar in all but one study (Newton 2005).

[3] Control group risk taken from the World Health Statistics 2010 (http://www.who.int/whosis/whostat/2010/en/index.html) for neonatal mortality rate. Estimates of neonatal mortality were based on rates of 30/1000 live births for Ghana (Kirkwood 2010) and Nepal (Katz 2000) recorded in 2008.

[4] Two out of seven studies reporting mortality. Both studies had very large sample sizes.

[5] Information taken from two sources. The World Health Statistics 2010 (http://www.who.int/whosis/whostat/2010/en/index.html) provided the low and high mortality rates at 1 year of age in the countries of the included studies (India and Zimbabwe). Based on the

proportion of global all cause mortality attributed to pneumonia (18%, reported in Black 2010), the CERs entered represent 18% of the national rates of mortality.

[6] Venkatarao 1996 had inadequate concealment of allocation. Both studies failed to address missing data appropriately.

[7] The confidence intervals include a 16% reduction and 300% increase (appreciable harm) in the risk of ARI related death

[8] Only two trials reported this outcome, and the meta-analysis may be affected by the non-disclosure of cause-specific mortality in the remaining studies.

[9] Information taken from two sources. The World Health Statistics 2010 (http://www.who.int/whosis/whostat/2010/en/index.html) provided the low and high mortality rates at 1 year of age in the countries of the included studies for 2008(India and Zimbabwe). Based on the proportion of global all cause mortality attributed to diarrhoea (15% reported in Black 2010), the events entered represent 15% of the national rates of mortality.

[10] The confidence intervals include a 28% reduction (appreciable benefit) and 900% increase (appreciable harm) in the risk of diarrhoea-related death.

[11] Single study (Venkatarao 1996) on which randomisation procedure and method of allocation concealment were not described, and incomplete outcome data was not addressed.

[12] A single small trial reported this outcome.

BACKGROUND

Description of the condition

Vitamin A deficiency (VAD) is a significant public health problem in low and middle income countries, especially in Africa and Southeast Asia. It is most serious when it affects young children and pregnant women. Estimates suggest that there are 127 million pre-school children with VAD (serum retinol < 0.70 mmol/L or displaying abnormal impression cytology) and 4.4 million pre-school children with xerophthalmia in the developing world (West 2002). More than 7.2 million pregnant women in the developing world are vitamin A deficient (serum or breast milk vitamin A concentrations < 0.70 µmol/L) and another 13.5 million have low vitamin A status (0.70 to 1.05 µmol/L) (West 2002). Annually, more than six million women develop night blindness (XN) during pregnancy (West 2002).

The main causes of childhood vitamin A deficiency in the developing world include maternal vitamin A deficiency resulting in low concentrations of vitamin A in breast milk, inadequate dietary intake of vitamin A during and after weaning, and repeated bouts of infectious illnesses, which further decrease vitamin A levels (Miller 2002). The current US recommended dietary allowance (RDA) established by the Institute of Medicine (IOM) for non-pregnant, non-lactating women aged 19 to 50 years is 700 µg of vitamin A per day (IOM 2001). The recommended dietary allowance increases to only 770 µg/d during pregnancy but nearly doubles to 1300 µg/d during lactation. Mothers in developing countries are commonly vitamin A deficient because they consume diets low in vitamin A. Median dietary intake of vitamin A is 403 µg/d in rural Bangladeshi women; which provides 57% of their RDA if they are not pregnant or lactating and only 31% of their RDA during lactation (Zeitlin 1992). Maternal vitamin A deficiency seems to have little effect on fetal status since even well-nourished women transfer very little vitamin A to the infant. Therefore, all babies are physiologically vitamin A 'depleted' at birth, having little in the way of vitamin A stores in their livers. Young infants in developing countries have even lower vitamin A stores (Miller 2002). However, during lactation well-nourished women transfer about 71,500 µg of vitamin A to their infant (130 L of breast milk consumed during the entire period of lactation containing 55 µg/dL vitamin A), whereas women in developing countries transfer only about half that amount because the average milk vitamin A concentrations are about 30 µg/dL (Wallingford 1986). As a result, during lactation breast-fed babies of well-nourished women accrue adequate stores whereas breast-fed babies of vitamin A-deficient women remain depleted. Furthermore, if weaning foods are lower in vitamin A than the breast milk they partially replace, the child's risk of vitamin A deficiency increases further when breast feeding stops. Dietary vitamin A reference intakes for infants and young children, established by the IOM in the United States and by the Food and Agricultural Organization (FAO), recommend intakes from 350 to 500 µg/d for infants and from 300 to 400 µg/d for one to six year old children (FAO/WHO 1988; IOM 2001). In studies of pre-school children in Egypt, Mexico, Kenya and India median intakes of animal sources of vitamin A were 174, 119, 50 and 33 µg/d, respectively, providing only 11% to 58% of the RDA and leaving these children largely dependent on plant sources (Calloway 1993; Ramakrishnan 1999). In a study of Bangladeshi children, virtually the only source of pre-formed vitamin A consumed was breast milk; weaned children consumed only negligible amounts of vitamin A from animal sources (Zeitlin 1992).

Description of the intervention

There are two approaches to supplementing vitamin A intake during the first half of infancy. Firstly, to supplement all lactating mothers so that their infants can increase vitamin A intake through breast milk. Secondly, to give vitamin A supplements to all infants when they come in contact with the healthcare system. Such possible contacts occur immediately after birth, during postnatal visits or during immunization visits. The International Vitamin A Consultative Group (IVACG) recommends that three 50,000 international unit (IU) doses of vitamin A should be given at the same time as infant vaccines during the first six months of life. Recent kinetic studies have indicated that this regimen would be safe and would maintain the infant's vitamin A stores even when the mother is also given 400,000 IU within the first six weeks after delivery (Ross 2002).

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). Vitamin A deficiency 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 severe illness and death from such common childhood infections as diarrhoeal disease and measles (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

The role of prophylactic vitamin A supplementation, given to apparently healthy children (more than six months of age) residing in low and middle income countries, in reducing childhood mortality has been the subject of several systematic and narrative reviews. For deficient children more than six months of age, vitamin A supplementation is estimated to reduce mortality by between 23% and 30% overall. Most of the reduction is due to the effect on diarrhoea and measles mortality (Beaton 1993; Fawzi 1993; Glasziou 1993). Periodic vitamin A supplementation to children over six months old is being implemented in more than 70 countries and is considered by many international agencies to be one of the most effective public health interventions ever undertaken (Fawzi 2006). Supplementation with a standard WHO protocol (200,000 IU to mothers early postpartum, 100,000 IU to infants at nine months and 200,000 IU at four to six month intervals thereafter) has been adopted as national policy in most developing countries (Darboe 2007). Side-effects of vitamin A supplementation are rare in children aged six months or older but there are reports of toxic effects in the first six months of life, such as raised intracranial pressure manifested by vomiting, bulging of the anterior fontanelle and irritability (Agoestina 1994; Baqui 1995; de Francisco 1993).

Because infants are at a higher risk of mortality when compared to older children, improving the vitamin A status of infants could potentially save the greatest number of lives. Therefore, the available evidence on the beneficial effects on mortality and morbidity of this intervention during the first six months of life needs to be systematically reviewed. Moreover, concern about the safety of vitamin A supplementation in young infants, particularly during the neonatal period, needs to be addressed and the optimum dose determined. Furthermore, the differential effects on mortality and morbidity with respect to the vitamin A status of mothers, birthweight and infant mortality rate need to be studied.

A focused review on vitamin A supplementation in term neonates in developing countries irrespective of maternal HIV status is under preparation (Haider 2008b).

Therefore, we have undertaken a systematic review of randomised controlled trials to evaluate the effect of prophylactic vitamin A supplementation on mortality and morbidity in infants six months of age or less in developing countries, with particular reference to supplementation of mothers during lactation and of infants at different times during the first half of infancy.

OBJECTIVES

1. To evaluate the effect of synthetic vitamin A supplementation in postpartum breast feeding mothers in low and middle income countries, irrespective of antenatal vitamin A supplementation status, on mortality, morbidity, and adverse effects in their infants until the age of one year (Comparison 1).

2. To evaluate the effect of synthetic vitamin A supplementation initiated in the first half of infancy (≤ 6 months of age) in low and middle income countries, irrespective of maternal antenatal or postnatal vitamin A supplementation status, on mortality, morbidity, and reactions until the age of one year (Comparison 2).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised or quasi-randomised placebo controlled trials which randomised at the level of the mother or infant or cluster (such as village) that involved synthetic vitamin A supplementation to the postpartum mother or infant (≤ 6 months of age), or both.

Types of participants

Comparison 1: Maternal supplementation

Mothers from low and middle income countries receiving synthetic vitamin A supplementation initiated in the postpartum period (≤ 6 weeks) irrespective of antenatal vitamin A supplementation.

Comparison 2: Infant supplementation

Apparently healthy infants from low and middle income countries, breast-fed or non-breast fed, receiving vitamin A supplementation initiated before the age of six months (irrespective of maternal supplementation during pregnancy and lactation).

We excluded trials which recruited selected subgroups of infants, such as those who were very low birth weight (< 1500 grams), 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 2007; Shey 2002; Wiysonge 2005).

Types of interventions

Synthetic oral vitamin A supplementation in one or more of the following forms were compared against a placebo.

1. Maternal supplementation (Comparison 1): synthetic vitamin A supplementation to lactating mothers (first six weeks postpartum). Synthetic oral vitamin A supplementation initiated in the postpartum mother within six weeks of delivery,

irrespective of the antenatal vitamin A supplementation status, was compared against a placebo. Infants in intervention and placebo groups should not have been supplemented with vitamin A but could have received placebo.

2. Infant supplementation (Comparison 2): synthetic vitamin A supplementation to infants less than six months of age (breast-fed or non-breast fed). Synthetic oral vitamin A supplementation initiated in infants below six months of age, irrespective of maternal postpartum vitamin A supplementation status, was compared against a placebo administered to the infant and either placebo or no supplementation in the mother. If such a comparison group was not available for the mother infant dyad, the intervention group was compared with the group in which the infant had received placebo while the mother had received supplementation identical to the intervention group.

Trials providing additional interventions were considered 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 which evaluated food fortification, consumption of vitamin A rich foods or beta-carotene supplementation.

Types of outcome measures

Primary outcomes

Mortality:

1. during infancy, in the period between initiation of intervention and the last follow-up, until the age of one year;
2. during the neonatal period between initiation of intervention and the last follow-up, until the age of one month.

Secondary outcomes

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

1. diarrhoea;
2. acute respiratory infections;
3. other causes.

Morbidity during infancy (as defined by the 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:

1. diarrhoea;
2. acute respiratory infection or respiratory difficulty;
3. cough or running nose;
4. ear infection;
5. fever;
6. vomiting.

Adverse effects within one week following the intervention:

1. bulging fontanel;
2. vomiting;
3. irritability;
4. diarrhoea;
5. fever.

Search methods for identification of studies

Electronic searches

We used the standard search strategy of the Cochrane Neonatal Review Group. The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 3), EMBASE and MEDLINE (1966 to October 15, 2010) via PubMed and clinical trials websites for example clinicaltrials.gov were searched 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 hand-searched reviews, bibliographies of books and abstracts. We contacted donor agencies, 'experts' and authors of recent vitamin A supplementation trials to identify any additional unpublished or ongoing trials.

Data collection and analysis

Selection of studies

Both review authors independently assessed the eligibility of the trials. We selected studies as being potentially relevant by screening the titles and abstracts, if available. The full text of the article was retrieved and reviewed if a decision could not be made by screening the title and the abstract. We retrieved the full texts of all potentially relevant articles and independently assessed study eligibility with forms designed in accordance with the specified inclusion criteria. We resolved disagreements by discussion. We requested additional data and information regarding definitions of outcomes from study investigators when required. In the case of conference abstracts we used the information provided in the abstract if additional data were not forthcoming.

Data extraction and management

We collected data using a data extraction form which we designed and piloted. We extracted data independently, and resolved differences by discussion. We contacted study investigators for additional information or data as required. For dichotomous outcomes, the total number of participants for each group and the number of participants experiencing an event were extracted. The relative risks and 95% confidence intervals (or standard errors) of treatment effects for the outcomes were extracted.

Assessment of risk of bias in included studies

We undertook a risk of bias assessment in accordance with recommendations from Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). We assessed the included studies for their risk of bias against the following key criteria:

1. adequate sequence generation;
2. allocation concealment;
3. blinding;
4. incomplete outcome data;
5. selective outcome reporting;
6. other biases.

Both review authors independently evaluated and agreed the risk of bias for the individual studies; help with the interpretation was made available by the Cochrane Collaboration Editorial Unit. We resolved disagreements by mutual discussion. Following this, another teleconference was arranged between the authors and the Cochrane Collaboration Editorial Unit to resolve disagreements with another ongoing review of neonatal vitamin A supplementation (Haider 2008b) for some domains in studies that were in both reviews.

Measures of treatment effect

Analysis of the outcome was based on the available case analysis. We used risk ratio (RR) to analyse data for dichotomous outcomes. In a hierarchical pattern, preference was given to the RR provided by authors with a recalculation using the stated 'raw' numbers. If the RR was not stated, it was computed with the following preference order for the denominator:

1. stated child-years;
2. numbers with definite outcome known, until completion of intervention period;
3. number randomised.

The RR and standard error (SE) were extracted or calculated for individually randomised trials and cluster randomised trials. We entered the SEs for cluster randomised studies which had taken account of the effect of clustering (see below).

Unit of analysis issues

Cluster randomised trials

The design effect-corrected SEs were calculated from the published data or we contacted the authors for the intra-cluster correlation (ICC) estimates. If required, the design effect for a study was calculated and the SE of the treatment effect was adjusted for use in the analysis based on the formula provided in Chapter 16 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008).

Studies with multiple treatment groups

In studies with multiple intervention groups (different methods or doses of vitamin A supplementation), the vitamin A groups were combined to create a single pair-wise comparison with the control (placebo) group.

Dealing with missing data

In studies where intention-to-treat data were available, the same was used in case the authors had reported otherwise.

Assessment of heterogeneity

We assessed heterogeneity among the trials by the visual inspection of forest plots and by measurement of the I^2 statistic.

Assessment of reporting biases

We evaluated publication bias and other reporting biases by preparing a funnel plot.

Data synthesis

Statistical meta-analyses were undertaken using Revman 5 (RevMan). We used Intercooled Stata version 9.2 for Windows Stata for the meta-regression (see Subgroup analysis and investigation of heterogeneity).

We calculated the RR and its standard error (SE) for individually randomised trials and combined these estimates with the RRs and SEs from cluster randomised trials (adjusted for the effect of clustering). We used the generic inverse variance method to permit the aggregation of the data.

We developed 'Summary of findings' tables in GRADEpro software for outcomes relating to mortality, morbidity and adverse effects. The quality ratings assigned to the outcome results were based on our assessments of study limitations, consistency and precision of the result, indirectness (such as population, intervention or definition of outcome not of primary interest to the review question) and possible impact of publication bias. More information on recommendations for the methods we applied are provided from GRADE.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses

The proposed subgroup analyses for the infant mortality component in the maternal postpartum supplementation (Comparsion 1) analysis were:

- cumulative vitamin A dose received by the mother: low dose (≤ 200,000 IU) versus high dose (≥ 200,000 IU);
- baseline maternal vitamin A status: maternal night blindness prevalences of < 5% (low) versus ≥ 5% (high), and mean maternal antenatal or postpartum serum retinol levels of ≥ 1.1 µmol/L (low) versus < 1.1 µmol/L (high);
- birth weight: < 2500 grams (low birth weight) versus ≥ 2500 grams (normal birth weight).

The proposed subgroup analyses for the infant mortality component in the infant supplementation analysis (Comparison 2) were:

- age at initiation of prophylactic vitamin A supplementation: neonatal period (0 to 1 month) versus post-neonatal period (1 to 6 months);
- cumulative vitamin A dose received by the infant until the age of six months: low dose (≤ 50,000 IU) versus high dose (≥ 50,000);
- maternal postpartum vitamin A supplementation: received versus not received;
- baseline maternal vitamin A status: maternal night blindness prevalences of < 5% (low) versus ≥ 5% (high), and mean maternal antenatal or postpartum serum retinol levels of ≥ 1.1 µmol/L (low) versus < 1.1 µmol/L (high);
- birth weight: < 2500 grams (low birth weight) versus ≥ 2500 grams (normal birth weight).

Investigation of heterogeneity

We considered heterogeneity to be substantial if the I^2 statistic exceeded 25% and visual inspection of the forest plot was indicative. We sought to explain heterogeneity in terms of subgroup analyses which considered the possible sources of variation as:

1. time point of initiation of vitamin A supplementation;
2. maternal postpartum vitamin A supplementation for Comparison 1 (yes or no);
3. cumulative dose of vitamin A supplementation;
4. vitamin A status of mother;
5. birth weight of neonate;
6. high baseline infant mortality.

Meta-regression was used to further explore heterogeneity.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

The search strategy identified 42 potentially eligible trials; of these we excluded 24 and 18 met the inclusion criteria of the review. In addition, we identified four ongoing trials (Bhandari 2010; Bhutta 2010; Edmond 2010; Fawzi 2010).

Included studies

A total of 18 studies were included because these supplied information on one or more of the outcomes for the maternal and infant supplementation analyses.

Comparison 1: Maternal supplementation

Information on outcomes was available from eight trials. Mortality was available from seven trials (Ayah 2007; Katz 2000; Kirkwood 2010; Klemm 2008; Malaba 2005; Newton 2005; Venkatarao 1996), morbidity from one trial (Venkatarao 1996) and adverse effects from two trials (Bhaskaram 1998; Venkatarao 1996).

Comparison 2: Infant supplementation

Information on outcomes was available from 15 trials. Mortality was available from nine trials (Benn 2008; Benn 2010; Humphrey 1996; Klemm 2008; Malaba 2005; Newton 2005; Rahmathullah 2003; West 1995; WHO 1998), morbidity in seven trials (Benn 2008; Benn 2010; Humphrey 1996; Rahmathullah 2003; Semba 2001; Venkatarao 1996; WHO 1998) and adverse effects in 13 trials (Ayah 2007; Baqui 1995; Benn 2008; de Francisco 1993; Humphrey 1996; Klemm 2008; Malaba 2005; Rahmathullah 2003; Semba 2001; Stabell 1995; Venkatarao 1996; West 1995; WHO 1998). The mortality analysis was done on 10 independent analytic components (that is 10 sets of comparisons) from nine trials to aid the subgroup analysis as one trial yielded two independent analytic components according to the age at which an infant received vitamin A supplementation (0 to 1 month and one to six months) (West 1995).

Characteristics of included studies summarizes the baseline characteristics of the trials included for all the outcomes for the maternal and young infant supplementation analyses.

Characteristics of included studies of maternal supplementation (Comparison 1)

All the seven trials reporting mortality (Ayah 2007; Katz 2000; Kirkwood 2010; Klemm 2008; Malaba 2005; Newton 2005; Venkatarao 1996) were conducted in developing countries (three in Asia, four in Africa). Only three trials (Katz 2000; Kirkwood

2010; Klemm 2008) were cluster randomised, and in all of them the cluster design-adjusted results were available. All of the trials were assessed to be double blind; allocation concealment was adequate in six studies; and loss to follow-up was below 10% in two trials. Antenatal vitamin A supplementation had also been given in three studies (Katz 2000; Kirkwood 2010; Klemm 2008). The cumulative vitamin A dose received by the postpartum mother was ≤ 200,000 IU in Newton 2005 and > 200,000 IU in the other six studies. The intervention had been given as a single dose in four studies and as multiple doses in three (Katz 2000; Kirkwood 2010; Klemm 2008). Information on prevalence of maternal night blindness was available in only three studies (> 5% in Malaba 2005 and ≤ 5% in Klemm 2008 and Kirkwood 2010). Mean maternal (antenatal or postnatal) serum retinol levels (micromoles per liter) in placebo group were documented in five trials, and were ≤ 1.1 in two (Ayah 2007; Katz 2000) and > 1.1 in three (Kirkwood 2010; Klemm 2008; Malaba 2005). Information on mean birth weight was available in three studies, and was above 2500 grams in two of them. The infants' follow-up age was ≤ 6 months in four trials and > 6 months in three studies (Kirkwood 2010; Malaba 2005; Venkatarao 1996).

Characteristics of included studies of infant supplementation (Comparison 2)

Nine trials reported mortality in 10 independent analytic components. All these studies (Benn 2008; Benn 2010; Humphrey 1996; Klemm 2008; Malaba 2005; Newton 2005; Rahmathullah 2003; West 1995; WHO 1998) were conducted in low and middle income countries (five in Asia, three in Africa, and one involved multiple centres from Asia, Africa and Latin America). Only two trials (Klemm 2008; West 1995) providing three analytic components were cluster randomised, and in all of them the cluster design-adjusted results were available. All the trials were assessed to be double blind; allocation concealment was adequate in nine of the 10 analytic components; and loss to follow-up was below 10% in seven. Infant vitamin A supplementation had been initiated between birth and one month of age in seven analytic components, and between one and six months of life in three (Newton 2005; West 1995; WHO 1998). In five studies participants were followed up to the age of ≤ 6 months, and in five they were followed up to > 6 months. Simultaneous maternal postpartum vitamin A supplementation (≥ 30% mothers in the intervention arm) had been used in four of the 10 analytic components (Benn 2008; Humphrey 1996; Rahmathullah 2003; West 1995). The cumulative vitamin A dose received by the infant in the first six months of life was ≤ 50,000 IU in seven analytic components and > 50,000 IU in three analytic components. This had been administered as a multiple dose in three analytic components (Newton 2005; Rahmathullah 2003; WHO 1998). Information on prevalence of maternal night blindness was available in only four analytic components; of these two recorded a prevalence > 5% (Malaba 2005; WHO 1998) and two ≤ 5% (Klemm 2008; Rahmathullah 2003). Mean maternal serum retinol levels (µmol/L) in the placebo group were documented in two analytic components, and were ≤ 1.1 in both. The mean infant serum retinol level in the placebo group was reported in only the multi-centre trial (WHO 1998), and was > 0.6 µmol/L. The mean birth weight was above 2500 grams in four of the six analytic components that had documented this information. However, three trials had presented results separately for low birth weight and non-low birth weight infants. One trial had been conducted exclusively in low birth weight infants (Benn 2010).

The notable general and individual study specific features in relation to data abstraction are summarized in Appendix 1.

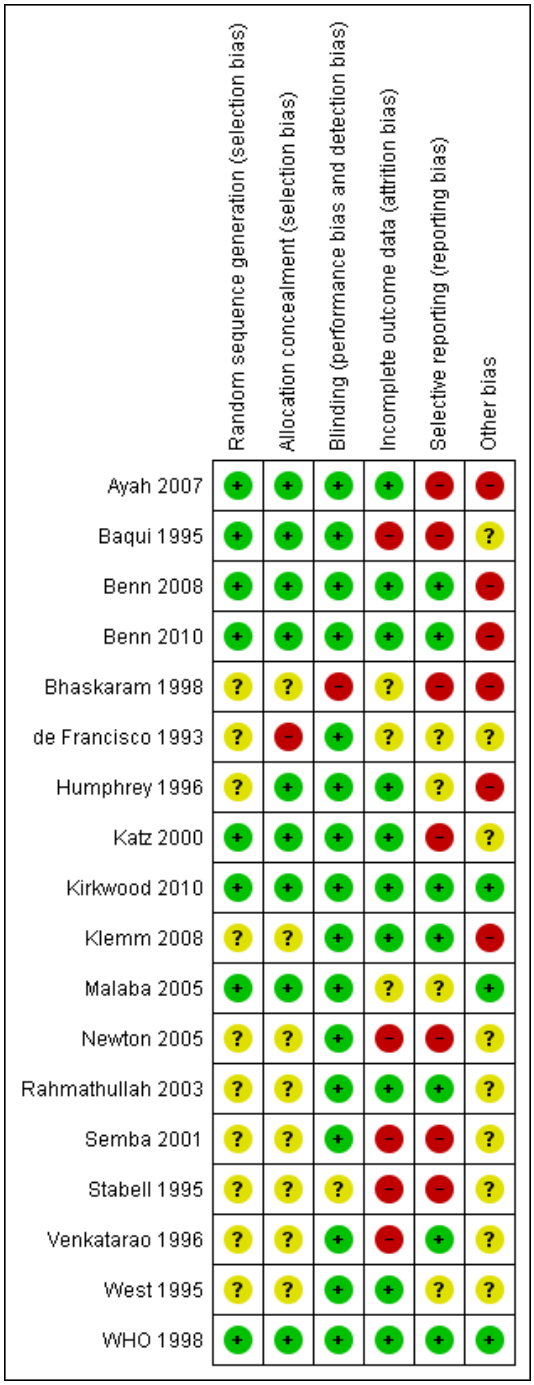
Excluded studies

The reasons for excluding the 24 studies are summarised in the table Characteristics of excluded studies. The reasons were: relevant outcomes not reported (N = 13 studies), conducted in HIV positive women (N = 5), not placebo controlled (N = 3), conducted on infants treated for diarrhea (N = 2), and only antenatal vitamin A supplementation (N = 1).

Risk of bias in included studies

The risk of bias table for individual included studies is summarised in the table Characteristics of included studies and Figure 1.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Comparison 1: Maternal supplementation

In the seven trials providing information on mortality the risk of bias for sequence generation was low in four and unclear in three trials, of which two were relatively small studies (Newton 2005; Venkatarao 1996). The allocation concealment was assessed to be adequate (low risk) in four trials and of unclear risk in three trials. The only trial providing information on morbidity had unclear risk of bias for sequence generation and allocation concealment. The two trials providing information on adverse effects had unclear risk of bias for sequence generation and allocation concealment.

