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October 2011

Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries

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Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries (Review)

Haider BA, Bhutta ZA

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Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries.
Cochrane Database of Systematic Reviews 2011, Issue 10. Art. No.: CD006980.
DOI: 10.1002/14651858.CD006980.pub2.

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[Intervention Review]

Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries

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Editorial group: Cochrane Neonatal Group.
Publication status and date: New, published in Issue 4, 2012.
Review content assessed as up-to-date: 30 November 2010.

Citation: Haider BA, Bhutta ZA. Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries. *Cochrane Database of Systematic Reviews* 2011, Issue 10. Art. No.: CD006980. DOI: 10.1002/14651858.CD006980.pub2.

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ABSTRACT

Background

Vitamin A deficiency is a major public health problem in developing countries. Vitamin A supplementation in children greater than six months of age has been found to be beneficial, with no effect of supplementation between one to five months. Supplementation in the neonatal period has been suggested to have an impact by increasing body stores in early infancy.

Objectives

To evaluate the role of vitamin A supplementation in term neonates in developing countries with respect to the prevention of mortality and morbidity.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, May 2010), EMBASE and MEDLINE (1966 to May 2010) via PubMed.

Selection criteria

Randomised and quasi-randomised controlled trials. Trials with factorial designs were also included.

Data collection and analysis

Two review authors independently assessed trial quality and extracted the data.

Main results

Seven trials (51,446 neonates) were included in this review, with only few trials reporting disaggregated data for term infants. Therefore, we analysed data and presented estimates for term infants (where specified) followed by all infants.

Data for term neonates from three studies showed a statistically significant effect on the risk of infant mortality at six months in the vitamin A group compared with the control group (typical risk ratio (RR) 0.82; 95% CI 0.68 to 0.99; I^2 63%). Analysis of data for all

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infants from five studies showed a 14% reduction in the risk of infant mortality at six months in neonates supplemented with vitamin A compared to control; this reduction was statistically significant (typical RR 0.86; 95% CI 0.77 to 0.97; I^2 39%). These findings should be interpreted with caution, however, due to the small number of included studies, wide confidence intervals with upper levels close to the null effect and statistical heterogeneity. Vitamin A supplementation failed to show any significant effect on infant mortality at 12 months of age compared to control (typical rate ratio 1.03; 95% CI 0.87 to 1.23; I^2 49%). Limited data were available for the outcomes of cause-specific mortality and morbidity, vitamin A deficiency, anaemia and adverse events.

Authors' conclusions

Considering mortality in early infancy being a major contributory cause of overall child mortality for the under five year old group in developing countries, it is critical to obtain sound scientific evidence of the effect of vitamin A supplementation in neonates. Evidence provided in this review does indicate a potential beneficial effect of supplementing neonates with vitamin A at birth for reducing mortality in the first half of infancy. Considering the absence of a clear indication of the biological mechanism and conflicting findings from individual studies in settings with varying levels of maternal vitamin A deficiency and infant mortality, and given four additional ongoing trials with approximately 100,000 neonates being enrolled, we propose a delay in any policy recommendations for neonatal vitamin A supplementation.

PLAIN LANGUAGE SUMMARY

Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries

Vitamin A is an important micronutrient that is required for the maintenance of normal functioning of the human body. In the developing world, many pregnant women are vitamin A-deficient. During pregnancy, additional vitamin A is required for the growth of the baby and for providing stores in the baby's liver. Deficiency of this micronutrient in the mother may also lead to its deficiency in the baby and may result in adverse effects on the baby's health. The benefits of giving vitamin A to children greater than six months of age, in reducing death and adverse effects on health, have been established but no evidence of this beneficial effect is available in infants one to five months of age. The potential benefits of vitamin A supplementation in the newborn period (during the first month of life) is under investigation and the review identified seven studies including 51,446 newborns with the intervention group supplemented with vitamin A in this period. There was a significant reduction in infant deaths at six months of age with the intervention when data for all infants were analysed. A similar reduction in the risk was observed for term neonates whose data were available from a subset of studies. These findings should be interpreted with caution because of the small number of studies used in these analyses and their estimates were close to the null effect of vitamin A. There are several large studies being conducted. The data from these, when available, will inform our analysis and help in establishing a definitive role of this intervention.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Neonatal vitamin A supplementation versus control for the prevention of mortality and morbidity in term neonates in developing countries

Patient or population: mortality and morbidity in term neonates
Settings: low and middle income countries
Intervention: neonatal vitamin A supplementation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	neonatal vitamin A supplementation				
All cause infant mortality at 6 months Follow-up: 6 months	**Low risk population**		**RR 0.82** (0.68 to 0.99)	22721 (3 studies)	⊕⊕◯◯ **low**[1,2,3]	
	13 per 1000	**11 per 1000** (9 to 13)				
	Medium risk population					
	15 per 1000	**12 per 1000** (10 to 15)				
	High risk population					
	28 per 1000	**23 per 1000** (19 to 28)				
All cause infant mortality at 12 months child years of follow-up Follow-up: 12 months	**Low risk population**[4]		**Rate ratio 0.95** (0.72 to 1.26)	5732 (2 studies)	⊕⊕◯◯ **low**[3,5,6]	

	13 per 1000	**12 per 1000** (9 to 16)			
	High risk population[4]				
	46 per 1000	**43 per 1000** (33 to 58)			
Adverse events: Bulging fontanelle Follow-up: 3 days	**Low risk population**		**RR 1.38** (1.04 to 1.82)	3158 (2 studies)	⊕⊕⊕⊕ **high**[3,7,8]
	25 per 1000	**35 per 1000** (26 to 46)			
	High risk population				
	94 per 1000	**130 per 1000** (98 to 171)			
Adverse events: Vomiting Follow-up: 3 days	**145 per 1000**	**128 per 1000** (107 to 152)	**RR 0.88** (0.74 to 1.05)	3159 (2 studies)	⊕⊕⊕◯ **moderate**[7,8,9]
Adverse events: Diarrhoea Follow-up: 3 days	**51 per 1000**	**47 per 1000** (39 to 56)	**RR 0.92** (0.77 to 1.09)	3159 (2 studies)	⊕⊕⊕◯ **moderate**[7,8,10]

*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.

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[1] The risk of bias assessment identified a possible issue over the stopping procedure in Klemm 2008. A higher rate of mortality was observed in the placebo group after 2/3 participants had been randomised. This study dominated the analysis (65% weight).

[2] The level of statistical heterogeneity between the results of the studies was moderate (I square 63%). The variation between the studies may have been related to differences between the study populations and settings in terms of infant mortality rates and baseline prevalence of vitamin A deficiency.

[3] It should be noted that there are a number of ongoing studies. The funnel plots did not indicate substantial asymmetry. The review concluded that firm policy recommendations could not be made until the studies are complete and contribute to the review.

[4] The rate reflects the number of events per 1000 years of child follow-up.

[5] Very high levels of statistical heterogeneity (I square 82%).

[6] The 95% confidence intervals include a substantial reduction in rate of mortality by 28% (translating to a reduction of 4 and 13 events/1000 child years in low and high risk populations), as well as a substantial increase in the mortality rate of 26% (translating to an increase of 3 and 12 events/1000 child years in low and high risk populations).

[7] The population for these outcomes includes all infants (i.e. term and pre-term).

[8] Only two of the included studies reported this outcome. The authors note that data reported on this outcome specified different timepoints and could not be formally used in the meta-analysis.

[9] In view of the high event rates for this outcome, the width of the confidence intervals lead to substantial variation in the absolute effect from a protective effect of vitamin A to an increase in the risk of vomiting.

[10] There was a high level of statistical heterogeneity (I square 80%).

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BACKGROUND

Description of the condition

Vitamin A deficiency is considered to be a major public health problem in the developing countries (WHO 2000; WHO 2009). Globally, 9.8 million pregnant women are affected by night blindness, with more than 19 million having low serum retinol concentrations (< 0.70 µmol/L). Night blindness affects 5.2 million preschool children and an estimated 190 million have low serum retinol concentrations. The prevalence of low serum retinol concentrations in pregnant women is highest in South-East Asia (17.3%) followed by Africa (13.5%), whereas the prevalence of night blindness is approximately the same in the two regions (9.9% in South-East Asia versus 9.8% in Africa) (WHO 2009).

Deficiency of vitamin A may be secondary to decreased ingestion, defective absorption and altered metabolism; or increased requirements. Factors such as low dietary fat intake or intestinal infections may also interfere with the absorption of vitamin A. Vitamin A deficiency is the most important cause of childhood blindness and contributes significantly to morbidity and mortality from common childhood infections. It is a significant contributing factor in the 2.2 million diarrhoea deaths each year among children under five years of age, and in the nearly one million measles deaths (SOWC 1998).

Description of the intervention

Vitamin A is an essential micronutrient that is required for the maintenance of normal functioning of the human body. It was the first fat soluble vitamin to be discovered and has been known to be an important dietary constituent for nearly a century (Hopkins 1912; McCollum 1915). Vitamin A is part of a family of compounds called retinoids; the naturally occurring retinoids are retinol, retinal and retinoic acid. For human physiology, retinol is the predominant form and 11-cis-retinol is the active form. The inactive retinoids, also known as provitamin A, are produced as plant pigments and are called carotenoids. Although many carotenoids occur in foods, approximately only 50% can be metabolized into the active retinoid forms. Beta-carotene, a retinol dimer, has the most significant provitamin A activity. Vitamin A is stored in the liver as retinyl esters and, when needed, is transported into blood where it is carried by retinol binding protein (RBP) for delivery to other tissues (Shenai 1993).

Vitamin A is important for the normal functioning of the visual system, immune response, gene expression, reproduction, embryogenesis and hematopoiesis (Sommer 1996). It is essential for the maintenance of normal epithelial tissues throughout the body (Wolbach 1925). Preformed vitamin A is found only in animal foods such as liver, fish and dairy products (such as milk, cheese and butter); it constitutes 65% to 75% of the dietary vitamin A intake. The remaining dietary vitamin A comes from carotenoids present in plant sources such as carrots, dark green leafy vegetables, red and orange fruits and red palm oil. The Recommended Dietary Allowances (RDAs) for vitamin A vary with age. For healthy breast-fed infants up to six months of age the average RDA is 400 µg/d, and for infants seven to 12 months of age the RDA is 500 µg/d. For children one to three years and four to eight years old, the RDA is 300 µg/d and 400 µg/d, respectively (DRI 2001).

Routine consumption of large amounts of vitamin A over a period of time can result in toxic symptoms which include liver damage, headaches, vomiting, skin desquamation, bone abnormalities, joint pain and alopecia. Hypervitaminosis A appears to be due to abnormal transport and distribution of vitamin A and retinoids that is caused by overloading of the plasma transport mechanisms (Smith 1976). A very high single dose can also cause transient acute toxic symptoms that may include a bulging fontanelle in infants; headaches in older children and adults; and vomiting, diarrhoea, loss of appetite and irritability in all age groups. Toxicity from ingestion of food sources of preformed vitamin A is rare (Hathcock 1997).

How the intervention might work

During pregnancy, women need additional vitamin A (an additional increment of 100 µg/day above basal requirements during the full gestation period) to sustain the growth of the fetus and to provide a limited reserve in the fetal liver as well as to maintain the woman's own tissue growth. Because therapeutic levels of vitamin A are generally higher than preventive levels, the safe intake level recommended during pregnancy is 800 µg retinol equivalents (RE)/day. Women who are or who might become pregnant should carefully limit their total daily vitamin A intake to a maximum of 3000 µg RE (10,000 IU) to minimize the risk of fetal toxicity (WHO/NUT 1998). Infants have very low levels of vitamin A stored in the liver at birth and are dependent on breast milk as a source of vitamin A in the first few months of life. Thus, maternal vitamin A deficiency during lactation, early weaning or artificial feeding may result in vitamin A deficiency in infants (Underwood 1994). The physiologic vitamin A needs of infants born to vitamin A-adequate mothers and fed breast milk with adequate vitamin A (in excess of 30 µg/dL or 1.05 µmol/L) are met for at least the first six months of life (Underwood 1994). Because of the need for vitamin A to support the growth rate in infancy, which can vary considerably, a requirement estimate of 180 µg RE/d seems appropriate. Average consumption of human milk by such infants is about 750 ml/day during the first six months (WHO/NUT/98.1 1998). Assuming an average concentration of vitamin A in human milk of about 1.75 mmol/l, the mean daily intake would have to be about 375 µg RE, which is therefore the recommended safe level.

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Why it is important to do this review

The role of vitamin A supplementation in children greater than six months of age is well established (Beaton 1993; Imdad 2010; Rice 2004). Beaton and colleagues in their meta-analysis showed that vitamin A supplementation in children six months to five years of age significantly reduced mortality by 23% (Beaton 1993). A recent Cochrane Review concluded that two oral doses of 200,000 IU of vitamin A on consecutive days in children less than two years of age with measles were associated with a reduced risk of overall mortality (RR 0.18; 95% CI 0.03 to 0.61); similarly with pneumonia-specific mortality (RR 0.33; 95% CI 0.08 to 0.92) (Huiming 2005). The World Health Organization (WHO) recommends administration of vitamin A during vaccination contacts in order to prevent vitamin A deficiency (WHO 1998). The policy has been to supplement 100,000 IU of vitamin A at the earliest possible opportunity after six months of age. However, it has now been recommended that an additional 50,000 IU of vitamin A be administered with each of the diphtheria-tetanus-pertussis (DTP) and polio vaccinations, which are usually given at six, 10 and 14 weeks of age (Sommer 2002). National and regional programmes of vitamin A supplementation are in place in over 60 countries worldwide and target children greater than six months of age. These programs are not only highly effective in reducing mortality and morbidity but, in countries in which vitamin A deficiency constitutes a public health problem, the programmes appear to be among the most cost-effective public health interventions available. Such programs address child survival in children greater than six months of age; this group accounts for a quarter of under five years of age deaths. In order to address the major proportion of deaths in children under five, children less than six months of age should be targeted. Supplementation with vitamin A between one and five months of age has not been found to have a beneficial effect (Daulaire 1992; Rahman 1995; WHO/CHD 1998). Supplementation of neonates has been suggested as a feasible approach to bolstering body stores of vitamin A in early infancy and, therefore, having an impact on mortality and morbidity (Sommer 1995; Sugana 1978).

