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

Haider BA, Sharma R, Bhutta ZA

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

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[Intervention Review]

Neonatal vitamin A supplementation for the prevention of mortality and morbidity in term neonates in low and middle income countries

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ABSTRACT

Background

Vitamin A deficiency is a major public health problem in low and middle income countries. Vitamin A supplementation in children six months of age and older has been found to be beneficial, but no effect of supplementation has been noted for children between one and five months of age. Supplementation during 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 for term neonates in low and middle income countries with respect to prevention of mortality and morbidity.

Search methods

We used the standard search strategy of the Cochrane Neonatal Review Group to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 2), MEDLINE via PubMed (1966 to 13 March 2016), Embase (1980 to 13 March 2016) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to 13 March 2016). We also searched clinical trials databases, conference proceedings and reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials.

Selection criteria

Randomised and quasi-randomised controlled trials. Also trials with a factorial design.

Data collection and analysis

Two review authors independently assessed trial quality and extracted study data. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of evidence.

Main results

We included 12 trials (168,460 neonates) in this review, with only a few trials reporting disaggregated data for term infants. Therefore, we analysed data and presented estimates for term infants (when specified) and for all infants.

Data for term neonates from three studies did not show 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) 0.80; 95% confidence interval (CI) 0.54 to 1.18; $I^2 = 63\%$). Analysis

of data for all infants from 11 studies revealed no evidence of a significant reduction in the risk of infant mortality at six months among neonates supplemented with vitamin A compared with control neonates (typical RR 0.98, 95% CI 0.89 to 1.07; $I^2 = 47\%$). We observed similar results for infant mortality at 12 months of age with no significant effect of vitamin A compared with control (typical RR 1.04, 95% CI 0.94 to 1.15; $I^2 = 47\%$). Limited data were available for the outcomes of cause-specific mortality and morbidity, vitamin A deficiency, anaemia and adverse events.

Authors' conclusions

Given the high burden of death among children younger than five years of age in low and middle income countries, and the fact that mortality in infancy is a major contributory cause, it is critical to obtain sound scientific evidence of the effect of vitamin A supplementation during the neonatal period on infant mortality and morbidity. Evidence provided in this review does not indicate a potential beneficial effect of vitamin A supplementation among neonates at birth in reducing mortality during the first six months or 12 months of life. Given this finding and the absence of a clear indication of the biological mechanism through which vitamin A could affect mortality, along with substantial conflicting findings from individual studies conducted in settings with potentially varying levels of maternal vitamin A deficiency and infant mortality, absence of follow-up studies assessing any long-term impact of a bulging fontanelle after supplementation and the finding of a potentially harmful effect among female infants, additional research is warranted before a decision can be reached regarding policy recommendations for this intervention.

PLAIN LANGUAGE SUMMARY

Neonatal vitamin A supplementation for prevention of mortality and morbidity among term neonates in low and middle income countries

Review question: Does vitamin A supplementation among term neonates in low and middle income countries prevent mortality and morbidity?

Background: Vitamin A is an important micronutrient that is required for 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 to promote growth of the baby and to provide stores in the baby's liver. Deficiency of this micronutrient in the mother may 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 older than six months of age for reducing death and adverse effects on health have been established, but no available evidence shows this beneficial effect among infants one to five months of age. Potential benefits of vitamin A supplementation during the newborn period (during the first month of life) are under investigation.

Study characteristics: The present review identified 12 studies including 168,460 newborns in which the intervention group was supplemented with vitamin A during the newborn period.

Key results: Analysis of data for all infants shows no significant reduction in infant deaths at six months of age with the intervention and similar findings for infant deaths at 12 months of age.

Quality of evidence: We judged the quality of evidence as high for the most important clinical outcomes, with the exception of two outcomes that we scored as having low and very low quality: 'diarrhoeal events during the first 48-72 hours post supplementation' and 'all-cause infant mortality at 6 months in term infants', respectively.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Neonatal vitamin A supplementation versus control for prevention of mortality and morbidity in term neonates in low and middle income countries

Neonatal vitamin A supplementation versus control for prevention of mortality and morbidity in term neonates in low and middle income 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)	Number 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: risk ratios based on cumulative risk (% adjusted for clustering) - term infants	Low-risk population		RR 0.80 (0.54 to 1.18) Risk ratios based on cumulative risk (%)	22,721 (3 studies)	⊕⊕⊕⊕ Very low a,b,c	The pooled estimate of data for term infants from 3 studies (Humphrey 1996; Klemm 2008; Malaba 2005) suggests that risk of death from any cause at 6 months of age for neonates who were supplemented with vitamin A was 20% lower than control and was not statistically significant (pooled RR 0.80, 95% CI 0.54 to 1.18; 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
	13 per 1000	10 per 1000 (7 to 15)				
	Medium-risk population					
	15 per 1000	12 per 1000 (8 to 18)				
	High-risk population					
	28 per 1000	22 per 1000 (15 to 33)				
All-cause infant mortality at 6 months: risk ratios based on cumulative risk (% adjusted for clustering) - all infants	Low-risk population		RR 0.98 (0.89 to 1.07) Risk ratios based on cumulative risk (%)	154,634 (11 studies)	⊕⊕⊕⊕ High	The pooled estimate of data for all infants from 11 studies (Benn 2008; Benn 2010; Bhutta 2016; Edmond 2015; Humphrey 1996; Klemm 2008; Malaba 2005; Masanja 2015; Mazumder 2015; Rahmathullah 2003; West 1995) showed no evidence of a significant effect on risk of death from any cause for neonates supplemented with vitamin A as compared with controls
	13 per 1000	13 per 1000 (12 to 15)				
	Medium-risk population					

(typical RR 0.98, 95% CI 0.89 to 1.07). The level of statistical heterogeneity for this analysis was 47% ([Analysis 1.1.2](#))

clustering) - all infants	15 per 1000	15 per 1000 (13 to 16)				
	High-risk population					
	28 per 1000	27 per 1000 (25 to 30)				
All-cause neonatal mortality: risk ratios based on cumulative risk (%; adjusted for clustering) - all infants	Low-risk population		RR 0.99	126,242	⊕⊕⊕⊕ High	Five included studies measured neonatal mortality in the first month of life (Bhutta 2016 ; Edmond 2015 ; Klemm 2008 ; Masanja 2015 ; Mazumder 2015). Data from these 5 studies were measured as risk ratios based on cumulative risk. The pooled estimate of data for all infants showed no evidence of a significant effect on risk of death from any cause at 1 month of age for neonates supplemented with vitamin A as compared with controls (typical RR 0.99, 95% CI 0.90 to 1.08)
			(0.90 to 1.08)	(5 studies)		
	Medium-risk population		Risk ratios based on cumulative risk (%)			
	High-risk population					
Adverse events during first 48-72 hours post supplementation - bulging fontanelle	7 per 1000	11 per 1000 (8 to 14)	RR 1.53 (1.11 to 2.11)	100,256 (5 studies)	⊕⊕⊕⊕ High ^d	Data for adverse events in all infants during the first 48 to 72 hours could be pooled from 5 studies (Benn 2008 ; Edmond 2015 ; Humphrey 1996 ; Masanja 2015 ; Mazumder 2015), and only 1 study (Benn 2008) presented adverse events at 1 month of age (Analysis 1.14 and Analysis 1.15)
						The risk of a bulging fontanelle during the first 48 to 72 hours for neonates supplemented with vitamin A was 53% higher than for controls, which is statistically significant (typical RR 1.53, 95% CI 1.11 to 2.11; $I^2 = 71\%$)
Adverse events during first 48-72 hours post supplementation - vomiting	34 per 1000	34 per 1000 (31 to 36)	RR 1.00 (0.93 to 1.07)	99,582 (5 studies)	⊕⊕⊕⊕ High	Typical RR 1.00 (95% CI 0.93 to 1.07) in vitamin A group vs control group
Adverse events during first 48-72 hours post supplementation - diarrhoea	43 per 1000	41 per 1000 (35 to 49)	RR 0.96 (0.81 to 1.13)	102,638 (5 studies)	⊕⊕⊕⊖ Low ^{e,f}	Pooled estimates from the 5 studies provided no evidence of a significant increase in diarrhoea (typical RR 0.96, 95% CI 0.81 to 1.13)

Vitamin A deficiency (serum retinol < 0.70 micromol/L) at 6 weeks of age	331 per 1000	311 per 1000 (248 to 394)	RR 0.94 (0.75 to 1.19) at 6 weeks	612 (1 study)	⊕⊕⊕⊕ High ^g	Vitamin A deficiency defined as serum retinol value < 0.70 µmol/L was available for all infants from 1 study only (Benn 2008), which showed no evidence of a significant effect of vitamin A supplementation on vitamin A deficiency as compared with control at 6 weeks (RR 0.94, 95% CI 0.75 to 1.19)
Vitamin A deficiency (serum retinol < 0.70 micromol/L) at 4 months of age	158 per 1000	162 per 1000 (101 to 257)	RR 1.02 (0.64 to 1.62) at 4 months	369 (1 study)	⊕⊕⊕⊕ High ^h	Vitamin A deficiency defined as serum retinol value < 0.70 µmol/L was available for all infants from 1 study only (Benn 2008), which provided no evidence of a significant effect of vitamin A supplementation on vitamin A deficiency as compared with control at 4 months (RR 1.02, 95% CI 0.64 to 1.62)

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on 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

^aRisk 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

^bThe lower confidence limit indicates a 46% reduction in mortality at 6 months, whereas the upper limit indicates an 18% increase

^cThe level of statistical heterogeneity between study results was moderate ($I^2 = 63\%$). Variation between studies may have been related to differences between study populations and settings in terms of infant mortality rates and baseline prevalence of vitamin A deficiency

^dAlthough level of statistical heterogeneity was substantial ($I^2 = 71\%$), all included studies indicated potential harm. Heterogeneity was caused by differences in strength of association among the included studies

^eModerate level of statistical heterogeneity ($I^2 = 58\%$)

^fThe lower confidence limit indicates a 19% reduction in diarrhoea, whereas the upper limit indicates a 13% increase

^gOnly one of the included studies reported this outcome at 6 weeks of age. Review authors noted that data reported on this outcome specified different time points and could not be formally used in the meta-analysis

^hOnly 1 of the included studies reported this outcome at 4 months of age. Review authors noted that data reported on this outcome specified different time points and could not be formally used in the meta-analysis

BACKGROUND

Description of the condition

Vitamin A deficiency is considered a major public health problem in low and middle income countries ([WHO 2009](#)). Globally, 9.8 million pregnant women are affected by night blindness, and more than 19 million have low serum retinol concentrations (< 0.70 $\mu\text{mol/L}$). 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 among 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 vs 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 infection may also interfere with 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 ([WHO 2016](#)).

Description of the intervention

Vitamin A is an essential micronutrient that is required for maintenance of normal functioning of the human body. It was the first fat-soluble vitamin to be discovered and for nearly a century has been known to be an important dietary constituent ([Hopkins 1912](#); [McCollum 1915](#)). Vitamin A is part of a family of compounds called retinoids; naturally occurring retinoids include retinol, retinal and retinoic acid. For human physiology, retinol is the predominant form and 11-*cis*-retinol is the active form. Inactive retinoids, also known as provitamin A, are produced as plant pigments and are called carotenoids. Although many carotenoids are found in foods, only about 50% can be metabolised into 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 ([Bowman 2001](#)).

Vitamin A is important for normal functioning of the visual system, as well as for immune response, gene expression, reproduction, embryogenesis and hematopoiesis. It is essential for maintenance of normal epithelial tissues throughout the body ([Bowman 2001](#)). 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 dietary vitamin A intake. Remaining dietary vitamin A is obtained from carotenoids present in plant sources such as carrots, dark green leafy vegetables, red and orange fruits and red palm oil. 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 $\mu\text{g/d}$, and for infants seven to 12 months of age, the RDA is 500 $\mu\text{g/d}$. For children one to three years and four to eight years old, the RDA is 300 $\mu\text{g/d}$ and 400 $\mu\text{g/d}$, respectively ([DRI 2001](#)).

Routine consumption of large amounts of vitamin A over time can result in toxic symptoms, which include liver damage, headaches, vomiting, skin desquamation, bone abnormalities, joint pain and alopecia ([Bowman 2001](#)). Hypervitaminosis A appears to be due

to abnormal transport and distribution of vitamin A and retinoids that is caused by overloading of plasma transport mechanisms. 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 $\mu\text{g/d}$ above basal requirements during the full gestation period) to sustain growth of the foetus and to provide a limited reserve in the foetal 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)/d. 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 minimise risk of foetal 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 during the first few months of life. Thus, maternal vitamin A deficiency during lactation, early weaning or artificial feeding may result in vitamin A deficiency among infants ([Underwood 1994](#)). The physiological vitamin A needs of infants born to vitamin A-adequate mothers and fed breast milk with adequate vitamin A (in excess of 30 $\mu\text{g/dL}$, or 1.05 $\mu\text{mol/L}$) are met for at least the first six months of life ([Underwood 1994](#)). Because of the need for vitamin A to promote growth in infancy, the rate of 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/d during the first six months ([WHO/NUT/98.1 1998](#)). If an average concentration of vitamin A in human milk of about 1.75 mmol/L is assumed, mean daily intake would have to be about 375 μg RE, which is therefore the recommended safe level.