Comparison 2: Infant supplementation

The risk of bias for sequence generation in trials providing data on mortality outcome was low in four trials while it was unclear in five trials (Humphrey 1996; Klemm 2008; Newton 2005; Rahmathullah 2003; West 1995). The allocation concealment was assessed to be adequate (low risk) in five trials and unclear in four trials. In the seven trials providing information on morbidity, sequence generation was adequate (low risk) in three and unclear in four studies; allocation concealment was adequate (low risk) in four and unclear in three trials. In the 13 trials providing information on adverse effects, sequence generation was adequate (low risk) in five and unclear in eight studies; allocation concealment was adequate (low risk) in six, inadequate (high risk) in one small trial, and unclear in six studies.

Blinding

Comparison 1: Maternal supplementation

In the seven trials providing information on mortality, blinding was adequate in all. The trial providing information on morbidity also had adequate (low risk) blinding. In the two trials providing information on adverse effects, blinding was adequate (low risk) and inadequate (high risk) in one trial each.

Comparison 2: Infant supplementation

All the nine trials providing data on mortality were adequately blinded. Similarly, in all the seven trials providing information on morbidity, blinding was assessed to be adequate (low risk). In the 13 trials providing information on adverse effects, blinding was adequate (low risk) in 12 trials and unclear in one study (Stabell 1995).

Incomplete outcome data

Comparison 1: Maternal supplementation

In the seven trials providing information on mortality, incomplete outcome data were addressed adequately (low risk) in four, it was unclear in one and inadequately (high risk) in two trials. The trial providing information on morbidity had not adequately addressed incomplete outcome data. In the two trials providing information on adverse effects: the risk of bias for incomplete outcome data was high and unclear in one trial each.

Comparison 2: Infant supplementation

In the nine trials providing data on mortality, incomplete outcome data were addressed adequately in seven, unclear in one and inadequately in one trial. Incomplete outcome data were addressed adequately in five trials and inadequately in two studies providing information on morbidity. In the 13 trials providing information on adverse effects, the risk of bias for incomplete data was low in seven studies, high in four studies and unclear in two studies.

Selective reporting

Comaprison 1: Maternal supplementation

In the seven trials providing information on mortality, the risk of bias for selective reporting was low in three, high in three and unclear in one. The trial providing information on morbidity was free of selective reporting. In the two trials providing information on adverse effects, the risk of bias for selective reporting was high and low in one trial each.

Comaprison 2: Infant supplementation

In the nine trials providing information on mortality, the risk of bias for selective reporting was low in five, high in one and unclear in three. In the seven trials providing information on morbidity, the risk of bias for selective reporting was low in five trials, high in one trial and unclear in one trial. In the 13 trials providing information on adverse effects, the risk of bias for selective reporting was low in five trials, high in four trials and unclear in four trials.

Other potential sources of bias

Comparison 1: Maternal supplementation

In the seven trials providing information on mortality, the risk of bias for other potential sources was low in two, high in two and unclear in three. In the trial providing information on morbidity it was unclear if there were other potential sources of bias. In the two trials providing information on adverse effects the risk of bias from other potential sources was high and unclear in one trial each.

Comparison 2: Infant supplementation

In the nine trials providing information on mortality, the risk of bias from other potential sources was low in two, high in four and unclear in three. In the seven trials providing information on morbidity, the risk of bias from other potential sources was low in one, high in three and unclear in three. In the 13 trials providing information on adverse effects, the risk of bias from other potential sources was low in two, high in four and unclear in seven.

Effects of interventions

See: **Summary of findings for the main comparison** Maternal vitamin A supplementation compared to placebo for the prevention of morbidity and mortality in infants up to six weeks of age; **Summary of findings 2** Young infant vitamin A supplementation compared to placebo for the prevention of morbidity and mortality in infants six months of age or less; **Summary of findings 3** Young infant vitamin A supplementation compared to placebo for the prevention of morbidity and mortality in infants six months of age or less

Comparison 1: Maternal vitamin A supplementation

Primary outcomes

The pertinent details of the vital events and denominators for the mortality analysis for each study are summarised in Table 1.

Table 1. Details of vital events for the mortality analysis in the maternal supplementation review

Author	Vitamin A						Placebo						Source of RR used in meta-analysis
	Number randomised	Number dead	Number alive	Number lost	Vital status known	Follow up duration (child yrs)	Number randomised	Number dead	Number alive	Number lost	Vital status known	Follow up duration (child yrs)	
Venkatar 1996	301	8	228	65	236	NM	297	9	228	60	237	NM	Calculated
Katz 2000	5583	382	4782	419	5164	NM	5202	334	4385	483	4719	NM	Stated
Malaba 2005^	2300	48	2013	239	2061	2119	2309	38	2028	243	2066	2120	Calculated^
Newton 2005	269	3	198	68	201	NM	277	2	204	71	206	NM	Calculated
Ayah 2007	282	23	227	32	250	NM	282	23	214	45	237	NM	Calculated
Klemm 2008	NC	121	2596	NC	2717	NM	NC	115	2517	NC	2632	NM	Calculated

Table 1. Details of vital events for the mortality analysis in the maternal supplementation review (*Continued*)

Kirkwood 2010	37042	1948	NM	NM	NM	30858	36710	1963	NM	NM	NM	30544	Stated

NM Not mentioned; NC Not calculable

ˆ The deaths also include those due to injuries and congenital defects (2 in Vitamin A and 2 in placebo), and RR calculated from child year denominator.

Outcome 1.1 (Mortality in the first year of life)

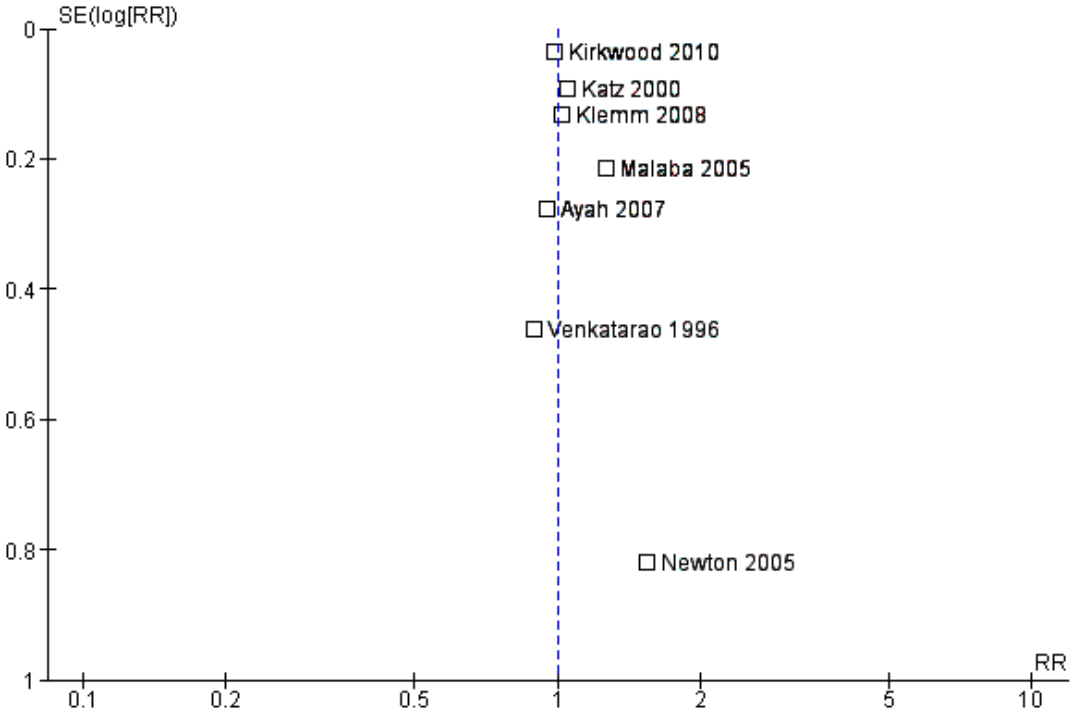
Relevant data for evaluating the pooled relative risk of all-cause mortality during infancy, in the period between initiation of intervention and the last follow-up until the age of one year, were available from seven studies.

Outcome 1.1.1 (Mortality after postpartum vitamin A supplementation)

There was no evidence of a reduced risk of mortality during infancy (Analysis 1.1). The pooled risk ratio for mortality was 1.00 (95% CI 0.94 to 1.06, P = 0.9; test for heterogeneity I^2 = 0%, P = 0.9). The result was identical with fixed-effect and random-effects models.

The funnel plot for the seven trials included in the main analysis was symmetrical suggesting the absence of publication bias, which was confirmed using the Egger's (weighted regression) method (P = 0.202) and the Begg's (rank correlation) method (continuity corrected P = 1.0) in Stata 9.2 (Figure 2).

Figure 2. Funnel plot of comparison: Maternal vitamin A supplementation versus placebo, outcome: 1.1.1 Mortality in the first year of life for the main analysis.



Outcome 1.1.2 (Mortality after postpartum vitamin A supplementation in presence of night blindness, prevalence < 5%)

In the two trials providing data (Kirkwood 2010; Malaba 2005), there was no evidence of a reduced risk of mortality in the presence of maternal night blindness, prevalence < 5% (random-effects model RR 1.02, 95% CI 0.85 to 1.22, P = 0.83; I^2 = 28%, test for heterogeneity P = 0.24) (Analysis 1.1). Similar estimates were derived from the fixed-effect model.

Outcome 1.1.3 (Mortality after postpartum vitamin A supplementation in presence of night blindness, prevalence ≥ 5%)

Only one trial had relevant data (Klemm 2008) and the effect was not significant (RR 1.02, 95% CI 0.79 to 1.32).

Outcome 1.1.4 (Mortality with cumulative vitamin A dose < 200,000 IU)

Only one trial had relevant data (Newton 2005) and the effect was not significant (RR 1.54, 95% CI 0.31 to 7.63).

Outcome 1.1.5 (Mortality with cumulative vitamin A dose > 200,000 IU)

There was no evidence of a reduced risk of mortality in six trials providing a cumulative vitamin A dose > 200,000 IU (random-effects model RR 1.00, 95% CI 0.93 to 1.06, P = 0.89; I^2= 0%, test for heterogeneity P = 0.86) (.Analysis 1.1). Similar estimates were derived with the fixed-effect model.

Outcome 1.1.6 (Mortality with maternal serum retinol ≤ 1.1 µmol/L)

From two studies (Ayah 2007; Katz 2000), there was no evidence of a reduced risk of mortality if maternal serum retinol was ≤ 1.1 µmol/L (random-effects model RR 1.04, 95% CI 0.88 to 1.23, P = 0.66; I^2= 0%, test for heterogeneity P = 0.73) (.Analysis 1.1). Similar estimates were derived with the fixed-effect model.

Outcome 1.1.7 (Mortality with maternal serum retinol > 1.1 µmol/L)

From three trials providing data, there was no evidence of a reduced risk of mortality if maternal serum retinol was > 1.1 µmol/L (random-effects model RR 0.99, 95% CI 0.92 to 1.06, P = 0.76; I^2 = 0%, test for heterogeneity P = 0.49) (.Analysis 1.1). Similar estimates were derived from the fixed-effect model.

With a univariate meta-regression neither the cumulative vitamin A dose received by the mother nor mean maternal serum retinol emerged as a significant predictor of heterogeneity (Table 2).

Table 2. Meta-regression analyses of all- cause infant mortality following maternal postpartum vitamin A supplementation

Study characteristic	Univariate analysis Ratio of RRs* (95% CI); I^2	P Value
Total vitamin A dose (units) received by mother *(Per unit change) (7 trials)*	1.00 (1.00, 1.00); 0.0	0.496
Mean maternal serum retinol (micromoles/L) (5 trials) *(Per unit change)*	0.81 (0.17, 3.99); 0.0	0.706

* When the study characteristic is a binary variable, the estimate of effect size is the ratio of relative risks for infant mortality (treated/control) in the two groups. When the study characteristic is continuous, the estimate of effect size is the ratio of relative risks for infant mortality multiplicatively per unit change in the characteristic.

Disaggregated data for low birth weight (< 2500 grams) and normal birth weight (≥ 2500 grams) were not available for subgroup analysis.

Outcome 1.2 (Mortality in the first month of life)

In two trials providing data (Katz 2000; Kirkwood 2010), there was no evidence of a reduced risk of neonatal mortality (random-effects model RR 0.98, 95% CI 0.87 to 1.11, P = 0.47; I^2= 28%, test for heterogeneity P=0.24) (Analysis 1.2).

Secondary outcomes

Outcome 1.3 (Cause-specific mortality in the first year of life)

Among the six trials providing data on mortality, only two documented information on the cause of death (Malaba 2005; Venkatarao 1996). We have requested information on this outcome from another recent trial (Benn 2010). The cause of death was ascertained by verbal autopsy or lay reporting.

With a random-effects model, there was no evidence of a reduced risk of deaths due to respiratory causes (outcome 1.3.1: RR 1.59, 95% CI 0.84 to 2.99, P = 0.154; I^2=0%, test for heterogeneity P = 0.321), diarrhoeal etiology (outcome 1.3.2: RR 2.65, 95% CI 0.83 to 8.50, P = 0.10; I^2=11.8%, test for heterogeneity P = 0.287), or causes other than respiratory or diarrhoeal morbidities (outcome 1.3.3: RR 1.04, 95% CI 0.51 to 2.10, P = 0.92; I^2 = 64.5%, test for heterogeneity P = 0.093) (Analysis 1.3). Similar results were obtained with fixed-effect modelling for both outcomes. The estimated RR for causes other than respiratory and diarrhoeal etiologies was 0.62 (95% CI 0.09 to 4.09, P = 0.618; I^2 = 64%, test for heterogeneity P = 0.09).

Morbidity during infancy

The following morbidity details were available only in one study, for diarrhoeal and acute respiratory infections (Venkatarao 1996). In relation to infant follow-up from birth to six months of age, the two intervention arms (only maternal supplementation and both maternal and child supplementation) were combined, as the child supplementation had been done at six months of age, and compared with the placebo group. There was no evidence of a decrease in either of the recorded morbidities, namely diarrhoeal (RR 1.08, 95% CI 0.94 to 1.24) or acute respiratory infection (RR 1.08, 95% CI 0.98 to 1.19). The morbidity comparison between six and 12 months of age was in relation to only maternal supplementation and placebo groups. In this age group there was no evidence of a decrease in either diarrhoeal (RR 1.10, 95% CI 0.99 to 1.23) or acute respiratory infection (RR 0.96, 95% CI 0.85 to 1.08).

Adverse effects within one week

Relevant information was reported in two studies (Bhaskaram 1998; Venkatarao 1996), but no adverse effects were observed in both the trials, in either the intervention or the control groups, during the follow-up.

Comparison 2: Infant vitamin A supplementation in the first six months of life

Primary outcomes

The pertinent details of the vital events and denominators for the mortality analysis for each study are summarised in Table 3.

Table 3. Details of vital events for the mortality analysis in the infant supplementation review

Study	Vitamin A						Placebo						Source of RR used in meta-analysis
	Number randomised	Number dead	Number alive	Number lost	Vital status known	Follow up duration (child yrs)	Number randomised	Number dead	Number alive	Number lost	Vital status known	Follow up duration (child yrs)	
West (0-1 mo) 1995	830	38	781	11	819	268.4	791	34	751	6	785	256.9	Stated
West (1-6 mo) 1995	5256	112	5061	83	5173	2356.9	5041	96	4852	93	4948	2260.2	Calculated*

Table 3. Details of vital events for the mortality analysis in the infant supplementation review (*Continued*)

Humphı 1996	1034	7	918	109	925	969.6	1033	19	895	119	914	957.1	Stated
WHO 1998	4716	97	4388	231	4485	NM	4708	99	4396	213	4495	NM	Stated
Rahmathullah 2003	5786	146	5217	423	5363	2713.0	5833	188	5220	425	5408	2719.1	Stated
Malaba 2005^	4599	93	NM	NM	NM	4195	2309	38	NM	NM	NM	2120	Calculated^
Newton 2005	539	10	397	132	407	NM	277	2	204	71	206	NM	Calculated
Benn 2008	2145	91	2015	39	2106	NM	2200	88	2081	31	2169	NM	Stated
Klemm 2008#	7956	306	7647	3	7953	NM	NC	115	2517	NC	2632	NM	Calculated #
Benn 2010	854	83	701	70	784	757	863	78	710	75	788	762	Stated

NM Not mentioned; NC Not calculable

* Values derived from Tables 1 and 2 of publication and RR calculated with child year denominator.

^ The deaths also include those due to injuries and congenital defects (5 in Vitamin A and 2 in placebo), and RR calculated from child year denominator.

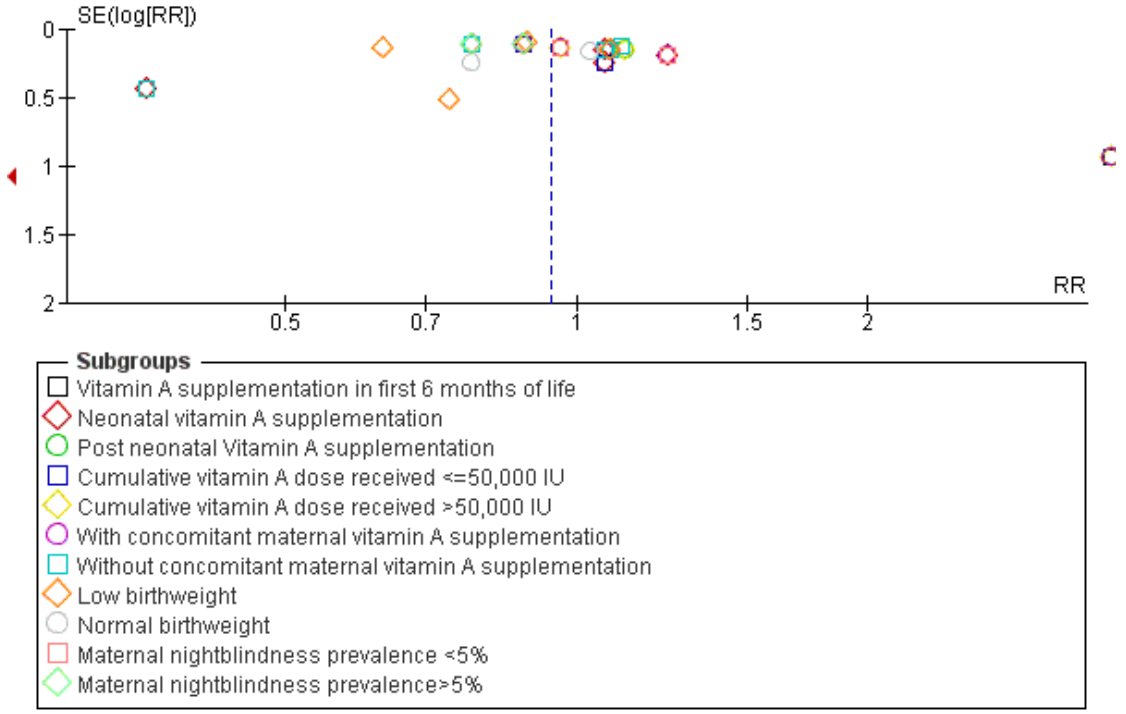
In the placebo group for this comparison, both mothers and newborns had received placebos. The RRs have been adjusted for the calculated design effect of 1.01769.

Outcome 2.1 (Mortality in the first year of life)

Relevant data for evaluating the pooled relative risk of mortality during infancy, in the period between initiation of intervention and the last follow-up until the age of one year, were available from nine trials, which contributed 10 independent analytic components for the subgroup analyses.

The funnel plot for the nine trials included in the main analysis was symmetrical suggesting the absence of publication bias. This was confirmed using the Egger's (weighted regression) method (P for bias = 0.566) and the Begg's (rank correlation) method (continuity corrected P = 0.118) in Stata 9.2 (Figure 3).

Figure 3. Funnel plot of comparison: 2 Young Infant vitamin A supplementation versus placebo, outcome: 2.1.1 Mortality in the first year of life for the main analysis.



We preferred to report the random-effects model for the pooled estimates in view of I^2 values which were above 25% in several of the analyses. The results from the fixed-effect model estimates are also reported for comparison.

The pertinent details of the vital events for the mortality analysis are summarised in Table 3.

Outcome 2.1.1 (Mortality after vitamin A supplementation in first six months)

In the main analysis of nine trials, the pooled risk ratio was 0.97 (95% CI 0.83 to 1.12, P = 0.65; test for heterogeneity I^2= 49%, P = 0.05) by the random-effects model and 0.95 (95% CI 0.86 to 1.05, P = 0.32) by the fixed-effect model (Analysis 2.1).

Outcome 2.1.2 (Mortality after neonatal vitamin A supplementation)

From the seven analytic components in which the intervention had been initiated in the neonatal period (0 to < 1 month), the pooled risk ratio was 0.94 (95% CI 0.79 to 1.12, P = 0.49; I^2 = 50%, test for heterogeneity P = 0.06) by the random-effects model and 0.92 (95% CI 0.82 to 1.03, P = 0.16) by the fixed-effect model (Analysis 2.1).

Outcome 2.1.3 (Mortality after vitamin A supplementation in one to six months)

From the three analytic components in which the intervention had been initiated between one to six months of life, the pooled risk ratio was 1.05 (95% CI 0.84 to 1.32, P = 0.66; test for heterogeneity I^2 = 13%, P = 0.32) by the random-effects model and 1.05 (95% CI 0.86 to 1.28, P = 0.66) by the fixed-effect model. The probability value from the test for statistical heterogeneity between the two subgroups (supplementation initiated in neonatal period and one to six months) was 0.285 (Stata 9.2).

Outcome 2.1.4 (Mortality after vitamin A supplementation, cumulative dose ≤ 50,000 IU)

From the seven analytic components, the pooled risk ratio was 0.94 (95% CI 0.79 to 1.12, P = 0.49; I^2 = 50%, test for heterogeneity P = 0.06) with random-effects modelling and 0.92 (95% CI 0.82 to 1.03, P = 0.16) with the fixed-effect model (Analysis 2.1).

Outcome 2.1.5 (Mortality after vitamin A supplementation, cumulative dose > 50,000 IU)

From the three analytic components, the pooled risk ratio was 1.05 (95% CI 0.84 to 1.32, P = 0.66; I^2 = 13%, test for heterogeneity P = 0.32) by random-effects modelling and 1.05 (95% CI 0.86 to 1.28, P = 0.66) with the fixed-effect model. The probability value for the test for statistical heterogeneity between the two subgroups (cumulative dose ≤ 50,000 and > 50,000) was 0.285 (Stata 9.2).

Outcome 2.1.6 (Mortality with concomitant maternal vitamin A supplementation)

From four trials, the pooled risk ratio was 1.0 (95% CI 0.81 to 1.23, P = 0.97; I^2 = 31%, test for heterogeneity P = 0.23) by random-effects modelling and 0.97 (95% CI 0.83 to 1.13, P = 0.70) with the fixed-effect model.

Outcome 2.1.7 (Mortality without concomitant maternal vitamin A supplementation)

From five trials, the pooled risk ratio was 0.93 (95% CI 0.74 to 1.17, P = 0.54; I^2 = 64%, test for heterogeneity P = 0.03) by random-effects modelling and 0.94 (95% CI 0.83 to 1.07, P = 0.34) by the fixed-effect model.

Outcome 2.1.8 (Mortality with vitamin A supplementation of low birthweight infants)

From four trials providing this data, the pooled risk ratio was 0.84 (95% CI 0.65 to 1.07, P = 0.16; I^2 = 58%, test for heterogeneity P = 0.07) by random-effects modelling and 0.85 (95% CI 0.74 to 0.97, P = 0.02) with the fixed-effect model.

Outcome 2.1.9 (Mortality with vitamin A supplementation of normal birthweight infants)

From three trials providing this data, the pooled risk ratio was 0.78 (95% CI 0.43 to 1.40, P = 0.40; I^2 = 64%, test for heterogeneity P = 0.06) by random-effects modelling and 0.92 (95% CI 0.70 to 1.19, P = 0.51) with the fixed-effect model.

Outcome 2.1.10 (Mortality with vitamin A supplementation in presence of night blindness in < 5% mothers)

From two trials providing this data, the pooled risk ratio was 1.06 (95% CI 0.83 to 1.34, P = 0.66; I^2 = 13%, test for heterogeneity P = 0.28) by random-effects modelling and 1.05 (95% CI 0.84 to 1.31, P = 0.66) by the fixed-effect model.

Outcome 2.1.11 (Mortality with vitamin A supplementation in presence of night blindness in ≥ 5% mothers)

In two trials providing this data, the pooled risk ratio was 0.83 (95% CI 0.71 to 0.96, P = 0.01; I^2 = 0%, test for heterogeneity P = 0.43). Results were identical with random-effects and fixed-effect modelling.

On univariate meta-regression none of these pre-specified variables (time point of initiation of vitamin A supplementation, simultaneous maternal administration of vitamin A supplementation, cumulative dose of vitamin A supplementation, vitamin A status of mother, and birth weight of neonates) could be identified as a statistically significant (P > 0.05) predictor of heterogeneity (Table 4).

Table 4. Meta-regression analyses of all cause infant mortality following vitamin A supplementation in the first six months of life

Study characteristic	Univariate analysis Ratio of RRs* (95% CI); I^2	P value
Vitamin A supplementation age *(Post-neonatal* versus *neonatal)*	1.13 (0.76, 1.68); 0.44	0.50
Maternal post-partum vitamin A supplementation *(Yes* versus *no)*	1.05 (0.72, 1.53); 0.48	0.77
Total vitamin A dose (units) received by infant *(Per unit change)*	1.00 (1.00, 1.00); 0.41	0.39
Maternal night blindness *(>5%* versus *≤5%) (components=5)*	0.78 (0.53, 1.14); 0.00	0.13

Table 4. Meta-regression analyses of all cause infant mortality following vitamin A supplementation in the first six months of life (*Continued*)

Birthweight *(<2500 grams* versus *>=2500 grams)* *(components = 4 for <2500 grams and 3 for >=2500 grams)*	1.02 (0.49, 2.15); 0.61	0.94

* When the study characteristic is a binary variable, the estimate of effect size is the ratio of relative risks for infant mortality (treated/control) in the two groups. When the study characteristic is continuous, the estimate of effect size is the ratio of relative risks for infant mortality multiplicatively per unit change in the characteristic.