OBJECTIVES

To evaluate the role of vitamin A supplementation in term neonates in developing countries with respect to the prevention of mortality and morbidity.

We prespecified the following subgroups to investigate heterogeneity:

1. maternal vitamin A supplementation;
2. birth weight of neonates;
3. HIV status of the mother and infant;
4. dose and frequency of vitamin A used;
5. high baseline infant mortality;
6. co-morbidities;
7. timing of vitamin A supplementation (either within the first 48 to 72 hours or later).

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials, both individual and cluster randomised and irrespective of publication status and language, evaluating the effects of vitamin A supplementation in term neonates in developing countries were included in the review. Studies using factorial design and quasi-randomised trials were also included.

Types of participants

All term neonates (born between 37 to 42 weeks of gestational age) up to 28 days after birth were included.

Types of interventions

Supplementation with vitamin A within the first 28 days of life was compared against a control (placebo or no supplementation). Any trial with continued supplementation beyond the first 28 days of life was excluded from the review. Co-interventions, if any, should have been identical in the two groups.

Types of outcome measures

Primary outcomes

1. All-cause infant mortality at six and 12 months

Secondary outcomes

1. Cause-specific infant mortality associated with acute respiratory infections and diarrhoea at six and 12 months
2. Infant morbidity at six months of age, associated with acute respiratory infections and diarrhoea, measured as at least one episode of morbidity
3. Biochemical indicator values of vitamin A deficiency (vitamin A deficiency measured as serum retinol < 0.70 µmol/L)
4. Blindness and signs of xerophthalmia (Bitot's spots and corneal lesions)

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5. Mean haemoglobin level or anaemia defined as haemoglobin less than the age-specific cut-off value as stated by the authors

6. Adverse events reported in trials due to vitamin A toxicity such as bulging fontanelles, vomiting and diarrhoea

Search methods for identification of studies

See: Cochrane Neonatal Review Group methods used in reviews

We used the standard search strategy of the Cochrane Neonatal Review Group. The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 14 June 2010), EMBASE and MEDLINE (1966 to May 2010) via PubMed were searched using the following search terms: (Newborn OR infan* OR neonat*) AND (vitamin A OR retino*) Limit: publication type clinical trial.

We limited the searches to human studies. We did not apply any language restrictions. We also searched related conference proceedings for relevant abstracts. We contacted organizations and researchers in the field for information on unpublished and ongoing trials. We searched reference lists of all trials identified by the above methods. For further identification of ongoing trials the websites www.clinicaltrials.gov and www.anzctr.com were searched.

Data collection and analysis

Selection of studies

Two review authors, Batool Haider (BAH) and Zulfiqar Bhutta (ZAB), independently assessed all the potential studies we identified as a result of the search strategy for inclusion. We resolved any disagreement through discussion.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors (BAH and ZAB) extracted the data using the agreed form. We resolved discrepancies through discussion. Data were entered into the Review Manager software (RevMan 2008) and checked for accuracy.

Assessment of risk of bias in included studies

Two review authors (BAH and ZAB) independently assessed the risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). We resolved any disagreement by discussion.

(1) Sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence, if it was in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk (adequate) (any truly random process, e.g. random number table; computer random number generator);
- high risk (inadequate) (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal the allocation sequence if in sufficient detail to determine whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk (adequate) (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk (inadequate) (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk.

(3) Blinding (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Studies were judged at low risk of bias if they were blinded or if we judged that the lack of blinding could not have affected the results.

We assessed the methods as:

- low risk (adequate), high risk (inadequate) or unclear risk for participants;
- low risk (adequate), high risk (inadequate) or unclear risk for personnel;
- low risk (adequate), high risk (inadequate) or unclear risk for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total number of randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. We assessed methods as:

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- low risk (adequate);
- high risk (inadequate);
- unclear risk.

(5) Selective reporting bias

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk (adequate) (where it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (inadequate) (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest were reported incompletely and so cannot be used; the study failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk.

(6) Other sources of bias

We described for each included study any important concerns we have about other possible sources of bias. We assessed whether each study was free of other problems that could put it at risk of bias as:

- yes;
- no;
- unclear.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). We explored the impact of the overall risk of bias by undertaking sensitivity analysis for primary outcomes. We considered a study to be of high quality if it was judged to have adequate sequence generation and allocation concealment, with either adequate blinding or methods for dealing with incomplete outcome data.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratios or rate ratios with 95% confidence intervals (CI).

Continuous data

There were no continuous outcomes in this review.

Unit of analysis issues

There were two cluster randomised trials (Klemm 2008; West 1995) included in this review. Klemm et al reported that the observed design effect was 0.9%. In West 1995, the 95% confidence intervals (CIs) of the effect estimates were inflated by 10% to account for the impact of design on the study findings. We estimated that the 10% increase in the 95% CIs gave an intracluster correlation coefficient (ICC) of 0.04 for the cohort of infants administered vitamin A.

Data synthesis

We analysed the data using a generic inverse variance approach to meta-analysis, using Review Manager software (RevMan 2008), and generated risk ratio or rate ratio estimates with 95% CIs for the dichotomous outcomes. For this approach, the data were entered as natural logarithms (as log risk ratios and SE of log risk ratio or log rate ratios and SE of log rate ratio) for each individual study, with data either extracted from the published papers or obtained from the authors if not presented in the papers. Data used for the infant mortality analyses along with their source are presented in 'Additional tables'. We used the fixed-effect method for combining data where trials were examining the same intervention and the trial populations and methods were judged to be sufficiently similar.

The review objective was to evaluate the effect of vitamin A supplementation in term neonates. The studies included in this review had enrolled all births that were identified in their study settings without using a restriction for gestational age, of either < 37 or ≥ 37 weeks, which would have allowed us to use the term data only. Birthweight was used as a criterion in two studies: Benn 2008 enrolled normal birthweight neonates (birthweight ≥ 2500 g) and Benn 2010 recruited low birthweight neonates (birthweight < 2500 g) only. Data for term neonates was presented separately only in the published paper of one study, for the infant mortality outcome at six months (Klemm 2008), whereas mortality data for term neonates only for other studies was obtained by contacting the study authors. Information about the gestational age was not available in West 1995 (Keith West; personnel communication 2008). Considering the small number of studies included in the review and the availability of data for primary outcomes, we analysed data for term neonates, where available, followed by the analysis for all infants. For all secondary outcomes, data in published papers were presented for all infants together and have been analysed as such. As the inclusion criterion of Benn 2008 was birthweight at least 2500 g, we assumed that a greater proportion of neonates would be term babies and have analysed its data as such in our term neonate analysis. We used the term 'all infants' to refer to aggregated term and preterm infants data throughout this review.

There were two studies which had maternal supplementation with vitamin A, either in the postpartum period (Malaba 2005) or dur-

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ing pregnancy (Klemm 2008). Malaba et al randomised mother-infant pairs to the four treatment arms (described in detail in the table 'Characteristics of included studies') whereas Klemm et al randomised neonates within each of three previously randomised treatment arms of a maternal supplementation trial of vitamin A. This resulted in two neonatal treatment arms in Klemm 2008 which were balanced across the maternal supplementation arms. Both studies reported no significant interaction between maternal and neonatal supplementation with vitamin A and we have used data for all neonates included in these studies on the basis of their randomisation to the neonatal vitamin A intervention or control group.

Subgroup analysis and investigation of heterogeneity

We measured heterogeneity among the trials by calculating the I^2 statistic. Values of the I^2 statistic greater than 50% were considered to represent substantial heterogeneity, in which case we planned to explore heterogeneity by undertaking prespecified subgroup analysis. However, the small number of studies included in the review precluded any evaluation of heterogeneity, when identified. We planned to investigate publication bias for outcomes with more than 10 included studies. However, we did not investigate the presence of this bias as the number of studies included was small.

RESULTS

Description of studies

Included studies

Seven studies including 51,446 neonates were included in this review.

The study by Humphrey et al was conducted in a single tertiary care hospital in Indonesia (Humphrey 1996) as a safety trial for vitamin A supplementation at the time of birth. This was a randomised double blind placebo controlled trial of 2067 infants with birthweight > 1500 g and without any critical illness. The infants were randomly assigned to receive a single oral dose of vitamin A (50,000 IU) or placebo within 24 hours of delivery. The two groups were similar at baseline for maternal, infant and household characteristics.

The study conducted by West et al (West 1995) in Nepal was part of a large cluster randomised, double blind, placebo controlled trial of vitamin A supplementation in preschool children. A total of 11,918 infants less than six months of age, of which 1621 were neonates, were enrolled and administered vitamin A (50,000 IU in < one month old infants and 100,000 in one to five month old infants) or placebo. Baseline characteristics of the two groups were similar.

The study conducted in India by Rahmatullah et al (Rahmathullah 2003) was also a randomised, double blind, placebo controlled trial in which all live born infants resulting from pregnancies within the participating villages were eligible for inclusion. A total of 11,619 newborn infants born to consenting mothers who were residing in the study area were enrolled. Infants were given two doses of vitamin A or placebo with the first dose being administered within the first 48 hours of delivery and the second dose within 24 hours of the first dose. Baseline characteristics of the families, mothers and infants were similar between the treatment groups.

The Zimbabwe study (Malaba 2005) was a randomised, double bind, placebo controlled trial using a two by two factorial design. Mother-infant pairs were eligible for inclusion if the mother planned to reside in the study area after delivery. None of the two had any life threatening illness and the infant's birthweight was > 1500 g. Around 14,110 infant-mother pairs were enrolled within 96 hours of delivery and were assigned to either of the following groups: Aa (vitamin A supplementation to both the mother and infant), Ap (vitamin A to the mother and placebo to infant), pa (placebo to mother and vitamin A to infant) and pp (placebo to both the mother and infant). The vitamin A dose for mothers was 400,000 IU and for infants it was 50,000 IU. All the treatment groups were similar at baseline for maternal, household and other related variables.

The study conducted by Klemm et al in Bangladesh (Klemm 2008) was a cluster randomised, double bind, placebo controlled trial which was nested within an ongoing parent trial of vitamin A supplementation in pregnant women. All infants born to consenting mothers of the original trial were included in the current trial. A total of 15,948 infants were administered vitamin A (50,000 IU) or placebo at home as soon as possible after birth. Baseline characteristics of the mothers and infants in this study were comparable at baseline.

Two studies were conducted in Guinea Bissau by Benn et al. Benn 2008 was a randomised, double blind, placebo controlled trial which included 4345 normal birthweight infants (birthweight at least 2500 g). For births occurring at the national hospital or local health centres, mothers were invited to participate in the study at the time of Bacille Calmette-Guérin (BCG) vaccination. For home births, mothers were invited to participate at the time of their visit to the local health centres for BCG vaccination. All infants with birthweight at least 2500 g, without any serious medical condition or malformation, for whom parental consent was available were randomised to either oral drops of vitamin A (50,000 IU) or placebo. The treatment groups were similar at baseline for various baseline characteristics. The other study by these investigators was conducted in parallel with Benn 2008. Benn 2010 was a two by two factorial, randomised, double blind, placebo controlled trial in low birth weight neonates (birthweight < 2500 g). This study included 1736 neonates randomised to either 25,000 IU vitamin

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A or placebo, as well as to early BCG vaccine or the usual late BCG vaccine.
See the table 'Characteristics of included studies' for further details.

Ongoing studies

There are four ongoing studies that are being conducted in Pakistan, India, Ghana and Tanzania. All four studies are randomised, double blind, placebo controlled trials, with the one in Pakistan using a cluster randomised design.
The inclusion criteria for Pakistan 2008 were live born infants without congenital malformations or serious birth injury from all pregnancies within participating villages, with a sample size of 7,400 infants. The study was designed as an effectiveness trial with vitamin A delivery through the Lady Health Workers program of the government of Pakistan. Intervention included routine postpartum care and vitamin A supplementation (50,000 IU) to the newborn within 48 to 72 hours of birth whereas the control group received routine postpartum care only. Outcomes to be evaluated were all-cause and cause-specific infant mortality at six months, incidence of serious infections (sepsis, pneumonia and diarrhoea), measurement of serum retinol values and rates of breastfeeding in the two groups. Recruitment and follow up for this study have been completed and data analysis is in progress.
The studies being planned in India, Ghana and Tanzania also aim to evaluate the effect of supplementation of 50,000 IU of vitamin A against control. The Indian study is being conducted in two districts in the state of Haryana with an estimated sample size of 40,200 neonates (India 2010). All births in the study area contacted by the enrolment team within the eligible age window and with the parent's consent to participate will be included. The eligible age window has been defined as up to 60 hours after birth. Outcomes that will be evaluated include infant mortality at six months, mortality in the neonatal period (during the first month of life); incidence of severe morbidity, defined as hospitalizations due to any illness in the first six months of infancy; potential adverse effects of vitamin A; and vitamin A status in a subgroup of newborns at two weeks and three months of age and their caregivers.
The methodologies of the studies in Ghana and Tanzania were found to be similar. The Ghana study will be conducted in seven contiguous districts in the Brong Ahafo region of central rural Ghana (Ghana 2010) with a target sample size of 28,000 neonates. The Tanzanian study will be conducted in Dar-es-Salaam and the Kilombero and Ulanga districts in Ifakara (Tanzania 2010). The estimated sample size for this study is 32,000 neonates. Inclusion criteria in both studies are all births in the study area that are contacted by the study team on the day of birth or in the next two days. Both singleton and multiple births are eligible for inclusion and each infant will be provided a unique identification number. Intervention includes vitamin A 50,000 IU once orally within the first three days of life, keeping a minimum period of two hours between birth and dosing. Similar outcomes will be evaluated in the two studies, which are all-cause infant mortality assessed at six months of age, all-cause neonatal mortality assessed at one month of age, incidence of severe morbidity defined as hospitalisations due to any illness in the first six months of infancy, potential adverse effects of vitamin A, and vitamin A and C reactive protein (CRP) status in a subsample of infants at two weeks and three months of age.
See the table 'Characteristics of ongoing studies' for further details.