Why it is important to do this review

The role of vitamin A supplementation for children older 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 given on consecutive days to children younger than two years of age with measles were associated with reduced risk of overall mortality (risk ratio (RR) 0.18, 95% confidence interval (CI) 0.03 to 0.61) and 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 to prevent vitamin A deficiency ([WHO 1998](#)). The policy of WHO has been to supplement vitamin A by providing 100,000 IU at the earliest possible opportunity after six months of age. However, it is now recommended that an additional 50,000 IU of vitamin A be administered with each of the diphtheria-tetanus-pertussis (DTP) and polio vaccinations, which usually are given at six, 10 and 14 weeks of age ([Sommer 2002](#)). National and regional programmes of vitamin A supplementation, which are in place in more than 60 countries worldwide, target children older than six months of age ([Fawzi 2006](#)). Not only are these programmes highly effective in reducing mortality and morbidity, but in countries in which vitamin A deficiency constitutes a public

health problem, they appear to be among the most cost-effective public health interventions available. Such programmes seek to maximise child survival among children older than six months - the group that accounts for a quarter of deaths in children younger than five years of age. To address the major proportion of deaths in children younger than five, programmes should target children younger than six months of age. Supplementation with vitamin A between one and five months of age has been found to have no 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 during early infancy, thereby having an impact on mortality and morbidity (Sommer 1995). Several randomised clinical trials and systematic reviews have evaluated this approach (Benn 2008; Benn 2010; Benn 2014; Bhutta 2016; Edmond 2015; Haider 2011; Haider 2015; Humphrey 1996; Klemm 2008; Malaba 2005; Masanja 2015; Mazumder 2015; Rahmathullah 2003; West 1995). This review updates the previous Cochrane review on this topic, which was published in 2011 (Haider 2011), and includes trials published since the time of the previous publication.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

We included in this review all randomised controlled trials (RCTs), both individually randomised and cluster-randomised, irrespective of publication status and language, conducted to evaluate effects of vitamin A supplementation for term neonates in low and middle income countries. We also included studies using a factorial design and quasi-randomised trials.

Types of participants

We included all term neonates (born between 37 and 42 weeks' gestational age) up to 28 days after birth.

Types of interventions

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

Types of outcome measures

Primary outcomes

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

Secondary outcomes

- Cause-specific infant mortality associated with acute respiratory infection and diarrhoea at six months and 12 months
- Infant morbidity at six months of age, associated with acute respiratory infection and diarrhoea, measured as at least one episode of morbidity

- Biochemical indicator values of vitamin A deficiency (vitamin A deficiency measured as serum retinol < 0.70 µmol/L)
- Blindness and signs of xerophthalmia (Bitot's spots and corneal lesions)
- Mean haemoglobin level or anaemia defined as haemoglobin less than the age-specific cut-off value as stated by study authors
- Adverse events reported in trials due to vitamin A toxicity such as bulging fontanelles, vomiting and diarrhoea
- All-cause neonatal mortality (between supplementation and 28 days of age)

Search methods for identification of studies

For the March 2016 update:

- We conducted a comprehensive search including Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 2) in the Cochrane Library; MEDLINE via PubMed (1966 to 13 March 2016); Embase (1980 to 13 March 2016); and Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to 13 March 2016) using the following search terms: (vitamin A OR retinol OR retinoid OR retinoic OR vitamin A [MeSH]), plus database-specific limiters for RCTs and neonates (see [Appendix 1](#) for full search strategies for each database). We applied no language or date restrictions.
- We searched clinical trials registries for ongoing and recently completed trials (clinicaltrials.gov; World Health Organization's International Trials Registry and Platform - www.whoint/ictrp/search/en/ and the [ISRCTN Registry](http://www.isrctn.com)).

For prior searches:

- We used the standard search strategy of the Cochrane Neonatal Review Group. We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 14 June 2010) in the Cochrane Library; and Embase and MEDLINE (1966 to May 2010) via PubMed using the following search terms: (Newborn OR infan* OR neonat*) AND (vitamin A OR retino*). We limited our search to the clinical trial publication type.
- We limited searches to human studies and applied no language restrictions. We also searched related conference proceedings for relevant abstracts. We contacted organisations and researchers in the field for information on unpublished and ongoing trials and searched reference lists of all trials identified by the above methods. For further identification of ongoing trials, we searched the websites www.clinicaltrials.gov and www.anzctr.com.

Data collection and analysis

Selection of studies

Two review authors independently assessed for inclusion all potential studies identified as a result of the search strategy. We resolved disagreements through discussion.

Data extraction and management

We designed a form on which to record extracted data. For eligible studies, two review authors extracted data using the agreed form. We resolved discrepancies through discussion. We entered data into Review Manager software (RevMan 2008) and checked them for accuracy.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias (low, high or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2011) for the following domains.

- Selection bias.
- Performance bias.
- Attrition bias.
- Reporting bias.
- Any other bias.

We resolved disagreements by discussion or by consultation with a third assessor. See Appendix 2 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

Dichotomous data

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

Continuous data

We included no continuous outcomes in this review.

Unit of analysis issues

We included in this review three cluster-randomised trials (Bhutta 2016; Klemm 2008; West 1995). For Bhutta 2016, study investigators reported that the observed design effect and intraclass correlation coefficient (ICC) for neonatal mortality were 1.29 and 0.01, respectively. For infant mortality at six months, the observed design effect and ICC were 1.27 and 0.01. Klemm 2008 reported that the observed design effect was 0.9%. For West 1995, 95% CIs of effect estimates were inflated by 10% to account for the impact of design on study findings. We estimated that the 10% increase in 95% CIs yielded an 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 via Review Manager software (RevMan 2008) and generated risk ratio or rate ratio estimates with 95% CIs for dichotomous outcomes. For this approach, we entered data as natural logarithms (as log risk ratios and log rate ratios and standard error (SE) of log risk ratios and SE of log rate ratios) for each individual study, using data extracted from published papers or obtained from study authors if not presented in papers. We have presented data used for infant mortality analyses along with their sources in 'Additional tables'. We used the fixed-effect method for combining data when trials were examining the same intervention, and when we judged trial populations and methods as sufficiently similar.

The review objective was to evaluate the effect of vitamin A supplementation in term neonates. Studies included in this review had enrolled all births identified in their study settings without restriction for gestational age of < 37 or ≥ 37 weeks, which would have allowed us to use only term data. Three studies used birth weight as a criterion: Benn 2008 and Benn 2014 enrolled normal birth weight neonates (birth weight ≥ 2500 grams), and Benn 2010 recruited only low birth weight neonates (birth weight

< 2500 grams). One study presented data for term neonates separately only in the published paper for the infant mortality outcome at six months (Klemm 2008). West 1995 (Keith West; personal communication, 2008) did not provide information about gestational age. Given the small number of studies included in the review and limited available data for primary outcomes, we analysed data for term neonates, when available, then performed analyses of data for all infants. For all secondary outcomes, investigators presented data for all infants together in published papers, and we analysed these data as such. As the inclusion criterion for both Benn 2008 and Benn 2014 was birth weight of at least 2500 grams, we assumed that a greater proportion of neonates would be term babies and analysed their data as such in our term neonate analysis. We used the term 'all infants' to refer to aggregated term and preterm infant data throughout this review.

Two studies provided maternal supplementation with vitamin A in the postpartum period (Malaba 2005) or during pregnancy (Klemm 2008). Malaba and colleagues randomised mother-infant pairs to four treatment arms (described in detail in the Characteristics of included studies table), whereas Klemm and associates 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 maternal supplementation arms. Both studies reported no significant interaction between maternal and neonatal supplementation with vitamin A, and we included data for all neonates provided by these studies on the basis of their randomisation to the neonatal vitamin A intervention or control group.

Quality of evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes.

- All-cause infant mortality at six months.
- All-cause neonatal mortality (between supplementation and 28 days of age).
- Blindness and signs of xerophthalmia (Bitot's spots and corneal lesions).
- Adverse events reported in trials due to vitamin A toxicity: bulging fontanelles.
- Adverse events reported in trials due to vitamin A toxicity: vomiting.
- Adverse events reported in trials due to vitamin A toxicity: diarrhoea.
- Biochemical indicator values of vitamin A deficiency (vitamin A deficiency measured as serum retinol < 0.70 µmol/L).

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

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

- High: We are very confident that the true effect lies close to the estimate of effect.
- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different.
- Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.
- Very low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

We prespecified the following subgroups to investigate heterogeneity.

- Maternal vitamin A supplementation.
- Birth weight of neonates.
- HIV status of mother and infant.
- Dose and frequency of vitamin A used.
- High baseline infant mortality.
- Comorbidities.

- Timing of vitamin A supplementation (within the first 48 to 72 hours or later).
- Sex of the neonate.
- Geographic region.

We measured heterogeneity among trials by calculating the I^2 statistic. We considered values of the I^2 statistic greater than 50% 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 evaluation of heterogeneity, when identified. We conducted subgroup analysis by geographic region and sex of the infant for mortality outcomes for all infants in response to the special interest of the scientific community in evaluating this differential effect.

We planned to investigate publication bias for outcomes if we identified more than 10 studies for inclusion. However, we did not investigate this bias as the number of studies included was small.

RESULTS

Description of studies

Included studies

We included in this review 12 studies including 168,460 neonates ([Figure 1](#)).

Figure 1. Study flow diagram: review update.

[Humphrey 1996](#) was conducted in a single tertiary care hospital in Indonesia as a safety trial for vitamin A supplementation at the time of birth. In this randomised double-blind placebo-controlled trial of 2067 infants with birth weight > 1500 grams and without critical illness, researchers randomly assigned infants to receive a single oral dose of vitamin A (50,000 IU) or placebo within 24 hours of delivery. Maternal, infant and household characteristics were similar in the two groups at baseline.

[West 1995](#) was part of a large cluster-randomised, double-blind, placebo-controlled trial of vitamin A supplementation for preschool children conducted in Nepal. Investigators enrolled a total of 11,918 infants younger than six months, of whom 1621 were neonates, and administered vitamin A (50,000 IU to infants < one month old and 100,000 IU to infants one to ≤ five months old) or placebo. Baseline characteristics of the two groups were similar.

[Rahmathullah 2003](#) was also a randomised, double-blind, placebo-controlled trial conducted in India in which all live-born infants within participating villages were eligible for inclusion. Investigators enrolled a total of 11,619 newborn infants born to consenting mothers who were residing in the study area and administered two doses of vitamin A or placebo - the first dose within the first 48 hours of delivery and the second dose within 24 hours of the first dose. Baseline characteristics of families, mothers and infants were similar between treatment groups.

[Malaba 2005](#) was a randomised, double-blind, placebo-controlled trial conducted in Zimbabwe in which investigators used 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; if neither of the two had a life-threatening illness; and if the infant's birth weight was > 1500 grams. Researchers enrolled around 14,110 infant-mother pairs within 96 hours of delivery and assigned them to one of the following groups: Aa (vitamin A supplementation for both mother and infant), pa (placebo for mother and vitamin A for infant) and pp (placebo for both mother and infant). The vitamin A dose for mothers was 400,000 IU, and for infants 50,000 IU. All treatment groups were similar at baseline in terms of maternal, household and other related variables.

[Klemm 2008](#) was a cluster-randomised, double-blind, placebo-controlled trial conducted in Bangladesh that was nested within an ongoing parent trial of vitamin A supplementation for pregnant women. All infants born to consenting mothers from the original trial were included in the current trial. A total of 15,948 infants received vitamin A (50,000 IU) or placebo at home as soon as possible after birth. Baseline characteristics of mothers and infants in this study were comparable at baseline.

Benn et al conducted three studies in Guinea Bissau. [Benn 2008](#) was a randomised, double-blind, placebo-controlled trial that included 4345 normal birth weight infants (birth weight ≥ 2500 grams). For births occurring at the national hospital or at local health centres, researchers invited mothers to participate in the study at the time of Bacille Calmette-Guérin (BCG) vaccination. For home births, they invited mothers to participate at the time of their visit to the local health centre for BCG vaccination. Study investigators randomised all infants with birth weight at least 2500 grams, with no serious medical condition or malformation and for whom parental consent was available, to oral drops of vitamin A (50,000 IU) or to placebo. Treatment groups were similar at baseline in terms of various

characteristics. 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 (birth weight < 2500 grams) that included 1736 neonates randomised to 25,000 IU vitamin A or to placebo, as well as to early BCG vaccine or the usual late BCG vaccine. Investigators in [Benn 2014](#), a double-blind, placebo-controlled randomised trial that included 6048 healthy normal birth weight neonates (> 2500 grams), randomly assigned infants in a 1:1:1 ratio to three different treatment groups: 50,000 IU of vitamin A; 25,000 IU of vitamin A; or placebo, concurrent with BCG vaccination.

Recent studies conducted in Ghana, Tanzania, India and Pakistan aimed to evaluate the effect of neonatal supplementation of 50,000 IU of vitamin A against control. All four studies were randomised, double-blind, placebo-controlled trials; the study conducted in Pakistan used a cluster-randomised design.