Outcome 2.2 (Mortality in the first month of life)

In three trials providing this data, the pooled risk ratio was 0.90 (95% CI 0.75 to 1.08, P = 0.27; I^2= 0%, test for heterogeneity P = 0.83). Results were identical with random-effects and fixed-effect modelling (Analysis 2.2).

Outcome 2.3 (Cause-specific mortality in the first year of life)

Among the nine trials providing data on mortality, only seven documented information on the cause of death. All of these studies were conducted in low and middle income countries: three in Asia (Humphrey 1996; Rahmathullah 2003; West 1995); three in Africa (Benn 2008; Benn 2010; Malaba 2005); and one was multi-centre, from Asia, Africa and Latin America (WHO 1998). The cause of death had been ascertained by verbal autopsy or lay reporting. In the trial with two independent analytic components for the all-cause mortality analysis, information on the cause of death was not available by the strata for the age group when intervention was initiated (West 1995).

Outcome 2.3.1 (Cause-specific mortality due to diarrhoea)

The pooled risk ratio was 1.01 (95% CI 0.72 to 1.41, P = 0.96; I^2 = 33%, test for heterogeneity P = 0.17) by random-effects modelling and 1.01 (95% CI 0.79 to 1.30, P = 0.92) by the fixed-effect model (Analysis 2.3).

Outcome 2.3.2 (Cause-specific mortality due to acute respiratory infection)

The pooled risk ratio was 1.12 (95% CI 0.91 to 1.39, P = 0.29; I^2 = 0%, test for heterogeneity P = 0.99). Results were identical with random-effects and fixed-effect modelling (Analysis 2.3).

Outcome 2.3.3 (Cause-specific mortality due to other causes)

The pooled risk ratio was 0.81 (95% CI 0.64 to 1.02, P = 0.07; I^2 = 63%, test for heterogeneity P = 0.01) by the random-effects model and 0.85 (95% CI 0.75 to 0.97, P = 0.01) with a fixed-effect model (Analysis 2.3).

In the trial of neonatal supplementation from India (Rahmathullah 2003), one report (Tielsch 2007) had recorded relative case fatality rates following episodes of common morbidities with follow-up to 60 days after onset. It could not be ascertained whether death during follow-up was causally related to the specific morbidity. At the last follow-up (60 days post-onset) case fatalities for diarrhoea and fever were significantly reduced in the vitamin A group compared with placebo (relative case fatality of 0.50, 95% CI 0.27 to 0.90; and 0.60, 95% CI 0.40 to 0.88, respectively). However, the relative case fatality rates were not statistically different during the episode of diarrhoea and fever (relative case fatality 0.54, 95% CI 0.24 to 1.22; 1.20, 95% CI 0.59 to 2.43, respectively). Also at the last follow-up (60 days post-onset) there were no significant differences for relative case fatality for dysentery (relative case fatality 0.83, 95% CI 0.25 to 2.70) and various definitions of acute respiratory infections, namely cough and fever (0.66, 95% CI 0.35 to 1.21); difficulty breathing and fever (0.52, 95% CI 0.22 to 1.21); and cough, difficulty breathing and fever (0.40, 95% CI 0.12 to 1.28). The numbers of deaths from this data set (assuming that the morbidities occurred independently) were only 249 out of a total of 334 (75%) deaths recorded in the primary study. There was no evidence that the treatment effects were modified by birth weight.

Outcome 2.4 (Morbidity in the first year of life)

We evaluated seven trials for the morbidities outcome, all of which were conducted in low and middle income countries: four in Asia (Humphrey 1996; Rahmathullah 2003; Semba 2001; Venkatarao 1996), two in Africa (Benn 2008; Benn 2010), and one was multi-centre from Asia, Africa and Latin America (WHO 1998). There were no cluster randomised studies. Simultaneous maternal vitamin A supplementation had been given in two trials (Rahmathullah 2003; Venkatarao 1996). Infant intervention had been initiated in the neonatal period in four studies (Benn 2008;

Benn 2010; Humphrey 1996; Rahmathullah 2003). The total vitamin A dose received by the infant was ≤ 50,000 IU in four trials (Benn 2008; Benn 2010; Humphrey 1996; Rahmathullah 2003) and > 50,000 IU in three studies. A single intervention dose had been given in four trials (Benn 2008; Benn 2010; Humphrey 1996; Rahmathullah 2003) and multiple doses in the other three studies. The follow-up age was > 6 months in four trials.

Outcome 2.4.1 (Diarrhea)

In six trials providing this data, the pooled risk ratio was 1.02 (95% CI 0.99 to 1.06, P = 0.19; I^2= 0%, test for heterogeneity P = 0.55). Results were identical with random-effects and fixed-effect modelling (Analysis 2.4).

Outcome 2.4.2 (Acute respiratory infection or respiratory distress)

In four trials providing this data, the pooled risk ratio was 1.04 (95% CI 0.95 to 1.15, P = 0.38; I^2 = 61%, test for heterogeneity P = 0.05) by random-effects modelling and 1.07 (95% CI 1.02 to 1.13, P = 0.004) with the fixed-effect model (Analysis 2.4).

Outcome 2.4.3 (Cough or running nose)

In three trials providing data the pooled risk ratio was 0.98 (95% CI 0.85 to 1.13, P = 0.77; I^2 = 69%, test for heterogeneity P = 0.04) by random-effects modelling and 1.01 (95% CI 0.99 to 1.04, P = 0.34) with the fixed-effect model (Analysis 2.4).

Outcome 2.4.4 (Ear infection)

No trial provided data for this outcome.

Outcome 2.4.5 (Fever)

In three trials providing this data, the pooled risk ratio was 0.92 (95% CI 0.76 to 1.11, P = 0.39; I^2 = 69%, test for heterogeneity P = 0.04) by random-effects modelling and 1.02 (95% CI 0.98 to 1.07, P = 0.24) with the fixed-effect model (Analysis 2.4).

Outcome 2.4.6 (Vomiting)

No trial provided data for this outcome (classified as morbidity).

Outcome 2.5 (Adverse effects)

Of the 13 trials reporting adverse effects, three (Rahmathullah 2003; Stabell 1995; Venkatarao 1996) had not recorded any adverse effect (including bulging fontanelle) in either group during the follow-up. In a companion publication to one of these trials (Rahmathullah 2003), it was stated that "side effects, defined as morbidity of the infant associated close in time to the receipt of the study treatment, were uncommon, with six cases occurring in the placebo group and three cases in the vitamin A group" (Tielsch 2007); specific adverse effect data could not therefore be extracted. Pooled estimates of adverse effects were based on data from 10 trials. All these studies were conducted in developing countries (six in Asia, three in Africa, and one was multi-centre from Asia, Africa and Latin America). Klemm 2008 and West 1995 were cluster randomised. Of the 10 trials, nine were assessed to be double blind, all had adequate allocation concealment, and loss to follow-up was < 10% in 8, ≥ 10% in one, and unknown in one. Simultaneous maternal postpartum vitamin A supplementation (≥ 30% mothers in the intervention arm) had been resorted to in four studies. The vitamin A dose received by the infant was < 50,000 IU in three trials and ≥ 50,000 IU in seven studies. A physician had recorded the adverse effect (bulging fontanelle) in five trials.

Outcome 2.5.1 (Bulging fontanelle following any dose of vitamin A)

In the 10 trials providing this data, the pooled risk ratio was 1.55 (95% CI 1.05 to 2.28, P = 0.03; I^2 = 68%, test for heterogeneity P = 0.0009) by random-effects modelling and 1.16 (95% CI 0.99 to 1.35, P = 0.06) with the fixed-effect model (Analysis 2.5).

Outcome 2.5.2 (Bulging fontanelle following first dose of vitamin A)

From seven trials providing data, the pooled risk ratio was 1.37 (95% CI 0.98 to 1.91, P = 0.06; I^2 = 63%, test for heterogeneity P = 0.01) by random-effects modelling and 1.12 (95% CI 0.96 to 1.31, P=0.15) with the fixed-effect model (Analysis 2.5).

Outcome 2.5.3 (Bulging fontanelle following second dose of vitamin A)

In the two trials providing this data, the pooled risk ratio was 3.60 (95% CI 1.65 to 7.87, P = 0.001; I^2 = 0%, test for heterogeneity P = 0.82). Results were identical with random-effects and fixed-effect modelling (Analysis 2.5).

Outcome 2.5.4 (Bulging fontanelle following third dose of vitamin A)

In the two trials providing this data, the pooled risk ratio was 3.14 (95% CI 1.72 to 5.74, P = 0.0002; I^2 = 0%, P = 0.32). Results were identical with random-effects and fixed-effect modelling (Analysis 2.5).

Outcome 2.5.5 (Vomiting)

In the four trials providing this data, the pooled risk ratio was 0.81 (95% CI 0.58 to 1.12, P = 0.20; I^2= 77%, test for heterogeneity

P = 0.005) by the random-effects model and 0.88 (95% CI 0.78 to 0.99, P = 0.03) by the fixed-effect model (Analysis 2.5).

Outcome 2.5.6 (Irritability)

In the four trials providing this data, the pooled risk ratio was 0.98 (95% CI 0.87 to 1.11, P = 0.78; I^2 = 0%, test for heterogeneity P = 0.50). Results were identical with random-effects and fixed-effect modelling (Analysis 2.5).

Outcome 2.5.7 (Diarrhea)

In the five trials providing this data, the pooled risk ratio was 0.99 (95% CI 0.75 to 1.31, P = 0.94; I^2= 73%, test for heterogeneity P = 0.03) by random-effects modelling and 0.97 (95% CI 0.84 to 1.12, P = 0.69) with the fixed-effect model (Analysis 2.5).

Outcome 2.5.8 (Fever)

In the three trials providing this data, the pooled risk ratio was 1.07 (95% CI 0.96 to 1.20, P = 0.21; I^2= 0%, test for heterogeneity P = 0.79). Results were identical with random-effects and fixed-effect modelling (Analysis 2.5).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Young Infant Vitamin A Supplementation compared to placebo for the prevention of morbidity and mortality in infants six months of age or less

Patient or population: patients with the prevention of morbidity and mortality in infants six months of age or less
Settings: Low middle income countries
Intervention: Young Infant Vitamin A Supplementation
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	Young Infant Vitamin A Supplementation				
All-cause mortality in the first year of life Follow-up: 6-12 months	**Low risk population**[1]		**RR 0.97** (0.83 to 1.12)	59402 (9 studies)	⊕⊕⊕◯ **moderate**[2,3]	Data analysed as risk ratios. Cumulative risk and incidence ratios from studies were combined to generate a pooled risk ratio. CER from external source.
	22 per 1000	**21 per 1000** (18 to 25)				
	Medium risk population[1]					
	51 per 1000	**49 per 1000** (42 to 57)				
	High risk population[1]					
	117 per 1000	**113 per 1000** (97 to 131)				
All-cause mortality at 1 month Follow-up: 1 months	**Low risk population**[4]		**RR 0.90** (0.75 to 1.08)	17000 (3 studies)	⊕◯◯◯ **very low**[5,6,7]	Data analysed as risk ratios. Cumulative risk and incidence ratios from studies were combined to generate a pooled risk ra-

						tio. CERs from external source.
	19 per 1000	**17 per 1000** (14 to 21)				
	High risk population[4]					
	45 per 1000	**40 per 1000** (34 to 49)				
Diarrhoea-related mortality in the first year of life verbal autopsy or lay reporting	**Low risk population**[8]		**RR 1.01** (0.72 to 1.41)	47998 (7 studies)	⊕⊕◯◯ **low**[9,10]	Data analysed as risk ratios. Cumulative risk and incidence ratios from studies were combined to generate a pooled risk ratio. CER from external sources.
	3 per 1000	**3 per 1000** (2 to 5)				
	Medium risk population[8]					
	8 per 1000	**8 per 1000** (6 to 11)				
	High risk population[8]					
	18 per 1000	**18 per 1000** (13 to 25)				
ARI-related mortality in the first year of life verbal autopsy or lay reporting	**Low risk population**[11]		**RR 1.12** (0.91 to 1.39)	47998 (7 studies)	⊕⊕⊕◯ **moderate**[6,9]	Data analysed as risk ratios. Cumulative risk and incidence ratios from studies were combined to generate a pooled risk ratio. CER from included studies.
	4 per 1000	**4 per 1000** (4 to 6)				
	Medium risk population[11]					
	9 per 1000	**10 per 1000** (8 to 13)				

	High risk population[11]					
	21 per 1000	**24 per 1000** (19 to 29)				
Morbidity in the first year of life - Diarrhoea Follow-up: 2-12 months	**Medium risk population**[12]		**RR 1.02** (0.99 to 1.06)	24802 (6 studies)	⊕⊕◯◯ **low**[13,14]	Data were analysed from ratios of rates and risk. Estimate of cumulative risk comes from an included study (WHO 1998).
	100 per 1000	**102 per 1000** (99 to 106)				
Morbidity in the first year of life - Acute respiratory infection or respiratory difficulty Follow-up: 4-12 months	**Medium risk population**[12]		**RR 1.04** (0.95 to 1.15)	24019 (4 studies)	⊕⊕◯◯ **low**[15,16]	Data were analysed from ratios of rates and risk. Estimate of cumulative risk comes from an included study (WHO 1998).
	34 per 1000	**35 per 1000** (32 to 39)				
Adverse effects of vitamin A supplementation - Bulging fontanelle following any dose of vitamin A	**18 per 1000**	**28 per 1000** (19 to 41)	**RR 1.55** (1.05 to 2.28)	32978 (10 studies)	⊕⊕◯◯ **low**[17,18]	We believe that further research is unlikely to affect the direction of effect, but that it may improve the precision of the estimated increase in risk.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Information taken from the World Health Statistics 2010 (http://www.who.int/whosis/whostat/2010/en/index.html) based on the lowest, medium and highest mortality rates at 1 year of age recorded in 2008 in the countries of the included studies (Bangladesh, Ghana, Guinea-Bissau, India, Indonesia, Nepal, Peru, Zimbabwe).

[2] Five studies were at an unclear risk of selection bias due to insufficient reporting (Humphrey 1996: allocation generation; Klemm 2008, Newton 2005, Rahmathullah 2003, West 1995: allocation generation and concealment). However, this was not considered to pose a serious bias for this outcome (unlikely risk of high bias - lack of clarity primarily due to inadequate reporting with intervention and control arms being reasonably balanced for confounders likely to influence mortality estimates). All trials had a low risk of bias for blinding. One small trial (Newton 2005) was at high risk of bias for incomplete outcome data reporting. Selective outcome reporting was not considered to pose a risk of bias for this outcome. Three trials (Benn 2008, Benn 2010, Humphrey 1996) at high risk of bias for depicting post hoc sub-group comparisons were not considered to pose a bias for this outcome. Partial funding from Vitamin A manufacturer was not considered to pose a risk of bias (Humphrey 1996). One trial terminated early was considered to pose a high risk of bias (Klemm 2008). The weighting of the two trials (Klemm 2008, Newton 2005) with a high risk of bias on one or more key domains was 17.6%. Thus overall, the data was not considered to have serious limitations of design.

[3] A moderate to high level of heterogeneity (I squared: 49%, $p = 0.05$) was observed between the results of the studies. This variation could not be fully explained by supplementation age, maternal postpartum vitamin A supplementation, total dose received, maternal night blindness and birth weight at baseline. Humphrey 1996 and Rahmathullah 2003 were the only studies to find a statistically significant benefit for vitamin A.

[4] Information taken from the World Health Statistics 2010 (http://www.who.int/whosis/whostat/2010/en/index.html) based on the lowest, medium and highest mortality rates at 1 month of age in the countries of the included studies (Bangladesh, Guinea-Bissau, Indonesia).

[5] Two studies were at an unclear risk of selection bias due to insufficient reporting (Humphrey 1996: allocation generation; Klemm 2008: allocation generation and concealment). However, this was not considered to pose a serious bias for this outcome (unlikely risk of bias - lack of clarity primarily due to aspects of reporting, with intervention and control arms reasonably balanced for confounders likely to influence mortality estimates). Blinding, incomplete data and selective reporting were not considered to significantly bias the results. Two trials (Benn 2008, Humphrey 1996) at high risk of bias for depicting post hoc sub-group comparisons were not considered to pose a bias for this outcome. Partial funding from Vitamin A manufacturer was not considered to pose a risk of bias (Humphrey 1996). Reporting on neonatal mortality with most (~75%) of the participants being followed-up only at one year of age after intervention within 48 hours of birth was considered to pose a high risk of bias (Humphrey 1996). One trial with terminated early was considered to pose a high risk of bias (Klemm 2008). The weighting of the two trials (Humphrey 1996, Klemm 2008) with a high risk of bias on one or more key domains was 95.4%. Thus overall, the data was considered to have serious limitations of design.

[6] The 95% confidence intervals around the pooled effect estimate include both (i) no effect and (ii) appreciable benefit or appreciable harm.

[7] Only three studies reported this outcome. Selective reporting bias cannot be excluded.

[8] Information taken from two sources. World Health Statistics 2010 (http://www.who.int/whosis/whostat/2010/en/index.html) provided the lowest, medium and highest mortality rates at 1 year of age from the countries where the included studies were performed (Ghana, Guinea-Bissau, India, Indonesia, Nepal, Peru, Zimbabwe). Based on the proportion of global all cause mortality attributed to diarrhoea (15% reported in Black 2010), the events entered represent 15% of each of the national rates of mortality.

[9] Three studies were at an unclear risk of selection bias due to insufficient reporting (Humphrey 1996: allocation generation; Rahmathullah 2003, West 1995: allocation generation and concealment). However, this was not considered to pose a serious bias for this outcome (unlikely risk of high bias - lack of clarity primarily due to aspects of reporting, with intervention and control arms being reasonably balanced for confounders likely to influence mortality estimates). All trials had a low risk of bias for blinding. Selective outcome reporting was not considered to pose a risk of bias for this outcome. Three trials (Benn 2008, Benn 2010, Humphrey 1996) at high risk of bias for depicting post hoc sub-group comparisons were not considered to pose a bias for this outcome. Partial funding from Vitamin A

manufacturer was not considered to pose a risk of bias (Humphrey 1996). Thus overall, the data was not considered to have serious limitations of design.

[10] The 95% confidence intervals around the pooled effect estimate include both appreciable benefit and appreciable harm.

[11] Information taken from two sources. World Health Statistics 2010 (http://www.who.int/whosis/whostat/2010/en/index.html) provided the lowest, medium and highest mortality rates at 1 year of age from the countries where the included studies were performed (Ghana, Guinea-Bissau, India, Indonesia, Nepal, Peru, Zimbabwe). Based on the proportion of global all cause mortality attributed to pneumonia (18% reported in Black 2010), the events entered represent 18% of each of the national rates of mortality.

[12] Derived from multi-country trial (WHO 1998).

[13] Only one study (WHO 1998) described an adequate sequence generation, and two studies had adequate allocation concealment (Humphrey 1996, WHO 1998). For the remaining studies there was a high risk of selection bias. Blinding was adequately reported in all studies. Two studies (Semba 2001, Venkatarao 1996) were at high risk of attrition bias, and two studies (Humphrey 1996, Semba 2001) were at risk of selective reporting. Only WHO 1998 was considered to be free of other sources of bias.

[14] Only six of the studies contributing data were included. Selective reporting bias cannot be excluded.

[15] Only one study (WHO 1998) described an adequate sequence generation, and two studies had adequate allocation concealment (Humphrey 1996, WHO 1998). For the remaining studies there was a high risk of selection bias. Blinding was adequately reported in all studies. Venkatarao 1996 was at high risk of attrition bias, and one study (Humphrey 1996) was at risk of selective reporting bias. Only WHO 1998 was considered to be free of other sources of bias.

[16] Only four of the studies contributing data were included. Selective reporting bias cannot be excluded.

[17] Five studies had unclear sequence generation (de Francisco 1993, Humphrey 1996, Klemm 2008; Semba 2001; West 1995), and four studies had unclear or inappropriate allocation concealment (de Francisco 1993, Klemm 2008, Semba 2001, West 1995). For the remaining studies there was a low risk of selection bias. Blinding was adequately reported in all studies. Three studies (Baqui 1995; de Francisco 1993, Semba 2001) were at high risk of attrition bias, and only three studies (Benn 2008, Klemm 2008, WHO 1998) were free of selective reporting bias. Only Malaba 2005 and WHO 1998 were judged to be free of other biases.

[18] A high level of statistical heterogeneity was observed between the results of the studies (I squared: 68%, P = 0.0009). Three studies (de Francisco 1993, Humphrey 1996 and WHO 1998) found a statistically significant increase in the risk of bulging fontanelle after vitamin A supplementation when compared to placebo.

Young Infant Vitamin A Supplementation compared to Placebo for the prevention of morbidity and mortality in infants six months of age or less

Patient or population: patients with the prevention of morbidity and mortality in infants six months of age or less
Settings: Low middle income countries
Intervention: Young Infant Vitamin A Supplementation
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Young Infant Vitamin A Supplementation				
Mortality in the first year of life - Neonatal vitamin A supplementation Follow-up: 6-12 months	**Low risk population**[1]		**RR 0.94** (0.79 to 1.12)	38865 (7 studies)	⊕⊕⊕◯ **moderate**[2,3]	This was a subgroup estimate. Meta-regression gave a non-significant Ratio of the subgroup RRs of 1.13, 95% CI 0.76 to 1.68.
	22 per 1000	**21 per 1000** (17 to 25)				
	Medium risk population[1]					
	51 per 1000	**48 per 1000** (40 to 57)				
	High risk population[1]					
	117 per 1000	**110 per 1000** (92 to 131)				
Mortality in the first year of life - Post neonatal Vitamin A supplementation Follow-up: 6-9 months	**Low risk population**[1]		**RR 1.05** (0.84 to 1.32)	20537 (3 studies)	⊕⊕⊕◯ **moderate**[4,5]	This was a subgroup estimate. Meta-regression gave a non-significant Ratio of the subgroup RRs of 1.13, 95% CI 0.76 to 1.68.

	22 per 1000	**23 per 1000** (18 to 29)
	Medium risk population[1]	
	41 per 1000	**43 per 1000** (34 to 54)
	High risk population[1]	
	52 per 1000	**55 per 1000** (44 to 69)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Information taken from the World Health Statistics 2010 (http://www.who.int/whosis/whostat/2010/en/index.html) based on the lowest, medium and highest mortality rates at 1 year of age recorded in 2008 in the countries of the included studies

[2] Four studies were at an unclear risk of selection bias due to insufficient reporting (Humphrey 1996: allocation generation; Klemm 2008, Rahmathullah 2003, West 1995: allocation generation and concealment). However, this was not considered to pose a serious bias for this outcome (unlikely risk of high bias - lack of clarity primarily due to reporting aspects with intervention and control arms being reasonably balanced for confounders likely to influence mortality estimates). All trials had a low risk of bias for blinding. Selective outcome reporting was not considered to pose a risk of bias for this outcome. Three trials (Benn 2008, Benn 2010, Humphrey 1996) were at a high risk of bias for depicting post-hoc subgroup comparisons were not considered to pose a bias for this outcome. Partial funding from Vitamin A manufacturer was not considered to pose a risk of bias (Humphrey 1996). One trial terminated prematurely was considered to pose a high risk of bias (Klemm 2008); and contributed 22% weight of the estimated effect. Thus overall, the data were not considered to have serious limitations of design.

[3] I square for the subgroup estimate in neonatal children was moderately high (50%, P = 0.06).

[4] Two studies were at an unclear risk of selection bias due to insufficient reporting (Newton 2005, West 1995: allocation generation and concealment). However, this was not considered to pose a serious bias for this outcome (unlikely risk of high bias - lack of clarity

primarily due to reporting aspects with intervention and control arms being reasonably balanced for confounders likely to influence mortality estimates). All trials had a low risk of bias for blinding. One small trial (Newton 2005) was at high risk of bias for incomplete outcome data reporting. Selective outcome reporting was not considered to pose a risk of bias for this outcome. The weighting of the trial (Newton 2005) with a high risk of bias on one or more key domains was only 2.2%. Thus overall, the data was not considered to have serious limitations of design.

[5] The confidence intervals include both a reduction in the risk of all cause mortality of 16% and an appreciable increase in the risk of mortality of 32%.

DISCUSSION

Summary of main results

The main results are depicted in the summary of findings tables, separately for the maternal (Summary of findings for the main comparison) and young infant (Summary of findings 2; Summary of findings 3) supplementation components of the review.

Comparison 1: Maternal supplementation

(Summary of findings for the main comparison)
There was no evidence of a reduced risk of all-cause mortality during infancy (high quality evidence) or the neonatal period (moderate quality evidence). Limited data from one to two trials did not indicate a reduced risk of mortality and morbidity due to diarrhoea or acute respiratory infections (ARI) but the quality of evidence was very low (very uncertain of effect). Only two studies reported on adverse effects but no events were recorded in either of them.

Comparison 2: Infant supplementation

(Summary of findings 2)
There was no evidence of a reduced risk of all-cause mortality during infancy (moderate quality evidence with possibilities including 17% benefit and 12% harm). There was considerable heterogeneity between the results of the nine trials (I^2 = 49%, P = 0.05), which could not be explained by any of the pre-specified variables including timing of supplementation (neonatal or post-neonatal). The pre-specified subgroup estimates for supplementation within the neonatal and post-neonatal periods did not identify strong evidence of a reduced risk of all-cause mortality during infancy (Summary of findings 3; moderate quality evidence; a possible 21% reduction and 12% increase in the risk for neonatal supplementation; a possible 16% reduction and 32% increase in the risk for post-neonatal supplementation). There was considerable heterogeneity between the results of the seven trials for neonatal supplementation (I^2 = 50%, P = 0.06). There was no strong evidence that vitamin A reduced the risk of neonatal mortality (the confidence interval around the estimated RR included a possible 25% reduction and 8% increase in the risk of mortality (Summary of findings 2; very low quality evidence). There was no evidence of a reduced risk of mortality and morbidity due to diarrhoea or ARI (moderate quality evidence for ARI-related mortality and low quality evidence for others). However, in 10 trials (32,978 participants) there was weak evidence of an increased risk of bulging fontanelle following any dose of vitamin A (random-effects model RR 1.55, 95% CI 1.05 to 2.28, P = 0.03) but the quality of evidence was graded as low due to limitations in design and inconsistency (I^2 = 68%, P = 0.0009).