Excluded studies

Two studies were excluded from the review (Bezzera 2009; Bhaskaram 1998). Bezzera 2009 included vitamin A supplementation of mothers only in the immediate postpartum period; their neonates were not supplemented. Bhaskaram 1998 supplemented mothers only with vitamin A within 24 hours of delivery while all neonates were given oral poliovirus vaccine (OPV) between 48 and 72 hours after birth.

Risk of bias in included studies

Three studies adequately randomised neonates to the treatment groups (Benn 2008; Benn 2010; Malaba 2005) with a clear description of the method used for generating the randomisation sequence. Four studies did not provide sufficient details to allow judgement of the adequacy of their methods (Humphrey 1996; Klemm 2008; Rahmathullah 2003; West 1995). The method of allocation concealment was clearly described in four studies (Benn 2008; Benn 2010; Humphrey 1996; Malaba 2005) whereas it was not described in sufficient detail in Klemm 2008, Rahmathullah 2003 and West 1995. Blinding of participants, study personnel and outcome assessors was clearly described and achieved in all included studies. The post randomisation attrition and exclusion of participants was: 1.6% (Benn 2008), 18.7% (Benn 2010), 11% (Humphrey 1996), 7% (Klemm 2008), 41.8% (Malaba 2005) and 18.9% (Rahmathullah 2003), with reasons for attrition and exclusion of the participants described in the papers. Exclusion and attrition were 1.04% in West 1995 and details of these were not provided. Evaluation of selective outcome reporting by reviewing either trial registration documents, if available, or methodology in published papers showed that all trials have reported their findings for prespecified or expected outcomes except for Humphrey 1996 where it was unclear. We identified three trials with potential high risk of other bias: Benn 2008 and Benn 2010 conducted post hoc analyses after assuming that vitamin A might be more beneficial to boys whereas Klemm 2008 was terminated after randomisation of two-thirds of the planned number of infants due to the significantly higher mortality in the control group. Malaba 2005 was found to be free of other bias and the risk of other bias was uncertain in the remaining three trials due to insufficient information (Humphrey 1996; Rahmathullah 2003; West 1995).

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See the table 'Characteristics of included studies' for further details on risk of bias in included studies. A graphical presentation of our individual judgments per item per study is provided in Figure 1 and a summary graph is given in Figure 2.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

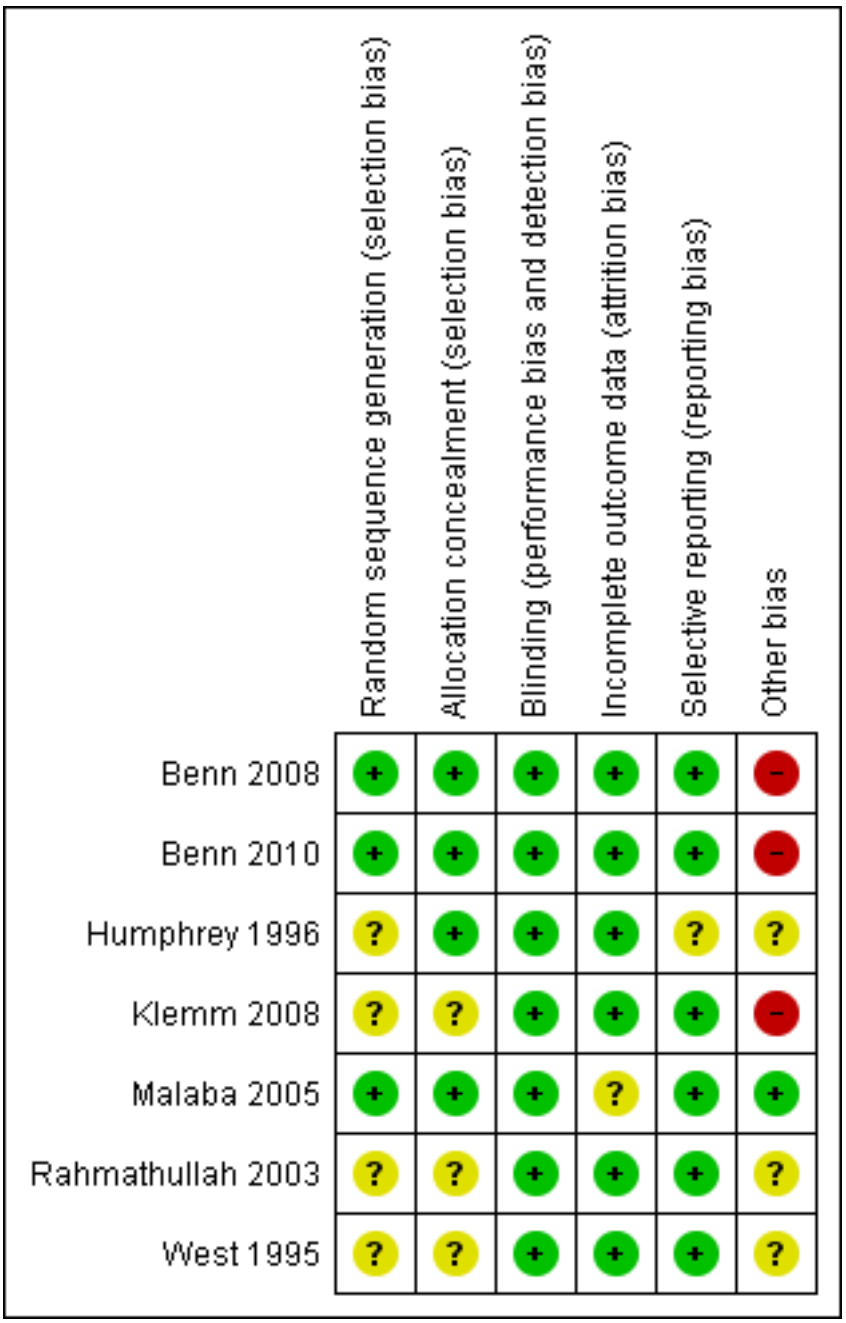

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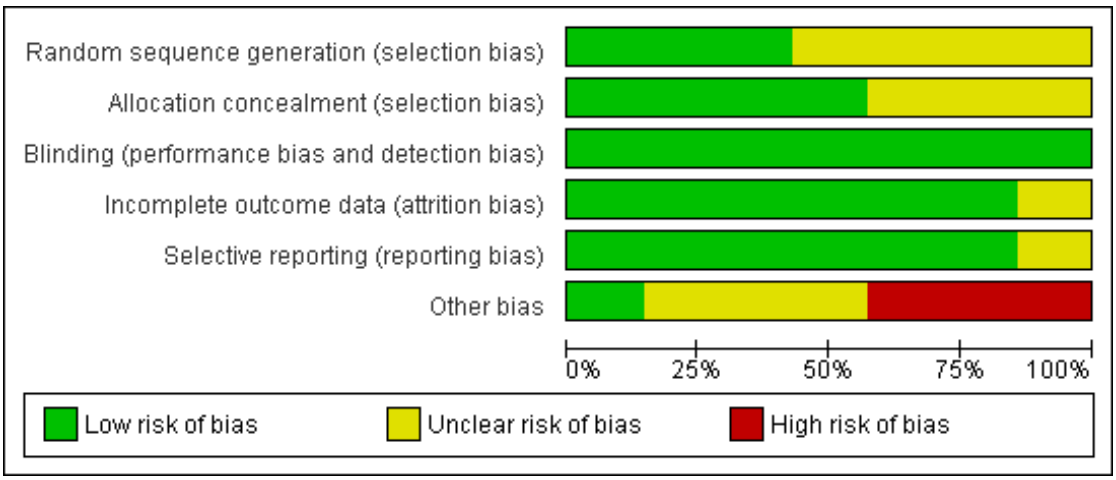
Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Effects of interventions

See: **Summary of findings for the main comparison** Neonatal vitamin A supplementation versus control for the prevention of mortality and morbidity in term neonates in developing countries
A summary of findings table based on the outcomes in term neonates has been included in this review, which is in accordance with the methodology recommended by GRADE (Summary of findings for the main comparison).

Neonatal vitamin A supplementation versus placebo

Primary outcomes

All-cause infant mortality at six months of age

An overview of the type and source of data for this outcome is presented in Table 1.
Six included studies (Benn 2008; Benn 2010; Humphrey 1996; Klemm 2008; Malaba 2005; Rahmathullah 2003) measured infant mortality at six months of age. West 1995 measured mortality at four months of age and this data has been included in the six month mortality analysis.

All-cause infant mortality at six months of age: risk ratios based on cumulative risk (%) (Outcome 1.1)

Data from five studies were measured as risk ratios based on cumulative risk.
The pooled estimate of data for term infants from three studies (Humphrey 1996; Klemm 2008; Malaba 2005) suggests that the risk of death from any cause at six months of age for neonates who were supplemented with vitamin A is 18% lower than control, which is statistically significant (typical RR 0.82; 95% CI 0.68 to 0.99) (Analysis 1.1.1). The level of statistical heterogeneity in this analysis was 63%. As the number of studies included was small, a subgroup analysis to investigate heterogeneity was not considered reliable. Given substantial statistical heterogeneity and the small number of included studies, these findings should be interpreted with caution.
The pooled estimate of the data for all infants from five studies (Humphrey 1996; Klemm 2008; Malaba 2005; Rahmathullah 2003; West 1995) showed a statistically significant reduction of 14% in the risk of death from any cause for neonates supplemented with vitamin A as compared to control (typical RR 0.86; 95% CI 0.77 to 0.97). The level of statistical heterogeneity for this analysis was less than 50% (I^2 39%) (Analysis 1.1.2).
There was only one high quality study included in these analyses (Malaba 2005), hence a sensitivity analysis on the basis of study quality was not undertaken.

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All-cause infant mortality at six months of age: rate ratios (per years of follow up) (Outcome 1.2)

Data from four studies were analysed as rate ratios (per year of follow up).

Pooled estimates for term neonates from Benn 2008 and Rahmathullah 2003 showed no evidence of a significant effect on the rate of death from any cause at six months of age in those that received vitamin A as compared to control (typical rate ratio 0.91; 95% CI 0.73 to 1.13) (Analysis 1.2.1). Analysis for all infants data from four studies (Benn 2008; Benn 2010; Rahmathullah 2003; West 1995) also did not reach statistical significance (typical rate ratio 0.91; 95% CI 0.77 to 1.06) (Analysis 1.2.2). The levels of statistical heterogeneity were: I^2 statistic 51% and 28% for term and all infants analyses, respectively.

Analysis of two high quality studies showed similar effects of vitamin A on the rate of death at six months as compared to control (typical rate ratio 0.89; 95% CI 0.75 to 1.05) (Rahmathullah 2003; Benn 2008; Benn 2010) (data not shown).

All-cause infant mortality at 12 months of age (Outcomes 1.3 and 1.4)

An overview of the type and source of data for this outcome is presented in Table 2.

Four included studies (Benn 2008; Benn 2010; Humphrey 1996; Malaba 2005) measured infant mortality at 12 months of age.

Analysis of term neonate data from two studies as rate ratios (Benn 2008; Humphrey 1996) showed no evidence of a significant effect on infant mortality from any cause at 12 months of age in neonates supplemented with vitamin A as compared to control, with statistical heterogeneity of 82% (typical rate ratio 0.95; 95% CI 0.72 to 1.26) (Analysis 1.4). Further subgroup analysis was not undertaken due to the small number of studies included. The pooled estimate for all infants data from four studies also showed no evidence of a significant effect of supplementation of neonates with vitamin A on infant mortality at 12 months of age compared to controls (typical risk ratio 1.02; 95% CI 0.87 to 1.20; typical rate ratio 1.03; 95% CI 0.87 to 1.23) (Analysis 1.4 and 1.4.2). The level of statistical heterogeneity was lower than 50% (I^2 49% for both risk and rate ratios). Three high quality studies (Benn 2008; Benn 2010; Malaba 2005) showed similar effects on infant mortality at 12 months of age (typical risk ratio 1.07; 95% CI 0.91 to 1.27) (data not shown).

Secondary outcomes

Cause-specific infant mortality at six months of age: diarrhoea and acute respiratory infections (Outcomes 1.5 and 1.6)

Infant mortality related to diarrhoea and acute respiratory infections at six months of age was measured by two studies (Humphrey 1996; Rahmathullah 2003). Data for all infants for Humphrey 1996 were measured as risk ratios based on cumulative risk, which showed no significant effect of vitamin A supplementation on diarrhoea and respiratory infections as compared to control (diarrhoea-specific infant mortality: risk ratio 0.20; 95% CI 0.02 to 1.68; and acute respiratory infection-specific infant mortality: risk ratio 0.66; 95% CI 0.11 to 3.91). Data for all infants from Rahmathullah 2003 were presented as rate ratios (per years of follow up) and showed a similar non-significant effect of vitamin A on the rate of diarrhoea-specific and acute respiratory infection-specific infant mortality at six months of age as compared to control (diarrhoea-specific infant mortality: rate ratio 0.67; 95% CI 0.32 to 1.39; and acute respiratory infection-specific infant mortality: rate ratio 1.00; 95% CI 0.56 to 1.79).