[Edmond 2015](#), [Masanja 2015](#) and [Mazumder 2015](#) recruited participants who were at least two hours old; were identified at home or in facilities on the day of birth or over the next two days; were able to feed orally; were likely to stay in the study area for at least six months; and had received parental consent to participate. In all three studies, infant and maternal baseline characteristics were similar between intervention and control groups. Investigators conducted [Edmond 2015](#) in seven contiguous districts in the Brong Ahafo region of central rural Ghana, with a sample size of 22,955 neonates; [Masanja 2015](#), in the Morogoro and Dar es Salaam regions of Tanzania, with a sample size of 31,999 neonates; and [Mazumder 2015](#), in two districts (Faridabad and Palwal) in the state of Haryana, India, with a sample size of 44,984 neonates. [Masanja 2015](#) and [Mazumder 2015](#) considered infants from both singleton and multiple births as eligible for enrolment.

Soofi and colleagues conducted a community-based, cluster-randomised, placebo-controlled trial in two districts (Sukkur and Jehlum) of rural Pakistan ([Bhutta 2016](#)). All live-born infants within participating villages were potentially eligible for inclusion, and infants with obvious congenital malformations and birth weight less than 1500 grams were ineligible. Investigators randomised a total of 11,028 consecutively delivered neonates to receive vitamin A or placebo. Baseline characteristics of the two study arms were comparable.

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

Ongoing studies

[McDonald 2014](#) is a double-blind, randomised, placebo-controlled trial conducted in a peri-urban area of The Gambia. Researchers recruited two hundred mother-infant pairs at the Sukuta Health Centre, a government health clinic in the Western coastal region of The Gambia. Inclusion criteria were singleton birth, birth weight ≥ 1500 grams, mothers over 18 years of age, residency within the study area and administration of birth vaccinations and vitamin A supplementation within 48 hours of birth. Exclusion criteria were infants with a congenital disease, a serious infection at birth or inability to feed, and mothers who were seriously ill at the time of enrolment, were participating in other studies and/or were HIV positive. Within 48 hours of birth, investigators randomised neonates to receive an oral dose of 50,000 IU vitamin A or placebo. The primary outcome is frequency of circulating T regulatory (Treg)

cells expressing gut homing receptors in infants at 17 weeks post supplementation. Secondary outcomes are differences in thymus size, B cell immune responses and improved mucosal barrier function in infant participants. Recruitment and follow-up for this study are complete and data analysis is in progress.

See the [Characteristics of ongoing studies](#) table for additional details.

Excluded studies

We excluded five studies from the review ([Ahmad 2014](#); [Bezzera 2009](#); [Bhaskaram 1998](#); [Mathew 2015](#); [Schmiedchen 2016](#)). [Bezzera 2009](#) provided vitamin A supplementation to mothers only in the immediate postpartum period and did not supplement neonates. [Bhaskaram 1998](#) supplemented only mothers with vitamin A within 24 hours of delivery and gave all neonates oral poliovirus vaccine (OPV) between 48 and 72 hours after birth. [Ahmad 2014](#) reported no relevant outcomes. [Mathew 2015](#) was a commentary on an included study ([Mazumder 2015](#)). [Schmiedchen 2016](#) included infants with birth weight < 1500 grams and gestational age < 33 weeks.

Risk of bias in included studies

Allocation

Eight studies adequately randomised neonates to treatment groups ([Benn 2008](#); [Benn 2010](#); [Benn 2014](#); [Bhutta 2016](#); [Edmond 2015](#); [Malaba 2005](#); [Masanja 2015](#); [Mazumder 2015](#)) and provided a clear description of the method used to generate the randomisation sequence. Four studies did not provide sufficient details to allow judgement of the adequacy of study methods ([Humphrey 1996](#); [Klemm 2008](#); [Rahmathullah 2003](#); [West 1995](#)). Nine studies clearly described the method of allocation concealment ([Benn 2008](#); [Benn 2010](#); [Benn 2014](#); [Bhutta 2016](#); [Edmond 2015](#); [Humphrey 1996](#); [Malaba 2005](#); [Masanja 2015](#); [Mazumder 2015](#)), whereas [Klemm 2008](#), [Rahmathullah 2003](#) and [West 1995](#) did not provide sufficient details.

Blinding

All included studies clearly described and achieved blinding of participants, study personnel and outcome assessors.

Incomplete outcome data

Rates of postrandomisation attrition and exclusion of participants were as follows: 1.6% ([Benn 2008](#)), 18.7% ([Benn 2010](#)), 1.87% ([Benn 2014](#)), 6.7% ([Bhutta 2016](#)), 1.1% ([Edmond 2015](#)), 11% ([Humphrey 1996](#)), 7% ([Klemm 2008](#)), 41.8% ([Malaba 2005](#)), 3.5% ([Masanja 2015](#)), 0.1% ([Mazumder 2015](#)) and 18.9% ([Rahmathullah 2003](#)); papers described reasons for attrition and exclusion of participants. [West 1995](#) reported exclusion and attrition of 1.04% and provided no details.

Selective reporting

Evaluation of selective outcome reporting by review of trial registration documents, if available, or of methods presented in published papers revealed that all trials had reported findings for prespecified or expected outcomes, except for [Humphrey 1996](#), for which reporting was unclear.

Other potential sources of bias

We identified three trials with potentially 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 owing to significantly higher mortality in the control group. We found [Malaba 2005](#) to be free of other bias and determined that risk of other bias was uncertain in the remaining eight trials owing to insufficient information ([Benn 2014](#); [Bhutta 2016](#); [Edmond 2015](#); [Humphrey 1996](#); [Masanja 2015](#); [Mazumder 2015](#); [Rahmathullah 2003](#); [West 1995](#)).

See the [Characteristics of included studies](#) table for additional details on risk of bias in included studies. We have provided in [Figure 2](#) a graphical presentation of our individual judgements per item per study and a summary graph in [Figure 3](#).

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Benn 2008	+	+	+	+	+	-
Benn 2010	+	+	+	+	+	-
Benn 2014	+	+	+	+	+	?
Bhutta 2016	+	+	+	+	+	?
Edmond 2015	+	+	+	+	+	?
Humphrey 1996	?	+	+	+	?	?
Klemm 2008	?	?	+	+	+	-
Malaba 2005	+	+	+	?	+	+
Masanja 2015	+	+	+	+	+	?
Mazumder 2015	+	+	+	+	+	?
Rahmathullah 2003	?	?	+	+	+	?
West 1995	?	?	+	+	+	?

Figure 3. 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 prevention of mortality and morbidity in term neonates in low and middle income countries](#)

We have included in this review [Summary of findings for the main comparison](#) based on outcomes in term neonates, which was prepared in accordance with the method 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

We have presented in [Table 1](#) an overview of the type and source of data for this outcome.

Ten included studies ([Benn 2008](#); [Benn 2010](#); [Bhutta 2016](#); [Edmond 2015](#); [Humphrey 1996](#); [Klemm 2008](#); [Malaba 2005](#); [Masanja 2015](#); [Mazumder 2015](#); [Rahmathullah 2003](#)) measured infant mortality at six months of age. [West 1995](#) measured mortality at four months of age, and we have included these data in the six-month mortality analysis.

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

Eleven studies measured data 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 risk of death from any cause at six months of age for neonates supplemented with vitamin A is 20% lower than for control infants and was not statistically significant (pooled risk ratio 0.80, 95% CI 0.54 to 1.18; [Analysis 1.1.1](#)). The level of statistical heterogeneity in this analysis was 63%. As the number of studies included was small,

we considered a subgroup analysis to investigate heterogeneity as not reliable. Given substantial statistical heterogeneity and the small number of included studies, the reader should interpret these findings with caution.

The pooled estimate of data for all infants from 11 studies ([Benn 2008](#); [Benn 2010](#); [Bhutta 2016](#); [Edmond 2015](#); [Humphrey 1996](#); [Klemm 2008](#); [Malaba 2005](#); [Masanja 2015](#); [Mazumder 2015](#); [Rahmathullah 2003](#); [West 1995](#)) showed no evidence of a significant effect on risk of death from any cause for neonates supplemented with vitamin A as compared with control neonates (typical risk ratio 0.98, 95% CI 0.89 to 1.07). The level of statistical heterogeneity for this analysis was 47% ([Analysis 1.1.2](#)).

For gender-specific subanalyses, the pooled estimate of data for all male infants from five studies ([Bhutta 2016](#); [Edmond 2015](#); [Klemm 2008](#); [Masanja 2015](#); [Mazumder 2015](#)) showed no evidence of a significant effect (typical risk ratio 1.01, 95% CI 0.92 to 1.12). The level of statistical heterogeneity for this analysis was less than 50% ($I^2 = 11\%$; [Analysis 1.1.3](#)). Likewise, analysis of data for all female infants from five studies ([Bhutta 2016](#); [Edmond 2015](#); [Klemm 2008](#); [Masanja 2015](#); [Mazumder 2015](#)) did not reach statistical significance (typical risk ratio 0.95, 95% CI 0.84 to 1.08; $I^2 = 41\%$; [Analysis 1.1.4](#)).

For the analysis based on geographic region, the pooled estimate from studies conducted in Asia showed a statistically significant reduction in risk of mortality at six months (typical risk ratio 0.89, 95% CI 0.80, 0.99; $I^2 = 29\%$), whereas the pooled estimate from studies conducted in Africa indicated higher risk of mortality at six months ($P = 0.05$; typical risk ratio 1.10, 95% CI 1.00 to 1.21; $I^2 = 0\%$).

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

We analysed data from five studies 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 given vitamin A as compared with control neonates (typical rate ratio 0.93, 95% CI 0.67 to 1.30; [Analysis 1.2.1](#)). Analysis of data for all infants from five studies ([Benn 2008](#); [Benn 2010](#); [Masanja 2015](#); [Rahmathullah 2003](#); [West 1995](#)) did not show statistical significance (typical rate ratio 0.99, 95% CI 0.84 to 1.17; [Analysis 1.2.2](#)). Levels of statistical heterogeneity were as follows: $I^2 = 51\%$ and 46% for analyses of term and all infants, respectively.

For gender-specific subanalyses, the pooled estimate of data for all male infants from two studies ([Masanja 2015](#); [Rahmathullah 2003](#)) showed no evidence of a significant effect on the rate of death from any cause at six months of age in those who received vitamin A as compared with control infants (typical rate ratio 0.88, 95% CI 0.58 to 1.35; [Analysis 1.2.3](#)). Analysis of data for all female infants from two studies ([Masanja 2015](#); [Rahmathullah 2003](#)) also did not show statistical significance (typical rate ratio 1.01, 95% CI 0.79 to 1.30; [Analysis 1.2.4](#)). Levels of statistical heterogeneity were as follows: $I^2 = 82\%$ and 46% for analyses of all male infants and all female infants, respectively.

For geography-specific subanalyses, the pooled estimate from two studies conducted in Asia showed a non-significant effect on the rate of mortality at six months (typical rate ratio 0.85, 95% CI 0.64 to 1.13; $I^2 = 33\%$). Similarly, a pooled estimate from three studies conducted in Africa showed no significant impact on mortality at six months (typical rate ratio 1.09, 95% CI 0.96 to 1.23; $I^2 = 0\%$).

All-cause infant mortality at 12 months of age

We have presented in [Table 2](#) an overview of the type and source of data for this outcome.

Eight included studies ([Benn 2008](#); [Benn 2010](#); [Benn 2014](#); [Edmond 2015](#); [Humphrey 1996](#); [Malaba 2005](#); [Masanja 2015](#); [Mazumder 2015](#)) measured infant mortality at 12 months of age.

All-cause infant mortality at 12 months of age: risk ratios based on cumulative risk (%) (Outcome 1.3)

Eight studies measured data as risk ratios based on cumulative risk. The pooled estimate of data for all infants from the eight studies ([Benn 2008](#); [Benn 2010](#); [Edmond 2015](#); [Humphrey 1996](#); [Malaba 2005](#); [Masanja 2015](#); [Mazumder 2015](#)) showed no evidence of a significant effect on risk of death from any cause at 12 months of age for neonates supplemented with vitamin A as compared with control neonates (typical risk ratio 1.04, 95% CI 0.94 to 1.15). The level of statistical heterogeneity for this analysis was less than 50% ($I^2 = 47\%$; [Analysis 1.3.1](#)).

For gender-specific subanalyses, the pooled estimate of data for all male infants from three studies ([Edmond 2015](#); [Masanja 2015](#); [Mazumder 2015](#)) showed no evidence of a significant effect on risk of death from any cause at 12 months of age for neonates supplemented with vitamin A as compared with control neonates (typical risk ratio 1.00, 95% CI 0.88 to 1.14). The level of statistical heterogeneity for this analysis was less than 50% ($I^2 = 46\%$; [Analysis 1.3.2](#)). Analysis of the data for all female infants from three studies ([Edmond 2015](#); [Masanja 2015](#); [Mazumder 2015](#)) also did not show statistical significance (typical risk ratio 1.04, 95% CI 0.90 to 1.20). The level of statistical heterogeneity for this analysis was 56% ([Analysis 1.3.3](#)).

For geography-specific analyses, the pooled estimate of data from studies conducted in Asia showed no evidence of a significant effect on risk of death from any cause at 12 months of age (typical risk ratio 0.65, 95% CI 0.26 to 1.60; $I^2 = 78\%$). The pooled estimate for studies conducted in Africa showed an indication of higher risk of mortality at 12 months of age (typical risk ratio 1.08, 95% CI 1.00 to 1.17; $I^2 = 0\%$).