Overall completeness and applicability of evidence

The ensuing description is pertinent to understanding how the results of the review fit into the context of current global practice. The current WHO guidelines on vitamin A supplementation (WHO 2009) were published in 1997 (WHO/UNICEF/IVACG 1997) and 1998 (WHO/MI 1998). In 2000, WHO commissioned reviews of the scientific literature to examine the current state of knowledge concerning the use of vitamin A supplements to control vitamin A deficiency and convened a Technical Consultation on vitamin A supplementation in Yverdon-les-Bains, Switzerland (March 1 to 3, 2000). The objectives of the Consultation were to undertake a critical review of the safety and efficacy of vitamin A supplementation in order to provide WHO with guidance on the use of vitamin A supplementation as a public health measure to prevent and treat vitamin A deficiency. The review and conclusions of the Consultation were published in a special issue of the Food and Nutrition Bulletin in 2001 (de Benoist 2001). However, these have not been published as formal WHO guidelines. Additional research has been conducted since 2001 and the official WHO guidelines on vitamin A supplementation are currently being revised in a systematic manner using the current evidence (WHO 2008).

Comparison 1: Maternal supplementation

The studies were conducted in participants and settings directly relevant to the review, namely in low and middle income countries in Asia and Africa, which have endemic vitamin A deficiency and high neonatal and infant mortality rates. However, data specifically restricted to high risk groups (high prevalence of maternal night blindness and low birth weight) were relatively limited.
The WHO/MI 1998 guidelines on supplementation for mothers in the first six months postpartum recommend "single high-dose supplement above 25,000 IU, and usually at a level 200,000 IU, during the safe period of postpartum infertility for mothers in vitamin A deficient areas". These recommendations have not as yet been adopted universally at national levels. The subsequent technical consultation (de Benoist 2001) suggested that: (i) "the postpartum dose of vitamin A to mothers should be increased to 400,000 IU and should be given as two doses of 200,000 IU" and (ii) "as an alternative to large-dose supplementation, mothers can receive vitamin A at any time postpartum, given as a low dose not exceeding 10,000 IU per day or 25,000 IU per week". These recommendations too are not widely adopted in low and middle income countries. In this review, the cumulative dose of vitamin A received by the postpartum mothers was 200,000 IU or more; it was delivered as a single megadose in four studies and as weekly low-dose supplementation in three trials. Thus, the included trials address interventions relevant to the current WHO guidelines for supplementation in vitamin A deficient areas.
Mortality during infancy was reported in seven trials (96,203 par-

ticipants) whereas neonatal mortality was documented in two large studies (84,537 participants). The identified studies thus sufficiently addressed mortality outcomes, and in particular mortality during infancy, which is the main question of our review. However, cause-specific mortality (two studies), morbidities (one study) and adverse effects (two studies) were not addressed sufficiently to develop firm recommendations.

Comparison 2: Infant supplementation

The studies were conducted in participants and settings directly relevant to the review, namely in Asia and Africa in low and middle income countries which had endemic vitamin A deficiency and high neonatal and infant mortality rates. Vitamin A supplementation was either initiated in the neonatal period (seven analytic components) or between one to six months of life (three analytic components). Data on low birth weight babies was available in three studies while one trial was conducted exclusively on low birth weight babies. However, data specifically restricted to mothers with high prevalence of night blindness was relatively limited. The WHO/MI 1998 guidelines on direct supplementation of infants before six months of age in areas of endemic vitamin A deficiency state that "firm evidence of benefits to breast-feeding infants of direct supplementation before six months of age is insufficient. Studies are in progress to clarify the benefits/risks of single supplementation at 50,000 IU at birth or thereafter, or multiple supplementation at 25,000 IU. Infants who are not breast-fed and who are not given fortified breast-milk substitutes should receive a 50,000 IU supplement, preferably by about 2 months of age - otherwise at any time within the first six months of life. As an alternative two doses of 25,000 IU can be given within an interval of a month or more in between". The subsequent technical consultation (de Benoist 2001) suggested that: "Infants should receive three 50,000 IU (15,000 µgRE) doses of vitamin A within the first six months of life. The three diphtheria-tetanus-pertussis (DTP) immunization contacts at 6, 10, and 14 weeks are thought to be some of the best opportunities to deliver and record these doses". In this review, the cumulative dose of vitamin A received was 25,000 IU to 50,000 IU in trials involving neonatal supplementation and more than 50,000 IU in trials involving supplementation to infants between one to six months of age. Thus the included trials address interventions relevant to framing the current WHO guidelines (WHO 2009) for supplementation in vitamin A-deficient areas.

Mortality during infancy was reported in nine trials (59,402 participants); the identified studies thus sufficiently addressed the main question of the review. Neonatal mortality (three trials), cause-specific mortality (seven studies) and morbidities (four to six studies) were partially addressed but not in a robust manner. The critical safety outcome of bulging fontanelle (10 trials) was addressed in a sufficient number of participants but not in a robust manner.

Quality of the evidence

Comparison 1: Maternal supplementation

Data on all-cause mortality in the first year of life were available for 96,203 participants from seven trials; the quality of evidence was high with no serious limitations. Neonatal mortality was documented for 84,537 participants in two large trials; the quality of evidence was rated as moderate due to publication bias. The data on cause-specific mortality (5207 participants in two studies) and morbidities (598 participants in one study) were assessed to have very low quality due to serious limitations of study design (allocation concealment and addressing incomplete outcome data) and imprecision or publication bias. Interpretation was not feasible for adverse effects as no events were recorded in the intervention and control groups amongst 700 participants in two studies (Summary of findings for the main comparison).

Comparison 2: Infant supplementation

Data on all-cause mortality in the first year of life were available for 59,402 participants from nine trials. We downgraded the quality of evidence due to inconsistency which could not be adequately explained (I^2 = 49%, P = 0.05). Neonatal mortality was documented for 17,000 participants in three trials; the quality of evidence was rated as very low due to limitations in design, imprecision and publication bias. The data on cause-specific mortality (47,998 participants in seven studies) were assessed to have low to moderate quality due to imprecision. The data on morbidities (diarrhoea in 24,802 participants in six studies and respiratory infections in 24,019 participants in four studies) were assessed to have low quality due to limitations of study design and publication bias. Data on adverse effects (bulging fontanelle following any dose of vitamin A in 32,978 participants in 10 studies) were also assessed to have low quality due to serious limitations of study design (one or more aspects in several studies) and inconsistency (heterogeneity I^2 = 68%, P = 0.0009) (Summary of findings 2).

For the pre-specified subgroup analyses for supplementation during the neonatal and post-neonatal periods, data on all-cause mortality in the first year of life were available for 38,865 participants from seven analytic components for neonatal supplementation and 20,537 participants from three analytic components for post-neonatal supplementation. The quality of evidence was rated as moderate due to inconsistency (unexplained heterogeneity I^2 = 50%, P = 0.06) and imprecision, respectively (Summary of findings 3).

Potential biases in the review process

Comparison 1: Maternal supplementation

Strengths

The main conclusion regarding all-cause mortality during the first year of life remained stable over a large spectrum of pre-specified subgroup analyses and there was no heterogeneity (I^2 = 0%). The results were invariably synchronous with the use of either random-effects or fixed-effect models. Analysis of seven trials, though admittedly not robust proof, did not indicate evidence of publication bias. Cluster and individually randomised trials were appropriately combined by design effect correction for the primary outcome. Diligent efforts were made to include all relevant trials.

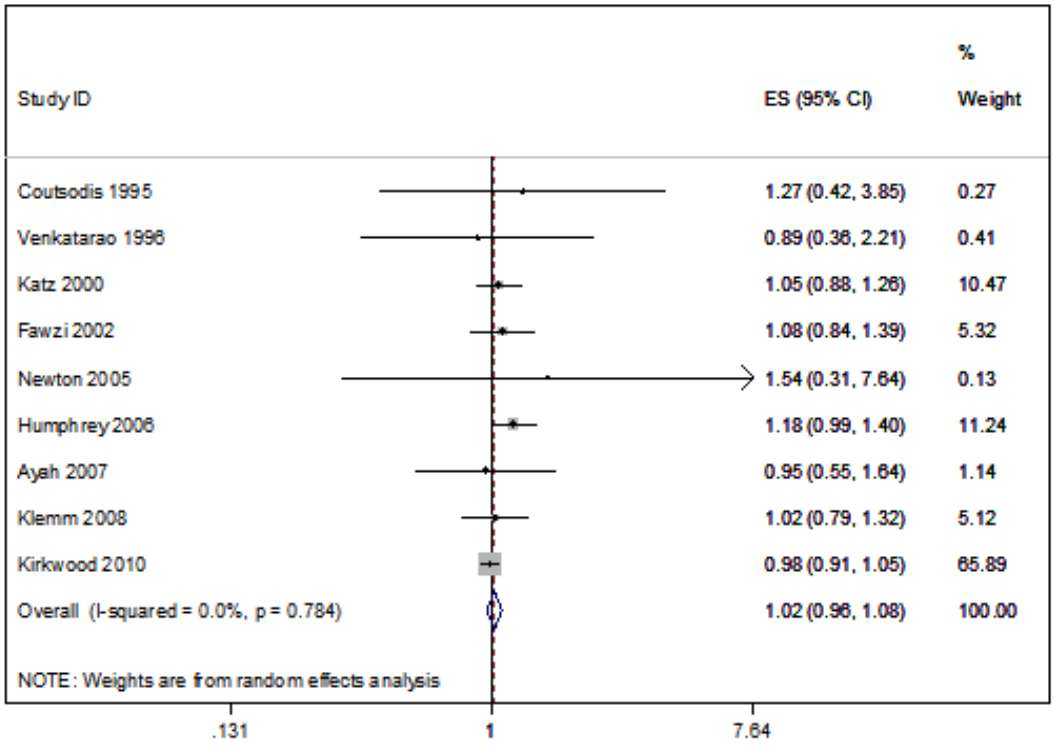
Limitations

There were only a few studies providing information on specific high risk groups (maternal night blindness prevalence > 5% and low birth weight infants), which limited the statistical power to detect differences in treatment effect in such participants. Similarly, due to the small number of trials for meta-regression analysis, the statistical power was limited. The initiation of intervention and the follow-up duration were variable, which precluded constitution of a uniform measure across the studies to explore the possibility of a lower RR of mortality in settings with high baseline infant mortality. For cause-specific mortality, we pooled data from studies reporting single or multiple reasons for death, with the underlying philosophy that the assessed cause had contributed to mortality either partially or wholly. We did multiple subgroup and meta-regression analyses for important pre-specified variables, which increased the possibility of false positive results.

Breast feeding is the sole link in transferring vitamin A to the neonate. Breast feeding rates could be documented only in three trials reporting mortality and were 100%. The authors of three other trials were contacted for relevant data but this information was not available. Trials without breast feeding rates were also conducted in countries with a high traditional prevalences of breast feeding and there is no reason to believe that the breast feeding rates in these studies would be any different.

We excluded trials in which participants were HIV positive to factor for potential effect modification by an immunosuppressive condition. In some settings, however, for public health programmes it would be impossible to distinguish such participants from HIV negative participants. However, on including infants born to HIV positive mothers also (Coutsoudis 1999; Fawzi 2002; Humphrey 2006), there was no evidence of a reduced risk of mortality during infancy (random-effects model RR 1.02, 95% CI 0.96 to 1.08, P = 0.597; I^2 = 0%) (Figure 4).

Figure 4. Forest plot for all cause mortality during infancy following maternal postpartum supplementation of Vitamin A after including HIV positive mothers also. The report Humphrey 2006 also includes the data for HIV negative mothers from Malaba 2005.



We excluded controlled trials that did not provide placebo to obviate the possibility of bias due to non-blinding and the 'Hawthorne effect', which has been a contentious issue in relation to defining child survival effect associated with vitamin A supplementation (Adamson 2006; Cravioto 1990; Gopalan 1992; Kapil 2005). Only two trials were excluded due to this reason (Basu 2003; Roy 1997), and in neither of these was information on the primary outcomes available.

Comparison 2: Infant supplementation

Strengths

Analysis of nine trials, though admittedly not robust proof, indicated no formal evidence of publication bias. Cluster and individually randomised trials were appropriately combined by design effect correction for the primary outcomes. Diligent efforts were made to include all relevant trials. Subgroup and meta-regression analyses relevant to public health policy were performed.

Limitations

There were only a few studies providing information on the specific high risk group of maternal night blindness prevalence > 5%, which limited the statistical power to detect differences in mortality risk in such participants. Similarly, due to the small number of trials for meta-regression analysis, the statistical power was limited.The adverse effects were unadjusted for design effect in the two cluster randomised trials. The follow-up duration was variable, which precluded constitution of a uniform measure to explore baseline mortality as a predictor. To evaluate cause-specific mortality, we pooled data from trials reporting a single cause or multiple causes of death, with the underlying philosophy that the assessed cause had contributed to mortality. We did multiple subgroup and meta-regression analyses for important pre-specified variables, which increased the possibility of false positive results. A moderate to high level of heterogeneity (I^2 = 49%, P = 0.05) was observed between the results of the studies. This could not be explained by the pre-specified variables including supplementation age (neonatal or post-neonatal), maternal postpartum vitamin A

supplementation, total dose received, maternal night blindness and birth weight at baseline. Additional variables, not examined by us, have been proposed to explain the observed differences.

1. Effects of micronutrient supplementation are hypothesized to be different between boys and girls, possibly due to variations in micronutrient deficiency prevalences (Webb 2007; Wieringa 2007).

2. Divergent results may be explained by differences in vaccination intensity because vitamin A supplementation may interact negatively with DPT vaccine in girls (Benn 2008a). In the Guinea-Bissau trial (Benn 2008), a post hoc analysis suggested that once children received DPT vaccine, mortality in girls who had received VAS at birth was significantly two-fold higher compared with girls who had received placebo at birth (Benn 2008a). We could not explore this hypothesis due to paucity of relevant information in the included trials.

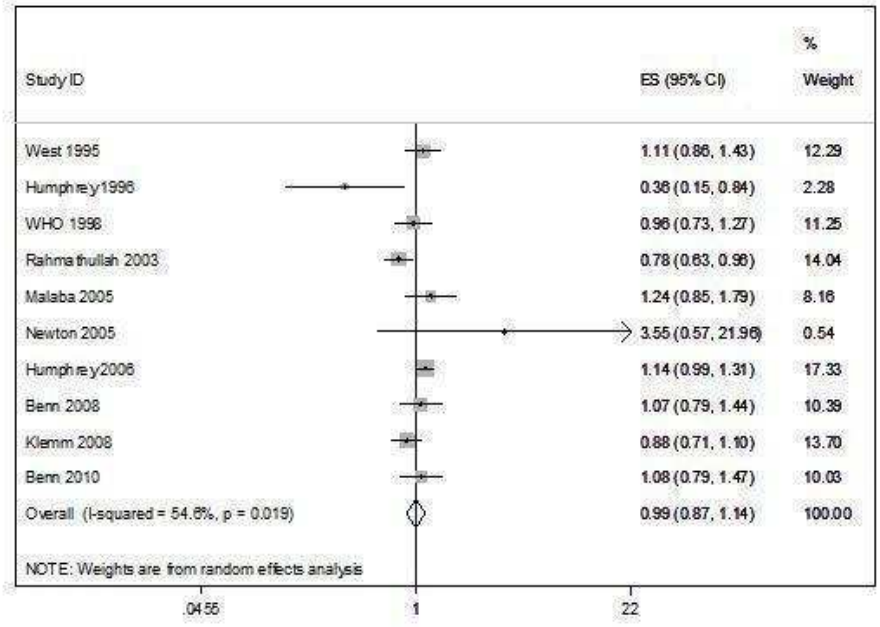
3. The possibility of a strong interaction with season in one trial (Benn 2008) could not be examined in other trials.

4. The relationship with infant feeding practices was not analysed in the trials.

We excluded controlled trials that did not provide placebo to obviate the possibility of bias due to non-blinding and the 'Hawthorne effect', which has been a contentious issue in relation to defining the child survival effect of vitamin A supplementation (Adamson 2006; Cravioto 1990; Gopalan 1992; Kapil 2005). However, no such additional trial was identified.

We excluded trials conducted on HIV positive participants and neonates born to HIV positive mothers to factor for potential effect modification by an immune-suppressive condition. However, programmatically in some settings, it would be impossible to distinguish such participants from normal HIV negative participants. There was no evidence of a reduced risk of all-cause mortality during infancy on including data from HIV positive mothers (Humphrey 2006) (random-effects model RR 0.99, 95% CI 0.87 to 1.14, P = 0.934; I^2 = 55%, P = 0.019) (Figure 5).

Figure 5. Forest plot for all cause mortality during the first year of life following vitamin A supplementation from birth to six months of age including participants born to HIV positive mothers. Random-effects model estimate was used for pooling.



A key issue for data abstraction in multi-arm and factorial design trials is the choice of the comparison group. The following reasoning influenced our choice of the control group, which comprised participants who were given placebo and whose mothers had received either placebo or no supplementation.

1. The most satisfactory comparison for policy should replicate envisaged programmatic intervention, and currently simultaneous neonatal or young infant and maternal supplementation is not formally recommended by the WHO and nor is it widely practised. Thus for an appropriate control group, neither the mothers nor the infants should have received the intervention.

2. Vitamin A transferred through breast milk may interact with the neonatal intervention. Postpartum Vitamin A supplementation to HIV positive mothers whose infants remained polymerase chain reaction-negative at six weeks (Miller 2006) increased their mortality by two years of age (hazards ratio 1.82, 95% CI 0.99 to 3.31, P = 0.05). Other trials of antenatal or postnatal maternal supplementation (Katz 2000; Malaba 2005) also documented an increased mortality risk for offspring (RR 1.05 and 1.26; P > 0.05). Including maternal supplementation in the control group could thus conceivably inflate survival benefit by increasing mortality in the neonatal placebo group.

3. Relevant factorial-designed trials (Klemm 2008; Malaba 2005) were only powered to detect effect sizes pooled across the various subgroups (maternal supplementation arms). Such pooling is usually justified by post hoc subgroup analyses that show no significant interaction between maternal and newborn supplementation. However, these analyses are underpowered to reveal realistic interactions; the power was only 10% to detect an interaction term (0.88) equivalent to the observed effect size in the maternal placebo subgroup in one study (Klemm 2008). Trials with 80% power for the overall effect have only 29% power to detect an interaction effect of the same magnitude, and even less power for the smaller interactions that are more likely to occur in practice (Brookes 2004). We evaluated the stability of our estimate (random-effects model) by altering the chosen comparison and control groups in the two relevant factorial-designed trials (Klemm 2008; Malaba 2005). On choosing neonatal intervention and control groups irrespective of maternal supplementation status, the sample size of the control component increased in these two trials while the pooled estimate was similar (random-effects model RR 0.98, 95% CI 0.86 to 1.11, P = 0.729; I^2 = 58%, P = 0.011). On restricting the analysis to neonatal intervention and control groups whose mothers were either receiving placebo or no supplementation, the sample size of the intervention component diminished in these two trials while the pooled estimates increased marginally (random-effects model RR 0.99, 95% CI 0.86 to 1.13, P = 0.865; I^2 = 53%, P = 0.022). Thus the conclusion regarding mortality during infancy remained stable irrespective of the chosen comparison and control groups.

In the Indian trial (Rahmathullah 2003), it is stated that "all analyses were based on intention to treat". However, for a 'purist' intention-to-treat analysis (Higgins 2008), their mortality risk estimate should also have included "infants whose mothers were randomised but who were not enrolled and received supplementation with vitamin A" (vide Figure 3 of the publication). With such intention-to-treat analysis reconstruction, the trial RR was actually 0.87 (95% CI 0.74 to 1.03, P = 0.109; fixed-effect model), which marginally strengthened the meta-analysis conclusion regarding mortality during infancy (RR 0.98, 95% CI 0.86 to 1.11, P = 0.74; I^2 = 40%, P for heterogeneity 0.10; random-effects model).

Agreements and disagreements with other studies or reviews

Comparison 1: Maternal supplementation

We were unable to identify a similar systematic review for comparison. However, a recent systematic review evaluated the effect of prenatal or postnatal vitamin A supplementation, or both, on the risk of mother-to-child transmission (MTCT) of HIV and other pregnancy outcomes (Kongnyuy 2009). The review included five trials totaling 7528 women (four trials of prenatal and one trial of postnatal supplementation). Overall, there was no evidence of an effect of prenatal or postnatal vitamin A supplementation on the risk of MTCT of HIV (RR 1.06, 95% CI 0.89 to 1.26). However, prenatal vitamin A supplementation significantly improved birth weight (WMD 89.78, 95% CI 84.7 to 94.8), but there was no evidence of an effect on stillbirths (RR 0.99, 95% CI 0.68 to 1.43), preterm births (RR 0.88, 95% CI 0.65 to 1.19), death before 24 months among live births (RR 1.08, 95% CI 0.91 to 1.29) and maternal death (RR 0.83, 95% CI 0.59 to 1.17). These findings are in agreement with our results for mortality during infancy among live births in non-HIV infected mothers.

Comparison 2: Infant supplementation

We could not identify an earlier systematic review focusing on vitamin A supplementation in participants aged between zero and six months or one and six months.

The findings of this review for the subgroup analysis for neonatal supplementation are concordant with our recent systematic review on neonatal vitamin A supplementation (Gogia 2009) for mortality and morbidity outcomes. However, our earlier review did not document an increased risk of bulging fontanelle, which could be related to exclusion of trials providing the intervention between one to six months of age.

The findings of our subgroup analysis for neonatal supplementation are at variance with a recent review (Bhutta 2008) which states "we identified three reported trials of vitamin A supplementation in the neonatal period in low income countries; they showed a 20% reduction in mortality in babies younger than six months (RR 0.80, 95% CI 0.66 to 0.96)". The following factors could explain the variation from this earlier estimate.

1. The authors did not explicitly state the inclusion and exclusion criteria, time window of supplementation, choice of control group and analytic plan to derive their estimate (Haider 2008), which makes direct comparison nebulous.

2. Their comparison group was probably neonatal placebo irrespective of maternal supplementation status, which is different from ours.

3. Relevant but negative data from four trials (Benn 2008; Benn 2010; Malaba 2005; West 1995) were excluded from their pooling (Haider 2008). In a subsequent reappraisal following correspondence questioning their finding (Sachdev 2008), the authors included data from two of the earlier excluded sources (Bhutta 2008b). This pooled estimate also did not document any convincing evidence of mortality reduction (RR 0.88, 95% CI 0.73 to 1.06, P = 0.19) following supplementation within three days of birth, which is in consonance with our findings.

4. They selectively evaluated mortality reduction until six months of age (Bhutta 2008b) when three (now four) trials had follow-up extending until one year.

A recent meta-analysis (Kirkwood 2010b) assessed the survival effect of vitamin A given to neonates within a few days of birth in six trials. It documented a pooled RR of 0.93 (95% CI 0.80 to 1.07; I^2 = 58%, P for heterogeneity 0.005; random-effects model). These findings are in consonance with our subgroup analysis for neonatal supplementation despite exclusion of older neonates from a trial (West 1995) and inclusion of newborns of HIV positive mothers (Humphrey 2006).

It is difficult to explain the differences between the earlier systematic reviews (Beaton 1993; Fawzi 1993; Glasziou 1993) documenting 23% to 30% reduction in childhood mortality following intervention after the age of six months and the findings of our review. However, the following possibilities deserve consideration.

1. These systematic reviews are quite old and do not take account of several relevant trials which have become available.

2. There was no evidence of child survival benefit in a trial conducted recently on one million Indian rural children (RR 0.96, 99% CI 0.88 to 1.05), which as yet remains unpublished (Awasthi 2007).

3. Trials included in the current systematic review have been more recent, when the magnitude and severity of vitamin A deficiency in populations may have diminished.

4. Causes of mortality in the neonatal period and in early infancy are different from those after six months of age.

5. In high risk settings, a vitamin A-deficient state is much more likely after the age of six months, when supplementation is more likely to have a beneficial effect.

AUTHORS' CONCLUSIONS

Implications for practice

Comparison 1: Maternal supplementation

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

Comparison 2: Infant supplementation

It is very difficult to justify a public health programme of VAS in the first six months of life because there is no convincing evidence of a mortality (moderate quality evidence) or morbidity (low quality evidence) benefit and simultaneously there is a possibility of an increased risk of an adverse effect of bulging fontanelle (low quality evidence). However, policy formulation would be based on deliberation of additional consequences including infant vitamin A status, long-term safety and cost-effectiveness. The four ongoing studies, on over 100,000 participants, are likely to provide further quality evidence on these issues and address the information gaps. It would therefore be logical to await the results of these trials before formulating any policy.

Implications for research

Comparison 1: Maternal supplementation

Considerable research has already been conducted to evaluate the effect of maternal postpartum VAS on infant outcomes. The quality of available evidence for mortality during infancy was rated as high and that for neonatal mortality as moderate. The need for conducting further studies designed solely to evaluate mortality outcomes is therefore questionable. However, there are some information gaps, which must be addressed if any future trials are contemplated: (i) population-based studies examining the role of VAS in specific high risk conditions like high prevalence of maternal night blindness and low birth weight infants; (ii) effect on morbidities, and (iii) adverse reactions.