Cause-specific infant mortality at 12 months of age: diarrhoea and acute respiratory infections (Outcomes 1.7 and 1.8)

Infant mortality related to diarrhoea and acute respiratory infections at 12 months of age was measured by three studies (Benn 2008; Humphrey 1996; Malaba 2005).

Data for all infants for Humphrey 1996 were measured as risk ratios based on cumulative risk and showed no evidence of a significant effect of vitamin A on death due to diarrhoea and acute respiratory infections as compared to control (diarrhoea-specific infant mortality: risk ratio 0.40; 95% CI 0.08 to 2.03 and acute respiratory infection-specific infant mortality: risk ratio 0.66; 95% CI 0.11 to 3.95). Benn 2008 and Malaba 2005 analysed data for all infants as rate ratios. Pooled data suggested no evidence of a significant effect of vitamin A on diarrhoea-specific and acute respiratory infections-specific infant mortality at 12 months of age as compared to control (typical rate ratios: 1.32; 0.80 to 2.16; I^2 0%; and 1.10; 0.48 to 2.50; I^2 0%, respectively).

Cause-specific infant morbidity at 6 months of age: diarrhoea and acute respiratory infection (Outcomes 1.9 and 1.10)

Two trials (Malaba 2005; Rahmathullah 2003) measured infant morbidity at six months of age as rate ratios (per year of follow up). Pooled estimates showed no significant effect of vitamin A as compared to control on the rate of diarrhoea and acute respiratory infections in infants at six months of age (typical rate ratio: 1.05; 0.99 to 1.10; I^2 0%; and 1.01; 95% CI 0.96 to 1.05; I^2 85%, respectively). A subgroup analysis to investigate heterogeneity was not considered due to the small number of studies contributing data to this analysis.

Vitamin A deficiency (Outcomes 1.11 and 1.12)

Vitamin A deficiency defined as serum retinol value < 0.70 µmol/L was available for all infants from one study only (Benn 2008), which showed no evidence of a significant effect of vitamin A

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supplementation on vitamin A deficiency as compared to control (at 6 weeks: risk ratio 0.94; 0.75 to 1.19; and at four months: risk ratio: 1.02; 0.64 to 1.62).

Anemia (Outcome 1.13)

The impact on anaemia was measured in only one study (Malaba 2005), for all infants born to both HIV positive and negative women. Vitamin A supplementation in neonates did not lead to a significant impact on anaemia (haemoglobin (Hb) < 105 g/L) at 8 to 14 months of age (risk ratio 0.97; 95% CI 0.87 to 1.07) compared to control.

Adverse events (Outcomes 1.14 and 1.15)

Data for adverse events in all infants during the first 48 to 72 hours could be pooled only from two studies (Benn 2008; Humphrey 1996), and only one study (Benn 2008) presented adverse events at one month of age. Pooled estimates suggested no evidence of a significant increase in adverse events during the first 48 to 72 hours, specifically bulging fontanelle (typical risk ratio 1.38; 95% CI 1.04 to 1.82), diarrhoea (typical risk ratio 0.92; 95% CI 0.77 to 1.09) and vomiting (typical risk ratio 0.88; 95% CI 0.74 to 1.05), in the vitamin A group versus the control group. Benn 2008 showed no evidence of a significant increase in adverse events during the first month post supplementation (risk ratio diarrhoea 1.07; 0.46 to 2.51; and vomiting 1.22; 0.57 to 2.58).

Other outcomes

The included studies did not measure the impact of neonatal vitamin A supplementation on blindness and xerophthalmia.

DISCUSSION

The objective of this review was to evaluate the effect of supplementing term neonates with vitamin A as compared to unsupplemented controls. As the term neonatal outcome data were only available for a small number of studies, and then for infant mortality outcomes only, we analysed and presented estimates for both term neonates (where specified) and all infants for the various prespecified outcomes. Our analysis for all infants provided evidence of a 14% (95% CI 3% to 23%) reduction in the risk of death at six months of age in the vitamin A supplemented group as compared to the controls. This was statistically significant. Analysis of the term neonatal outcome included data from a subset of studies included in the all infant analysis and also showed a significant reduction in the risk of death in the first six months of life (reduction of 18%; 95% CI 1% to 32%). These findings should be interpreted with caution due to the small number of studies contributing data to these analyses, statistical heterogeneity and wide confidence intervals that are close to the null effect. Three studies (Benn 2008; Benn 2010; Rahmathullah 2003) had analysed data as rates (per year of follow up) which precluded their inclusion in this analysis. They have been analysed separately, whereas the study by West et al did not include information on gestational age. Further assessment of the effect in term neonates is needed, with data for all studies included in the review.

Analysis of the effect on infant mortality at 12 months of age of vitamin A supplementation in neonates provided no evidence of a significant effect on this outcome. Of four included studies, only one by Humphrey et al in Indonesia (Humphrey 1996) showed a highly significant effect on mortality at the end of the first year of life. Overall, the review findings suggest a potential effect of this intervention in the first half of infancy only.

Deficiency of vitamin A is a major nutritional concern in many countries of the world. All studies included in this review were conducted in developing countries with varying levels of vitamin A deficiency and infant mortality. The first trial of vitamin A in neonates was conducted as a safety trial in Indonesia (Humphrey 1996). This trial had shown significant reduction in the risk of mortality, with a difference in survival between the groups notable after the first month of life and becoming consistent after four months of age. However, maternal serum retinol levels from a subset of this study population showed mean (± SD) levels of 1.79 (± 0.53) and 1.75 (± 0.56) µmol/L in the vitamin A and control groups respectively, suggesting little vitamin A deficiency. The infant mortality rate in the control group (7.2 per 1000 child years) was well below that in the general population and the authors state that the families included in their study were relatively privileged (Humphrey 1996). It has been suggested that though the serum retinol levels were adequate, this finding does not preclude low hepatic reserves in this study group (Tielsch 2008a). Of the other included trials, two were conducted in India (Rahmathullah 2003) and Bangladesh (Klemm 2008), which are characterized by high infant mortality and vitamin A deficiency. The trial in India showed a reduction of 22% in the risk of infant mortality at six months whereas the trial in Bangladesh showed a 15% reduction in the vitamin A group compared with the control group. In the Indian setting, 5% to 6% of included women reported a history of night blindness, which is a clinical manifestation of vitamin A deficiency, and it was not significantly different between the two groups (P = 0.26). The authors noted that the impact on mortality was evident from two weeks of age and continued until three months, after which no further effect was observed. Similar observations were noted in the Bangladesh trial, which reported a difference in the mortality of infants as early as after the first week of life that persisted till four months of age. There were approximately 9.5% of the pregnant women in each group who reported night blindness in their most recent pregnancy. A subsample of this study population was measured for serum retinol in the first trimester and showed a suboptimal vitamin A status (defined as

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serum retinol < 1.05 µmol/L) in approximately 41% of women in the vitamin A group and 36% of women in the control group. These findings of an effect of vitamin A on the risk of mortality between the early weeks of life until four months does indicate a common biological mechanism of vitamin A.

Conflicting results were shown by studies conducted in Nepal, Zimbabwe and Guinea Bissau. The Nepal trial (West 1995) was conducted as part of a larger vitamin A supplementation trial in preschool children. The infants supplemented in the neonatal period did not show a significant effect on infant mortality, which was evaluated at four months of age. To note, this study setting was characterized by endemic vitamin A deficiency and high infant mortality. This finding was in contrast to findings from other studies conducted in similar settings. Studies conducted in Zimbabwe (Malaba 2005) and Guinea Bissau (Benn 2008) reported non-significant effects of vitamin A on both six and 12 months infant mortality outcomes. Infant mortality was measured in the other trial by Benn et al in Guinea Bissau (Benn 2010) at 12 months, which also showed no effect on the outcome. The vitamin A status of mothers provided evidence of minimal deficiency in these study settings with mean (± SD) serum retinol values in a subset of Zimbabwean women in the control group of 1.09 (± 0.29) and 1.19 (± 0.42) µmol/L at six weeks postpartum. In Guinea Bissau, less than 1% women were found to have low retinol binding proteins (retinol binding proteins < 1.11 µmol/L). This study also measured serum retinol values in infants at six weeks and four months of age and showed no evidence of an effect of vitamin A supplementation on vitamin A deficiency. An important feature of this trial was that all eligible children were provided free consultations and essential drugs for any illness during the first year of life. The mechanism through which vitamin A supplementation in children older than six months of age improves survival has partly been explained by a reduction in the severity rather than the incidence of infections (Sommer 1996). We believe that provision of free consultations and essential drugs for illnesses in the Guinea Bissau trial masked any beneficial effect of vitamin A supplementation that would have occurred through reducing severe illness episodes. The reasons for possible differences in the results of vitamin A supplementation trials conducted in different geographic regions are uncertain and could be a chance observation. However, these findings could represent genuine differences in population attributable risks of micronutrient deficiencies. The studies included neonates of mothers with varying levels of baseline vitamin A deficiency, both low birth weight and normal birth weight neonates and varying rates of baseline infant mortality. These factors could affect the generalizability of study findings. It should be noted that in contrast to the observed benefits of vitamin A supplementation among mothers in Nepal (West 1999), a large trial of maternal vitamin A supplementation in Ghana (Kirkwood 2010) did not show any benefits.

Reasons for these conflicting findings are unclear and there is no clear indication of the biological mechanisms through which vitamin A could lower the risk of death when given in the neonatal period. Various mechanisms have been proposed. Newborns have marginal reserves of vitamin A in their liver and they depend on breast milk as a source of this vitamin in the first few months of life. Hence, low maternal vitamin A levels translate into vitamin A deficiency in the newborns (Underwood 1994). Deficiency of vitamin A could also begin very early in life with the colostrum being discarded or breastfeeding being inadequate. Colostrum and early breast milk have been found to be very rich sources of vitamin A, which can significantly augment vitamin A stores in the neonates (Wallingford 1986). Along with inadequate breastfeeding, introduction of artificial feeds also hinders with the establishment of good breastfeeding practices, thereby denying infants of this critical source of vitamin A throughout the breastfeeding period (Haskell 1999). Artificial feeds early in life also increase the risk of gastrointestinal infections in these infants. Vitamin A supplementation has also been proposed to have an impact on infant mortality through the development and maintenance of the integrity of the intestinal and respiratory epithelia, and enhanced local and systemic immunity (Sommer 1996; Tielsch 2007). These pathways may provide an explanation of the effect in settings where the practice of discarding colostrum, inadequate breastfeeding or artificial feeds and infections are common. Alternatively, the early initiation of feeding of colostrum and exclusive breastfeeding could explain an absence of a beneficial effect of vitamin A received as a supplement. However, in this review we could not study these proposed mechanisms as only a few included studies presented limited information on breastfeeding practices and the use of artificial feeds.

There has been considerable debate on the issue of supplementing neonates with vitamin A due to conflicting findings from the studies and variability in the results of pooled analyses (Abrams 2008; Bhutta 2008; Gogia 2009; Sachdev 2008; Tielsch 2008a). The current review includes data from several new studies published since these earlier reviews and additional data that were obtained by contacting the study authors. Our findings corroborate those published in the earlier Lancet Undernutrition Series (Bhutta 2008) that included three neonatal supplementation trials published until then and used available data for analysing infant mortality outcomes separately at six months and 12 months. It showed a reduction of 20% (95% CI 4% to 34%) in the vitamin A supplemented group compared to the unsupplemented control group at six months of age. The earlier review also showed a non-significant impact of vitamin A on infant mortality at 12 months of age compared to the unsupplemented control (RR 0.90; 95% CI 0.61 to 1.32). A similar review by Gogia et al (Gogia 2009) analysed infant mortality data from six trials by pooling all deaths between the period of initiation of intervention till the last follow up, either at six or 12 months, and suggested no protective effect on mortality during the first year of life (RR 0.92; 95% CI 0.75 to 1.12). We believe that such an approach would mask any bene-

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ficial effects of the intervention in early infancy and could also be influenced by routine vitamin A supplementation practices after six months of age in the given population. Given that vitamin A supplementation to infants after six months of age is relatively well established in developing countries, adjunctive benefits of neonatal vitamin A supplementation could provide complementary benefits in young infants.

Limited data were available for the outcomes of cause-specific mortality and morbidity; and vitamin A deficiency, measured as serum retinol values in infants. Data on adverse events, specifically bulging fontanelle, vomiting or diarrhoea, were also limited and showed no significant increase within the first 48 to 72 hours of supplementation. An evaluation of these outcomes is needed with the inclusion of data from all studies that have measured these outcomes and additional new trials that are being planned in Ghana (Ghana 2010), India (India 2010) and Tanzania (Tanzania 2010). These trials have been designed to evaluate the effect of 50,000 IU of vitamin A on infant mortality at six months of age, their primary outcome. Another smaller effectiveness trial in Pakistan (Pakistan 2008) has completed recruitment and follow up and the data are being analysed. These additional trials will greatly contribute towards the evidence base and consensus on the value or otherwise of neonatal vitamin A supplementation.