All-cause infant mortality at 12 months of age: rate ratios (per years of follow up) (Outcome 1.4)

We analysed data from six studies as rate ratios (per year of follow-up).

Analysis of term neonate data from three studies expressed as rate ratios ([Benn 2008](#); [Benn 2014](#); [Humphrey 1996](#)) showed no evidence of a significant effect on infant mortality from any cause at 12 months of age among neonates supplemented with vitamin A as compared with control infants, with statistical heterogeneity of 72% (typical rate ratio 0.94, 95% CI 0.59 to 1.50; [Analysis 1.4.1](#)). The pooled estimate of data for all infants from six studies ([Benn 2008](#); [Benn 2010](#); [Benn 2014](#); [Humphrey 1996](#); [Malaba 2005](#); [Masanja 2015](#)) also did not reach statistical significance (typical rate ratio 1.06, 95% CI 0.92 to 1.22; [Analysis 1.4.2](#)). The level of statistical heterogeneity was lower than 50% ($I^2 = 31\%$).

Analysis of data for all male infants from five studies ([Benn 2008](#); [Benn 2010](#); [Benn 2014](#); [Humphrey 1996](#); [Masanja 2015](#)) showed no evidence of a significant effect of supplementation of neonates with vitamin A on infant mortality at 12 months of age compared with control (typical rate ratio 0.89, 95% CI 0.66 to 1.19; [Analysis 1.4.3](#)). In contrast, the pooled estimate for all female infants from five studies ([Benn 2008](#); [Benn 2010](#); [Benn 2014](#); [Humphrey 1996](#); [Masanja 2015](#)) did reach statistical significance (typical rate ratio 1.21, 95% CI 1.05 to 1.41; [Analysis 1.4.3](#)). However, differences between subgroups were not statistically significant ($P = 0.06$). Levels of statistical heterogeneity included the following: $I^2 = 58\%$ and 0% for analyses of all male infants and all female infants, respectively.

For geography-specific analyses, the pooled estimate of data from three studies conducted in Asia showed no evidence of a significant effect on risk of death from any cause at 12 months of age (typical rate ratio 0.94, 95% CI 0.69 to 1.29; $I^2 = 65\%$). Similarly, the estimate for three studies conducted in Africa showed no impact on mortality at 12 months of age (typical rate ratio 1.13, 95% CI 0.94 to 1.36; $I^2 = 0\%$).

Secondary outcomes

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

Two studies ([Humphrey 1996](#); [Rahmathullah 2003](#)) measured infant mortality related to diarrhoea and acute respiratory infection at six months of age. Investigators in [Humphrey 1996](#) provided data for all infants as risk ratios based on cumulative risk, which showed no significant effect of vitamin A supplementation on diarrhoea and respiratory infection as compared with control (diarrhoea-specific infant mortality: risk ratio 0.20, 95% CI 0.02 to 1.68; acute respiratory infection-specific infant mortality: risk ratio 0.66, 95% CI 0.11 to 3.91). [Rahmathullah 2003](#) presented data for all infants as rate ratios (per years of follow-up) and showed a similar non-significant effect of vitamin A on rates of diarrhoea-specific and acute respiratory infection-specific infant mortality at six months of

age as compared with control (diarrhoea-specific infant mortality: rate ratio 0.67, 95% CI 0.32 to 1.39; 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 infection (Outcomes 1.7 and 1.8)

Three studies (Benn 2008; Humphrey 1996; Malaba 2005) measured infant mortality related to diarrhoea and acute respiratory infection at 12 months of age.

Humphrey 1996 provided data for all infants 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 infection as compared with control (diarrhoea-specific infant mortality: risk ratio 0.40, 95% CI 0.08 to 2.03; 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 provided no evidence of a significant effect of vitamin A on diarrhoea-specific and acute respiratory infection-specific infant mortality at 12 months of age as compared with control (typical rate ratio 1.32, 95% CI 0.80 to 2.16; $I^2 = 0\%$; and rate ratio 0.97, 95% CI 0.67 to 1.42; $I^2 = 0\%$, respectively).

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

Three trials (Benn 2008; 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 with control on rates of diarrhoea and acute respiratory infection among infants at six months of age (typical rate ratio 0.89, 95% CI 0.69 to 1.14; $I^2 = 89\%$; and rate ratio 1.05, 95% CI 0.91 to 1.21; $I^2 = 85\%$, respectively). We did not consider performing a subgroup analysis to investigate heterogeneity because of the small number of studies contributing data to this analysis.

Vitamin A deficiency (Outcomes 1.11 and 1.12)

One study only (Benn 2008) reported vitamin A deficiency defined as serum retinol value $< 0.70 \mu\text{mol/L}$ for all infants and showed no evidence of a significant effect of vitamin A supplementation on vitamin A deficiency as compared with control (at six weeks: risk ratio 0.94, 95% CI 0.75 to 1.19; at four months: risk ratio 1.02, 95% CI 0.64 to 1.62).

Anaemia (Outcome 1.13)

Only one study (Malaba 2005) measured the impact of the intervention on anaemia for all infants born to both HIV-positive and HIV-negative women. Vitamin A supplementation in neonates did not lead to a significant impact on anaemia (haemoglobin (Hb) $< 105 \text{ g/L}$) at eight to 14 months of age (risk ratio 0.97, 95% CI 0.87 to 1.07) compared with control.

Adverse events (Outcomes 1.14 and 1.15)

We were able to pool data from five studies (Benn 2008; Edmond 2015; Humphrey 1996; Masanja 2015; Mazumder 2015) for adverse events in all infants during the first 48 to 72 hours, and only one study (Benn 2008) presented adverse events at one month of age (Analysis 1.14 and Analysis 1.15). Risk of a bulging fontanelle during the first 48 to 72 hours for neonates supplemented with vitamin A was 53% higher than for control neonates, and this finding is statistically significant (typical risk ratio 1.53, 95% CI 1.11 to 2.11;

$I^2 = 71\%$). Pooled estimates from the five studies provided no evidence of a significant increase in diarrhoea (typical risk ratio 0.96, 95% CI 0.81 to 1.13) or vomiting (typical risk ratio 1.00, 95% CI 0.93 to 1.07) in the vitamin A group versus the control group. Likewise, analyses from three studies (Edmond 2015; Masanja 2015; Mazumder 2015) indicated no significant increase in fever (typical risk ratio 1.04, 95% CI 0.98 to 1.09), inability to suck or feed (typical risk ratio 1.00, 95% CI 0.81 to 1.23) and convulsions (typical risk ratio 1.12, 95% CI 0.66 to 1.88). Estimates from one study (Mazumder 2015) showed no statistically significant differences in excessive crying (typical risk ratio 0.99, 95% CI 0.93 to 1.05), jaundice (typical risk ratio 1.07, 95% CI 0.96 to 1.19), eye infection (typical risk ratio 0.99, 95% CI 0.88 to 1.12), skin infection (typical risk ratio 0.94, 95% CI 0.82 to 1.09), umbilical infection (typical risk ratio 0.97, 95% CI 0.81 to 1.15), respiratory infection (typical risk ratio 1.08, 95% CI 0.94 to 1.24), feeding problems (typical risk ratio 1.01, 95% CI 0.88 to 1.16) or other adverse events during the first 48 to 72 hours (typical risk ratio 0.93, 95% CI 0.84 to 1.02). Benn 2008 showed no evidence of a significant increase in adverse events during the first month post supplementation (diarrhoea: risk ratio 1.07, 95% CI 0.46 to 2.51; vomiting: risk ratio 1.22, 95% CI 0.57 to 2.58).

All-cause neonatal mortality (Outcomes 1.16 and 1.17)

We have presented in Table 3 an overview of the type and source of data for this outcome.

Five included studies measured neonatal mortality in the first month of life (Bhutta 2016; Edmond 2015; Klemm 2008; Masanja 2015; Mazumder 2015). Investigators measured data for these five studies as risk ratios based on cumulative risk. The pooled estimate of data for all infants showed no evidence of a significant effect on risk of death from any cause at one month of age for neonates supplemented with vitamin A as compared with control neonates (typical risk ratio 0.99, 95% CI 0.90 to 1.08). Analyses for all male infants and for all female infants also did not reach statistical significance (male: typical risk ratio 1.01, 95% CI 0.87 to 1.17; female: typical risk ratio 1.03, 95% CI 0.89 to 1.19). The level of statistical heterogeneity for all three analyses was 0%.

Masanja 2015 analysed data as rate ratios (per year of follow-up) and showed no significant effect on neonatal mortality for all infants (typical rate ratio 1.04, 95% CI 0.86 to 1.25), all male infants (typical rate ratio 0.99, 95% CI 0.77 to 1.27) or all female infants (typical rate ratio 1.10, 95% CI 0.82 to 1.49) supplemented with vitamin A as compared with control infants.

Other outcomes

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

DISCUSSION

Summary of main results

We conducted this review to compare the effect of supplementing term neonates with vitamin A as compared with not providing vitamin A supplementation. As term neonatal outcome data were available for only a small number of studies, and then for infant mortality outcomes only, we analysed and presented estimates for both term neonates (when specified) and all infants for various prespecified outcomes. Our analysis of data provided for all infants provided evidence of a non-significant reduction in risk of death

at six months of age in the vitamin A supplemented group as compared with the control group. Analysis of term neonatal outcomes included data from a subset of studies included in the all-infant analysis and revealed a non-significant reduction in risk of death in the first six months or 12 months of life. The reader should interpret these findings with caution because of the small number of studies contributing data to these analyses, statistical heterogeneity and wide confidence intervals that are close to the null effect. In addition to these results, our analysis of data from Asia on all infants based on geographical region showed a significant reduction in risk of death at six months as a result of vitamin A (reduction 11%; 95% confidence interval (CI) 1% to 20%). On the contrary, studies from Africa showed an effect that ranged from no impact to a 21% increase in risk of mortality. Overall, our review findings do not suggest a potential effect of this intervention on infant mortality.

Overall completeness and applicability of evidence

This review included a total of 12 trials conducted to evaluate the effect of vitamin A supplementation for neonates. These include all trials conducted to date to assess this intervention. Inclusion of these studies, which we identified through extensive searches of the literature and of additional data obtained by contacting study authors, represents the overall completeness of evidence.

Deficiency of vitamin A is a major nutritional concern in many countries of the world. All studies included in this review were conducted in low and middle income countries with varying levels of vitamin A deficiency and infant mortality. These studies have demonstrated a mix of effects on infant mortality resulting from supplementation with vitamin A, and studies conducted in areas with vitamin A deficiency indicate a potential beneficial effect of supplementation; however, studies conducted in regions with less deficiency suggest no benefit of supplementation and potential for harm.

Reasons for these conflicting findings are unclear, and data show no clear indication of the biological mechanisms through which vitamin A could lower risk of death when given during the neonatal period. Investigators have proposed various mechanisms. Newborns have marginal reserves of vitamin A in their liver, and they depend on breast milk as a source of this vitamin during the first few months of life. Hence, low maternal vitamin A levels translate into vitamin A deficiency among newborns ([Underwood 1994](#)). Deficiency of vitamin A could begin very early in life if colostrum is discarded or breastfeeding is inadequate. Colostrum and early breast milk have been found to be very rich sources of vitamin A that can significantly augment vitamin A stores among neonates ([Wallingford 1986](#)). Along with inadequate breastfeeding, introduction of artificial feeds hinders establishment of good breastfeeding practices, thereby denying infants this critical source of vitamin A throughout the breastfeeding period ([Haskell 1999](#)). Artificial feeds early in life also increase the risk of gastrointestinal infection among these infants. It has been proposed that vitamin A supplementation may have an impact on infant mortality through development and maintenance of the integrity of intestinal and respiratory epithelia, and by provision of enhanced local and systemic immunity ([Sommer 1996](#); [Tielsch 2008](#) - a report on [Rahmathullah 2003](#)). These pathways may provide an explanation for the effect of supplementation in settings where the practice of discarding colostrum, the presence of inadequate breastfeeding or reports of artificial feeds and infections are common. Alternatively,

early initiation of feeding of colostrum and exclusive breastfeeding could explain 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.

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.

Quality of the evidence

We graded the evidence for most outcomes as high quality, with the exception of two outcomes that we scored as having low and very low quality: 'diarrhoeal events during the first 48-72 hours post supplementation' and 'all-cause infant mortality at six months in term infants', respectively ([Summary of findings for the main comparison](#)). We downgraded the former outcome for inconsistency and imprecision, a moderate level of statistical heterogeneity ($I^2 = 58\%$) and wide confidence intervals, with the lower confidence limit indicating a 19% reduction in diarrhoeal events and the upper limit indicating a 13% increase. We downgraded the latter outcome, 'all-cause infant mortality at six months in term infants', to very low quality, although the previous review judged this outcome as low quality. This change reflected adoption of a random-effects model; the estimate changed from a risk ratio (RR) of 0.82 (95% CI 0.68 to 0.99) to an RR of 0.80 (95% CI 0.54 to 1.18), with the wider confidence interval indicating less precision. It should be noted that we considered the evidence for all-cause infant mortality at six months in all infants as high quality, despite inclusion of three studies with the outcome for term infants. With the introduction of eight new studies into the analysis of data for all infants, the relative influence of the three previously included studies decreased. Unclear risk of bias from [Klemm 2008](#) was no longer a reason to downgrade the quality of the entire analysis because it had little effect on the overall risk ratio. Likewise, heterogeneity was lower ($I^2 = 47\%$), and imprecision was not indicated as serious.