Comparison 2: Infant supplementation

Considerable research has already been conducted to evaluate the effect of VAS in the first six months of life on infant outcomes. The quality of available evidence for mortality during infancy was rated as moderate, for neonatal mortality as very low, and for other

outcomes as low. There is also limited information in participants with a high prevalence of maternal night blindness. The four ongoing studies on over 100,000 participants are designed to address the outstanding issues of quality and information gaps. It would therefore be logical to await the results of these trials before any further research is contemplated.

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* *Indicates the major publication for the study*

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	Number: 564 Inclusion criteria: recently delivered women with live singleton neonate Exclusion criteria: none
Interventions	(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 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 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 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 age with DPT and OPV vaccines; n=139) All pregnant women received presumptive malarial treatment in their second and third trimesters.
Outcomes	Maternal supplementation: mortality; morbidity and adverse effects not reported; follow-up at 14 weeks Infant supplementation: adverse effects; mortality and morbidity not reported; follow-up after infant dosing at 14 and 26 weeks
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 Maternal supplementation: • Mortality extracted until 14 weeks only; differential mortality in the 4 groups not depicted after 14 weeks when infant intervention commenced • Adverse effect of bulging fontanel is recorded as a comparison of infants receiving vitamin A or placebo; the stratification according to factorial design is not available, and thus adverse effects cannot be extracted for the intervention and comparison groups as specified Infant supplementation: • Mortality given as a composite from 0 to 6 months; data not extractable after starting intervention in infants (14 weeks to 6 months) in the 4 treatment arms • Adverse effect of bulging fontanel is recorded as a comparison of infants receiving vitamin A or placebo irrespective of maternal vitamin A supplementation In our analyses for the effects of maternal supplementation, we have combined group

Ayah 2007 (*Continued*)

	Aa and group Ap for the vitamin A group, and we have combined group Pa and group Pp for the placebo group.

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 randomisation 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	All analyses were by intention-to-treat
Selective reporting (reporting bias)	High risk	Not all relevant outcomes reported
Other bias	High risk	Sample size calculation reported, but a protocol was not reported a priori Supported by Hoffmann-La Roche Ltd (Basel, Switzerland)

Baqui 1995

Methods	Randomised, double-blind, placebo-controlled trial Data collection: 1993
Participants	Number: 167 Inclusion criteria: infants registered in local demographic surveillance system aged between 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)

Baqui 1995 (*Continued*)

Interventions	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 Follow-up on days 1, 2 ,3, and 8
Notes	Location: Slum population, Dhaka city, Bangladesh (Asia)

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 randomisation 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	High risk	9.7% of infants lost to follow up and not accounted for in the analysis
Selective reporting (reporting bias)	High risk	Not all relevant outcomes reported
Other bias	Unclear risk	No a priori research protocol reported Study funded by the US Agency for International Development (USAID) under grant No. DPE-5986-A-00-1009-00 with the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B)

Benn 2008

Methods	Randomised, double-blind, placebo-controlled trial
Participants	Number: 4345 Inclusion criteria: infants weighing at least 2500 g at birth with no signs of overt illness or malformations; infants were recruited at the time of Bacillus Calmette-Guérin (BCG) vaccination. Exclusion criteria: birth weight < 2500 g; signs of illness
Interventions	1. Vitamin A (0.5 mL vegetable oil containing 50,000 IU of vitamin A as retinyl palmitate and 10 IU vitamin E, 1 dose at the time of BCG vaccination; n=2145) 2. Control (10 IU of vitamin E was given into the mouth of child at the time of BCG vaccination; n=2200) Other: BCG vaccine was given as co-intervention in both groups
Outcomes	• Mortality at 12 months of age • Cause-specific mortality at 12 months of age • Retinol-binding protein (RBP) concentration at 6 weeks and 4 months of age (low RBP defined as serum retinol < 0.70 μ/L) • Adverse effects (bulging fontanelle, hospitalizations, irritability, fever, frequent stools, vomiting, mother thinks the child is not well) • Morbidity (cough and running nose) Follow-up every 3 months until 1 year of age
Notes	Location: Guinea-Bissau (Africa) Setting: 6 urban districts in capital of Guinea-Bissau which is classified as an area of sub-clinical vitamin A deficiency and high infant mortality; HIV prevalence among women in the study area was 3% to 5% Since the trial authors did not have information about the gestational age at delivery and the inclusion criteria was infants with birth weight of at least 2500g, we included data as such assuming that none were preterm infants The adverse effects and morbidity components were reported in Nante 2007. For this outcome, attrition was 4.66%. The intervention group had 1086 participants and the placebo group had 1059 participants. The follow-up was done daily for first 3 days following supplementation and then weekly follow-up during the first month following supplementation. In this report in Table 1 captioned for adverse effects, the outcomes diarrhoea and vomiting are considered as adverse effects whereas cough and running nose were considered as morbidity as these have not been reported as adverse effects in the literature

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The mother drew a lot from an envelope prepared by the study supervisor. Each envelope contained 100 lots-50 marked "1" and 50 marked "2"-indicating from which of two numbered bottles, "1" or "2," the child should receive the supplement.The

Benn 2008 (*Continued*)

		lots were folded, making it impossible to tell what was written on them before they were opened."
Allocation concealment (selection bias)	Low risk	"The code was kept at the pharmacy until 12 months after the last child was included."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Apart from the randomisation number, the bottles looked alike". Small differences in taste and colour of the contents were judged as "unimportant owing to the recipients' age." "blinding of mothers and assistants was successful" and "assistants of the registration system and the special team were unaware.....vaccination card and follow up forms"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 1.6%; reasons for attrition and distribution in the 2 groups are provided
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	High risk	A protocol was provided but post hoc analyses were conducted after assuming that vitamin A might be more beneficial to boys The study was funded by the EU (ICA4-CT-2002-10053), the Danish Medical Research Council, University of Copenhagen, March of Dimes, and the Ville Heise Foundation

Benn 2010

Methods	Randomised, placebo controlled, 2 x 2 factorial trial
Participants	Number: 1717 Inclusion criteria: low birthweight (< 2.5 kg) children born at the national hospital about to be discharged; medical officer ascertained that they were sufficiently well to be discharged Exclusion criteria: severe malformations
Interventions	1. Vitamin A (25,000 IU vitamin A as retinyl palmitate and 10 IU vitamin E per 0.5 mL oil; n=854) 2. Control (10 IU vitamin E per 0.5 mL oil; n=863) Other: all infants were also assigned to early Bacillus Calmette-Guérin (BCG) vaccine or the usual late BCG vaccine

Benn 2010 (*Continued*)

Outcomes	• Infant mortality and cause-specific infant mortality at 12 months • Morbidity • Adverse effects Follow-up at home within the first 3 days and at 2, 6, and 12 months of age
Notes	Location: Guinea Bissau, Africa Detailed data on RR and 95% CI for cause-specific mortality received through a personal communication (depicted only as a graph in report). Authors intend to report the morbidity and adverse effects data separately and do not wish to share the unpublished information for this review The morbidity data on diarrhoea was reported in Diness 2010 for a sub-sample of 287 infants during annual rotavirus epidemic from Januray through March 2005. No evidence of an interaction between BCG and vitamin A supplementation in neonates (P value = 0.73) Vitamin A was administered within the first 48 h of life to 878 (51%) of the 1717 children

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Low birth weight infants were randomly allocated in a two by two factorial design to early BCG vaccination or the usual delayed BCG vaccination and to 25,000 IU vitamin A or placebo..... ... the mother drew an envelope from a bag. Each bag was prepared by the study supervisor and contained 48 envelopes; each envelope contained a lot name. Within each bag were 12 envelopes with lots marked "BCG 6", 12 marked "BCG 7", and 12 marked "no BCG 7". The numbers "6" and "7" indicated from which of the two numbered bottles, "6" or "7", the child should receive treatment (that is, either 25,000 IU vitamin A or placebo). Twins were allocated the same treatment to prevent confusion regarding who had been vaccinated and supplemented".
Allocation concealment (selection bias)	Low risk	"The envelopes were closed and non-transparent, making it impossible to identify the allocation before the envelopes were opened"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Apart from the bottle number, the vitamin A and placebo bottles looked alike. Small

Benn 2010 (*Continued*)

		differences in the taste and colour of the contents were judged as unimportant owing to the recipients' age. The assistant and the nurse who were responsible for the randomisation procedure had no idea which bottles contained vitamin A or which had placebo when asked. The follow-up assistants were unaware of the allocated treatment, "6" or "7", because they were not present during enrolment and the information was not transferred to the children's vaccination card or follow up forms."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions and attrition were 18.72%; reasons and distribution in the 2 groups are provided
Selective reporting (reporting bias)	Low risk	All expected outcomes, as per protocol are reported or are under preparation (personal communication from the author)
Other bias	High risk	A protocol was provided but *post hoc* analyses were conducted after assuming that vitamin A might be more beneficial to boys The study was funded by the EU (ICA4-CT-2002-10053), the Danish Medical Research Council, University of Copenhagen, March of Dimes, and the Ville Heise Foundation

Bhaskaram 1998

Methods	Randomised, double-blind, placebo-controlled trial
Participants	Number: 102 Inclusion criteria: recently delivered mothers with neonates born at the end of a healthy term pregnancy Exclusion criteria: complicated full term deliveries
Interventions	1. Vitamin A (mother received 200,000 IU vitamin A as retinyl palmitate within 24 h after delivery; n=50) 2. Control (mother received placebo; n=52) Other: all infants given oral polio vaccine within 72 h after birth; all infants breast fed, followed up at 6 months
Outcomes	• Infant serum retinol concentration • Breast milk retinol concentration • Corneal lesions

Bhaskaram 1998 (*Continued*)

	Follow-up for first 5 days of life
Notes	Location: Hyderabad, India (Asia) 100% followed up until 6 weeks, 87% followed up until 3 months, and 46% followed up until 6 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The mothers were randomly allocated into two groups"
Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding (performance bias and detection bias) All outcomes	High risk	Information not provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not provided
Selective reporting (reporting bias)	High risk	Most clinically relevant outcomes are not reported
Other bias	High risk	Study protocol not provided, small sample size Source of funding not provided

de Francisco 1993

Methods	Randomised, double-blind, placebo-controlled trial
Participants	Number: 191 Inclusion criteria: neonates Exclusion criteria: none
Interventions	1. Vitamin A (50,000 IU vitamin A (palmitate in peanut oil and transport media) at 1.5, 2.5, and 3.5 months of age) 2. Control group (soybean oil and the same transport media as above at 1.5, 2.5, and 3.5 months of age) Infants were examined on days 1, 2, 3, and 8 after supplementation.
Outcomes	• Mortality: not recorded • Morbidity: not recorded • Adverse effects Follow-up on days 1, 2, 3, and 8

de Francisco 1993 (*Continued*)

Notes	Location: rural Bangladesh (Asia)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"A computerised randomisation procedure had been used to assign a bottle code to each infant."
Allocation concealment (selection bias)	High risk	"The first 42 infants (22%) were given the first dose and then monitored for 24 h. These infants were randomised to receive either an A or B bottle according to their order of arrival at the hospital."
Blinding (performance bias and detection bias) All outcomes	Low risk	"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." Outcome assessors were unaware of the bottle code.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Losses of follow up were minimal and equally distributed in the vitamin A and placebo groups"
Selective reporting (reporting bias)	Unclear risk	Not all clinically relevant outcomes reported
Other bias	Unclear risk	No a priori research protocol reported Study funded by the US Agency for International Development (USAID) under grant No. DPE-5986-A-00-1009-00 with the International Centre for Diarrhoea1 Disease Research, Bangladesh (ICDDR,B)

Humphrey 1996

Methods	Randomised, placebo-controlled trial Data collection: 18 June 1992 to 3 June 1993
Participants	Number: 2067 Inclusion criteria: all neonates within 24 h of birth Exclusion criteria: birth weight < 1500 g; severe respiratory distress syndrome; major congenital anomalies; paralysis; sepsis; hypoglycaemia; hypocalcaemia; and hypoxia

Humphrey 1996 (*Continued*)

Interventions	1. Vitamin A (1 oral dose of 52 µmol vitamin A (as retinyl palmitate) plus 23 µmoL vitamin E on day 1 of life; n=1034) 2. Control (<0.10 µmoL vitamin A + 23 µmoL vitamin E; n=1033)
Outcomes	• Mortality at 4, 6, and 12 months in 1 subgroup (n=470) and at 12 months in other subgroup (n=1597); follow up in per 1000 child year • Morbidity at 4, 6, and 12 months in 1 subgroup (n=470) • Adverse effects (bulging fontanelle, vomiting, fever, loose stool, irritability, intracranial haemorrhage, resistive index) Adverse effects reported in Agoestina 1994.
Notes	Location: Bandung, Indonesia (Asia) The adverse effects are recorded in Agoestina 1994 by follow-up until 48 h of life; attrition for this outcome was 0.5% Treatment groups were comparable at baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"by simple randomisation, blocked within the birth weight strata"
Allocation concealment (selection bias)	Low risk	"The randomisation scheme and coded supplement packets were prepared by a team in Baltimore, none of whom was involved in recruitment or follow-up of infants in Indonesia."
Blinding (performance bias and detection bias) All outcomes	Low risk	Supplements were individually coded, odourless, and identical in appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 11% and reasons for it are provided. Missing outcome data for mortality unlikely to be affected as there were no significant differences in baseline factors between the treatment groups among those who were lost to follow up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement Adverse events were reported in a separate publication (Agoestina 1994)
Other bias	High risk	Agoestina 1994 mentioned a protocol, but no further details were provided Supported by a grant from Johns Hopkins

Humphrey 1996 (*Continued*)

		University and assistance from Hoffmann-LaRoche industry (Basel, Switzerland), a manufacturer of Vitamin A. Several unplanned subgroup analyses reported including gender, birth weight, ponderal index). In Discussion, it is stated "Although the study was not designed to investigate subgroups.....". Unclear as to how the mortality rates for all subjects were derived between 1 and 4 months of age when the majority were to be followed-up only at one year of age.

Katz 2000

Methods	Randomised, cluster, placebo-controlled trial Data collection: July 1994 to October 1997
Participants	Number: 10,785 Inclusion criteria: women of child-bearing age Exclusion criteria: families moving into the study area
Interventions	1. Vitamin A (23,300 IU vitamin A weekly to the women of childbearing age until 24 weeks postpartum; n=5583 infants born alive) 2. Control group (peanut oil to women; n=5202 infants born alive) All capsules contained 5 mg dl-alpha-tocopherol (Roche, Basel, Switzerland)
Outcomes	• Mortality • Morbidity: not recorded • Adverse effects: not recorded Follow-up at 3 and 6 months postpartum
Notes	Location: Sarlahi district, Nepal (Asia) Setting: 270 wards in 30 subdistricts (9 wards each) with total population of around 176,000 Generalized-estimating-equations logistic regression model with exchangeable correlation structure in which survival as modelled as a function of the treatment assignment, adjusted for the correlation within the units of randomisation (the ward) and stratification (by village development community) Miscarriages and stillbirths included in mortality data, maternal deaths not included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"30 subdistrict areas (village development communities), each composed of 9 wards, were enrolled in the study. Within each

Katz 2000 (*Continued*)

		subdistrict, each of the 9 wards were randomly assigned to receive 1 of the 3 treatments, resulting in 90 wards assigned to each treatment group."
Allocation concealment (selection bias)	Low risk	"All capsules ..... were shipped to Nepal in opaque plastic bottles labelled with 1 of 3 masked, numeric codes. The bottles were relabeled with individual ward numbers that had been assigned to the specific codes."
Blinding (performance bias and detection bias) All outcomes	Low risk	"gelatin capsules of identical appearance"; "This committee and the data analysts were unmasked to the treatment codes, but the codes were made available to study investigators only at the end of the trial" Comment: participants and outcome assessors were blinded; people responsible for analysing data were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	8.1% of attrition, however intention-to-treat analysis was conducted
Selective reporting (reporting bias)	High risk	Not all relevant outcomes for infants were provided
Other bias	Unclear risk	Supported by the Johns Hopkins University, Baltimore; the Office of Health and Nutrition, USAgency for International Development (USAID); the Task Force Sight and Life, Roche, Basel, Switzerland; and the Sushil Kedia Foundation, Hariaun, Sarlahi, Nepal, under cooperative agreement DAN 0045-A-005094-00 Unclear if study protocol was published a priori

Kirkwood 2010

Methods	Randomised, cluster, placebo-controlled trial Data collection: December 2000 to October 2008
Participants	Number: 73,752 Inclusion criteria: women of reproductive age (15 to 45 years) who gave informed consent and who planned to remain in the area for at least 3 months Exclusion criteria: families moving into the study area

Interventions	1. Vitamin A (25,000 IU vitamin A weekly; n=37,042) 2. Control (placebo; n=36,710)
Outcomes	• Mortality • Morbidity: not recorded • Adverse effects: not recorded Follow-up monthly
Notes	Location: Ghana (Africa) Setting: 1086 small geographical clusters of compounds with fieldwork areas consisting of 4 contiguous clusters Intention-to-treat analyses to compare treatment groups with random-effects regression to account for the cluster-randomised design was used Trial registration: ClinicalTrials.gov, number NCT00211341.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation was blocked and based on an independent, computer-generated list with two clusters in each fieldwork area allocated to vitamin A supplementation and two to placebo."
Allocation concealment (selection bias)	Low risk	"A computer-generated randomisation list was prepared for the capsule manufacturers by an independent statistician on the data monitoring and ethics committee. The capsules were packaged in labelled jars, for each cluster for each week of the trial. Trial personnel had no access to the randomisation list or to any information that would allow them to deduce or change the cluster allocation."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Placebo capsules were identical in taste and appearance to the vitamin A capsules."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants enrolled were accounted for in the analysis
Selective reporting (reporting bias)	Low risk	All planned outcomes on the published protocol were subsequently reported in the main publication

Other bias	Low risk	A protocol was published a priori with details of sample size calculation and outcomes Funded by the UK Department for International Development, and USAID, and Roche (Basel, Switzerland) donated vitamin A palmitate

Klemm 2008

Methods	Double-masked, cluster-randomised, placebo-controlled trial
Participants	Number: 5349 mothers, 10585 infants (see details under Interventions below) Inclusion criteria: infants born to consenting mothers participating in the parent trial Exclusion criteria: infants of consenting mothers who had died before they could be supplemented by staff, those who were born outside the study area, and infants who were not supplemented after repeated staff visits during the first 30 days following birth
Interventions	1. (Group=Aa) Maternal vitamin A (vitamin A 23,300 IU weekly during pregnancy until 12 weeks postpartum) and newborn vitamin A (vitamin A 50,000 IU after birth) (n=2531) 2. (Group=Ap) Maternal vitamin A (vitamin A 23,300 IU weekly during pregnancy until 12 weeks postpartum) and newborn placebo (placebo after birth) (n=2717) 3. (Group=Ba) Maternal beta carotene (beta carotene weekly during pregnancy until 12 weeks postpartum) and newborn vitamin A (vitamin A 50,000 IU after birth) (n=2700) 4. (Group=Bp) Maternal beta carotene (beta carotene weekly during pregnancy until 12 weeks postpartum) and newborn placebo (placebo after birth) (n=2635) 5. (Group=Pa) Maternal placebo (placebo weekly during pregnancy until 12 weeks postpartum) and newborn vitamin A (vitamin A 50,000 IU after birth) (n=2722) 6. (Group=Pp) Maternal placebo (placebo weekly during pregnancy until 12 weeks postpartum) and newborn placebo (after birth) (n=2632) The numbers refer to infants whose vital status was known at 24 weeks of life; only 3 of the 7956 infants were lost to follow-up in the vitamin A supplemented infants and 8 of the 7992 infants were lost to follow up in the placebo supplemented infants. The number randomised in each of the six groups above cannot be depicted as loss to follow-up stratified by groups is not reported Maternal supplementation Mortality outcome: Intervention - (Group=Ap) Maternal vitamin A (vitamin A 23,300 IU weekly during pregnancy until 12 weeks postpartum) and newborn placebo (placebo after birth) (n=2717) Control - (Group=Pp) Maternal placebo (placebo weekly during pregnancy until 12 weeks postpartum) and newborn placebo (after birth) (n=2632) Infant supplementation Mortality outcome: Intervention - (Groups Aa, Ba and Pa) Newborn vitamin A (vitamin A 50,000 IU after

	birth) irrespective of maternal supplementation status (n=7953) Control - (Group=Pp) Maternal placebo (placebo weekly during pregnancy until 12 weeks postpartum) and newborn placebo (after birth) (n=2632) Adverse effects: Intervention - (Groups Aa, Ba and Pa) Newborn vitamin A (vitamin A 50,000 IU after birth) irrespective of maternal supplementation status (n=7953) Control - (Groups Ap, Bp and Pp) Newborn placebo (placebo after birth) irrespective of maternal supplementation status (n=7984). The control group could not be the same as for mortality outcome because the adverse effects were not reported for each subgroup of newborn placebo intake
Outcomes	Maternal supplementation: • Mortality • Morbidity: not recorded • Adverse effects: not recorded Infant supplementation: • Mortality • Morbidity: not recorded • Adverse effects Follow-up weekly at home for the first 12 weeks of life by field staff and then again at 24 weeks of age
Notes	Location: districts of Gaibandha and Rangpur, Bangladesh (Asia) Setting: community-based The trial was nested into and balanced across the treatment arms of an ongoing placebo-controlled, weekly, low-dose vitamin A or beta carotene supplementation trial among pregnant women, underway since August 2001 to evaluate effects on pregnancy-related mortality; risk ratio and 95% confidence intervals adjusted for design effect by generalised estimating equation logistic regression model with log link and exchangeable correlation to adjust for the design effect Randomisation of sectors was done in a manner to produce 2 infant supplementation groups that were balanced across the maternal supplementation trial arms An expected 6 month infant mortality rate 64 deaths per 1000 live birth Approximately 84% infants supplemented within the first 48 h after birth Treatment groups were comparable at baseline Analysis was adjusted for cluster design

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The study area was divided into 596 smaller community groups of comparable size, each with a median number of households of 228 (interquartile range [IQR]: 200-263), called "sectors," which served as units of randomisation. Sectors were listed in geographically contiguous order and were randomised in blocks of 4 within

Klemm 2008 (*Continued*)

		each of 3 previously randomised maternal supplementation trial treatment arms (i.e., vitamin A,-carotene, and placebo, each 200 sectors) for newborns to receive 50 000 IU of vitamin A or placebo in oil as soon as possible after birth." However, in the description, the method used to generate the randomisation sequence is not described in sufficient detail to permit judgement.
Allocation concealment (selection bias)	Unclear risk	"administered a sector-coded supplement containing either 50 000 IU of vitamin A or placebo"
Blinding (performance bias and detection bias) All outcomes	Low risk	"The supplements for both groups were opaque gelatinous capsules identical in shape, size, and colour containing edible oil."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions and attrition was 7%. Reasons for attrition and exclusions; and numbers in each intervention group are reported. Attrition and reasons for attrition were balanced across the treatment groups.
Selective reporting (reporting bias)	Low risk	Comment: results of all outcomes mentioned in the methods section of the published paper and trial registration document were presented in the paper
Other bias	High risk	An independent data safety and monitoring board (DSMB) halted the study "for reasons of efficacy of the intervention in reducing infant mortality" Results adjusted by cluster effect. Source of funding: Johns Hopkins University (GHS-A-00-03-00019-00), Bill and Melinda Gates Foundation

Malaba 2005

Methods	Randomised, placebo-controlled, 2 x 2 factorial design trial Data collection: 25 November 1997 to 29 January 2000
Participants	Number: 4639 women, 6908 infants Inclusion criteria: newly delivered mother and her infant Exclusion criteria: birth weight < 1500 g; severe congenital anomalies; life-threatening illness; families intending to move out of study area

Interventions	(Aa group) Maternal vitamin A, infant vitamin A (mother received 400,000 IU vitamin A, infant received 50,000 IU vitamin A within 96 hours of delivery; n=2319) (Pa group) Maternal placebo, infant vitamin A (mother received placebo, infant received 50,000 IU vitamin A within 96 hours of delivery; n=2280) (Ap group) Maternal vitamin A, infant placebo (mother received 400,000 IU vitamin A, infant received placebo within 96 hours of delivery; n=2300) (Pp group) Maternal placebo, infant placebo (mother received placebo, infant received placebo within 96 hours of delivery; n=2309) • Maternal supplementation vitamin A group (vitamin A 400,000 IU, 1 dose, within 96 h of delivery; n=2300) • Maternal comparison group (placebo; n=2309) • Infant supplementation vitamin A group (50,000 IU vitamin A, 1 dose within 96 h of birth; n=4599) • Infant comparison group (placebo; n=2309)
Outcomes	• Mortality • Morbidity: not recorded • Adverse effects Follow up at 6 weeks, 3 months, and then 3 monthly until 1 year For maternal supplementation review only mortality
Notes	Location: Harare, Zimbabwe (Africa) HIV-negative mothers (Zimbabwe is categorized by the World Health Organization as a high-risk area for vitamin A deficiency. HIV is endemic in Zimbabwe nearly 25% are HIV-positive.) Infants were randomly assigned within 96 h of delivery to 1 of the 4 treatment groups: mothers and infants received vitamin A; mothers received vitamin A and infants received placebo; mothers received placebo and infants received vitamin A; and both mothers and infants received placebo. The vitamin A dose in the mothers was 400,000 IU and in the infants was 50,000 IU The adverse effects were documented in Iliff 1999 with follow-up for 2 days after supplementation. The attrition was 6%. In the intervention vitamin A group (n=398), infant received 50,000 IU vitamin A within 24 h of life and the mother received 400,000 IU vitamin A within 24 h following delivery. In the control group (n=390) placebo was given to the infant and mother. The HIV status of mothers is not stated The trial included multiple intervention groups employing a factorial design. Data were abstracted and pooled for comparison of vitamin A-supplemented infants (irrespective of maternal vitamin A supplementation status) with controls receiving placebo (mothers received no intervention or placebo). If comparison with a "pure" placebo group (infants receiving placebo with mothers receiving no intervention or placebo) was not possible from the available data, comparisons were performed with infants receiving placebo whose mothers had received supplementation analogous to the infant intervention group (s). Strictly speaking, a subsequent report (Humphrey 2006) from this trial presenting data on HIV positive women (an exclusion criteria for this review) should have been classified along with this study. However, to prevent confusion in an already long review with different comparisons, we have preferred to show the Humphrey 2006 report as an

	excluded study under the various headings in this review. The description in this table pertains only to the HIV negative mothers (one of the inclusion criteria for this review).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A separate team at Johns Hopkins University prepared the study capsule packets. Study identification numbers were randomly allocated to the treatment groups by computer in blocks of 12. The numbers were printed on adhesive labels and affixed to amber-coloured zip-lock plastic bags that were packed with the assigned capsules. Capsule packets were prepared separately for each of the 4 treatment groups and were then merged into numeric order before shipping to Zimbabwe, where a series of packets were distributed to each recruitment site. As each mother- infant pair was recruited, the capsules in the next sequential bag were administered, and the associated study number was assigned to the pair.
Allocation concealment (selection bias)	Low risk	"Lists linking the study number to the treatment were kept in sealed envelopes and encrypted computer files."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Treatment and placebo capsules appeared identical" "separate team at Johns Hopkins University prepared the study capsule packets" and "neither participants nor nurses who administered the capsules or assessed outcomes were aware of treatment group assignment"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Only infants of mothers who remained HIV-negative to 12 mo postpartum were included in the current analysis." Attrition was 11.5% It is unclear, in the absence of a trial protocol, as to why the entire trial data on HIV negative and HIV positive mothers was not reported as a single publication.