AUTHORS' CONCLUSIONS

Implications for practice

Considering the high burden of deaths of children under the age of five years in developing countries, and mortality in infancy being a major contributory cause, it is critical to obtain sound scientific evidence of the effect of vitamin A supplementation in the neonatal period on infant mortality and morbidity. Evidence provided in this review does indicate a potential beneficial effect of supplementing neonates with vitamin A at birth in reducing mortality in the first half of infancy. Considering the absence of a clear indication of the biological mechanism through which vitamin A could affect mortality in early infancy, substantial conflicting findings from individual studies in settings with potentially varying levels of maternal vitamin A deficiency and infant mortality; and given that data from at least four new trials will be available in the foreseeable future, we propose to delay any policy recommendations for neonatal vitamin A supplementation pending these findings.

Implications for research

Future research and trials should examine the effects of vitamin A supplementation in the neonatal period on infant mortality in the first half of infancy. These trials should also include measures of maternal micronutrient status (vitamin A deficiency), the effect of maternal vitamin A supplementation, dose of vitamin A, maternal HIV status, breastfeeding patterns and breast milk vitamin A concentrations. Efforts should be made to stratify effects by age after birth of vitamin A administration, prematurity and intrauterine growth retardation. Research should also be conducted to identify biologic mechanisms and indicators for vitamin A in reducing the risk of death and to explain the differences observed in vitamin A supplementation trials conducted in settings with varying levels of baseline vitamin A deficiency.

ACKNOWLEDGEMENTS

We would like to thank the trial authors who provided additional data for this review; the Cochrane Editorial Unit, particularly Toby Lasserson who provided statistical advice and drafted the summary of findings tables, Karla Soares-Weiser and Harriet MacLehose for comments on the 'Risk of bias' tables; and Furqan Bin Irfan who assisted in protocol writing. In addition, we would like to thank the staff at the editorial office of the Neonatal Cochrane Review Group for their support in the preparation of this review and, in particular, the Coordinating Editor Dr Roger Soll and Managing Editor Diane Haughton. We would also like to thank the peer reviewers who provided helpful feedback on the review.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Benn 2008

Methods	Randomised, double blind placebo controlled trial.
Participants	Inclusion criteria were infants weighing at least 2500 g at birth with no signs of overt illness or malformations. Infants were recruited at the time of BCG vaccination. Number of participants in vitamin A group was 2145 and that in the placebo was 2200
Interventions	0.5 ml vegetable oil, either containing 50,000 IU of vitamin A as retinyl palmitate and 10 IU vitamin E, or only 10 IU of vitamin E was given into the mouth of child at the time of BCG vaccination
Outcomes	Mortality at 12 month of age, cause specific mortality at 12 months of age, scar, in vivo and ex vivo PPD response to BCG, retinol binding protein (RBP) concentration at 6 weeks and 4 months of age (low RBP defined as serum retinol <0.70 micromol/L) and adverse effects (bulging fontanelle, hospitalizations, irritability, fever, frequent stools, vomiting, mother thinks the child is not well)
Notes	Study was conducted in 6 urban districts in capital of Guinea-Bissau which is classified as an area of subclinical vitamin A deficiency (by UNICEF) and high infant mortality. The HIV prevalence among women in the study area was 3-5% Since the authors did not have information about the gestational age at delivery and the inclusion criteria was infants with birth weight of at least 2500 g, we included data as such in the term neonate analysis assuming that a greater proportion of these were term infants

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "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" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "lots were folded, making it impossible to tell what was written on them before they were opened. A new envelope was not taken into use before the previous envelope had been completely emptied. The result of the randomisation was noted on the inclusion form and the lot was stapled to the inclusion form.", "The dark glass bottles

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Benn 2008 (*Continued*)

		were prepared at Skanderborg Pharmacy" and "The code was kept at the pharmacy until 12 months after the last child was included" Comment: probably done
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "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" and "Apart from the randomisation number, the bottles looked alike; we judged small differences in taste and colour of the contents as unimportant owing to the recipients" Comment: blinding of participants, study personnel and outcome assessors probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 1.6%. Reasons for attrition and distribution in the two groups were provided. Infant lost to follow up were similar to those who were followed in baseline anthropometric characteristics
Selective reporting (reporting bias)	Low risk	Comment: results of all expected outcomes were presented in several publications of the study
Other bias	High risk	A protocol was provided but post hoc analyses were conducted after assuming that Vit 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, two by two factorial trial.
Participants	Inclusion criteria were infants weighing < 2500 g at birth with no severe malformations. Number of participants in vitamin A group was 864 and that in the placebo was 872
Interventions	Neonates < 2500 g at birth were assigned to 25,000 IU vitamin A as retinyl palmitate and 10 IU vitamin E per 0.5ml oil or placebo which contained only 10 IU vitamin E per 0.5ml oil, as well as to early BCG vaccine or the usual late BCG vaccine

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Outcomes	Infant mortality and cause-specific infant mortality at 12 months
Notes	• Study was conducted in 6 urban districts in capital of Guinea-Bissau which is classified as an area having moderate to severe vitamin A deficiency (by WHO) and high infant mortality. • No evidence of an interaction between BCG and vitamin A supplementation in neonates (P=0.73). • Vitamin A was administered within the first 48 hours 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	Quote: "randomly allocated in a two by two factorial design" and"mother drew an envelope from a bag. Each bag was prepared... 12 marked "no BCG 6," and 12 marked "no BCG 7", "The numbers 6 and 7 indicated from which of two numbered bottles, 6 or 7, the child should receive treatment (that is, either 25 000 IU vitamin A or placebo) ." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "The envelopes were closed and non-transparent, making it impossible to identify the allocation before the envelopes were opened.", "The result of the randomisation was noted on the inclusion form and, furthermore, the lot name was stapled on the form." and "The code of which treatment was in which bottle was kept at the pharmacy until 12 months after the last child was included." Comment: probably done
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "numbers "6" and "7" indicated from which of two numbered bottles, "6" or "7," the child should receive treatment", "vitamin A and placebo bottles looked alike" and "assistant and the nurse who were responsible for the randomisation procedures had no idea which bottles contained vitamin A or which had placebo" and "follow-up assistants were unaware of the allocated treatment,

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Benn 2010 (*Continued*)

		Comment: blinding of participants, study personnel and outcome assessors probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions and attrition were 18.72%. Reasons and distribution in the two groups were provided. Numbers were balanced across the treatment groups
Selective reporting (reporting bias)	Low risk	Comment: All expected outcomes, as per protocol were 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 Vit 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

Humphrey 1996

Methods	Randomised placebo controlled trial.
Participants	All neonates within 24 hours of birth were eligible for inclusion. Very low birthweight babies (<1500 gm) and those with life threatening illnesses such as severe respiratory distress syndrome, major congenital anomalies, paralysis, hypoglycaemia, hypocalcaemia, clinical evidence of ischaemic hypoxia, or sepsis were excluded. A total of 2067 were enrolled within the 24-hour inclusion period
Interventions	One oral dose of 52 µmol vitamin A (as retinyl palmitate) plus 23 µmol vitamin E in the treatment group. Placebo (<0.10 µmol vitamin A + 23 µmol vitamin E) in the control group. Intervention n=1034 and placebo n=1033
Outcomes	Mortality at 6 and 12 months of age, cause specific mortality at 12 month of age, morbidity at 4 months of age, adverse effects of VAS (bulging fontanelle, vomiting, fever, loose stool, irritability, intracranial haemorrhage, resistive index), development at 3 years of age
Notes	• Infants born at Hasan Sadikin Hospital in Bandung, Indonesia, from June 18, 1992 to June 3, 1993 were considered. • Mean age of dosing was 16.2 (SD=8.2) hours, 88.2% were dosed in first 24 hours of life birth. • Treatment groups were comparable at baseline.

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Humphrey 1996 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "simple randomisation blocked within the birth weight strata" Comment: method used to generate the randomisation sequence is not described in sufficient detail to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "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" Comment: probably done
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "supplements were individually coded, odourless.....follow-up of infants in Indonesia" Comment: blinding of participants, study personnel and outcome assessors probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 11% and reasons for it were provided. Distribution was balanced in the two groups. Infants lost to follow up were not significantly different from those who were followed
Selective reporting (reporting bias)	Unclear risk	Comment: Insufficient information to permit judgement Adverse events were reported in a separate publication (Agoestina 1994)
Other bias	Unclear risk	Agoestina 1994 mentioned a protocol, but no further details were provided. Supported by a grant from John HopkinsUniversity and assistance from Hoffmann-LaRoche industry (Basel, Switzerland)

Klemm 2008

Methods	Community based double masked, cluster randomised, placebo controlled trial
Participants	Infants born to consenting mothers who were participating in the parent trial were eligible for inclusion in the study Vitamin A group infants whose mothers consented=8525 Placebo group infants whose mothers consented=8591 Infants of consenting mothers who had died before they could be supplemented by staff, those who were born outside of the study area, and infants who could not be reached to

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	receive a supplement after repeated staff visits during the first 30 days after birth were excluded
Interventions	Intervention= 50,000 IU of vitamin A or a placebo in oil given as soon as possible after birth
Outcomes	Infant mortality at 6 months of age and adverse effects
Notes	• The trial was nested into 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. The present study began in January 2004 in districts of Gaibandha and Rangpur, Bangladesh. • Randomisation of sectors was done in a manner to produce 2 infant supplementation groups that were balanced across the maternal supplementation trial arms. Interaction between maternal and vitamin A supplementation was non-significant. • Approx 84% supplemented within the first 48 hours 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	Quote: "cluster randomised" and "sectors were listed in geographically contiguous order and were randomised in blocks of 4" Comment: method used to generate the randomisation sequence is not described in sufficient detail to permit judgement
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient detail to permit judgement.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "sector-coded supplement", "supplements for both groups were opaque gelatinous capsules identical in shape, size, and colour containing edible oil"; "double-masked" Comment: blinding of participants, study personnel and outcome assessors probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions and attrition was 7%. Reasons and distribution in the two groups were provided. Attrition and reasons for attrition were balanced across the treatment groups

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Klemm 2008 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: results of all outcomes mentioned in methods section of the published paper and those in trial registration document were presented in the paper
Other bias	High risk	Study halted before conclusion because mortality on the placebo group was significantly higher than intervention group after 2/3 of infants were randomised. Results adjusted by cluster effect. Source of funding: John Hopkins University (GHS-A-00-03-00019-00), Bill and Melinda Gates Foundation

Malaba 2005

Methods	Randomised placebo controlled two by two factorial design trial
Participants	Mother and infant pairs enrolled within 96 hrs of delivery. Pairs were eligible if neither of the pairs have an acutely life threatening condition, the infant was a singleton with birthweight >1500gms, and the mother planned to stay in Harare after delivery Mothers and infants were assigned into the following 4 groups 1. Mothers received 400,000 IU vitamin A and infants received 50 000 IU vitamin A (Aa group)=3529 2. Mothers received 400,000 IU vitamin A and infants received placebo (Ap group)=3529 3. Mothers received placebo and infants received 50,000 IU vitamin A (Pa group)=3530 4. Both mothers and infants received placebo (Pp group)=3522
Interventions	Mothers received 400,000 IU vitamin A and infants received 50,000 IU vitamin A. Both treatment and placebo contained a soy oil base with vitamin E (50 IU per maternal capsule; 10 IU per infant capsule).
Outcomes	Infant mortality at 6 and 12 months, cause-specific infant mortality at 12 months, anaemia and haemoglobin in infants and MTCT of HIV in infants born to HIV positive mothers
Notes	• Zimbabwe is categorized by WHO as a high risk area for vitamin A deficiency. HIV is endemic in Zimbabwe nearly 25% are HIV infected. • From 25 November 1997 to 29 January 2000 in Harare, Zimbabwe. • Three-quarters of the pairs received their treatment dose within 24 hours, and 94% received it within 48 hours of delivery. • Interaction between maternal and infant vitamin A supplementation was not significant (P=0.60).
Risk of bias	

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Malaba 2005 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "study identification numbers were randomly allocated to the treatment groups by computer in blocks of 12", "A separate team at Johns Hopkins University prepared the study capsule packets" and "Lists linking the study number to the treatment were kept in sealed envelopes and encrypted computer files." Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: "numbers were printed on adhesive labels and affixed to amber-coloured ziplock plastic bags" and "capsules in the next sequential bag were administered..... files" Comment: probably done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "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" Comment: blinding of participants, study personnel and outcome assessors probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Exclusions and attrition were 41.8%. Reasons for exclusion included being HIV-positive or HIV-indeterminate at baseline or those who seroconverted. Reasons for attrition were not provided
Selective reporting (reporting bias)	Low risk	Comment: results of all expected outcomes were presented in various publications
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

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		was provided by the Rockefeller Foundation (New York) and BASF (Ludwigshafen, Germany)."