Potential biases in the review process

This update of the review includes additional data published since the time of the last update. We conducted an extensive literature search to identify new studies or new publications of previously included studies available since the last search was conducted. Two review authors independently screened the updated search for identification of studies, eligibility assessment, risk of bias evaluation and extraction of data from selected studies. Given that we applied the Cochrane methods described above, the findings of this review are unlikely to be affected by biases in the review process.

Agreements and disagreements with other studies or reviews

Considerable debate has surrounded the issue of supplementing neonates with vitamin A owing to conflicting study findings and variability in the results of pooled analyses ([Abrams 2008](#); [Bhutta 2008](#); [Gogia 2009](#); [Haider 2015](#); [Sachdev 2008](#); [Tielsch 2008](#)). The

current review includes most of the up-to-date data available on neonatal vitamin A supplementation and additional data provided when we contacted study authors.

Two of the included trials, one conducted in India ([Rahmathullah 2003](#)) and one in Bangladesh ([Klemm 2008](#)), examined a population characterised by high infant mortality and vitamin A deficiency. The trial in India showed a reduction of 22% in risk of infant mortality at six months, whereas the trial in Bangladesh showed a 15% reduction in risk of infant mortality 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 this event was not significantly different between the two groups ($P = 0.26$). Study authors noted that the impact of vitamin A supplementation on mortality was evident from two weeks of age and continued until three months, after which no further effect was apparent. The Bangladesh trial reported similar observations, including a difference in mortality among infants as early as after the first week of life that persisted until four months of age. Approximately 9.5% of pregnant women in each group reported night blindness during their most recent pregnancy. Investigators measured a subsample of this study population for serum retinol in the first trimester and showed suboptimal vitamin A status (defined as serum retinol $< 1.05 \mu\text{mol/L}$) in approximately 41% of women in the vitamin A group and 36% of those in the control group. These findings of an effect of vitamin A on risk of mortality between the early weeks of life until four months do indicate a common biological mechanism of vitamin A. Of the three large recent trials funded by the World Health Organization (WHO), the trial conducted in India by Mazumder et al examined a population with moderate vitamin A deficiency (about 40% of mothers in this setting had low vitamin A status). Researchers reported a significant reduction of 10% in risk of infant mortality at six months of age with vitamin A supplementation for neonates. This beneficial effect was evident in survival curves after a few weeks of supplementation and was sustained until 12 months of age. This study observed no significant interaction between the intervention effect and sex of the infant in terms of mortality at six months. [Humphrey 1996](#), an Indonesian trial, was the first trial of vitamin A supplementation in neonates that was conducted as a safety trial. Although this trial had reported significant benefit for survival that was notable after the first month and became consistent after four months of birth, trial authors had noted that the mother included in the study had little vitamin A deficiency (based on serum retinol levels for a subset of the study population). The infant mortality rate in the control group (7.2 per 1000 child-years) was well below that reported for families included in this study, which were relatively privileged ([Humphrey 1996](#)). Although serum retinol levels were adequate, these findings provide no information on hepatic reserves, which may have been low in this study group ([Tielsch 2008](#)).

Studies conducted in Nepal, Zimbabwe, Guinea Bissau, Ghana and Tanzania reported conflicting results. [West 1995](#), the Nepal trial, was part of a larger vitamin A supplementation trial in preschool children. Infants supplemented during the neonatal period did not show a significant effect on infant mortality, which investigators evaluated at four months of age. Of note, this study setting was characterised by endemic vitamin A deficiency and high infant mortality. This finding contrasted with 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-month and 12-month infant mortality outcomes. Benn and associates ([Benn 2010](#)) measured infant mortality in a study conducted in Guinea Bissau at 12 months and reported no effect on this outcome. The vitamin A status of mothers provided evidence of minimal deficiency in these study settings, with mean ($\pm$ standard deviation (SD)) serum retinol values in a subset of Zimbabwean women in the control group of $1.09 (\pm 0.29)$ and $1.19 (\pm 0.42) \mu\text{mol/L}$ at six weeks postpartum. In Guinea Bissau, less than 1% of women had low retinol binding proteins (retinol binding proteins $< 1.11 \mu\text{mol/L}$). This study also measured serum retinol values among infants at six weeks and four months of age and found no evidence of an effect of vitamin A supplementation on vitamin A deficiency. An important feature of this trial is 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 been explained in part by a reduction in severity rather than the incidence of infection ([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 might have occurred by reducing episodes of severe illness. Recent large trials in Ghana ([Edmond 2015](#)) and Tanzania ([Masanja 2015](#)) also reported no significant beneficial effect of vitamin A supplementation on infant mortality at six months. Results of these trials indicated potential for harm. Study sites for these recent studies included districts with long-running demographic surveillance programmes for supplementation of women to address the problem of micronutrient deficiencies. As a result, less than 3% of women in Ghana and 5% to 8% of those in Tanzania had biochemical vitamin A deficiency.

This update also found differences in the effect of vitamin A supplementation for neonates on infant mortality at six months by geographic region, with studies conducted in Asia showing a beneficial effect of supplementation and those in Africa indicating potential for harm. [Haider 2015](#) noted this in another pooled analysis of data. The reasons for possible differences in results of trials conducted in different geographic regions are uncertain. However, these findings could represent genuine differences in population-attributable risks of micronutrient deficiencies. As noted above, 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 generalisability of study findings. It should be noted that in contrast to observed benefits of vitamin A supplementation among mothers in Nepal ([West 1999](#)), a large trial of maternal vitamin A supplementation in Ghana ([Kirkwood 2010](#)) reported no benefit.

Another concern raised by some trial authors is the presence of a differential effect of vitamin A supplementation for neonates on infant mortality by sex ([Benn 2014](#)). In the current review, we conducted a subgroup analysis by sex of the infant, when data were available. Although results showed no significant difference in infant mortality at six months of age, findings were statistically significantly different for infant mortality at 12 months, with significantly higher risk noted in the subgroup of female infants (RR 1.21, 95% CI 1.05 to 1.41). [Benn 2014](#) reported similar findings in an assessment and pooled analysis of infant mortality among children six to 12 months of age; however, recent trials did not observe significant interaction of effects of interventions on infant mortality

at six months by sex. Given these differences in study findings, additional research is warranted to further study this effect.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence provided in this review does not indicate a potential beneficial effect of vitamin A supplementation for neonates at birth in reducing mortality during the first six months or 12 months of life. Analyses based on geographical region, however, demonstrated a beneficial effect of supplementation in studies from Asia and potential for harm in studies from Africa. Given this finding and the absence of a clear indication of the biological mechanism through which vitamin A could affect mortality during early infancy, along with substantial conflicting findings from individual studies conducted in settings with potentially varying levels of maternal vitamin A deficiency and infant mortality; the absence of follow-up studies assessing the long-term impact of a bulging fontanelle after supplementation; and the finding of a potentially harmful effect among female infants, additional research is warranted before a decision can be reached regarding any policy recommendations for this intervention.

Implications for research

Future research should seek to identify biological mechanisms and indicators for vitamin A in reducing risk of death, and to

explain the differences observed in vitamin A supplementation trials conducted in different geographical settings with varying levels of baseline vitamin A deficiency. Longer follow-up studies should evaluate neurodevelopmental outcomes for neonates supplemented with vitamin A at birth to ensure the safety of this intervention. Future investigators should make every effort to stratify effects by sex of the infant, age after birth of vitamin A administration, prematurity and intrauterine growth retardation.

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REFERENCES

References to studies included in this review

Benn 2008 {published data only}

Age S, Kiraly N, Da Costa K, Byberg S, Bjerregaard-Andersen M, Fisker AB, et al. Neonatal vitamin A supplementation associated with increased atopy in girls. *Allergy* 2015;**70**(8):985-94. [DOI: [10.1111/all.12641](https://doi.org/10.1111/all.12641)]

* Benn CS, Diness BR, Roth A, Nante E, Fisker AB, Lisse IM, et al. Effect of 50,000 IU vitamin A given with BCG vaccine on mortality in infants in Guinea-Bissau: randomised placebo controlled trial. *BMJ* 2008;**336**(7658):1416-20. [DOI: [10.1136/bmj.39542.509444.AE](https://doi.org/10.1136/bmj.39542.509444.AE)]

Diness BR, Christoffersen D, Pedersen UB, Rodrigues A, Fischer TK, Andersen A, et al. The effect of high-dose vitamin A supplementation given with bacille Calmette-Guerin vaccine at birth on infant rotavirus infection and diarrhea: a randomized prospective study from Guinea-Bissau. *The Journal of Infectious Diseases* 2010;**202**(Suppl 1):S243-251. [DOI: [10.1086/653569](https://doi.org/10.1086/653569)]

Diness BR, Fisker AB, Roth A, Yazdanbakhsh M, Sartono E, Whittle H, et al. Effect of high-dose vitamin A supplementation on the immune response to Bacille Calmette-Guerin vaccine. *The American Journal of Clinical Nutrition* 2007;**86**(4):1152-9. [PUBMED: 17921396]

Fisker AB, Aaby P, Rodrigues A, Frydenberg M, Bibby BM, Benn CS. Vitamin A supplementation at birth might prime the response to subsequent vitamin A supplements in girls. Three year follow-up of a randomized trial. *PLoS One* 2011;**6**(8):e23265.

Fisker AB, Benn CS, Diness BR, Martins C, Rodrigues A, Aaby P, et al. The effect of 50000IU vitamin A with BCG vaccine at birth on growth in the first year of life. *Journal of Tropical Medicine* 2011;**2011**:Article Number: 570170.

Fisker AB, Lisse IM, Aaby P, Erhardt JG, Rodrigues A, Bibby BM, et al. Effect of vitamin A supplementation with BCG vaccine at birth on vitamin A status at 6 wk and 4 mo of age. *The American Journal of Clinical Nutrition* 2007;**86**(4):1032-9. [PUBMED: 17921381]

Jorgensen MJ, Fisker AB, Sartono E, Andersen A, Erikstrup C, Lisse IM, et al. The effect of at-birth vitamin A supplementation on differential leucocyte counts and in vitro cytokine production: an immunological study nested within a randomised trial in Guinea-Bissau. *The British Journal of Nutrition* 2013;**109**(3):467-77. [DOI: [10.1017/S0007114512001304](https://doi.org/10.1017/S0007114512001304)]

Nante JE, Diness BR, Ravn H, Roth A, Aaby P, Benn CS. No adverse events after simultaneous administration of 50 000 IU vitamin A and Bacille Calmette-Guerin vaccination to normal-birth-weight newborns in Guinea-Bissau. *European Journal of Clinical Nutrition* 2008;**62**(7):842-8. [DOI: [10.1038/sj.ejcn.1602796](https://doi.org/10.1038/sj.ejcn.1602796)]

Benn 2010 {published data only}

* Benn CS, Fisker AB, Napirna BM, Roth A, Diness BR, Lausch KR, et al. Vitamin A supplementation and BCG vaccination at birth

in low birthweight neonates: two by two factorial randomised controlled trial. *BMJ* 2010;**340**:c1101. [DOI: [10.1136/bmj.c1101](https://doi.org/10.1136/bmj.c1101)]

Biering-Sørensen S, Fisker AB, Ravn H, Camala L, Monteiro I, Aaby P, et al. The effect of neonatal vitamin A supplementation on growth in the first year of life among low-birth-weight infants in Guinea-Bissau: two by two factorial randomised controlled trial. *BMC Pediatrics* 2013;**13**:87. [DOI: [10.1186/1471-2431-13-87](https://doi.org/10.1186/1471-2431-13-87)]

Kiraly N, Benn CS, Biering-Sorensen S, Rodrigues A, Jensen KJ, Ravn H, et al. Vitamin A supplementation and BCG vaccination at birth may affect atopy in childhood: long-term follow-up of a randomized controlled trial. *Allergy* 2013;**68**(9):1168-76. [DOI: [10.1111/all.12216](https://doi.org/10.1111/all.12216)]

Benn 2014 {published data only}

Benn CS, Diness BR, Balde I, Rodrigues A, Lausch KR, Martins CL, et al. Two different doses of supplemental vitamin A did not affect mortality of normal-birth-weight neonates in Guinea-Bissau in a randomized controlled trial. *The Journal of Nutrition* 2014;**144**(9):1474-9.

Bhutta 2016 {unpublished data only}

Bhutta Z, Soofi S, Ariff S, Sadiq K, Habib A, Ahmad I, et al. Evaluation of the uptake and impact of neonatal vitamin A supplementation delivered through the Lady Health Worker Program on neonatal and infant morbidity and mortality in rural Pakistan; an effectiveness trial.