Malaba 2005 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	It is unclear, in the absence of a trial protocol, whether all the pre-specified outcomes were reported. Adverse effects reported only in a subset (irrespective of HIV status) early in the course of trial (Illif 1999). Iliff 1999 states "The main hypotheses of this study (the ZVITAMBO Project) are that vitamin A supplementation of mothers and/or babies will reduce (i) infant mortality, (ii) vertical transmission of HIV through breast milk and (iii) HIV infection, during the first year postpartum, of mothers seronegative at delivery." A later report (Humphrey 2006) presents HIV infection data but this was not done for HIV negative women in Malaba 2005.
Other bias	Low risk	"The ZVITAMBO Project was primarily supported by the Canadian International Development Agency (R/C Project 690/M3688), the US Agency for International Development (cooperative agreement no. HRN-A-00-97-00015-00 between Johns Hopkins University and the Office of Health and Nutrition of the USAID), and a grant from the Bill and Melinda Gates Foundation (Seattle); additional support was provided by the Rockefeller Foundation (New York) and BASF (Ludwigshafen, Germany)."

Newton 2005

Methods	Randomised, placebo-controlled, 2 x 2 factorial design trial Data collection: November 1996 to January 1999
Participants	Number: 470 women, 816 infants Inclusion criteria: newly delivered mother and her infant Exclusion criteria: families intending to move out of the study area
Interventions	(Aa group) Maternal vitamin A, infant vitamin A (mother received 200,000 IU vitamin A within 24 hours of delivery; infant received 25,000 IU vitamin A at 6,10 and 14 weeks age with DPT and OPV vaccines; n=274) (Pa group) Maternal placebo, infant vitamin A (mother received placebo within 24 hours of delivery; infant received 25,000 IU vitamin A at 6,10 and 14 weeks age with DPT and OPV vaccines; n=265) (Ap group) Maternal vitamin A, infant placebo (mother received 200,000 IU vitamin A

	within 24 hours of delivery; infant received placebo at 6,10 and 14 weeks age with DPT and OPV vaccines; n=269 (Pp group) Maternal placebo, infant placebo (mother received 200,000 IU vitamin A within 24 hours of delivery; infant received 25,000 IU vitamin A at 6,10 and 14 weeks age with DPT and OPV vaccines; n=277) • Maternal supplementation vitamin A group (vitamin A 2,00,000 IU, 1 dose, 3 to 4 weeks postpartum; n=269) • Maternal comparison group (placebo; n=277) • Infant supplementation vitamin A group (vitamin A 25,000 IU at 6, 10, and 14 weeks; n=539) • Infant comparison group (placebo; n=277)
Outcomes	Maternal supplementation: • Mortality • Morbidity: not recorded • Adverse effects: not recorded Infant supplementation: • Mortality • Morbidity: not recorded • Adverse effects Follow-up at 6 months
Notes	Location: Kintampo, Ghana (Africa) Breast feeding rate was almost 100% and 51% of children aged < 5 years in the area had serum retinol concentrations less than 0.70 micromol/L 3 vitamin A supplementation strategies were investigated: (1) supplementation of breast-feeding mothers with 60 mg retinol equivalent (RE) vitamin A within 4 wk of delivery; (2) Expanded Program on Immunization (EPI)-linked supplementation of infants with 7.5 mg RE vitamin A at 6, 10, and 14 wk; and (3) 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 randomisation scheme."
Allocation concealment (selection bias)	Unclear risk	Not reported
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)	High risk	Not all clinically relevant outcomes were reported
Other bias	Unclear risk	Enrolment of participants was extended to higher than planned lost to follow up; sample size calculation provided, but unclear whether a protocol was published a priori Supported by a grant from the Wellcome Trust

Rahmathullah 2003

Methods	Randomised, placebo-controlled, community-based trial Data collection: June 1998 and March 2001
Participants	Number: Pregnant mothers 13294. Of these, only 11,619 newborns received the intervention in the village (excluding migrations, stillbirths, early infant deaths and refusals) . These newborns were enrolled and followed up. Inclusion criteria: infants born to pregnant females residing in the study area Exclusion criteria: miscarriages/stillbirths; delivery 20 km outside the study area; or infants who died before the study team reached
Interventions	1. Vitamin A (vitamin A 24,000 IU on days 1 and 2 of life; n=5786) 2. Control (placebo; n=5833)
Outcomes	• Mortality and cause specific mortality • Morbidity • Adverse effects Follow-up fortnightly for 6 months
Notes	Location: 2 rural districts of Tamil Nadu, India (Asia) Miscarriages and still births not included in mortality data No bulging fontanelle (adverse effect) in either group Tielsch 2007 had recorded case fatality following common morbidities

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomisation was at the individual level, stratified by geographical area in blocks of four."
Allocation concealment (selection bias)	Unclear risk	"Investigators, study staff, and mothers were masked to the assigned treatment. Treatment codes were kept in a sealed en-

Rahmathullah 2003 (*Continued*)

		velope in a locked filing cabinet in Baltimore."
Blinding (performance bias and detection bias) All outcomes	Low risk	"treatment doses were in an edible oil solution packaged in identical gelatin capsules" and "investigators, study staff, and mothers were masked to the assigned treatment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions and attrition was 18.9%; reasons for attrition and exclusions, and numbers in each intervention group are reported
Selective reporting (reporting bias)	Low risk	All planned outcomes reported on the main study
Other bias	Unclear risk	Supported by a grant from Johns Hopkins University and the Bill and Melinda Gates Foundation No information about the protocol provided

Semba 2001

Methods	Randomised, double-blind, placebo-controlled clinical trial
Participants	Number: 467 Inclusion criteria: infants < 6 weeks of age Exclusion criteria: none
Interventions	1. Vitamin A group 1 (25,000 IU vitamin A at 6, 10, and 14 weeks of life; n=156) 2. Vitamin A group 2 (50,000 IU vitamin A at 6, 10, and 14 weeks of life; n=155) 3. Control group (placebo; n=156) Co-intervention with oral polio vaccine (OPV) and diphtheria, pertussis (whooping cough), and tetanus (DPT) vaccine at each visit
Outcomes	• Mortality: not recorded • Morbidity • Adverse effects Follow-up within 24 h of first visit at 6 weeks in 293 infants; follow-up at 10 and 14 weeks and at 9, 10, and 15 months
Notes	Location: Indonesia (Asia)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Semba 2001 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"Randomly allocated by number table in blocks of ten"
Allocation concealment (selection bias)	Unclear 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	High risk	Exclusions and attrition was 8.4%; reasons for attrition and exclusions not reported
Selective reporting (reporting bias)	High risk	Not all clinically relevant outcomes were reported
Other bias	Unclear risk	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, US Agency for International Development (Cooperative Agreement DAN-0045-A-5094-00)." Protocol mentioned but no details given

Stabell 1995

Methods	Double-blind, placebo-controlled trial
Participants	Number: 68 Inclusion criteria: infants 6 month of age Exclusion criteria: none
Interventions	1. Vitamin A (vitamin A 100,000 IU 1 dose; n=32) 2. Control (placebo; n=36) Co-administration of vitamin A and measles vaccine
Outcomes	1. Mortality: not recorded 2. Morbidity: not recorded 3. Adverse effects Daily follow-up for first 2 days following supplementation

Stabell 1995 (*Continued*)

Notes	Location: Guinea-Bissau (Africa) No episodes of bulging fontanelle recorded in either group Compliance monitoring not recorded Attrition = 10.3% Intention-to-treat data unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind; details not provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for attrition and exclusions not reported
Selective reporting (reporting bias)	High risk	Not all clinically relevant outcomes reported
Other bias	Unclear risk	Source of funding not mentioned No mention of any research protocol published a priori

Venkatarao 1996

Methods	Randomised, double-blind, placebo-controlled trial
Participants	Inclusion criteria: newly delivered mother and her infant Exclusion criteria: none
Interventions	1. Maternal vitamin A, infant vitamin A (vitamin A 300,000 IU to the mother, 1 dose, 7 to 14 days postpartum; vitamin A 200,000 IU to the infant, 1 dose, at 6 months of age; n=311) 2. Maternal vitamin A, infant placebo (vitamin A 300,000 IU to the mother, 1 dose, 7 to 14 days postpartum; placebo to the infant, 1 dose, at 6 months of age; n=301) 3. Maternal placebo, infant placebo (placebo to the mother, 1 dose, 7 to14 days postpartum; placebo to the infant, 1 dose, at 6 months of age; n=297
Outcomes	Maternal supplementation: • Mortality • Morbidity • Adverse effects follow-up at least fortnightly for 6 months Infant supplementation:

Venkatarao 1996 (*Continued*)

	• Mortality: not recorded • Morbidity • Adverse effects follow-up at least fortnightly for 6 months
Notes	Location: India (Asia) For the maternal supplementation comparison, the data on mortality outcome pertains to Ap and Pp groups only as the mortality after 6 months of age cannot be ascertained according to the different treatment arms. For the infant supplementation comparison, the data on mortality after initiating vitamin A supplementation (mortality after 6 months) cannot be extracted, and hence this outcome could not be included. For recalculating for the morbidity analyses, for Ap + Aa groups *versus* Pp for 0 to 6 months, Ap *versus* Pp for 6 to 12 months, and Aa *versus* Pp for 6 to 12 months, the total number of person years was taken from the number stated by the author (denominator) in Table 2 (page 283) No adverse effects were observed in any of the 3 groups

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"...randomly allocated"; no further details given
Allocation concealment (selection bias)	Unclear risk	"the Medical Officer...administered the appropriate capsules to the mother from the sealed envelope supplied by the Statistical Section at the Camp Office"
Blinding (performance bias and detection bias) All outcomes	Low risk	"...capsules that were similar in colour and consistency"
Incomplete outcome data (attrition bias) All outcomes	High risk	Exclusions and attrition were 23%; intention-to-treat analyses not performed
Selective reporting (reporting bias)	Low risk	All key expected outcomes reported
Other bias	Unclear risk	Source of funding not provided No mention of research protocol

West 1995

Methods	Cluster-randomised, double-masked, placebo-controlled Data collection: September 1989 to December 1991
Participants	Number:11918 Inclusion criteria: infants $\leq$ 6 months Exclusion criteria: none

West 1995 (*Continued*)

Interventions	1. Vitamin A (1 oral dose 50,000 IU vitamin A (3 drops of oil) for neonates, 100,000 IU (6 drops of oil) for 1 to 5 months of age; n= 6086) 2. Control group (1 oral dose of placebo, 75 RE (250 IU) for neonates or 150 RE (500 IU) for 1 to 5 months of age; n= 5832) All supplements also contained ~3.3 IU vitamin E per drop, added as an antioxidant
Outcomes	1. Mortality 2. Morbidity: not recorded 3. 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)) Variance inflated by 22% for cluster adjustment 1621 infants enrolled before 1 month of age (830 in intervention group and 791 in control group) Adverse effects recorded in West 1992 by follow-up at 24 h after supplementation then daily until bulging fontanel subsided. Intervention group (n=1461) and placebo (n= 1379). No irritability (adverse effect) recorded in either group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"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." However, in the description, the method used to generate the randomisation sequence is not described in sufficient detail to permit judgement.
Allocation concealment (selection bias)	Unclear risk	The method used for allocation concealment is not described in sufficient detail to permit judgement.
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.

West 1995 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	"All analyses were performed on an intention-to-treat basis, that is, by randomised 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 pre-specified outcomes were reported
Other bias	Unclear risk	Supported by a grant from Johns Hopkins University and assistance from Hoffmann-LaRoche industry (Basel, Switzerland) A protocol is described but no details are provided

WHO 1998

Methods	Randomised, double-blind, multi-centre trial	
Participants	Number: 9424 Inclusion criteria: pregnant women and those with newborn babies Exclusion criteria: families intending to leave study site	
Interventions	Vitamin A (mothers 21 to 42 days postpartum in Ghana and 18 to 28 days postpartum in India and Peru received 200,000 IU vitamin A 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) Control (placebo to both mothers and infants at the same time as the vitamin A group; n=4708) At 9 months, with measles immunisation, infants in the vitamin A group were given 25,000 IU vitamin A, whereas those in control group received 100,000 IU vitamin A. Vitamin A was provided as retinol palmitate with minute amounts of vitamin E; placebo was soy bean oil.	
Outcomes	1. Mortality 2. Morbidity 3. Adverse effects Follow-up: 4 weekly until 9 months of age	
Notes	Location: Ghana, India, Peru Compliance monitoring: direct Attrition: 2.6% Intention-to-treat data: yes	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

WHO 1998 (*Continued*)

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 two groups are provided
Selective reporting (reporting bias)	Low risk	All clinically relevant outcomes reported
Other bias	Low risk	Sample size calculation reported; protocol and study SOP available in the World Health Organization, Geneva on request Supported by Child Health and Development Division, WHO (Geneva), Indian Council of Medical Research and John Hopkins Family Health and Child Survival Co-operative agreement with USAID

HIV: human immunodeficiency virus.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Basu 2003	Not placebo controlled
Benn 2000	Relevant outcomes not reported
Bhaskaram 1997	Relevant outcomes not reported
Coles 2001	Relevant outcomes not reported
Coutsoudis 1999	Trial conducted on HIV positive women
Dimenstein 2007	Relevant outcomes not reported
Fawzi 2002	Trial conducted on HIV positive women
Humphrey 2006	Trial reports data only on HIV positive women
Kumwenda 2002	Trial conducted on HIV positive women
Mahalanabis 1997	Trial done on infants treated for diarrhoea (before discharge from hospital)
Miller 2006	Trial predominantly (81.1%) on infants born to HIV positive mothers
Newton 2007	Relevant outcomes not reported
Rahman 1995	Trial done on infants treated for diarrhoea (before discharge from hospital)
Rahman 1996	Relevant outcomes not reported
Rahman 1997	Relevant outcomes not reported
Rahman 1998	Relevant outcomes not reported
Rahman 1999	Relevant outcomes not reported
Rao 1976	Relevant outcomes not reported
Rice 1999	Relevant outcomes not reported
Rice 2000	Relevant outcomes not reported
Roy 1997	Not placebo controlled
Schmidt 2002	Maternal supplementation only in the antenatal period

(*Continued*)

Stoltzfus 1993	Relevant outcomes not reported
Vinutha 2000	Not placebo controlled

Characteristics of ongoing studies *[ordered by study ID]*

Bhandari 2010

Trial name or title	Bhandari N, et al. Efficacy of neonatal vitamin A supplementation in improving child survival in Haryana, India: generation of evidence necessary for informing global policy - NeoVitA Trial
Methods	Individually randomised double blind placebo controlled trials Location: Faridabad and Palwal Districts of Haryana, India
Participants	Estimated number: 40,200 Inclusion Criteria: Consent to participate; All births in the study area that are contacted by enrolment team within the eligible age window (on the day of birth or in the next 2 days keeping a minimum period of 2 hours between birth and dosing) Exclusion Criteria: Unable to feed on offering feeds, as reported by the mother; mother does not intend to stay in the study area for at least 6 months
Interventions	Vitamin A Capsules: Retinol Palmitate (50,000 IU) and minute amounts of Vitamin E in Soybean Oil orally as a single dose to neonates (on the day of birth or in the next 2 days keeping a minimum period of 2 hours between birth and dosing) Control: Placebo capsules containing minute amounts of Vitamin E in Soybean Oil orally as a single dose to neonates (on the day of birth or in the next 2 days keeping a minimum period of 2 hours between birth and dosing)
Outcomes	Primary: Risk of death in the period between receiving the intervention/placebo and six months of age Secondary: Risk of death in the neonatal period (dosing to-28 days age); risk of death in infancy (dosing to 365 days age), risk of hospital admissions in the follow up period, adverse events in a 3-day period following supplementation, and vitamin A status of a random sample of neonates in the intervention and placebo groups at 2 weeks and 3 months of age.
Starting date	June 2010
Contact information	Dr. Nita Bhandari, 45 Kalu Sarai, New Delhi 110016. E-mail: CHRD@sas.org.in
Notes	

Bhutta 2010

Trial name or title	Bhutta ZA, et al. Newborn Vitamin A (VA) Supplementation Pilot Project, Pakistan
Methods	Community based, cluster randomised, double blinded, placebo controlled trial Estimated completion date: December 2009 Location: Rural area, Karachi, Pakistan
Participants	Estimated number: 7400 Inclusion criteria: Live born infants from all pregnancies within participating villages Exclusion criteria: Child born with congenital malformation, serious birth injury, neonate with birth asphyxia and serious infections, gestational age less than 32 weeks, birth weight less than 1500 gms, refuse to participate
Interventions	Routine Post-partum Care and Vitamin A supplementation (50,000 IU) to the Newborn (within 48 hours of birth; maximum of 15 days after birth) Control: Routine Post-partum Care with Placebo to the Newborn (within 48 hours of birth; maximum of 15 days after birth)
Outcomes	Mortality and morbidity until six months of age
Starting date	January 2007
Contact information	Prof. Zulfiqar A. Bhutta, Aga Khan University, Karachi, Pakistan. E-Mail: zulfiqar.bhutta@aku.edu
Notes	

Edmond 2010

Trial name or title	Edmond K, et al. Efficacy of newborn vitamin A supplementation in improving child survival in rural Ghana: generation of evidence necessary for informing global policy - - NeoVitA
Methods	Individually randomised double blind placebo controlled trials Location: Rural areas Ghana
Participants	Estimated number: 28000 Inclusion Criteria:Consent to participate; all births in the study area that are contacted by enrolment team within the eligible age window (on the day of birth or in the next 2 days keeping a minimum period of 2 hours between birth and dosing) Exclusion Criteria: Unable to feed on offering feeds, as reported by the mother; mother does not intend to stay in the study area for at least 6 months
Interventions	Vitamin A Capsules: Retinol Palmitate (50,000 IU) and minute amounts of Vitamin E in Soybean Oil orally as a single dose to neonates (on the day of birth or in the next 2 days keeping a minimum period of 2 hours between birth and dosing) Control: Placebo capsules containing minute amounts of Vitamin E in Soybean Oil orally as a single dose to neonates (on the day of birth or in the next 2 days keeping a minimum period of 2 hours between birth and dosing)
Outcomes	Primary: Risk of death in the period between receiving the intervention/placebo and six months of age Secondary: Risk of death in the neonatal period (dosing to-28 days age); risk of death in infancy (dosing to

Edmond 2010 (*Continued*)

	365 days age), risk of hospital admissions in the follow up period, adverse events in a 3-day period following supplementation, and vitamin A status of a random sample of neonates in the intervention and placebo groups at 2 weeks and 3 months of age.
Starting date	August 2010
Contact information	Dr Karen Edmond, London School of Hygiene and Tropical Medicine, Keppel St London, WC1E7HT, United Kingdom. Email: karen.edmond@lshtm.ac.uk
Notes	

Fawzi 2010

Trial name or title	Fawzi W, et al. Efficacy of newborn vitamin A supplementation in improving child survival in Tanzania: generation of evidence necessary for informing global policy - Neovita
Methods	Individually randomised double blind placebo controlled trials Location: Rural areas Tanzania
Participants	Estimated number: 32000 Inclusion Criteria:Consent to participate; All births in the study area that are contacted by enrolment team within the eligible age window (on the day of birth or in the next 2 days keeping a minimum period of 2 hours between birth and dosing) Exclusion Criteria:Unable to feed on offering feeds, as reported by the mother; mother does not intend to stay in the study area for at least 6 months
Interventions	Vitamin A Capsules: Retinol Palmitate (50,000 IU) and minute amounts of Vitamin E in Soybean Oil orally as a single dose to neonates (on the day of birth or in the next 2 days keeping a minimum period of 2 hours between birth and dosing) Control: Placebo capsules containing minute amounts of Vitamin E in Soybean Oil orally as a single dose to neonates (on the day of birth or in the next 2 days keeping a minimum period of 2 hours between birth and dosing)
Outcomes	Primary: Risk of death in the period between receiving the intervention/placebo and six months of age Secondary: Risk of death in the neonatal period (dosing to-28 days age); risk of death in infancy (dosing to 365 days age), risk of hospital admissions in the follow up period, adverse events in a 3-day period following supplementation, and vitamin A status of a random sample of neonates in the intervention and placebo groups at 2 weeks and 3 months of age.
Starting date	August 2010
Contact information	Dr. Honorati Masanja, Ifakara Health Institute P. O. Box 78373 Dar es Salaam, Tanzania, United Republic Of. Tel: +255 22 2150503. E-mail: hmasanja@ihi.or.tz
Notes	

DATA AND ANALYSES

Comparison 1. Maternal vitamin A supplementation versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality in the first year of life	7		Risk Ratio (Random, 95% CI)	Subtotals only
1.1 Postpartum vitamin A supplementation	7		Risk Ratio (Random, 95% CI)	1.00 [0.94, 1.06]
1.2 Maternal nightblindness prevalence <5%	2		Risk Ratio (Random, 95% CI)	1.02 [0.85, 1.22]
1.3 Maternal nightblindness prevalence >5%	1		Risk Ratio (Random, 95% CI)	1.02 [0.79, 1.32]
1.4 Cumulative vitamin A dose<200000 IU	1		Risk Ratio (Random, 95% CI)	1.54 [0.31, 7.63]
1.5 Cumulative vitamin A dose>200000 IU	6		Risk Ratio (Random, 95% CI)	1.00 [0.93, 1.06]
1.6 Maternal serum retinol ≤1.1 µmol/l	2		Risk Ratio (Random, 95% CI)	1.04 [0.88, 1.23]
1.7 Maternal serum retinol>1.1µmol/l	3		Risk Ratio (Random, 95% CI)	0.99 [0.92, 1.06]
2 Mortality in the first month of life	2		Risk Ratio (Random, 95% CI)	0.98 [0.87, 1.11]
3 Cause specific mortality in the first year of life	2		Risk Ratio (Random, 95% CI)	Subtotals only
3.1 ARI	2		Risk Ratio (Random, 95% CI)	1.59 [0.84, 2.99]
3.2 Diarrhoea	2		Risk Ratio (Random, 95% CI)	2.57 [0.72, 9.12]
3.3 Others	2		Risk Ratio (Random, 95% CI)	0.62 [0.09, 4.09]

Comparison 2. Young infant vitamin A supplementation versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality in the first year of life	9		Risk Ratio (Random, 95% CI)	Subtotals only
1.1 Vitamin A supplementation in first 6 months of life	9		Risk Ratio (Random, 95% CI)	0.97 [0.83, 1.12]
1.2 Neonatal vitamin A supplementation	7		Risk Ratio (Random, 95% CI)	0.94 [0.79, 1.12]
1.3 Post neonatal Vitamin A supplementation	3		Risk Ratio (Random, 95% CI)	1.05 [0.84, 1.32]
1.4 Cumulative vitamin A dose received <=50,000 IU	7		Risk Ratio (Random, 95% CI)	0.94 [0.79, 1.12]