Rahmathullah 2003

Methods	Randomised, placebo controlled, community based trial.
Participants	Live born infants that resulted from all pregnancies within participating villages were eligible for participation. Pregnant women (>12 weeks) were identified for recruitment from a variety of sources. The infants were randomly assigned to receive either the intervention, or placebo Exclusions after randomisation were stillbirths, miscarriages, delivery more than 20 km outside the study area, and infants, who died before the study team reached
Interventions	Infants received 24,000 IU of vitamin A twice within a 24 hour interval, beginning within 48 hours of birth, or placebo
Outcomes	Infant mortality at 6 months, cause-specific mortality at 6 months, incidence of common morbidities and pneumococcal colonization
Notes	• Conducted between June 1998 and March 2001 in two rural districts of Tamil Nadu, southern India. • These areas are characterized by endemic vitamin A deficiency. • An expected infant mortality at 6 months of age of 52.5 per 1000 live births. • Approximately 80% of participants were supplemented within 48 hours of birth. • Treatment groups were comparable at baseline.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomisation was at the individual level, stratified by geographical area in blocks of four." Comment: method used to generate the randomisation sequence is not described in sufficient detail to permit judgement
Allocation concealment (selection bias)	Unclear risk	Quote: "For twins, the first born received the assigned treatment and the second born the other treatment. For triplets, the first two born infants were handled as twins and the third born received the originally assigned treatment." Comment: insufficient information provided to judge allocation concealment for singleton births. However, for triplets (only

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Rahmathullah 2003 (*Continued*)

		2 in the data set), allocation concealment did not hold
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "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" Comment: blinding of participants, study personnel and outcome assessors was probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions and attrition was 18.9%. Reasons and distributions in the two treatment groups were reported. Mortality in infants born alive but not enrolled was similar in treatment groups
Selective reporting (reporting bias)	Low risk	Comment: outcomes mentioned in the methods section were reported. All expected outcomes were presented in published reports
Other bias	Unclear risk	Supported by a grant from John Hopkins Universityand the Bill and Melinda Gates Foundation

West 1995

Methods	This trial was part of a large, cluster randomised, double masked, placebo controlled community trial in Nepal
Participants	Infants ≤5 months of age were eligible for inclusion. No exclusion criteria given
Interventions	Intervention group received an oral dose of vitamin A [15,000 RE (50,000 IU) in 3 drops of oil for neonates (< 1 mo of age) and 30,000 RE (100 000 IU) in 6 drops of oil for infants 1-5 mo of age or placebo [75 RE (250 IU) or 150 RE (500 IU), respectively]. A total of 11,918 infants (infants ≤5 months: intervention= 6086, control= 5832) were enrolled. Among these, the distribution of neonates was: intervention=791, control= 830
Outcomes	4 month mortality, cause specific mortality and adverse effect noted after 24 hours of dosing (vomiting, loose stools, fever, irritability, bulging fontanelles)
Notes	• Was conducted in district of Sarlahi, Nepal between September 1989 and December 1991. • Evaluated the effect of VAS every 4 month on preschool child mortality. • No information about gestational age and birth weight recorded and almost all neonates were supplemented after the first week of life (Keith West; personnel

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	communication 2008) • Treatment groups were comparable at baseline. • The 4-month mortality estimates have been included in the 6 month mortality analysis • This trial measured adverse effects approximately 24 hours after supplementation whereas 2 other trials reported adverse effects 48-72 hours after supplementation. Because of the difference in the timing of measurement of adverse effects, we did not include the 24 hour measurements from this trial in the analysis. This trial found no difference in the incidence of various adverse effects after 24 hours of supplementation in the two groups of neonates.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "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. " Comment: method used for the first random assignment is not described in sufficient detail to permit judgement
Allocation concealment (selection bias)	Unclear risk	Comment: It is unclear as the wards were assigned systematically
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "gelatinous capsules of identical appearance, size (8*16mm), and taste" and "double-masked" and "capsule codes were broken" (noted from methods section of the larger trial paper) Comment: blinding of participants, study personnel and outcome assessors was probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition among neonates was 1.04% reasons for which were not provided. All analyses 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)	Low risk	Comment: published reports included all expected outcomes.

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Other bias	Unclear risk	Supported by a grant from John Hopkins University and assistance from Hoffmann-LaRoche industry (Basel, Switzerland). A protocol is described but no details are provided

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

Study	Reason for exclusion
Bezzera 2009	This study included supplementation of mothers only with vitamin A supplements in the immediate postpartum period and there was no supplementation of neonates with vitamin A
Bhaskaram 1998	This study included supplementation of mothers only with vitamin A supplements within 24 hours of delivery while all neonates were given oral poliovirus vaccine (OPV) between 48 and 72 hours after birth

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

Ghana 2010

Trial name or title	Efficacy of newborn vitamin A supplementation in improving child survival in rural Ghana: generation of evidence necessary for informing global policy (Neovita)
Methods	Double blind, randomised, placebo controlled trial in 7 contiguous districts (Kintampo North, Kintampo South, Wenchi, Tain, Techiman, Nkoranza North and Nkoranza South) in the Brong Ahafo region of central rural Ghana
Participants	Inclusion criteria is all births in the study area that are contacted by the study team on the day of birth or in the next 2 days. Both singleton and multiple births are eligible for inclusion in this study and each infant will be provided with their own unique study identification number. Infants will be included even if they were not identified during pregnancy surveillance Exclusion criteria is if the neonate is unable to feed on offering feeds, as reported by the mother or the mother does not intend to stay in the study area for at least 6 months
Interventions	Intervention includes vitamin A 50,000 International Units (IU) once orally within the first 3 days of life keeping a minimum period of 2 hours between the birth and the dosing Placebo capsule of soy bean oil once orally within the first 3 days of life
Outcomes	All cause early infant mortality (0-5 months) assessed at 6 months of age, all cause neonatal mortality (0-1 month) assessed at 1 month, incidence of severe morbidity defined as hospitalisations due to any illness in the first 6 months of infancy, potential adverse effects of vitamin A such as bulging fontanelle, vomiting, irritability, fever, diarrhoea, inability to suck or feed, convulsions or any other condition that caused parents to be concerned, in the 3 days period following administration of the supplement, and vitamin A and C reactive protein (CRP) status of a subsample of infants at 2 weeks and 3 months of age

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Ghana 2010 (*Continued*)

Starting date	Anticipated date of first participant enrolment: Aug 16, 2010
Contact information	Karen Edmond London School of Hygiene and Tropical Medicine, Keppel St London, WC1E7HT, UK Email: karen.edmond@lshtm.ac.uk
Notes	Target sample size: 28000

India 2010

Trial name or title	Efficacy of Neonatal Vitamin A Supplementation in Improving Child Survival in Haryana, India: Generation of Evidence Necessary for Informing Global Policy (NeoVitA Trial)
Methods	Double blind, randomised, placebo controlled trial in two districts in the state of Haryana, India
Participants	Inclusion criteria is all births in the study area that are contacted by the enrolment team within the eligible age window (up to 60 hours of birth) and parent's consent to participate Exclusion criteria is neonate unable to feed on offering feeds, as reported by the mother or mother does not intend to stay in the study area for at least 6 months
Interventions	Intervention includes 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 of birth keeping a minimum period of 2 hours between the birth and the dosing Placebo capsules will contain minute amounts of vitamin E in soybean oil
Outcomes	Infant mortality at 6 months, mortality in the neonatal period (first month of life), incidence of severe morbidity defined as hospitalizations due to any illness in the first 6 months of infancy; bulging fontanelle, vomiting, irritability, fever, diarrhea, inability to suck or feed, convulsions or any other conditions that caused parents to be concerned, in the 3 day period following administration of the supplement; and vitamin A status in a subgroup of newborns and caregivers
Starting date	June 2010
Contact information	Nita Bhandari Society for Applied Studies New Delhi, Delhi, India, 110016 00 91 11 46043751-55 ext 201 Email: CHRD@sas.org.in
Notes	Estimated enrolment: 40200 Estimated study completion date: November 2013

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Pakistan 2008

Trial name or title	Feasibility study of delivering a neonatal dose of vitamin A through the Lady Health Workers (LHWs) program in Pakistan
Methods	Cluster randomised, double blind, placebo controlled trial in Sukkhur and Jehlum districts in Pakistan
Participants	Inclusion criteria is live born infants from all pregnancies within participating villages Exclusion criteria is a child born with congenital malformation, serious birth injury, birth asphyxia, serious infections, gestational age less than 32 weeks, birthweight less than 1500 gms and refuse to participate
Interventions	Intervention includes routine postpartum care and vitamin A supplementation (50,000 IU) to the newborn within 48-72 hours of birth Control group receives routine postpartum care and placebo.
Outcomes	All cause infant mortality at 6 months, cause-specific infant mortality at 6 months of age, serum retinol values, rates of breastfeeding and incidence of serious infections (sepsis, pneumonia and diarrhoea)
Starting date	January 2007
Contact information	Zulfiqar A Bhutta Division of Women & Child Health The Aga Khan University, Karachi 74800, Pakistan Email : zulfiqar.bhutta@aku.edu
Notes	Estimated enrolment: 7400 Expected completion date: April 2010

Tanzania 2010

Trial name or title	Efficacy of newborn vitamin A supplementation in improving child survival in Tanzania: generation of evidence necessary for informing global policy
Methods	Double blind, randomised, placebo controlled trial in Dar-es-Salaam, and Kilombero and Ulanga districts in Ifakara, Tanzania
Participants	Inclusion criteria is all births in the study area that are between two hours and two days of age, whose caretakers confirm of intention to remain in the study areas for a minimum of six months thereafter. Both singleton and multiple births are eligible for inclusion in this study and each infant will be provided with their own unique study identification number. Infants will be included even if they were not identified during pregnancy surveillance Exclusion criteria is if the neonate is unable to feed on offering feeds, the mother does not intend to stay in the study area for at least 6 months and women younger than 18 years old
Interventions	Intervention includes vitamin A 50,000 International Units (IU) as retinol palmitate and minute amounts of vitamin E in soybean oil, once orally within the first 3 days of life keeping a minimum period of 2 hours between the birth and the dosing Placebo capsule with minute amounts of vitamin E in soybean oil once orally within the first 3 days of life

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Tanzania 2010 (*Continued*)

Outcomes	Infant mortality assessed at 6 months of age, neonatal mortality (0-1 month) assessed at 1 month, incidence of severe morbidity defined as hospitalizations due to any illness in the first 6 months of infancy, potential adverse effects of vitamin A such as bulging fontanelle, vomiting, irritability, fever, diarrhoea, inability to suck or feed, convulsions or any other condition that caused parents to be concerned, in the 3 days period following administration of the supplement, and vitamin A and C reactive protein (CRP) status of a subsample of infants at 2 weeks and 3 months of age
Starting date	Anticipated date of first participant enrolment: July 1, 2010
Contact information	Honorati Masanja Ifakara Health Institute, PO Box 78373, Dar-es-Salaam, Tanzania Email: hmasanja@ihi.or.tz
Notes	Target sample size: 32,000

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DATA AND ANALYSES

Comparison 1. Neonatal vitamin A supplementation versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause infant mortality at 6 months: risk ratios based on cumulative risk (%, adjusted for clustering)	5		Risk Ratio (Fixed, 95% CI)	Subtotals only
1.1 Term infants	3	22721	Risk Ratio (Fixed, 95% CI)	0.82 [0.68, 0.99]
1.2 All infants	5	39040	Risk Ratio (Fixed, 95% CI)	0.86 [0.77, 0.97]
2 All-cause infant mortality at 6 months: rate ratios (per years of follow-up)	4		Rate Ratio (Fixed, 95% CI)	Subtotals only
2.1 Term infants	2		Rate Ratio (Fixed, 95% CI)	0.91 [0.73, 1.13]
2.2 All infants	4		Rate Ratio (Fixed, 95% CI)	0.91 [0.77, 1.06]
3 All-cause infant mortality at 12 months (all infants): risk ratios based on cumulative risk (%)	4	15731	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.87, 1.20]
4 All-cause infant mortality at 12 months: rate ratios (per years of follow-up)	4		Rate Ratio (Fixed, 95% CI)	Subtotals only
4.1 Term infants	2		Rate Ratio (Fixed, 95% CI)	0.95 [0.72, 1.26]
4.2 All infants	4		Rate Ratio (Fixed, 95% CI)	1.03 [0.87, 1.23]
5 Cause-specific infant mortality at 6 months (all infants): Diarrhea	2		(Fixed, 95% CI)	Totals not selected
5.1 Risk ratio	1		(Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Rate ratio	1		(Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Cause-specific infant mortality at 6 months (all infants): Respiratory infections	2		(Fixed, 95% CI)	Totals not selected
6.1 Risk ratio	1		(Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Rate ratio	1		(Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Cause-specific infant mortality at 12 months (all infants): Diarrhoea	3		(Fixed, 95% CI)	Subtotals only
7.1 Risk ratios	1		(Fixed, 95% CI)	0.40 [0.08, 2.03]
7.2 Rate ratios	2		(Fixed, 95% CI)	1.32 [0.80, 2.16]
8 Cause-speciifc infant mortality at 12 months (all infants): Respiratory infections	3		(Fixed, 95% CI)	Subtotals only
8.1 Risk ratios	1		(Fixed, 95% CI)	0.66 [0.11, 3.95]
8.2 Rate ratios	2		(Fixed, 95% CI)	0.97 [0.67, 1.42]
9 Infant morbidity at 6 months (rate ratio): Diarrhoea	2		Rate ratio (Fixed, 95% CI)	1.05 [0.99, 1.10]
10 Infant morbidity at 6 months (rate ratio): Respiratory infections	2		Rate ratio (Fixed, 95% CI)	1.01 [0.96, 1.05]

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11 Vitamin A deficient (serum retinol <0.70 micromol/L) at 6 weeks of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
12 Vitamin A deficient (serum retinol <0.70 micromol/L) at 4 months of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
13 Anaemia (haemoglobin <105g/L) at 8-14 months of age	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
14 Adverse events during the first 48-72 hours post supplementation	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Bulging fontanelle	2	3158	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.04, 1.82]
14.2 Diarrhoea	2	3159	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.77, 1.09]
14.3 Vomiting	2	3159	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.74, 1.05]
15 Adverse events during the first month post supplementation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
15.1 Diarrhoea	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Vomiting	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Neonatal vitamin A supplementation versus control, Outcome 1 All-cause infant mortality at 6 months: risk ratios based on cumulative risk (%, adjusted for clustering).