Edmond 2015 {published data only}

Bahl R, Bhandari N, Dube B, Edmond K, Fawzi W, Fontaine O, et al. NEOVITA Study Author Group. Efficacy of early neonatal vitamin A supplementation in reducing mortality during infancy in Ghana, India and Tanzania: study protocol for a randomized controlled trial. *Trials* 2012;**13**:22. [DOI: [10.1186/1745-6215-13-22](https://doi.org/10.1186/1745-6215-13-22)]

* Edmond KM, Newton S, Shannon C, O'Leary M, Hurt L, Thomas G, et al. Effect of early neonatal vitamin A supplementation on mortality during infancy in Ghana (Neovita): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;**385**(9975):1315-23. [DOI: [10.1016/S0140-6736\(14\)60880-1](https://doi.org/10.1016/S0140-6736(14)60880-1)]

Humphrey 1996 {published data only}

Agoestina T, Humphrey JH, Taylor GA, Usman A, Subardja D, Hidayat S, et al. Safety of one 52-mumol (50,000 IU) oral dose of vitamin A administered to neonates. *Bulletin of the World Health Organization* 1994;**72**(6):859-68. [PUBMED: 7867131]

Humphrey JH, Agoestina T, Juliana A, Septiana S, Widjaja H, Cerreto MC, et al. Neonatal vitamin A supplementation: effect on development and growth at 3 y of age. *The American Journal of Clinical Nutrition* 1998;**68**(1):109-17. [PUBMED: 9665104]

* Humphrey JH, Agoestina T, Wu L, Usman A, Nurachim M, Subardja D, et al. Impact of neonatal vitamin A supplementation on infant morbidity and mortality. *The Journal of Pediatrics* 1996;**128**(4):489-96. [PUBMED: 8618182]

Klemm 2008 {published data only}

Coles CL, Labrique A, Saha SK, Ali H, Al-Emran H, Rashid M, et al. Newborn vitamin A supplementation does not affect nasopharyngeal carriage of *Streptococcus pneumoniae* in Bangladeshi infants at age 3 months. *Journal of Nutrition* 2011;**141**(10):1907-11. [DOI: [10.3945/jn.111.141622](https://doi.org/10.3945/jn.111.141622)]

Klemm RD, Labrique AB, Christian P, Rashid M, Shamim AA, Katz J, et al. Newborn vitamin A supplementation reduced infant mortality in rural Bangladesh. *Pediatrics* 2008;**122**(1):e242-50. [DOI: [10.1542/peds.2007-3448](https://doi.org/10.1542/peds.2007-3448)]

Malaba 2005 {published and unpublished data}

Humphrey JH, Iliff PJ, Marinda ET, Mutasa K, Moulton LH, Chidawanyika H, et al. Effects of a single large dose of vitamin A, given during the postpartum period to HIV-positive women and their infants, on child HIV infection, HIV-free survival, and mortality. *The Journal of Infectious Diseases* 2006;**193**(6):860-71. [DOI: [10.1086/500366](https://doi.org/10.1086/500366)]

* Malaba LC, Iliff PJ, Nathoo KJ, Marinda E, Moulton LH, Zijenah LS, et al. Effect of postpartum maternal or neonatal vitamin A supplementation on infant mortality among infants born to HIV-negative mothers in Zimbabwe. *The American Journal of Clinical Nutrition* 2005;**81**(2):454-60. [PUBMED: 15699235]

Miller MF, Stoltzfus RJ, Iliff PJ, Malaba LC, Mbuya NV, Humphrey JH, Zimbabwe Vitamin A for Mothers and Babies Project (ZVITAMBO) Study Group. Effect of maternal and neonatal vitamin A supplementation and other postnatal factors on anemia in Zimbabwean infants: a prospective, randomized study. *The American Journal of Clinical Nutrition* 2006;**84**(1):212-22. [PUBMED: 16825698]

Masanja 2015 {published data only}

Bahl R, Bhandari N, Dube B, Edmond K, Fawzi W, Fontaine O, et al. NEOVITA Study Author Group. Efficacy of early neonatal vitamin A supplementation in reducing mortality during infancy in Ghana, India and Tanzania: study protocol for a randomized controlled trial. *Trials* 2012;**13**(22). [DOI: [10.1186/1745-6215-13-22](https://doi.org/10.1186/1745-6215-13-22)]

* Masanja H, Smith ER, Muhihi A, et al. for the Neovita Tanzania Study Group. Effect of neonatal vitamin A supplementation on mortality in infants in Tanzania: a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;**385**:1324-32.

Mazumder 2015 {published data only}

Bahl R, Bhandari N, Dube B, Edmond K, Fawzi W, Fontaine O, et al. Efficacy of early neonatal vitamin A supplementation in reducing mortality during infancy in Ghana, India and Tanzania: study protocol for a randomized controlled trial. *Trials* 2012;**13**(22).

* Mazumder S, Taneja S, Bhatia K, Yoshida S, Kaur J, Dube B, et al. Neovita India Study Group. Efficacy of early neonatal supplementation with vitamin A to reduce mortality in infancy in Haryana, India (Neovita): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;**385**(9975):1333-42. [DOI: [10.1016/S0140-6736\(14\)60891-6](https://doi.org/10.1016/S0140-6736(14)60891-6)]

Rahmathullah 2003 {published data only}

Coles CL, Rahmathullah L, Kanungo R, Thulasiraj RD, Katz J, Santhosham M, et al. Vitamin A supplementation at birth delays pneumococcal colonization in South Indian infants. *Journal of Nutrition* 2001;**131**(2):255-61. [PUBMED: 11160543]

* Rahmathullah L, Tielsch JM, Thulasiraj RD, Katz J, Coles C, Devi S, et al. Impact of supplementing newborn infants with vitamin A on early infant mortality: community based randomised trial in southern India. *BMJ* 2003;**327**(7409):254. [DOI: [10.1136/bmj.327.7409.254](https://doi.org/10.1136/bmj.327.7409.254)]

Tielsch JM, Rahmathullah L, Thulasiraj RD, Katz J, Coles C, Sheeladevi S, et al. Newborn vitamin A dosing reduces the case fatality but not incidence of common childhood morbidities in South India. *Journal of Nutrition* 2007;**137**(11):2470-4. [PUBMED: 17951487]

West 1995 {published data only}

Katz J, West KP, Khattri SK, Thapa MD, LeClerq SC, Pradhan EK, et al. Impact of vitamin A supplementation on prevalence and incidence of xerophthalmia in Nepal. *Investigative Ophthalmology and Visual Science* 1995;**36**(13):2577-83. [PUBMED: 7499080]

* West KP Jr, Katz J, Shrestha SR, LeClerq SC, Khattri SK, Pradhan EK, et al. Mortality of infants <6 mo of age supplemented with vitamin A: a randomized, double-masked trial in Nepal. *The American Journal of Clinical Nutrition* 1995;**62**(1):143-8. [PUBMED: 7598058]

West KP, Khattri SK, LeClerq SC, Adhikari R, See L, Katz J, et al. Tolerance of young infants to a single, large dose of vitamin A: a randomized community trial in Nepal. *Bulletin of the World Health Organization* 1992;**70**(6):733-9. [PUBMED: 1486669]

References to studies excluded from this review
Ahmad 2014 {published data only}

Ahmad SM, Raqib R, Qadri F, Stephensen CB. The effect of newborn vitamin A supplementation on infant immune functions: trial design, interventions, and baseline data. *Contemporary Clinical Trials* 2014;**39**(2):269-79. [DOI: [10.1016/j.cct.2014.09.004](https://doi.org/10.1016/j.cct.2014.09.004)]

Bezerra 2009 {published data only}

Bezerra DS, Araújo KF, Azevêdo GM, Dimenstein R. Maternal supplementation with retinyl palmitate during immediate postpartum period: potential consumption by infants. *Revista de Saude Publica* 2009;**43**(4):572-9. [PUBMED: 19547802]

Bhaskaram 1998 {published data only}

Bhaskaram P, Balakrishna N. Effect of administration of 200,000 IU of vitamin A to women within 24 hrs after delivery on response to PPV administered to the newborn. *Indian Pediatrics* 1998;**35**(3):217-22. [PUBMED: 9707874]

Mathew 2015 {published data only}

Mathew JL. Does early neonatal vitamin A supplementation reduce infant mortality?. *Indian Pediatrics* 2015;**52**(4):329-32. [PUBMED: 25929632]

Schmiedchen 2016 {published data only}

Schmiedchen B, Longardt AC, Loui A, Buhner C, Raila J, Schweigert FJ. Effect of vitamin A supplementation on the urinary retinol excretion in very low birth weight infants. *European Journal of Pediatrics* 2016;**175**(3):365-72. [DOI: [10.1007/s00431-015-2647-9](https://doi.org/10.1007/s00431-015-2647-9)]

References to ongoing studies

McDonald 2014 {published data only}

McDonald SLR, Savy M, Fulford AJC, Kendall L, Flanagan KL, Prentice AM. A double blind randomized controlled trial in neonates to determine the effect of vitamin A supplementation on immune responses: the Gambia protocol. *BMC Pediatrics* 2014;**14**:92. [DOI: [10.1186/1471-2431-14-92](https://doi.org/10.1186/1471-2431-14-92)]

Additional references

Abrams 2008

Abrams SA, Hilmers DC. Postnatal vitamin A supplementation in developing countries: an intervention whose time has come?. *Pediatrics* 2008;**122**(1):180-1. [DOI: [10.1542/peds.2008-0455](https://doi.org/10.1542/peds.2008-0455)]

Beaton 1993

Beaton GH, Martorell R, Aronson KJ, Edmonston B, McCabe G, Ross AC, et al. Effectiveness of vitamin A supplementation in the control of young child morbidity and mortality in developing countries. ACC/SCN State-of-the-Art Series policy discussion paper no. 13. Geneva, Switzerland: World Health Organization, 1993.

Bhutta 2008

Bhutta ZA, Ahmed T, Black RE, Cousens S, Dewey K, Giugliani E, et al. Maternal and Child Undernutrition Study Group. What works? Interventions for maternal and child undernutrition and survival. *Lancet* 2008;**371**(9610):417-40. [DOI: [10.1016/S0140-6736\(07\)61693-6](https://doi.org/10.1016/S0140-6736(07)61693-6)]

Bowman 2001

Solomons NW. Vitamin A and carotenoids. In: Bowman BA, Russell RM editor(s). *Present Knowledge in Nutrition*. 8th Edition. Washington, DC: ILSI Press, 2001.

Daulaire 1992

Daulaire NM, Starbuck ES, Houston RM, Church MS, Stukel TA, Pandey MR. Childhood mortality after a high dose of vitamin A in a high risk population. *BMJ* 1992;**304**(6821):207-10. [PUBMED: 1739794]

DRI 2001

Institute of Medicine (US) Panel on Micronutrients. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: National Academies Press, 2001. [DOI: [10.17226/10026](https://doi.org/10.17226/10026)]

Fawzi 2006

Fawzi WW. The benefits and concerns related to vitamin A supplementation. *Journal of Infectious Diseases* 2006;**193**(6):756-9. [DOI: [10.1086/500369](https://doi.org/10.1086/500369)]

Gogia 2009

Gogia S, Sachdev HS. Neonatal vitamin A supplementation for prevention of mortality and morbidity in infancy: systematic review of randomised controlled trials. *BMJ* 2009;**338**:b919. [DOI: [10.1136/bmj.b919](https://doi.org/10.1136/bmj.b919)]

GRADEpro GDT [Computer program]

Grade Working Group, McMaster University. GRADEpro [www.grade-pro.org]. Version 14, September 2016. Hamilton (ON): Grade Working Group, McMaster University, 2014.

Haider 2015

Haider BA, Bhutta ZA. Neonatal vitamin A supplementation: time to move on. *Lancet* 2015;**385**(9975):1268-71. [DOI: [10.1016/S0140-6736\(14\)62342-4](https://doi.org/10.1016/S0140-6736(14)62342-4)]

Haskell 1999

Haskell MJ, Brown KH. Maternal vitamin A nutriture and the vitamin A content of human milk. *Journal of Mammary Gland Biology and Neoplasia* 1999;**4**(3):243-57. [PUBMED: 10527467]

Hathcock 1997

Hathcock JN. Vitamins and minerals: efficacy and safety. *The American Journal of Clinical Nutrition* 1997;**66**(2):427-37. [PUBMED: 9250127]

Higgins 2011

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

Hopkins 1912

Hopkins FG. Feeding experiments illustrating the importance of accessory factors in normal diets. *The Journal of Physiology* 1912;**44**(5-6):425-60. [PUBMED: 16993143]

Huiming 2005

Huiming Y, Chaomin W, Meng M. Vitamin A for treating measles in children. *Cochrane Database of Systematic Reviews* 2005, Issue 4. [DOI: [10.1002/14651858.CD001479.pub3](https://doi.org/10.1002/14651858.CD001479.pub3)]

Imdad 2010

Imdad A, Herzer K, Mayo-Wilson E, Yakoob MY, Bhutta ZA. Vitamin A supplementation for preventing morbidity and mortality in children from 6 months to 5 years of age. *Cochrane Database of Systematic Reviews* 2010, Issue 12. [DOI: [10.1002/14651858.CD008524.pub2](https://doi.org/10.1002/14651858.CD008524.pub2)]

Kirkwood 2010

Kirkwood BR, Hurt L, Amenga-Etego S, Tawiah C, Zandoh C, Danso S, et al. ObaapaVitA Trial Team. Effect of vitamin A supplementation in women of reproductive age on maternal survival in Ghana (ObaapaVitA): a cluster-randomised, placebo-controlled trial. *Lancet* 2010;**375**(9726):1640-9. [DOI: [10.1016/S0140-6736\(10\)60311-X](https://doi.org/10.1016/S0140-6736(10)60311-X)]

McCollum 1915

McCollum EV, Davis M. The influence of certain vegetable fats on growth. *Journal of Biochemistry* 1915;**21**:179-82.