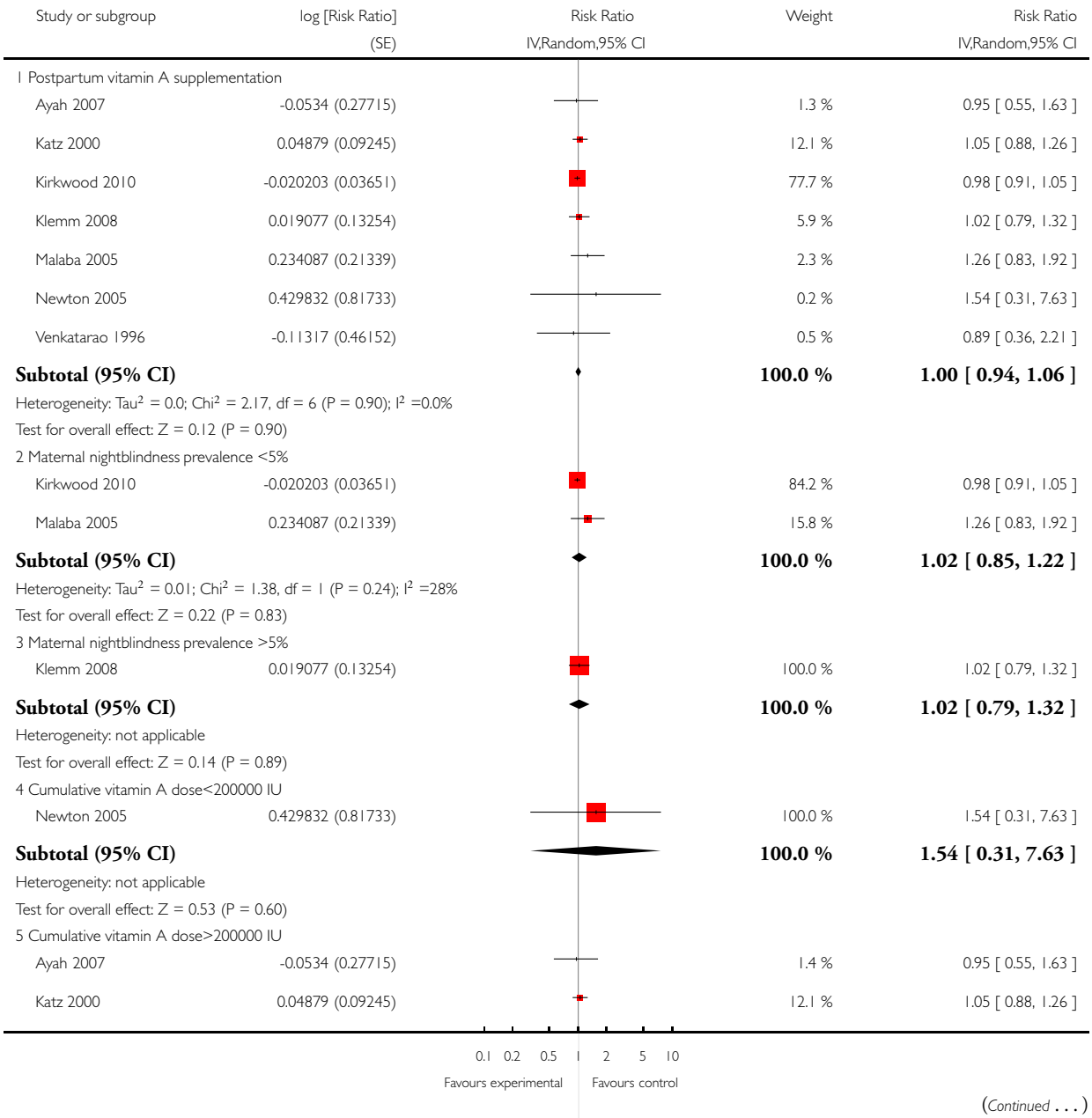
1.5 Cumulative vitamin A dose received >50,000 IU	3	Risk Ratio (Random, 95% CI)	1.05 [0.84, 1.32]
1.6 With concomitant maternal vitamin A supplementation	4	Risk Ratio (Random, 95% CI)	1.00 [0.81, 1.23]
1.7 Without concomitant maternal vitamin A supplementation	5	Risk Ratio (Random, 95% CI)	0.93 [0.74, 1.17]
1.8 Low birthweight	4	Risk Ratio (Random, 95% CI)	0.84 [0.65, 1.07]
1.9 Normal birthweight	3	Risk Ratio (Random, 95% CI)	0.78 [0.43, 1.40]
1.10 Maternal nightblindness prevalence <5%	2	Risk Ratio (Random, 95% CI)	1.06 [0.83, 1.34]
1.11 Maternal nightblindness prevalence>5%	2	Risk Ratio (Random, 95% CI)	0.83 [0.71, 0.96]
2 Mortality in the first month of life	3	Risk Ratio (Random, 95% CI)	0.90 [0.75, 1.08]
3 Cause specific mortality in the first year of life	7	Risk Ratio (Random, 95% CI)	Subtotals only
3.1 Diarrhoea	7	Risk Ratio (Random, 95% CI)	1.01 [0.72, 1.41]
3.2 ARI	7	Risk Ratio (Random, 95% CI)	1.12 [0.91, 1.39]
3.3 Others	7	Risk Ratio (Random, 95% CI)	0.81 [0.64, 1.02]
4 Morbidity in the first year of life	7	Risk Ratio (Random, 95% CI)	Subtotals only
4.1 Diarrhoea	6	Risk Ratio (Random, 95% CI)	1.02 [0.99, 1.06]
4.2 Acute respiratory infection or respiratory difficulty	4	Risk Ratio (Random, 95% CI)	1.04 [0.95, 1.15]
4.3 Cough or running nose	3	Risk Ratio (Random, 95% CI)	0.98 [0.85, 1.13]
4.4 Ear infection	0	Risk Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
4.5 Fever	3	Risk Ratio (Random, 95% CI)	0.92 [0.76, 1.11]
4.6 Vomiting	0	Risk Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
5 Adverse effects of vitamin A supplementation	10	Risk Ratio (Random, 95% CI)	Subtotals only
5.1 Bulging fontanelle following any dose of vitamin A	10	Risk Ratio (Random, 95% CI)	1.55 [1.05, 2.28]
5.2 Bulging fontanelle following first dose of vitamin A	7	Risk Ratio (Random, 95% CI)	1.37 [0.98, 1.91]
5.3 Bulging fontanelle following second dose of vitamin A	2	Risk Ratio (Random, 95% CI)	3.60 [1.65, 7.87]
5.4 Bulging fontanelle following third dose of vitamin A	2	Risk Ratio (Random, 95% CI)	3.14 [1.72, 5.74]
5.5 Vomiting	4	Risk Ratio (Random, 95% CI)	0.81 [0.58, 1.12]
5.6 Irritability	4	Risk Ratio (Random, 95% CI)	0.98 [0.87, 1.11]
5.7 Diarrhoea	3	Risk Ratio (Random, 95% CI)	0.99 [0.75, 1.31]
5.8 Fever	5	Risk Ratio (Random, 95% CI)	1.07 [0.96, 1.20]

Analysis 1.1. Comparison 1 Maternal vitamin A supplementation versus placebo, Outcome 1 Mortality in the first year of life.

Review: Vitamin A supplementation for the prevention of morbidity and mortality in infants six months of age or less

Comparison: 1 Maternal vitamin A supplementation versus placebo

Outcome: 1 Mortality in the first year of life



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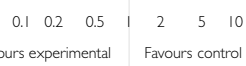
Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Kirkwood 2010	-0.020203 (0.03651)		77.8 %	0.98 [0.91, 1.05]
Klemm 2008	0.019077 (0.13254)		5.9 %	1.02 [0.79, 1.32]
Malaba 2005	0.234087 (0.21339)		2.3 %	1.26 [0.83, 1.92]
Venkatarao 1996	-0.11317 (0.46152)		0.5 %	0.89 [0.36, 2.21]
Subtotal (95% CI)			**100.0 %**	**1.00 [0.93, 1.06]**
Heterogeneity: Tau² = 0.0; Chi² = 1.89, df = 5 (P = 0.86); I² =0.0%				
Test for overall effect: Z = 0.14 (P = 0.89)				
6 Maternal serum retinol ≤1.1 mol/l				
Ayah 2007	-0.0534 (0.27715)		10.0 %	0.95 [0.55, 1.63]
Katz 2000	0.04879 (0.09245)		90.0 %	1.05 [0.88, 1.26]
Subtotal (95% CI)			**100.0 %**	**1.04 [0.88, 1.23]**
Heterogeneity: Tau² = 0.0; Chi² = 0.12, df = 1 (P = 0.73); I² =0.0%				
Test for overall effect: Z = 0.44 (P = 0.66)				
7 Maternal serum retinol>1.1mol/l				
Kirkwood 2010	-0.020203 (0.03651)		90.5 %	0.98 [0.91, 1.05]
Klemm 2008	0.019077 (0.13254)		6.9 %	1.02 [0.79, 1.32]
Malaba 2005	0.234087 (0.21339)		2.6 %	1.26 [0.83, 1.92]
Subtotal (95% CI)			**100.0 %**	**0.99 [0.92, 1.06]**
Heterogeneity: Tau² = 0.0; Chi² = 1.43, df = 2 (P = 0.49); I² =0.0%				
Test for overall effect: Z = 0.31 (P = 0.76)				

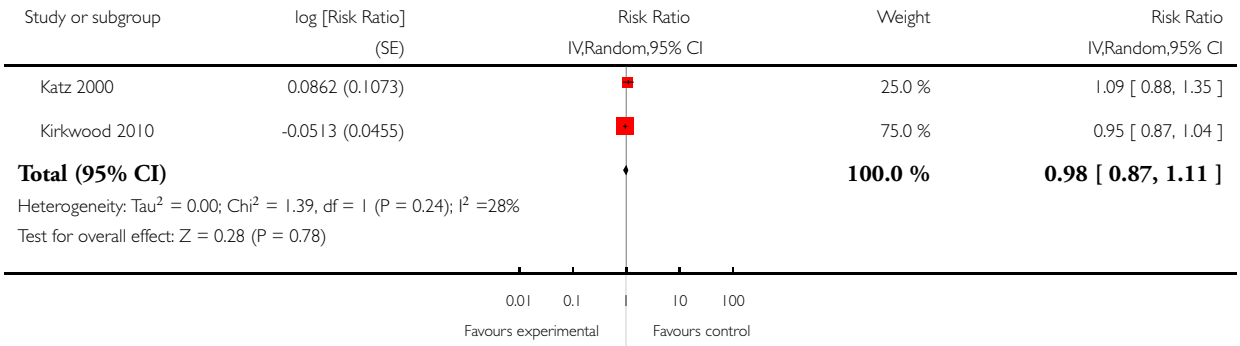


Analysis 1.2. Comparison 1 Maternal vitamin A supplementation versus placebo, Outcome 2 Mortality in the first month of life.

Review: Vitamin A supplementation for the prevention of morbidity and mortality in infants six months of age or less

Comparison: 1 Maternal vitamin A supplementation versus placebo

Outcome: 2 Mortality in the first month of life

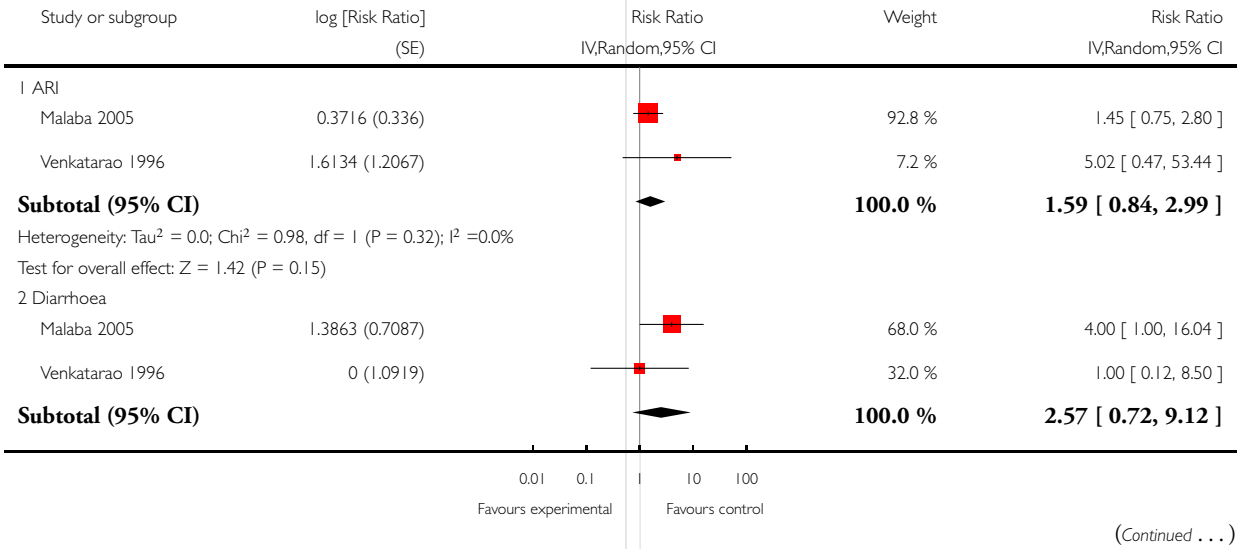


Analysis 1.3. Comparison 1 Maternal vitamin A supplementation versus placebo, Outcome 3 Cause specific mortality in the first year of life.

Review: Vitamin A supplementation for the prevention of morbidity and mortality in infants six months of age or less

Comparison: 1 Maternal vitamin A supplementation versus placebo

Outcome: 3 Cause specific mortality in the first year of life



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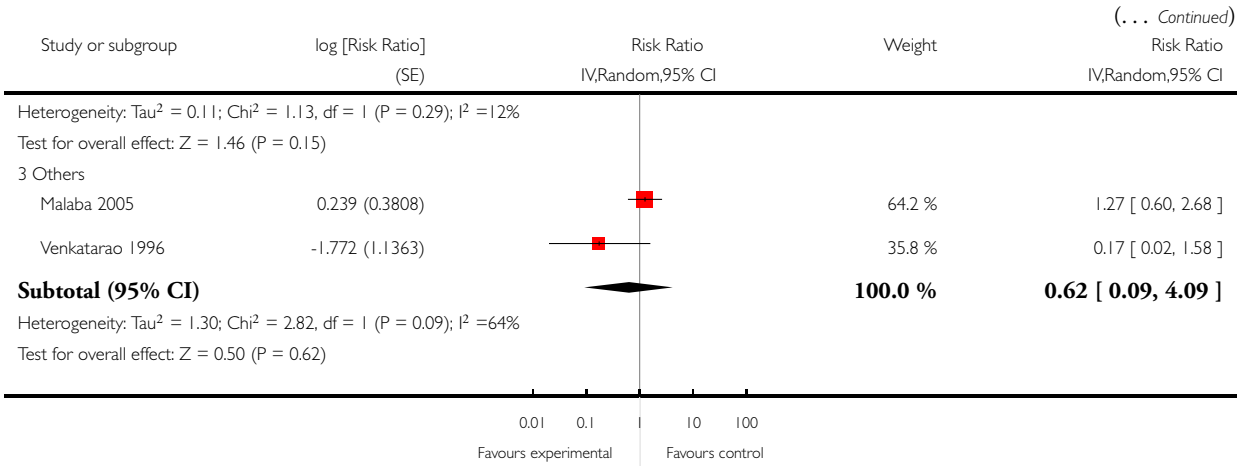
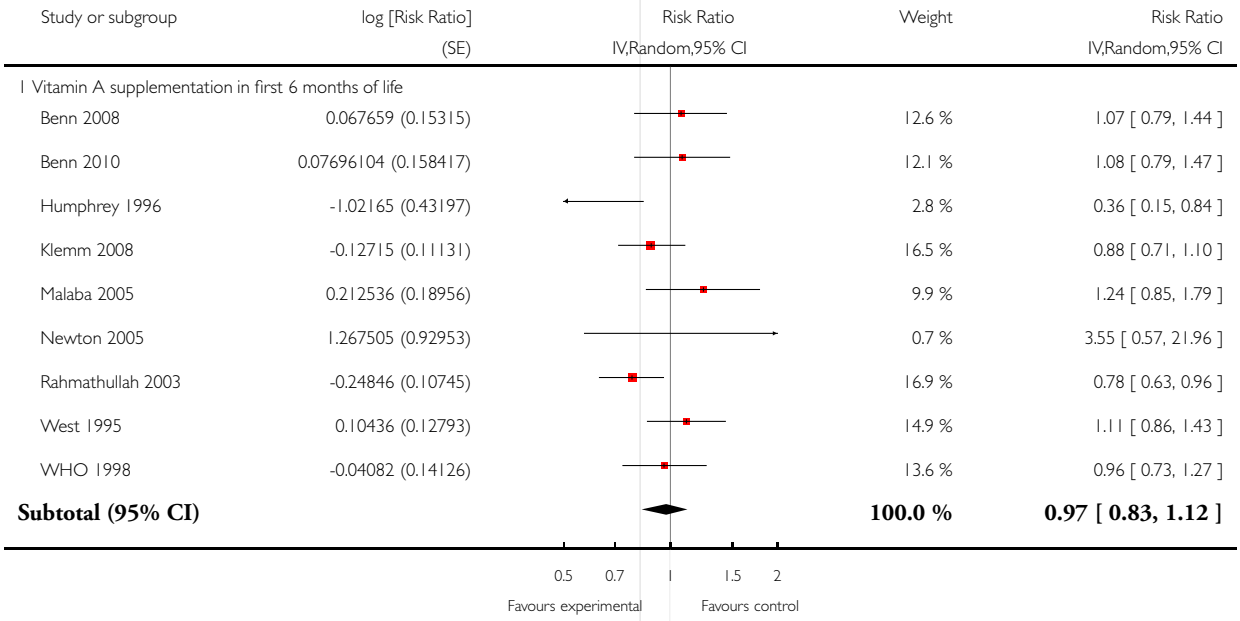


Analysis 2.1. Comparison 2 Young infant vitamin A supplementation versus placebo, Outcome 1 Mortality in the first year of life.

Review: Vitamin A supplementation for the prevention of morbidity and mortality in infants six months of age or less

Comparison: 2 Young infant vitamin A supplementation versus placebo

Outcome: 1 Mortality in the first year of life



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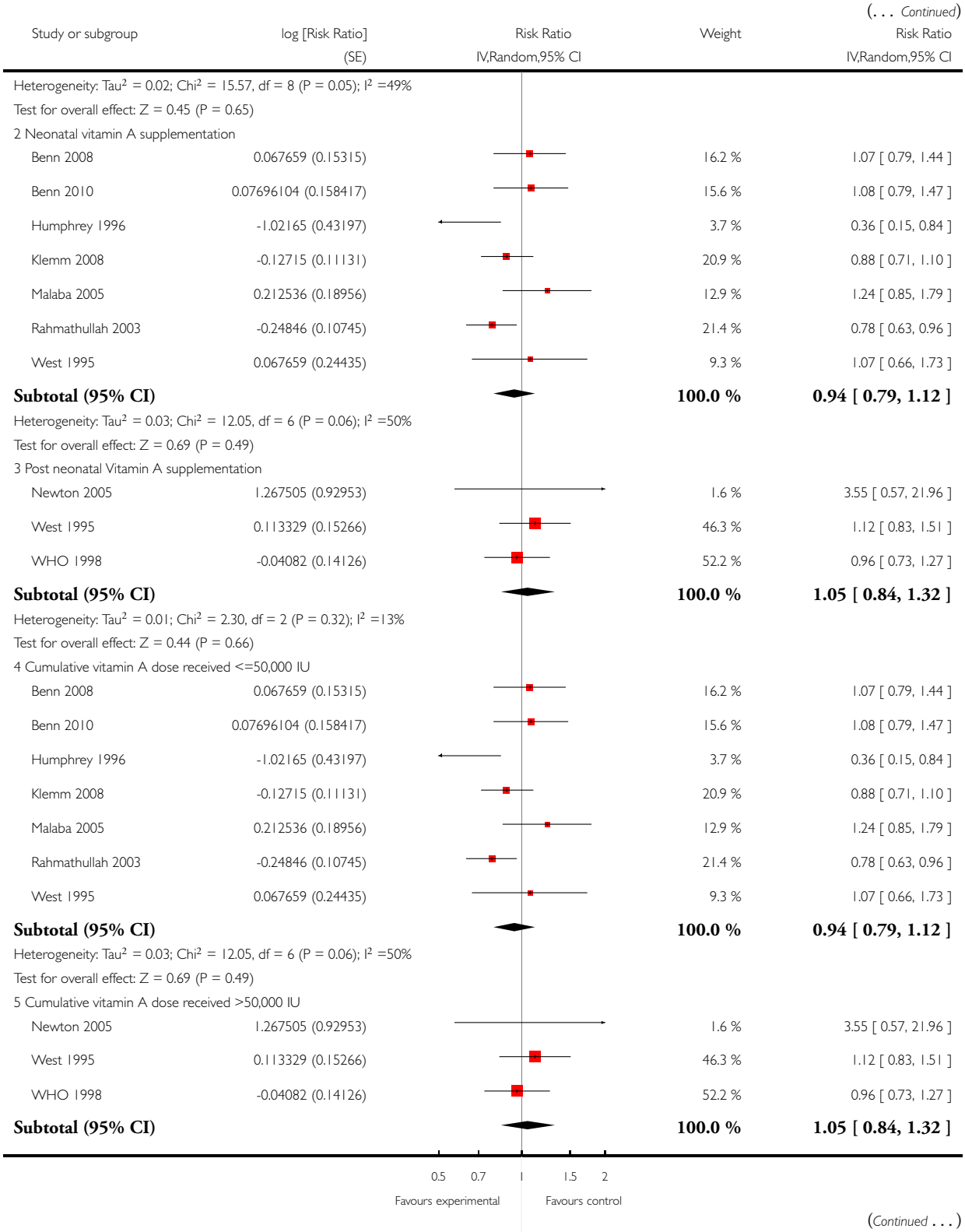

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Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Heterogeneity: Tau² = 0.01; Chi² = 2.30, df = 2 (P = 0.32); I² =13%				
Test for overall effect: Z = 0.44 (P = 0.66)				
6 With concomitant maternal vitamin A supplementation				
Klemm 2008	-0.12715 (0.11131)		42.9 %	0.88 [0.71, 1.10]
Malaba 2005	0.212536 (0.18956)		22.6 %	1.24 [0.85, 1.79]
Newton 2005	1.267505 (0.92953)		1.3 %	3.55 [0.57, 21.96]
WHO 1998	-0.04082 (0.14126)		33.3 %	0.96 [0.73, 1.27]
Subtotal (95% CI)			**100.0 %**	**1.00 [0.81, 1.23]**
Heterogeneity: Tau² = 0.01; Chi² = 4.35, df = 3 (P = 0.23); I² =31%				
Test for overall effect: Z = 0.04 (P = 0.97)				
7 Without concomitant maternal vitamin A supplementation				
Benn 2008	0.067659 (0.15315)		21.7 %	1.07 [0.79, 1.44]
Benn 2010	0.07696104 (0.158417)		21.2 %	1.08 [0.79, 1.47]
Humphrey 1996	-1.02165 (0.43197)		6.2 %	0.36 [0.15, 0.84]
Rahmathullah 2003	-0.24846 (0.10745)		26.6 %	0.78 [0.63, 0.96]
West 1995	0.10436 (0.12793)		24.4 %	1.11 [0.86, 1.43]
Subtotal (95% CI)			**100.0 %**	**0.93 [0.74, 1.17]**
Heterogeneity: Tau² = 0.04; Chi² = 11.12, df = 4 (P = 0.03); I² =64%				
Test for overall effect: Z = 0.61 (P = 0.54)				
8 Low birthweight				
Benn 2010	0.07696104 (0.158417)		27.2 %	1.08 [0.79, 1.47]
Humphrey 1996	-0.30110509 (0.523012)		5.2 %	0.74 [0.27, 2.06]
Klemm 2008	-0.11653382 (0.094074)		37.6 %	0.89 [0.74, 1.07]
Rahmathullah 2003	-0.46203546 (0.139707)		30.0 %	0.63 [0.48, 0.83]
Subtotal (95% CI)			**100.0 %**	**0.84 [0.65, 1.07]**
Heterogeneity: Tau² = 0.03; Chi² = 7.18, df = 3 (P = 0.07); I² =58%				
Test for overall effect: Z = 1.41 (P = 0.16)				
9 Normal birthweight				
Humphrey 1996	-2.40794561 (1.08382)		6.8 %	0.09 [0.01, 0.75]
Klemm 2008	-0.24846136 (0.253586)		42.1 %	0.78 [0.47, 1.28]
Rahmathullah 2003	0.0295588 (0.162845)		51.1 %	1.03 [0.75, 1.42]
Subtotal (95% CI)			**100.0 %**	**0.78 [0.43, 1.40]**
Heterogeneity: Tau² = 0.15; Chi² = 5.50, df = 2 (P = 0.06); I² =64%				
Test for overall effect: Z = 0.84 (P = 0.40)				
10 Maternal nightblindness prevalence <5%				
Malaba 2005	0.212536 (0.18956)		37.6 %	1.24 [0.85, 1.79]
WHO 1998	-0.04082 (0.14126)		62.4 %	0.96 [0.73, 1.27]

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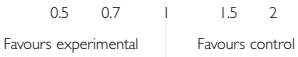
Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Subtotal (95% CI)			**100.0 %**	**1.06 [0.83, 1.34]**
Heterogeneity: Tau² = 0.00; Chi² = 1.15, df = 1 (P = 0.28); I² =13%				
Test for overall effect: Z = 0.44 (P = 0.66)				
11 Maternal nightblindness prevalence>5%				
Klemm 2008	-0.12715 (0.11131)		48.2 %	0.88 [0.71, 1.10]
Rahmathullah 2003	-0.24846 (0.10745)		51.8 %	0.78 [0.63, 0.96]
Subtotal (95% CI)			**100.0 %**	**0.83 [0.71, 0.96]**
Heterogeneity: Tau² = 0.0; Chi² = 0.61, df = 1 (P = 0.43); I² =0.0%				
Test for overall effect: Z = 2.46 (P = 0.014)				



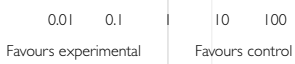
Analysis 2.2. Comparison 2 Young infant vitamin A supplementation versus placebo, Outcome 2 Mortality in the first month of life.