Review: Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries

Comparison: 1 Neonatal vitamin A supplementation versus control

Outcome: 1 All-cause infant mortality at 6 months: risk ratios based on cumulative risk (%, adjusted for clustering)

Study or subgroup	Favours vitamin A N	Control N	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Term infants						
Humphrey 1996	1011	1007	-0.9163 (0.4776)		4.2 %	0.40 [0.16, 1.02]
Klemm 2008	6109	6061	-0.2877 (0.1206)		65.5 %	0.75 [0.59, 0.95]
Malaba 2005	4253	4280	0.0862 (0.1773)		30.3 %	1.09 [0.77, 1.54]
Subtotal (95% CI)	**11373**	**11348**			**100.0 %**	**0.82 [0.68, 0.99]**
Heterogeneity: Chi² = 5.38, df = 2 (P = 0.07); I² =63%						
Test for overall effect: Z = 2.06 (P = 0.040)						
2 All infants						
Humphrey 1996	1034	1033	-0.9416 (0.4861)		1.6 %	0.39 [0.15, 1.01]
Klemm 2008	7953	7984	-0.1586 (0.0845)		52.1 %	0.85 [0.72, 1.01]
Malaba 2005	4309	4352	0.1133 (0.1717)		12.6 %	1.12 [0.80, 1.57]

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Study or subgroup	Favours vitamin A N	Control N	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Rahmathullah 2003	5363	5408	-0.2485 (0.1171)		27.1 %	0.78 [0.62, 0.98]
West 1995	819	785	0.0677 (0.2361)		6.7 %	1.07 [0.67, 1.70]
Subtotal (95% CI)	**19478**	**19562**			**100.0 %**	**0.86 [0.77, 0.97]**
Heterogeneity: Chi^2 = 6.57, df = 4 (P = 0.16); I^2 =39%						
Test for overall effect: Z = 2.39 (P = 0.017)						

Analysis 1.2. Comparison 1 Neonatal vitamin A supplementation versus control, Outcome 2 All-cause infant mortality at 6 months: rate ratios (per years of follow-up).

Review: Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries

Comparison: 1 Neonatal vitamin A supplementation versus control

Outcome: 2 All-cause infant mortality at 6 months: rate ratios (per years of follow-up)

Study or subgroup	log [Rate Ratio] (SE)	Rate Ratio IV,Fixed,95% CI	Weight	Rate Ratio IV,Fixed,95% CI
1 Term infants				
Benn 2008	0.131 (0.1948)		33.2 %	1.14 [0.78, 1.67]
Rahmathullah 2003	-0.2107 (0.1372)		66.8 %	0.81 [0.62, 1.06]
Subtotal (95% CI)			**100.0 %**	**0.91 [0.73, 1.13]**
Heterogeneity: Chi^2 = 2.06, df = 1 (P = 0.15); I^2 =51%				
Test for overall effect: Z = 0.87 (P = 0.39)				
2 All infants				
Benn 2008	0.13102826 (0.19420535)		16.8 %	1.14 [0.78, 1.67]
Benn 2010	0.0099 (0.1796)		19.7 %	1.01 [0.71, 1.44]
Rahmathullah 2003	-0.25059 (0.110311)		52.1 %	0.78 [0.63, 0.97]
West 1995	0.067434 (0.236067)		11.4 %	1.07 [0.67, 1.70]
Subtotal (95% CI)			**100.0 %**	**0.91 [0.77, 1.06]**
Heterogeneity: Chi^2 = 4.16, df = 3 (P = 0.25); I^2 =28%				
Test for overall effect: Z = 1.24 (P = 0.21)				

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Analysis 1.3. Comparison 1 Neonatal vitamin A supplementation versus control, Outcome 3 All-cause infant mortality at 12 months (all infants): risk ratios based on cumulative risk (%).

Review: Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries

Comparison: 1 Neonatal vitamin A supplementation versus control

Outcome: 3 All-cause infant mortality at 12 months (all infants): risk ratios based on cumulative risk (%)

Study or subgroup	Vitamin A n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Benn 2008	88/2106	86/2169		32.2 %	1.05 [0.79, 1.41]
Benn 2010	83/701	78/710		29.5 %	1.08 [0.81, 1.44]
Humphrey 1996 (1)	7/925	19/914		7.3 %	0.36 [0.15, 0.86]
Malaba 2005	88/4079	82/4127		31.0 %	1.09 [0.81, 1.46]
Total (95% CI)	**7811**	**7920**		**100.0 %**	**1.02 [0.87, 1.20]**
Total events: 266 (Vitamin A), 265 (Control)					
Heterogeneity: Chi^2 = 5.84, df = 3 (P = 0.12); I^2 =49%					
Test for overall effect: Z = 0.24 (P = 0.81)					
Test for subgroup differences: Not applicable					

(1) Contains 6% preterms

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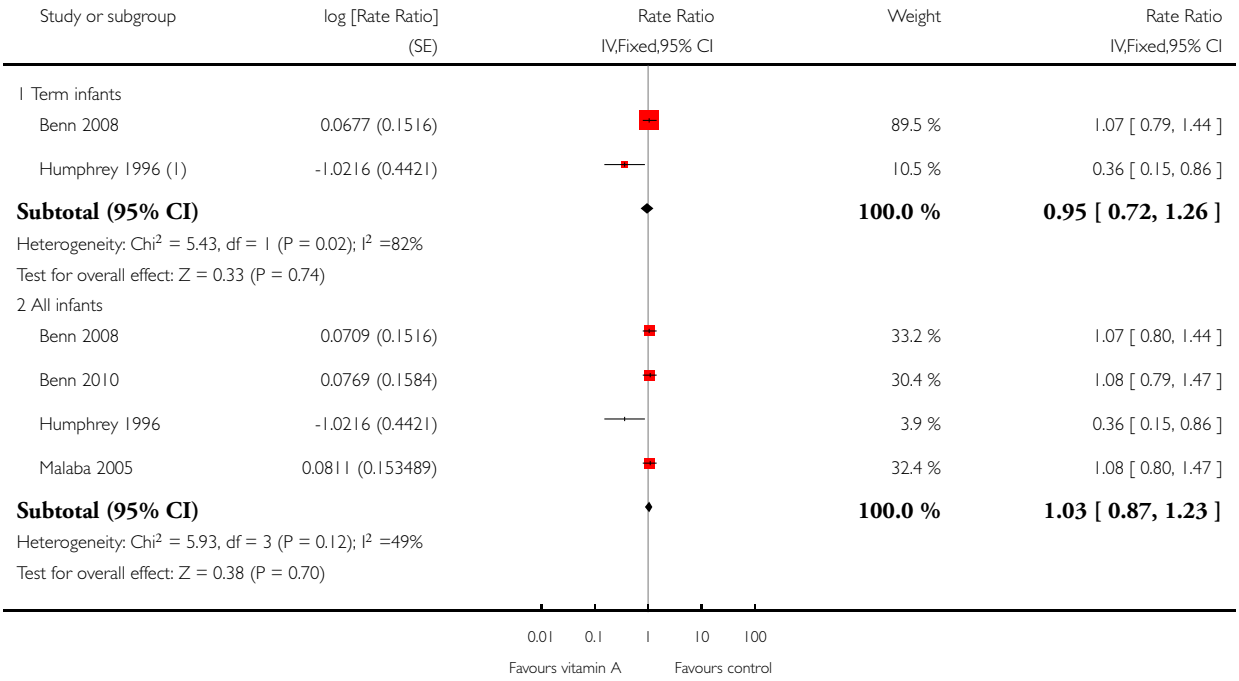
Analysis 1.4. Comparison 1 Neonatal vitamin A supplementation versus control, Outcome 4 All-cause infant mortality at 12 months: rate ratios (per years of follow-up).

Review: Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries

Comparison: 1 Neonatal vitamin A supplementation versus control

Outcome: 4 All-cause infant mortality at 12 months: rate ratios (per years of follow-up)



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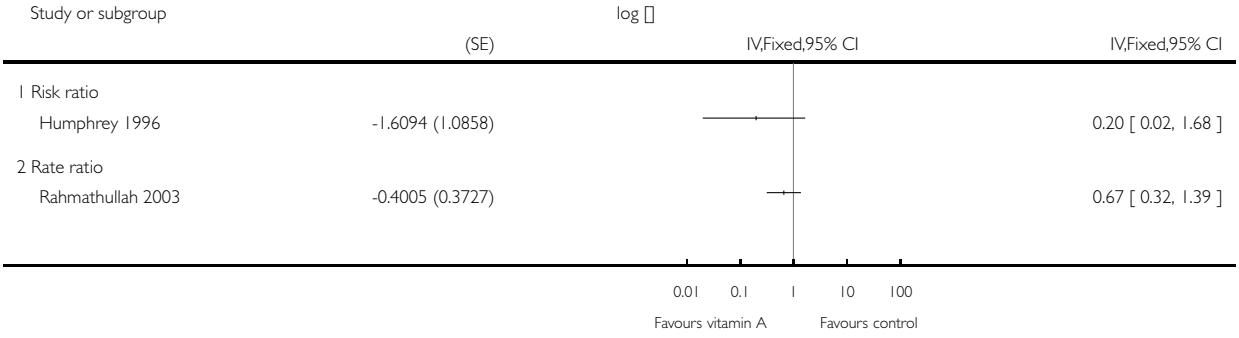
Analysis 1.5. Comparison 1 Neonatal vitamin A supplementation versus control, Outcome 5 Cause-specific infant mortality at 6 months (all infants): Diarrhea.

Review: Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries

Comparison: 1 Neonatal vitamin A supplementation versus control

Outcome: 5 Cause-specific infant mortality at 6 months (all infants): Diarrhea

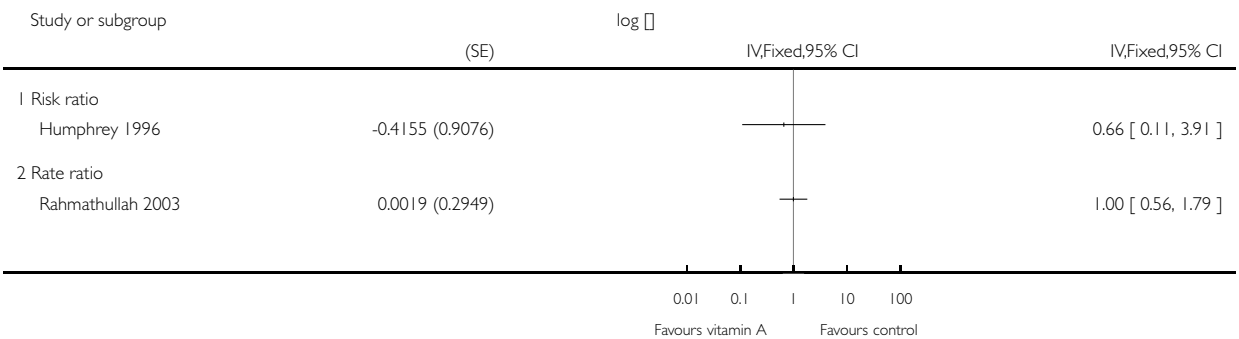


Analysis 1.6. Comparison 1 Neonatal vitamin A supplementation versus control, Outcome 6 Cause-specific infant mortality at 6 months (all infants): Respiratory infections.

Review: Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries

Comparison: 1 Neonatal vitamin A supplementation versus control

Outcome: 6 Cause-specific infant mortality at 6 months (all infants): Respiratory infections



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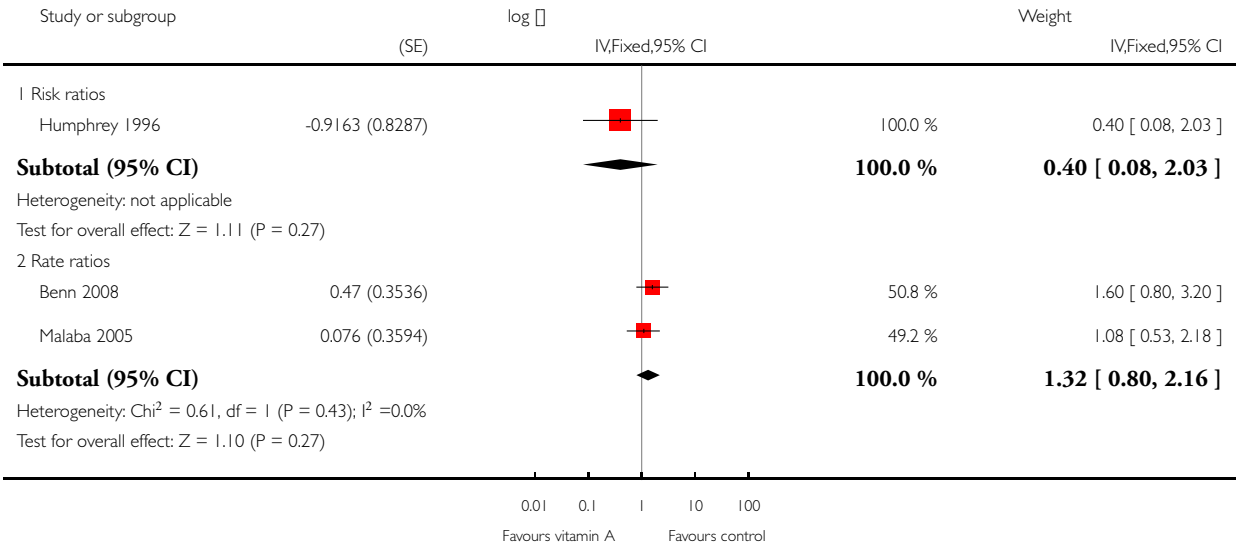
Analysis 1.7. Comparison 1 Neonatal vitamin A supplementation versus control, Outcome 7 Cause-specific infant mortality at 12 months (all infants): Diarrhoea.