Rahman 1995

Rahman MM, Mahalanabis D, Wahed MA, Islam MA, Habte D. Administration of 25,000 IU vitamin A doses at routine immunisation in young infants. *European Journal of Clinical Nutrition* 1995;**49**(6):439-45. [PUBMED: 7656887]

Rice 2004

Rice AL, West KP Jr, Black RE. Vitamin A deficiency. In: Ezzati M, Lopez AD, Rodgers A, Murray CJL editor(s). *Global and Regional Burden of Disease Attributable to Selected Major Risk Factors*. Vol. 1, Geneva: World Health Organization, 2004:211-56.

Sachdev 2008

Sachdev HP. Neonatal vitamin A supplementation and infant survival in Asia. *Lancet* 2008;**371**(9626):1746; author reply 1746-8. [DOI: [10.1016/S0140-6736\(08\)60750-3](https://doi.org/10.1016/S0140-6736(08)60750-3)]

Schünemann 2013

Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE Working Group. *GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations*. www.guidelinedevelopment.org/handbook. Updated October 2013.

Sommer 1995

Sommer A. *Vitamin A Deficiency and Its Consequences: A Field Guide to Their Detection and Control*. 3rd ed. Geneva: World Health Organization, 1995.

Sommer 1996

Sommer A, West KP Jr. *Vitamin A Deficiency: Health, Survival, and Vision*. New York: Oxford University Press, 1996.

Sommer 2002

Sommer A, Davidson FR. Assessment and control of vitamin A deficiency; Annecy Accords. *Journal of Nutrition* 2002;**132**(Suppl 9):2845S-50S. [PUBMED: 12221259]

Tielsch 2008

Tielsch JM. Vitamin A supplements in newborns and child survival. *BMJ* 2008;**336**(7658):1385-6. [DOI: [10.1136/bmj.39575.486609.80](https://doi.org/10.1136/bmj.39575.486609.80)]

Underwood 1994

Underwood BA. Maternal vitamin A status and its importance in infancy and early childhood. *The American Journal of Clinical Nutrition* 1994;**59**(2 Suppl):517S-24S. [PUBMED: 8304290]

Wallingford 1986

Wallingford JC, Underwood BA. Vitamin A deficiency in pregnancy, lactation, and the nursing child. In: Bauernfeind

CJ editor(s). *Vitamin A Deficiency and Its Control*. New York: Academic Press, 1986:101-52.

West 1999

West KP Jr, Katz J, Khatry SK, LeClerq SC, Pradhan EK, Shrestha SR, et al. Double blind, cluster randomised trial of low dose supplementation with vitamin A or beta carotene on mortality related to pregnancy in Nepal. The NNIPS-2 Study Group. *BMJ* 1999;**318**(7183):570-5. [PUBMED: 10037634]

WHO 1998

Global Programme for Vaccines and Immunizations. *Integration of Vitamin A Supplementation With Immunization: Policy and Programme Implications*. Geneva, Switzerland: World Health Organization (WHO/EPI/GEN/98.07), 1998.

WHO 2009

World Health Organization. *Global Prevalence of Vitamin A Deficiency in Populations at Risk 1995-2005*. WHO Global Database on Vitamin A Deficiency. Geneva, Switzerland: WHO, 2009.

WHO 2016

WHO. Micronutrient deficiencies: Vitamin A deficiency. <http://www.who.int/vmnis/vitamina/prevalence/en/> (accessed 28 May 2016).

WHO/CHD 1998

WHO/CHD Immunization-Linked Vitamin A Supplementation Study Group. Randomized trial to assess benefits and safety of vitamin A supplementation linked to immunization in early infancy. *Lancet* 1998;**352**(9136):1257-63. [PUBMED: 9788455]

WHO/NUT 1998

Safe vitamin A dosage during pregnancy and lactation. Geneva, Switzerland: World Health Organization (WHO/NUT/98.4), 1998.

WHO/NUT/98.1 1998

Complementary feeding of young children in developing countries: a review of current scientific knowledge. Geneva, Switzerland: World Health Organization (WHO/NUT/98.1), 1998.

References to other published versions of this review

Haider 2011

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. [DOI: [10.1002/14651858.CD006980.pub2](https://doi.org/10.1002/14651858.CD006980.pub2)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Benn 2008

Methods	Randomised, double-blind, placebo controlled trial
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Benn 2008 (Continued)

Participants	Inclusion criteria: infants weighing ≥ 2500 grams at birth with no signs of overt illness or malformation. Infants were recruited at the time of BCG vaccination. Number of participants in vitamin A group: 2145. Number in the placebo group: 2200
Interventions	0.5 mL vegetable oil, 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 child's mouth at the time of BCG vaccination
Outcomes	Mortality at 12 months 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), adverse effects (bulging fontanelle, hospitalisations, irritability, fever, frequent stools, vomiting, mother thinks the child is not well)
Notes	<p>Study was conducted in 6 urban districts in the capital of Guinea-Bissau, which is classified as an area of subclinical vitamin A deficiency (by UNICEF) and high infant mortality. HIV prevalence among women in the study area was 3% to 5%</p> <p>Given that study authors did not provide information about gestational age at delivery and that inclusion criteria included infants with birth weight ≥ 2500 grams, we included such data in the term neonate analysis while assuming that a greater proportion of these were term infants</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>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"</p> <p>Comment: probably done</p>
Allocation concealment (selection bias)	Low risk	<p>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 were prepared at Skanderborg Pharmacy"; and "The code was kept at the pharmacy until 12 months after the last child was included"</p> <p>Comment: probably done</p>
Blinding (performance bias and detection bias) All outcomes	Low risk	<p>Quote: "blinding of mothers and assistants was successful"; "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"</p> <p>Comment: blinding of participants, study personnel and outcome assessors probably done</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 1.6%. Reasons for attrition and distribution in the 2 groups were provided. Infants lost to follow-up were similar to those followed in terms of 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 it was assumed that vitamin A might be more beneficial for boys. The study was funded

Benn 2008 (Continued)

by the EU (ICA4-CT-2002-10053), the Danish Medical Research Council, the University of Copenhagen, the March of Dimes and the Ville Heise Foundation

Benn 2010

Methods	Randomised, placebo-controlled, 2-by-2 factorial trial
Participants	Inclusion criteria: infants weighing < 2500 grams at birth with no severe malformations. Number of participants in vitamin A group: 864. Number in placebo group: 872
Interventions	Neonates < 2500 grams at birth were assigned to 25,000 IU vitamin A as retinyl palmitate and 10 IU vitamin E per 0.5 mL oil or placebo, which contained only 10 IU vitamin E per 0.5 mL oil, as well as to early BCG vaccine or usual late BCG vaccine
Outcomes	Infant mortality and cause-specific infant mortality at 12 months
Notes	<ul style="list-style-type: none"> Study was conducted in 6 urban districts in the 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	<p>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)"</p> <p>Comment: probably done</p>
Allocation concealment (selection bias)	Low risk	<p>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"</p> <p>Comment: probably done</p>
Blinding (performance bias and detection bias) All outcomes	Low risk	<p>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"; "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"</p> <p>Comment: blinding of participants, study personnel and outcome assessors probably done</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Exclusions and attrition were 18.72%. Reasons and distribution in the 2 groups were provided. Numbers were balanced across treatment groups</p>

Benn 2010 (Continued)

Selective reporting (reporting bias)	Low risk	Comment: All expected outcomes, as per protocol, were reported or are under preparation (personal communication from study author)
Other bias	High risk	A protocol was provided, but post hoc analyses were conducted after it was assumed that vitamin A might be more beneficial for boys. The study was funded by the EU (ICA4-CT-2002-10053), the Danish Medical Research Council, the University of Copenhagen, the March of Dimes and the Ville Heise Foundation

Benn 2014

Methods	Randomised, double-blind, placebo-controlled trial in Guinea-Bissau
Participants	Eligible participants: healthy normal birth weight neonates who were due to be administered bacille Calmette-Guérin (BCG) vaccine. Exclusion criteria: weight < 2500 grams at presentation or overt illness/malformations
Interventions	Infants were randomly assigned in a 1:1:1 ratio to 3 different treatment groups: 50,000 IU of vitamin A; 25,000 IU of vitamin A; or placebo; concurrent with BCG vaccination
Outcomes	Infant mortality
Notes	<ul style="list-style-type: none"> The Bandim Health Project has a demographic surveillance system in 6 suburban districts of the capital of Guinea-Bissau covering ~102,000 inhabitants Enrolment into the trial took place between 29 November 2004, and 31 May 2007 Of 6053 infants invited to participate, 6048 were randomly allocated to each of the 3 treatment groups (50,000 IU vitamin A, 25,000 IU vitamin A, placebo)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "At each inclusion site, the randomization procedure was carried out by 1 carefully trained assistant every day except during short vacations. After providing consent, the mother drew a lot from an envelope"; and "the result of the randomization was noted on the inclusion form and the lot was also stapled on the inclusion form"</p> <p>Comment: probably done</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: "Each envelope was prepared by the data manager, who did not take part in the enrollment procedures, and contained 48 folded lots indicating from which of 3 numbered bottles—'3', '4', or '5'—the child should receive his or her supplement"; and "the code was kept at the pharmacy until follow-up had ended"</p> <p>Comment: probably done</p>
Blinding (performance bias and detection bias) All outcomes	Low risk	<p>Quote: "Apart from the randomization number the bottles looked alike, and small differences in taste and color of the contents were judged as being unimportant due to the recipients' age"; and "registration system assistants and the special team were unaware of the allocated treatment, because they were not present during enrollment, and the information was not transferred to the children's vaccination card or follow-up forms"</p> <p>Comment: probably done</p>

Benn 2014 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of 6053 children invited to participate, 6048 were randomly allocated to each of the 3 groups (50,000 IU vitamin A, 25,000 IU vitamin A, or placebo) (Fig. 1). The 3 randomly assigned groups were similar in terms of their background characteristics (Table 1). A total of 176 deaths occurred; 2 of these were due to accidents and were censored. Fourteen deaths occurred after the child had been eligible for a national vitamin A campaign. Hence, censoring for accidents and subsequent VAS, the cohort had 160 deaths during 4125 person-years of risk, corresponding to an MR of 39 per 1000 person-years"
Selective reporting (reporting bias)	Low risk	Comment: The published study reported on expected outcomes
Other bias	Unclear risk	<p>Quote: "We had based our sample size calculations on an infant mortality rate of 70, but in this trial it declined to 39. Although this clearly is a very positive development, it decreased our power to detect any differences between the randomly assigned groups. With the current MR, we only would have been able to show a difference of > 40% between the 2 doses. Because there was minimal difference between the 2 doses, we used the data to test findings made in our previous NVAS trial. All of these analyses were not a priori analyses pre-specified in the protocol but were formulated before we initiated the data analysis of the present trial. The trial was not sized to test these findings, and the results should be interpreted with appropriate caution"</p> <p>The Bandim Health Project receives support from the Danish International Development Agency. The Research Center for Vitamins and Vaccines (CVIVA) is funded by the Danish National Research Foundation (DNRF108). The funding agencies had no role in study design, data collection, data analysis, data interpretation or writing of the report</p>

Bhutta 2016

Methods	A community-based, cluster-randomised, placebo-controlled trial in 2 districts (Sukkhur and Jehlum) of rural Pakistan
Participants	All live-born infants within participating villages were potentially eligible for inclusion in the study. Infants with obvious congenital malformations and birth weight less than 1500 grams were excluded
Interventions	Intervention was vitamin A capsule containing (50,000 units) retinol palmitate in soybean oil. Placebo contained minute amounts of vitamin E (10 IU) in soybean oil
Outcomes	Primary outcome was all-cause mortality within the first six months of life. Secondary outcomes were common morbidities (febrile illness, diarrhoea or pneumonia)
Notes	<ul style="list-style-type: none"> • Trial was conducted between January 2007 and October 2010 • A total of 11,028 consecutively delivered newborns participated in the study; 5380 (49%) received VAS, and 5648 (51%) placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "This was a cluster randomized, placebo-controlled trial"; and "an external consultant generated the computerized allocation sequence of clusters to each study intervention to either group using Epi Info 3.5.3 with restricted randomization based on population size, expected births and LHW presence"

Bhutta 2016 (Continued)

Comment: probably done		
Allocation concealment (selection bias)	Low risk	Quote: "An external consultant generated the computerized allocation sequence of clusters to each study intervention to either group using Epi Info 3.5.3 with restricted randomization based on population size, expected births and LHW presence"
Comment: probably done		
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The capsules were identical in appearance (Banner Pharmacaps, Canada) and supplied through the courtesy of the Micronutrient Initiative (Ottawa, Canada). The capsules were packaged in containers labeled as A & B. The content of the capsules were masked from field staff and supervisors, and the codes were only known to the external consultant responsible for cluster randomization and the chair of the DSMB. The masking was maintained until the completion of the study"
Comment: probably done		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "We were able to follow 10,286 (93%) infants until death or 6 months of age"
Selective reporting (reporting bias)	Low risk	Comment: The published study reported on all expected outcomes
Other bias	Unclear risk	Protocol was not mentioned. This study was funded by PAIMAN (Pakistan Initiative for Mothers and Newborns)/John Snow Inc. via a grant funded by USAID, Award Number: Subagreement #36098-01 (USAID Co-operative Agreement #391-A-00-05-01037-00). The funding body provided clearance for the project design but, apart from field visits to review progress, did not influence the field trial or data analysis procedures