Review: Vitamin A supplementation for the prevention of morbidity and mortality in infants six months of age or less

Comparison: 2 Young infant vitamin A supplementation versus placebo

Outcome: 2 Mortality in the first month of life

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Benn 2008	0.0295 (0.4331)		4.6 %	1.03 [0.44, 2.41]
Humphrey 1996	0.2112 (0.6287)		2.2 %	1.24 [0.36, 4.24]
Klemm 2008	-0.1165 (0.0964)		93.2 %	0.89 [0.74, 1.08]
Total (95% CI)			**100.0 %**	**0.90 [0.75, 1.08]**
Heterogeneity: Tau² = 0.0; Chi² = 0.36, df = 2 (P = 0.83); I² =0.0%				
Test for overall effect: Z = 1.10 (P = 0.27)				

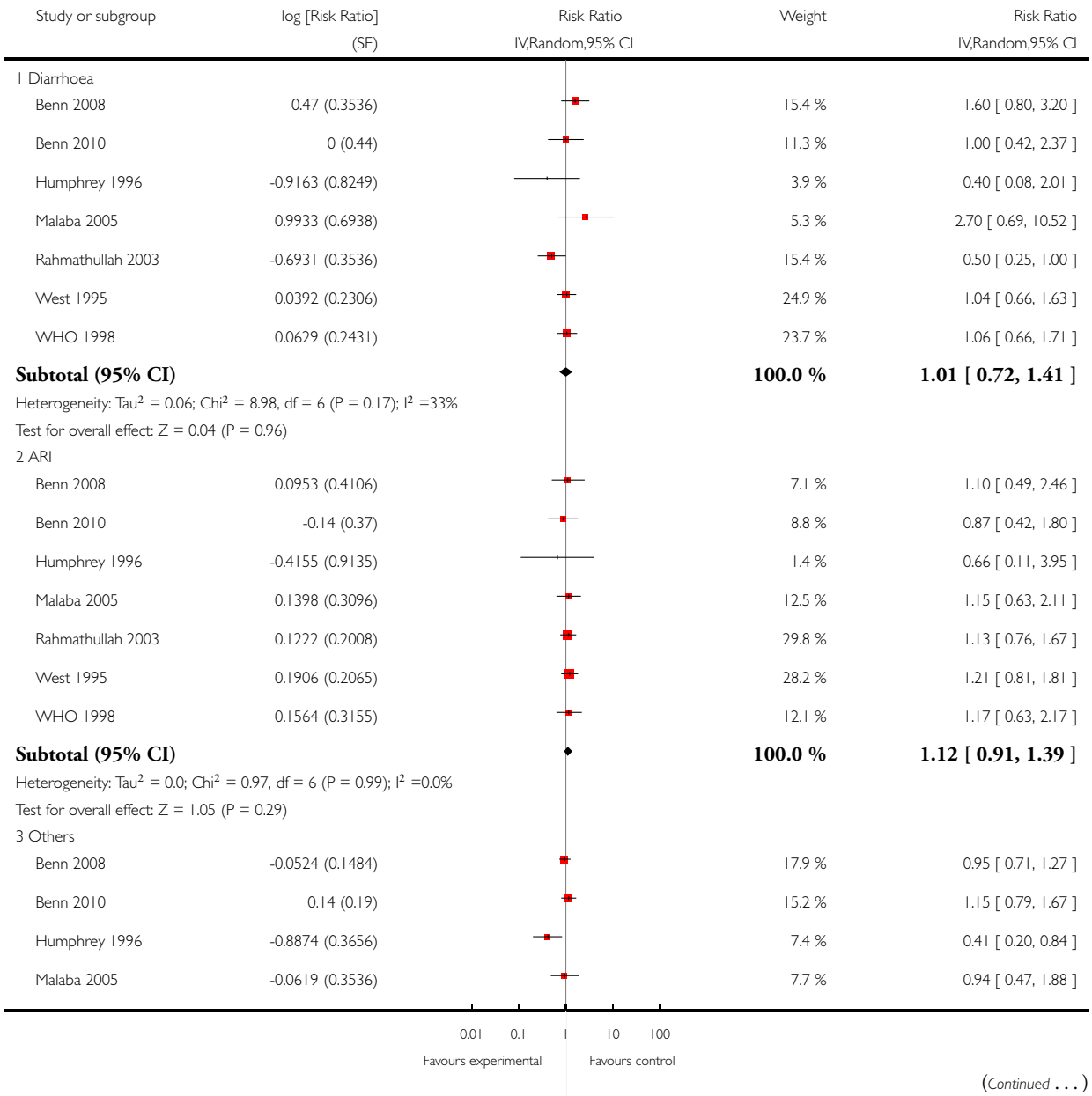


Analysis 2.3. Comparison 2 Young infant vitamin A supplementation versus placebo, Outcome 3 Cause specific mortality in the first year of life.

Review: Vitamin A supplementation for the prevention of morbidity and mortality in infants six months of age or less

Comparison: 2 Young infant vitamin A supplementation versus placebo

Outcome: 3 Cause specific mortality in the first year of life



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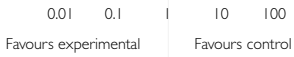
Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Rahmathullah 2003	-0.3711 (0.1455)		18.1 %	0.69 [0.52, 0.92]
West 1995	0.0129 (0.1219)		19.7 %	1.01 [0.80, 1.29]
WHO 1998	-0.6303 (0.2097)		14.0 %	0.53 [0.35, 0.80]
Subtotal (95% CI)			**100.0 %**	**0.81 [0.64, 1.02]**
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 16.20$, df = 6 (P = 0.01); $I^2 = 63\%$				
Test for overall effect: Z = 1.78 (P = 0.075)				



Analysis 2.4. Comparison 2 Young infant vitamin A supplementation versus placebo, Outcome 4 Morbidity in the first year of life.

Review: Vitamin A supplementation for the prevention of morbidity and mortality in infants six months of age or less

Comparison: 2 Young infant vitamin A supplementation versus placebo

Outcome: 4 Morbidity in the first year of life

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Diarrhoea				
Benn 2010	0.02 (0.13)		2.0 %	1.02 [0.79, 1.32]
Humphrey 1996	0.4762 (0.439)		0.2 %	1.61 [0.68, 3.81]
Rahmathullah 2003	0.0488 (0.0292)		40.0 %	1.05 [0.99, 1.11]
Semba 2001	0.0402 (0.2193)		0.7 %	1.04 [0.68, 1.60]
Venkatarao 1996	0.0677 (0.0548)		11.4 %	1.07 [0.96, 1.19]
WHO 1998	-0.0101 (0.0273)		45.8 %	0.99 [0.94, 1.04]
Subtotal (95% CI)			**100.0 %**	**1.02 [0.99, 1.06]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.98$, df = 5 (P = 0.55); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.31 (P = 0.19)				
2 Acute respiratory infection or respiratory difficulty				
Humphrey 1996	0.174 (0.4144)		1.4 %	1.19 [0.53, 2.68]
Rahmathullah 2003	0.1133 (0.0319)		39.6 %	1.12 [1.05, 1.19]

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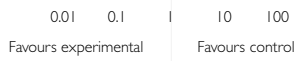
Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Venkatarao 1996	-0.0834 (0.0638)		26.4 %	0.92 [0.81, 1.04]
WHO 1998	0.0564 (0.0484)		32.6 %	1.06 [0.96, 1.16]
Subtotal (95% CI)			**100.0 %**	**1.04 [0.95, 1.15]**
Heterogeneity: Tau² = 0.01; Chi² = 7.77, df = 3 (P = 0.05); I² =61%				
Test for overall effect: Z = 0.89 (P = 0.38)				
3 Cough or running nose				
Benn 2008	-0.0834 (0.0606)		42.7 %	0.92 [0.82, 1.04]
Humphrey 1996	-1.772 (1.0764)		0.5 %	0.17 [0.02, 1.40]
Rahmathullah 2003	0.0392 (0.022)		56.9 %	1.04 [1.00, 1.09]
Subtotal (95% CI)			**100.0 %**	**0.98 [0.85, 1.13]**
Heterogeneity: Tau² = 0.01; Chi² = 6.40, df = 2 (P = 0.04); I² =69%				
Test for overall effect: Z = 0.29 (P = 0.77)				
4 Ear infection				
Subtotal (95% CI)			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable				
Test for overall effect: not applicable				
5 Fever				
Humphrey 1996	-0.5978 (0.3815)		5.9 %	0.55 [0.26, 1.16]
Rahmathullah 2003	0.0198 (0.015)		55.6 %	1.02 [0.99, 1.05]
Semba 2001	-0.1567 (0.0888)		38.5 %	0.85 [0.72, 1.02]
Subtotal (95% CI)			**100.0 %**	**0.92 [0.76, 1.11]**
Heterogeneity: Tau² = 0.02; Chi² = 6.42, df = 2 (P = 0.04); I² =69%				
Test for overall effect: Z = 0.86 (P = 0.39)				
6 Vomiting				
Subtotal (95% CI)			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable				
Test for overall effect: not applicable				

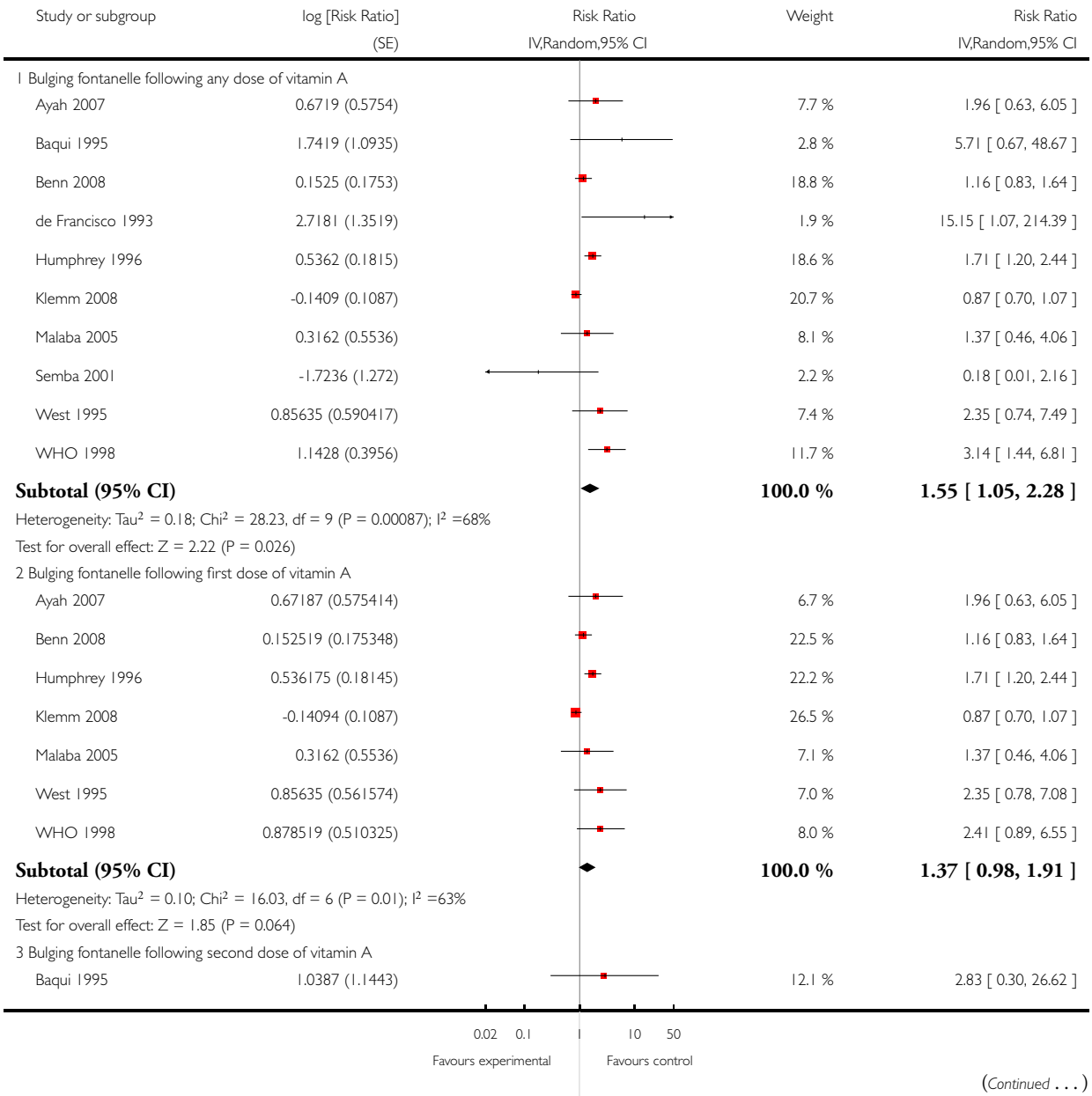


Analysis 2.5. Comparison 2 Young infant vitamin A supplementation versus placebo, Outcome 5 Adverse effects of vitamin A supplementation.

Review: Vitamin A supplementation for the prevention of morbidity and mortality in infants six months of age or less

Comparison: 2 Young infant vitamin A supplementation versus placebo

Outcome: 5 Adverse effects of vitamin A supplementation



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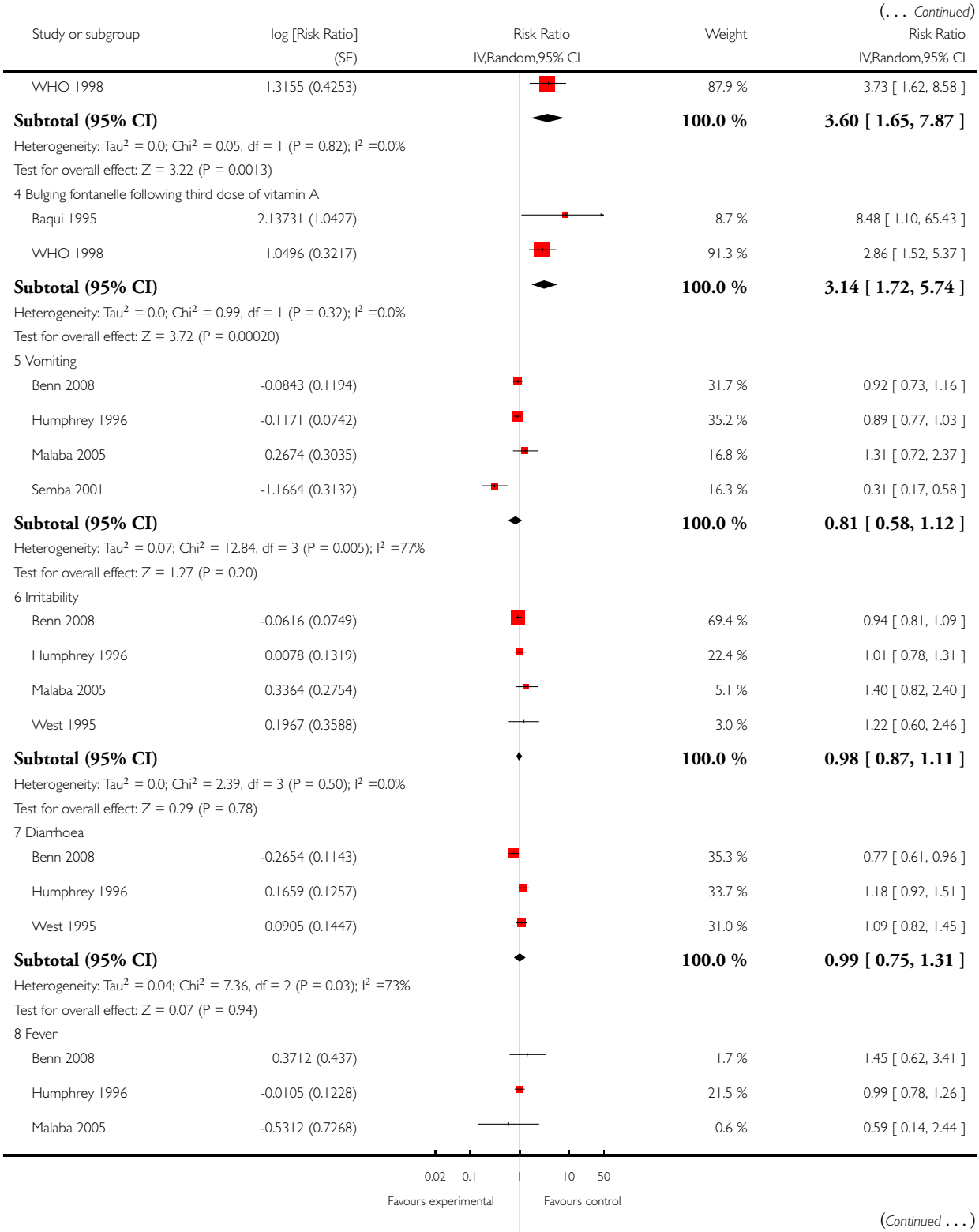

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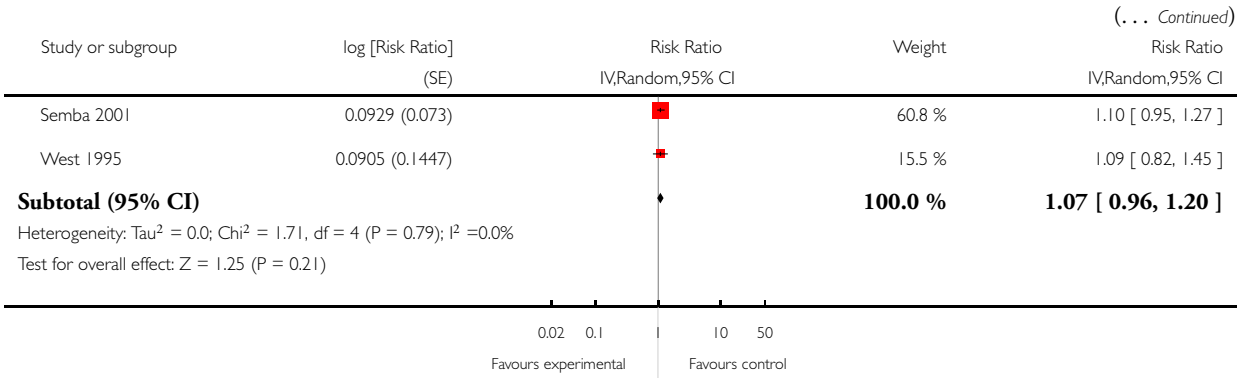

APPENDICES

Appendix 1. Data Abstraction

General

- For computing the summary relative risk, we required individual study risk ratio (RR) and 95% CI or standard error (SE). In a hierarchical pattern, we gave preference to the RR stated by authors with a recheck of the calculations from the stated numbers. If RR was not stated, it was computed with the following preference order for the denominator - stated child-years, numbers with definite outcome known till completion of intervention period, or number randomized.
- Where necessary and possible, an intention to treat analysis was reconstructed from the available data.
- In the case where no events (or all events) were observed in both groups the trial provided no information about relative probability of the event and was automatically omitted from the meta-analysis.
- If stratified data in relation to time point of starting supplementation was not available, then supplementation grouping was done as per the initiation time in >75% of participants.
- The term apparently healthy was used for the group of participants who had no obvious clinical morbidity and in whom HIV serology, if performed, was negative in > 75% of subjects.

Specific

Ayah 2007

Mortality outcome is available only till 14 weeks of age, the time point of initiating infant vitamin A supplementation. Thus for evaluating effect of maternal vitamin A supplementation in comparison to placebo, both groups of maternal supplementation (irrespective of infant vitamin A supplementation later) and both groups of maternal placebo (irrespective of infant vitamin A supplementation later) were merged for calculating RR and 95% CI.

Benn 2008

Actual death counts in the first seven days of life are available. However, the quantification of the small number of subjects recruited after seven days of life is not available. Thus the denominator for risk calculations was taken as the vital status known at the end of the study.

Benn 2010

The numbers for Additional Table 3 were derived from Figure 2 and Table 4 of the report.

The cause specific mortality, ascertained by verbal autopsy as a single cause of death, was depicted only as graph in Figure 5 in the publication. The authors responded to our request to provide detailed data. The rate ratios are adjusted for gender, randomization to BCG vaccine and inter-dependency for multiple births. Mortality due to diarrhea had a RR 1.0; 95% CI 0.42 to 2.38 (Vitamin A: 10/757 and Placebo: 10/762). Mortality due to respiratory infections had a RR 0.87; 95% CI 0.42 to 1.82 (Vitamin A: 13/757 and

Placebo: 15/762). Mortality due to causes other than diarrhea and respiratory infections had a RR 1.15; 95% CI 0.79 to 1.67 (Vitamin A: 60/757 and Placebo: 53/762).

The morbidity data on diarrhea was reported in Diness 2010 for a subsample of 287 infants during annual rotavirus epidemic from Januray through March 2005. We extracted the data for all diarrheal episodes (irrespective of etiology) till infancy from Tables 3 and 5 by combining non-rotavirus diarrhea and rota virus diarrhea for both age groups (1-5 months and 6-9 months). The calculated RR was 1.02; 95% CI 0.79 to 1.31 (Vitamin A:123/7377 and Placebo 137/8396 days at risk).

Humphrey 1996

Mean birth weight was calculated from percentages of birth-weight categories in Table 2 (page 492), assuming the mid point of birth-weight distributions for 1500-2499 g (2000 g), 2500 3499 g (3000 g), and 3500 g for the category $\geq$ 3500 g. The average of Vitamin A and control groups was computed as the mean birth-weight, which was 2.97 kg.

Klemm 2008

A recalculation of the RRs and 95% CIs was required for the two reviews, which was based on the stratified data provided by the authors of this study in the detailed Table 1. For this recalculation, appropriate adjustment was made for the design effect calculated (1.01769) from the numbers, and the stated RR and 95% CI for the mortality effect of neonatal vitamin A supplementation irrespective of maternal supplementation status. In the maternal supplementation review comparison, the intervention group comprised maternal vitamin A supplementation and neonatal placebo whereas the control group comprised placebo administration to both the newborn and the mother; the calculated RR and 95% CI were 1.0193 (0.7861, 1.3216). The numbers for Additional Table 1 of this review were derived from the Table 1 of the report; as this table or the text or tables elsewhere in the report do not mention the loss to follow-up in these sub-groups specifically, it is not possible to calculate the number randomized. In the young infant supplementation review comparison, the intervention group comprised neonatal vitamin A supplementation irrespective of maternal supplementation status whereas the control group comprised placebo administration to both the newborn and the mother; the calculated RR and 95% CI were 0.8806 (0.7080, 1.0953). The numbers for Additional Table 3 of this review were derived from the Figure 2 and Table 1 of the report; as this table or the text or tables elsewhere in the report do not mention the loss to follow-up in control subgroup specifically, it is not possible to calculate the number randomized for controls. A similar recalculation was not possible for the adverse effects analysis, in which the actual numbers were used (without design effect) for neonatal vitamin A supplemented and placebo groups irrespective of the maternal supplementation status.

Malaba 2005

For recalculation of the RRs according to all cause mortality, the number of deaths due to congenital abnormalities and injuries were added to each factorial group results in Table 4, page 459 (3 in Aa and 2 each in other groups) and the denominator taken as person years in Statsdirect software for RR meta-analysis. For infant mortality the intervention numbers were 93/4195 (Aa + Pa) and pure placebo (Pp) numbers were 38/2120; the calculated RR and 95% CI were 1.2368 (0.8534, 1.7942). For maternal mortality the intervention numbers (Ap) were 48/2119; the calculated RR and 95% CI were 1.2638 (0.8319, 1.9202). Mean maternal serum retinol values (postpartum) are not available. However, the percentage of serum retinol deficient women with the cut-off level of 1.05 micro moles/L was similar to that of Klemm, 2008 (18) for the first trimester. Assuming the same distribution of serum retinol, the mean serum retinol levels were presumed to be equal to this study.

Rahmathullah 2003

In the report Tielsch 2007, case fatality data is available following common morbidities for 60 day period following the episode, and numbers of deaths for this data (assuming no overlap of morbidities) are only 249 out of a total of 334 (75%) deaths recorded in the primary study . It is not possible to derive cause specific mortality data from this information. Information on the specific type of adverse effect recorded is missing as also the specific time period for recording adverse effects after the intervention.

The cause specific mortality was extracted from the web table of the publication. Mortality due to diarrhea had a RR 0.5; 95% CI 0.25 to 1.0 (Vitamin A: 12/2713 and Placebo: 24/2719 person-years). Moratlity due to respiratory causes (aspiration pneumonia, bronchopneumonia and respiratory distress syndrome) had a RR 1.13; 95% CI 0.76 to 1.67 (Vitamin A: 53/2713 and Placebo: 47/2719 person years). Mortality due to causes other than diarrhea and respiratory infections had a RR 0.69; 95% CI 0.52 to 0.92 (Vitamin A: 81/2713 and Placebo: 117/2719 person years).

For morbidity outcome, diarrhea and dysentery (Table 2) were combined as the two were mutually exclusive by definition; the pooled RR and 95% CI were calculated by generic inverse variance (fixed and random estimates were identical). ARI1 was categorized as cough or running nose and ARI2 as acute respiratory infection or respiratory difficulty.

Semba 2001

For the morbidity analyses, the two vitamin A intervention groups (25,000 IU and 50,000 IU) were pooled by the approximate method feasible in SPSS software.

Venkatarao 1996

For the maternal supplementation comparison, the data on mortality outcome pertains to AP and PP groups only as the mortality after 6 months age cannot be ascertained according to the different treatment arms. For the infant supplementation comparison, the data on mortality after initiating vitamin A supplementation (mortality after 6 months) cannot be extracted, and hence this outcome could not be included. For recalculating for the morbidity analyses, for AP + AA groups *versus* PP for 0-6 months, AP *versus* PP for 6-12 months, and AA *versus* PP for 6-12 months, the total number of person years was taken from the number stated by the author (denominator) in Table 2 (page 283).

No adverse effects were observed in any of the three groups.

West 1995

In the two independent analytic components (split according to the age of initiation of vitamin A supplementation, namely 0-1 months and 1-6 months), the RRs and 95% CIs were calculated according to the person-year follow-up given in Table 4 and inflated by 10% for cluster correction as per the methods section. The calculated RR and 95% CI for the mortality analysis in the 1-6 months group was 1.12 (0.83, 1.51).

WHO 1998

Of the 233 infants who had died by age 12 months, information on the cause of death was available for 203 deaths, which was sought from and received from the authors.

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 10, 2011

CONTRIBUTIONS OF AUTHORS

Both the authors prepared the protocol, applied the search strategy, retrieved the articles, extracted data, performed the risk of bias assessment, and did the statistical analysis. Both authors contributed to the drafting of the final version of the paper and act as joint guarantors.

DECLARATIONS OF INTEREST

None known

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Search strategy was reapplied on October 15, 2010 to include all relevant studies till that period. The Risk of Bias assessment was increased to include all the six headings now followed by The Cochrane Collaboration instead of the four specified earlier.