Review: Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries

Comparison: 1 Neonatal vitamin A supplementation versus control

Outcome: 7 Cause-specific infant mortality at 12 months (all infants): Diarrhoea



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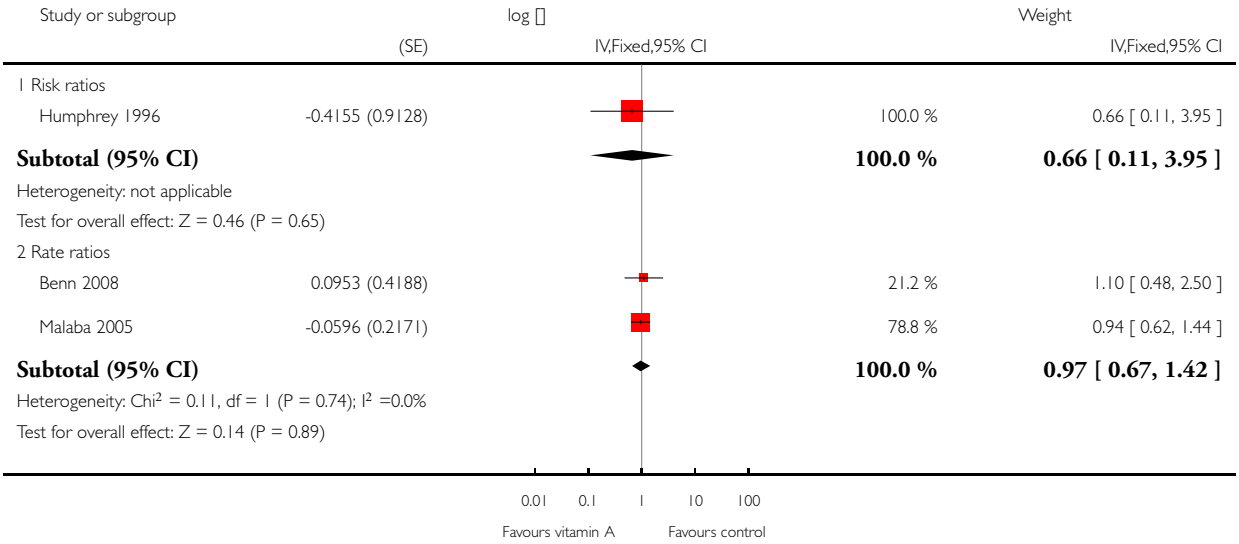
Analysis 1.8. Comparison 1 Neonatal vitamin A supplementation versus control, Outcome 8 Cause-speciifc infant mortality at 12 months (all infants): Respiratory infections.

Review: Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries

Comparison: 1 Neonatal vitamin A supplementation versus control

Outcome: 8 Cause-speciifc infant mortality at 12 months (all infants): Respiratory infections



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Analysis 1.9. Comparison 1 Neonatal vitamin A supplementation versus control, Outcome 9 Infant morbidity at 6 months (rate ratio): Diarrhoea.

Review: Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries

Comparison: 1 Neonatal vitamin A supplementation versus control

Outcome: 9 Infant morbidity at 6 months (rate ratio): Diarrhoea

Study or subgroup	log [Rate ratio] (SE)	Rate ratio IV,Fixed,95% CI	Weight	Rate ratio IV,Fixed,95% CI
Malaba 2005	0.0488 (0.0765)		12.3 %	1.05 [0.90, 1.22]
Rahmathullah 2003	0.0449 (0.0287)		87.7 %	1.05 [0.99, 1.11]
Total (95% CI)			**100.0 %**	**1.05 [0.99, 1.10]**

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² =0.0%

Test for overall effect: Z = 1.69 (P = 0.091)

Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 Neonatal vitamin A supplementation versus control, Outcome 10 Infant morbidity at 6 months (rate ratio): Respiratory infections.

Review: Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries

Comparison: 1 Neonatal vitamin A supplementation versus control

Outcome: 10 Infant morbidity at 6 months (rate ratio): Respiratory infections

Study or subgroup	log [Rate ratio] (SE)	Rate ratio IV,Fixed,95% CI	Weight	Rate ratio IV,Fixed,95% CI
Malaba 2005	-0.0202 (0.0253)		80.7 %	0.98 [0.93, 1.03]
Rahmathullah 2003	0.1293 (0.0518)		19.3 %	1.14 [1.03, 1.26]
Total (95% CI)			**100.0 %**	**1.01 [0.96, 1.05]**

Heterogeneity: Chi² = 6.73, df = 1 (P = 0.01); I² =85%

Test for overall effect: Z = 0.38 (P = 0.71)

Test for subgroup differences: Not applicable

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Analysis 1.11. Comparison 1 Neonatal vitamin A supplementation versus control, Outcome 11 Vitamin A deficient (serum retinol <0.70 micromol/L) at 6 weeks of age.

Review: Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries

Comparison: 1 Neonatal vitamin A supplementation versus control

Outcome: 11 Vitamin A deficient (serum retinol <0.70 micromol/L) at 6 weeks of age

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Benn 2008	91/292	106/320		0.94 [0.75, 1.19]

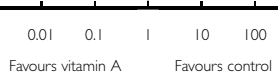
Analysis 1.12. Comparison 1 Neonatal vitamin A supplementation versus control, Outcome 12 Vitamin A deficient (serum retinol <0.70 micromol/L) at 4 months of age.

Review: Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries

Comparison: 1 Neonatal vitamin A supplementation versus control

Outcome: 12 Vitamin A deficient (serum retinol <0.70 micromol/L) at 4 months of age

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Benn 2008	30/186	29/183		1.02 [0.64, 1.62]



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Analysis 1.13. Comparison 1 Neonatal vitamin A supplementation versus control, Outcome 13 Anaemia (haemoglobin <105g/L) at 8-14 months of age.

Review: Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries

Comparison: 1 Neonatal vitamin A supplementation versus control

Outcome: 13 Anaemia (haemoglobin <105g/L) at 8-14 months of age

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Malaba 2005 (1)	368/809	369/783		0.97 [0.87, 1.07]

(1) Includes both HIV +/ - mothers but HIV status of the m/i did not modify the association b/w vitamin A supplementation and anaemia

Analysis 1.14. Comparison 1 Neonatal vitamin A supplementation versus control, Outcome 14 Adverse events during the first 48-72 hours post supplementation.

Review: Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries

Comparison: 1 Neonatal vitamin A supplementation versus control

Outcome: 14 Adverse events during the first 48-72 hours post supplementation

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Bulging fontanelle					
Benn 2008	60/551	56/599		68.2 %	1.16 [0.82, 1.65]
Humphrey 1996	46/1007	25/1001		31.8 %	1.83 [1.13, 2.95]
Subtotal (95% CI)	**1558**	**1600**		**100.0 %**	**1.38 [1.04, 1.82]**
Total events: 106 (Intervention), 81 (Control)					
Heterogeneity: Chi^2 = 2.25, df = 1 (P = 0.13); I^2 =56%					
Test for overall effect: Z = 2.24 (P = 0.025)					
2 Diarrhoea					
Benn 2008	103/551	146/599		60.8 %	0.77 [0.61, 0.96]
Humphrey 1996	104/1008	90/1001		39.2 %	1.15 [0.88, 1.50]
Subtotal (95% CI)	**1559**	**1600**		**100.0 %**	**0.92 [0.77, 1.09]**

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Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 207 (Intervention), 236 (Control)					
Heterogeneity: Chi^2 = 5.12, df = 1 (P = 0.02); I^2 =80%					
Test for overall effect: Z = 1.00 (P = 0.32)					
3 Vomiting					
Benn 2008	104/551	123/599		51.9 %	0.92 [0.73, 1.16]
Humphrey 1996	92/1008	109/1001		48.1 %	0.84 [0.64, 1.09]
Subtotal (95% CI)	**1559**	**1600**		**100.0 %**	**0.88 [0.74, 1.05]**
Total events: 196 (Intervention), 232 (Control)					
Heterogeneity: Chi^2 = 0.26, df = 1 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 1.43 (P = 0.15)					

Analysis 1.15. Comparison 1 Neonatal vitamin A supplementation versus control, Outcome 15 Adverse events during the first month post supplementation.

Review: Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in developing countries

Comparison: 1 Neonatal vitamin A supplementation versus control

Outcome: 15 Adverse events during the first month post supplementation

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Diarrhoea				
Benn 2008	11/991	10/964		1.07 [0.46, 2.51]
2 Vomiting				
Benn 2008	15/991	12/964		1.22 [0.57, 2.58]

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ADDITIONAL TABLES

Table 1. Data type and source: all-cause infant mortality at 6 months

Study ID	Analyzed as Rate/ Risk ratio	Data source (term/all infants)	Infants	Vitamin A group: Deaths	Vitamin A group: Child-years of follow-up	Vitamin A group: N	Control group: Deaths	Control group: Child-years of follow-up	Control group: N
Benn 2008	Rate ratio	Correspondence with study investigators	All infants	55	964	-	50	1003	-
Benn 2010	Rate ratio	Correspondence with study investigators	All infants	62	393	-	62	397	-
Humphrey 1996	Risk ratio	Correspondence with study investigators (denominators are number of neonates randomised)	All infants	7	-	1034	18	-	1033
			Term infants	6	-	1011	15	-	1007
Klemm 2008	Risk ratio	Klemm at al, Pediatrics 2008;122 (1):e242-50.	All infants	306	-	7953	360	-	7984
			Term infants	129	-	6109	171	-	6061
Malaba 2005	Risk ratio	Correspondence with study investigators. Data aggregated for the four treatment groups: Maternal	All infants	73	-	4309	66	-	4352

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Table 1. Data type and source: all-cause infant mortality at 6 months (*Continued*)

		vitamin A and infant vitamin A + maternal placebo and infant vitamin A versus maternal placebo and infant placebo + maternal vitamin A and infant placebo (For term infants, denominators are number of HIV negative mothers with term deliveries)	Term infants	62	-	4253	57	-	4280
Rahmathullah 2003	Rate ratio/ Risk ratio	Rahmathullah et al, BMJ 2003;327 (7409): 254.	All infants	146	2713	5363	188	2719.1	5408
		Correspondence with study investigators	Term infants	106	2348.7	-	130	2346.7	-
West 1995	Rate ratio/ Risk ratio	West et al, American Journal of Clinical Nutrition 1995;62 (1):143-8. Data were ex-	All infants	38	268.4	819	34	256.9	785

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Table 1. Data type and source: all-cause infant mortality at 6 months (*Continued*)

		tracted for infants under 1 month old who had been allocated to treatment							

Klemm 2008 was a cluster randomised study. The study authors reported that observed design effect was 0.9%.
West 1995 was a cluster randomised study. The study authors reported that the 95% confidence intervals of the effect estimates were inflated by 10% to account for the impact of the design on the study. We estimated that the 10% increase in the 95% CIs gave an ICC of 0.04 for the cohort of infants administered Vitamin A.

Table 2. Data type and source: all-cause infant mortality at 12 months

Study ID	Analyzed as Rate/ Risk ratio	Data source	Infants	Vitamin A group: Deaths	Vitamin A group: Child-years of follow-up	Vitamin A group: N	Control group: Deaths	Control group: Child-years of follow-up	Control group: N
Benn 2008	Rate ratio/ risk ratio	Benn et al, BMJ 2008;336 (7658): 1416-20.	All infants	88	1795	2106	86	1884	2169
Benn 2010	Rate ratio/ risk ratio	Benn et al, BMJ 2010;340: c1101.	All infants	83	757	701	78	762	710
Humphrey 1996	Rate ratio/ risk ratio	Humphrey et al, Journal of Pediatrics 1996;128 (4):489-96.	All infants (includes 6% preterms)	7	969.6	925	19	957.1	914
Klemm 2008	-	-	-	-	-	-	-	-	-
Malaba 2005	Rate ratio/ risk ratio	Malaba et al, The American Journal of	All infants	88	4195	4079	82	4239	4127

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Table 2. Data type and source: all-cause infant mortality at 12 months (*Continued*)

		Clinical Nutrition 2005;81 (2):454-60. Data aggregated for the four treatment groups: Maternal vitamin A and infant vitamin A + maternal placebo and infant vitamin A versus maternal placebo and infant placebo + maternal vitamin A and infant placebo							
Rahmathullah 2003	-	-	-	-	-	-	-	-	-
West 1995	-	-	-	-	-	-	-	-	-

WHAT'S NEW

Last assessed as up-to-date: 30 November 2010.

Date	Event	Description
13 March 2012	Amended	Minor typographical error corrected.

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HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 10, 2011

Date	Event	Description
14 May 2008	Amended	Reference correction
8 May 2008	Amended	Converted to new review format.
12 October 2007	New citation required and major changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

The review protocol was written by Batool A Haider (BAH) under the guidance of Zulfiqar A Bhutta (ZAB). Data extraction was done by BAH and ZAB. BAH entered the data, created the comparisons, did data analysis and wrote the text of the review. ZAB provided supervision and contributed to the writing process of the review.

DECLARATIONS OF INTEREST

Zulfiqar A Bhutta is a principal investigator of an ongoing neonatal vitamin A supplementation trial in Pakistan.

SOURCES OF SUPPORT

Internal sources

- The Aga Khan University Hospital, Pakistan.

External sources

- World Health Organization, Switzerland.

A grant was provided by the WHO to fund the completion of this Cochrane Review.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

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INDEX TERMS

Medical Subject Headings (MeSH)

*Developing Countries; *Infant Mortality; *Morbidity; Randomized Controlled Trials as Topic; Vitamin A [*administration & dosage]; Vitamin A Deficiency [prevention & control]; Vitamins [*administration & dosage]

MeSH check words

Humans; Infant, Newborn

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