Edmond 2015

Methods	Randomised, double-blind, 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	Trial participants were at least 2 hours old, were identified at home or at facilities on the day of birth or in the next 2 days, were able to feed orally, and were likely to stay in the study area for at least 6 months; at least 1 parent provided written informed consent for participation
Interventions	Intervention was retinol palmitate (50,000 IU) and minute amounts of vitamin E in soybean oil, given orally as a single dose to neonates on the day of birth or in the next 2 days after birth, with a minimum period of 2 hours between birth and dosing. Placebo capsules contained minute amounts of vitamin E (9.5–12.6 IU) in soybean oil
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, over 3 days following administration of the supplement; vitamin A and C-reactive protein (CRP) status of a subsample of infants at 2 weeks and 3 months of age
Notes	<ul style="list-style-type: none"> Study population was estimated at 600,000 and included about 120,000 women of reproductive age. This area had low HIV prevalence (2.0% in 2011)

Edmond 2015 (Continued)

- Infants born between 16 August 2010, and 7 November 2011, were considered
- 16,792 (73.2%) infants were dosed within 24 hours of birth

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The computerised block randomisation scheme was done with a block size of 20, so that in each block ten infants received vitamin A and ten received placebo" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "An independent statistician who was not part of the trial prepared the randomisation code at the WHO offices in Geneva, Switzerland. The code was available only to the Data Safety and Monitoring Board (DSMB) and their statistician" Comment: probably done
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The research team and parents were fully unaware of the content of the capsules, which were only labelled with the infant number. A manufacturer (Strides Arcolab Limited, Bangalore, India) supplied the capsules. Separate staff, who were not part of the trial, labelled all capsules" Comment: blinding of participants, study personnel and outcome assessors probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Our loss to follow-up was only 1.1% at the time of ascertainment of our primary outcome at 6 months and only 2.9% at 12 months" Comment: Mortality and attrition distribution in the 2 groups was provided and appeared balanced
Selective reporting (reporting bias)	Low risk	Comment: The published study reported on all expected outcomes
Other bias	Unclear risk	75 protocol violations occurred, and all protocol violations were included in the analyses. The published protocol is available. The trial was funded by a grant from the Bill & Melinda Gates Foundation to WHO

Humphrey 1996

Methods	Randomised, placebo-controlled trial
Participants	Eligible for inclusion: all neonates within 24 hours of birth. Exclusion criteria: very low birth weight babies (< 1500 grams); those with life-threatening illness such as severe respiratory distress syndrome, major congenital anomalies, paralysis, hypoglycaemia and hypocalcaemia; clinical evidence of ischaemic hypoxia or sepsis. 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; placebo, n = 1033
Outcomes	Mortality at 6 months and 12 months of age, cause-specific mortality at 12 months 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

Humphrey 1996 (Continued)

- Notes
- Infants born at Hasan Sadikin Hospital, in Bandung, Indonesia, from 18 June 1992, to 3 June 1993, were considered
 - Mean age of dosing was 16.2 (SD 8.2) hours; 88.2% were dosed in first 24 hours of life after birth
 - Treatment groups were comparable at baseline

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 2 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 provided no details. Supported by a grant from John Hopkins University and assistance from Hoffmann-LaRoche industry (Basel, Switzerland)

Klemm 2008

Methods	Community-based, double-masked, cluster-randomised, placebo-controlled trial
Participants	Eligible for inclusion in the study: infants born to consenting mothers who were participating in the parent trial Vitamin A group infants whose mothers consented = 8525 Placebo group infants whose mothers consented = 8591 Exclusion criteria: infants of consenting mothers who had died before they could be supplemented by staff, those who were born outside of the study area, infants who could not be reached to receive a supplement after repeated staff visits during the first 30 days after birth
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, adverse effects

Klemm 2008 (Continued)

Notes

- Trial was nested into an ongoing, placebo-controlled, weekly, low-dose vitamin A or beta-carotene supplementation trial among pregnant women, which was under way 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 maternal supplementation trial arms. Interaction between maternal and vitamin A supplementation was non-significant
- Approximately 84% were 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 were 7%. Reasons and distribution in the 2 groups were provided. Attrition and reasons for attrition were balanced across treatment groups
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 was halted before conclusions because mortality in the placebo group was significantly higher than in the intervention group after 2/3 of infants were randomised. Results were adjusted by cluster effect. Sources of funding: John Hopkins University (GHS-A-00-03-00019-00), Bill and Melinda Gates Foundation

Malaba 2005

Methods	Randomised, placebo-controlled, 2-by-2 factorial design trial
Participants	Mother and infant pairs were enrolled within 96 hours of delivery. Pairs were eligible if neither member of the pair had an acutely life-threatening condition, the infant was a singleton with birth weight > 1500 grams and the mother planned to stay in Harare after delivery Mothers and infants were assigned to the following 4 groups <ul style="list-style-type: none"> • Mothers received 400,000 IU vitamin A and infants received 50 000 IU vitamin A (Aa group) = 3529

Malaba 2005 (Continued)

- Mothers received 400,000 IU vitamin A and infants received placebo (Ap group) = 3529
- Mothers received placebo and infants received 50,000 IU vitamin A (Pa group) = 3530
- 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 months and 12 months, cause-specific infant mortality at 12 months, anaemia and haemoglobin in infants, MTCT of HIV in infants born to HIV-positive mothers
Notes	<ul style="list-style-type: none"> • Zimbabwe is categorised 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 treatment dose within 24 hours; 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>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"</p> <p>Comment: probably done</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: "numbers were printed on adhesive labels and affixed to amber-coloured zip-lock plastic bags"; and "capsules in the next sequential bag were administered..... files"</p> <p>Comment: probably done</p>
Blinding (performance bias and detection bias) All outcomes	Low risk	<p>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"</p> <p>Comment: blinding of participants, study personnel and outcome assessors probably done</p>
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Exclusions and attrition were 41.8%. Reasons for exclusion included HIV positive or HIV indeterminate at baseline or 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 was provided by the Rockefeller Foundation (New York) and BASF (Ludwigshafen, Germany)"

Masanja 2015

Methods	Randomised, double-blind, placebo-controlled trial of infants born in the Morogoro and Dar es Salaam regions of Tanzania
Participants	Eligible participants: neonates whose parents consented to participate, were likely to stay in the study area until at least 6 months of age and were able to feed orally at the time of enrolment Both singleton and multiple births were eligible for enrolment. Excluded were babies who were enrolled in other trials
Interventions	Intervention was retinol palmitate (50,000 IU) and minute amounts of vitamin E in soybean oil, given orally as a single dose to neonates on the day of birth or over the next 2 days after birth with a minimum period of 2 hours between birth and dosing. Placebo capsules contained minute amounts of vitamin E (9.5–12.6 IU) in soybean oil
Outcomes	Primary outcome was death between supplementation and 180 days of age (6 months). Secondary outcomes were defined as death between supplementation and 28 days of age, death between supplementation and 365 days of age and hospital admission during the first 6 months of life, which was defined as admission to hospital as an inpatient as reported by the mother. In the case of more than 1 hospital admission; each infant contributed only the first admission to the analysis. Adverse events were defined as any harmful or undesired effects reported by the family within 3 days of supplementation. These included death, presence of bulging fontanelle confirmed by research team through physical examination of the infant, vomiting, fever, diarrhoea, inability to suck or feed and convulsions
Notes	<ul style="list-style-type: none"> • In Dar es Salaam, mothers and newborn babies were enrolled from 10 large antenatal clinics and labour wards in catchment areas, and in the Morogoro region, the study was nested within the Ifakara Health Institute's health and demographic surveillance system (HDSS) • All births that occurred as part of the HDSS or at designated labour wards were eligible for screening • 34,133 live births between 26 August 2010, and 3 March 2013, were identified and were assessed for eligibility • Most (24,888; 78%) infants received vitamin A or placebo within 24 hours

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Block randomisation was done at WHO (Geneva, Switzerland) in block sizes of 20 (ten infants received vitamin A and ten received placebo)" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "Codes for the experimental regimens were kept with the data and safety monitoring board and broken during the analysis after a cleaned and locked database for the study was submitted to WHO" Comment: probably done
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The vitamin A and placebo capsules were identical in taste and appearance. Capsules were individually packed in blister packs of two capsules each; one for the dose and the second for the backup dose. Labels for the capsules were printed at WHO with country and infant study number in sequential order. Labels were first fixed on blister packs containing vitamin A capsules. The capsules were then packed in sealed boxes and removed from the packing room before the next treatment group was brought in. Investigators had no access to the randomisation list or to any information that would allow them to deduce the allocation. Participants' families, and trial personnel (including those distributing capsules and collecting, processing, and analysing data) were masked to treatment assignment for the duration of the trial"

Masanja 2015 (Continued)

		Comment: blinding of participants, study personnel and outcome assessors probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Our study had high ascertainment of the outcomes of interest, as shown by the low loss to follow-up rates both at 6 months (3.5%) and at 12 months of age (4.8%), despite many challenges throughout the implementation of the study" Comment: Mortality and attrition distribution in the 2 groups was provided and appeared balanced
Selective reporting (reporting bias)	Low risk	Comment: The published study reported on all expected outcomes
Other bias	Unclear risk	This trial was funded by a grant from the Bill & Melinda Gates Foundation to WHO. The published protocol is available. Study authors stated differences from the protocol and lack of power to detect differences between randomly assigned groups

Mazumder 2015

Methods	Double-blind, randomised, placebo-controlled trial in 2 districts (Faridabad and Palwal) in the state of Haryana, India
Participants	Eligible participants: neonates whose parents consented to participate, were likely to stay in the study area until at least 6 months of age and were able to feed orally at the time of enrolment Both singleton and multiple births were eligible for enrolment
Interventions	Intervention was retinol palmitate (50,000 IU) and minute amounts of vitamin E in soybean oil, given orally as a single dose to neonates on the day of birth or over the next 2 days after birth with a minimum period of 2 hours between birth and dosing. Placebo capsules contained minute amounts of vitamin E (9.5–12.6 IU) in soybean oil
Outcomes	Primary outcome was death between supplementation and 180 days of age (6 months). Secondary outcomes were deaths between supplementation and 28 days of age (neonatal period), deaths between supplementation and 365 days of age (12 months), admission of an infant to hospital 1 or more times because of any illness between supplementation and 180 days of age, potential adverse events during the 3-day period after supplementation and vitamin A status in a subsample of infants at 2 weeks and 3 months of age
Notes	<ul style="list-style-type: none"> • Neonates were screened between 24 June 2010, and 1 July 2012 • 44,984 neonates were randomly assigned to receive vitamin A (22,493) or placebo (22,491)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We randomly assigned infants using a block randomisation scheme with a block size of 20, so that in each block ten infants received vitamin A and ten received placebo" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation list was prepared offsite at WHO (Geneva, Switzerland) by a statistician not otherwise involved with the trial. After preparation of the supplements, the code was available only to the data safety monitoring board until trial termination"

Mazumder 2015 (Continued)

Comment: probably done

Blinking (performance bias and detection bias) All outcomes	Low risk	Quote: "The vitamin A and placebo capsules were identical in colour, shape, and size. Capsules were individually packaged in identical blister packs with two capsules, one for the dose and the other as a backup. Labels with a unique infant number based on the randomisation list were printed at WHO and under WHO staff supervision affixed on the appropriate capsule strips of vitamin A or placebo, which were then sent to the study site. The research team, parents, data analysis team, and safety board were unaware of the content of the capsules in the strip" Comment: blinding of participants, study personnel and outcome assessors probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up was extremely low (47/44,984; 0.1%) at 12 months. Mortality and attrition distribution in the 2 groups was provided and appeared balanced
Selective reporting (reporting bias)	Low risk	Comment: The published study reported on all expected outcomes
Other bias	Unclear risk	Quote: "The capsule could not be given to one infant randomly assigned to the vitamin A group. 4715 (21.6%) infants in the vitamin A group and 4552 (20.9%) in the placebo group received vitamin A supplementation not given by study investigators during follow-up" The trial was funded by a grant from the Bill & Melinda Gates Foundation to WHO. The published protocol is available

Rahmathullah 2003

Methods	Randomised, placebo-controlled, community-based trial
Participants	Eligible for participation: live-born infants who resulted from all pregnancies within participating villages. Pregnant women (> 12 weeks) were identified for recruitment from a variety of sources. Infants were randomly assigned to receive the intervention or placebo Exclusions after randomisation: stillbirths, miscarriages, delivery more than 20 km outside the study area, infants who died before the study team was 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 colonisation
Notes	<ul style="list-style-type: none"> Conducted between June 1998 and March 2001 in 2 rural districts of Tamil Nadu, southern India These areas are characterised by endemic vitamin A deficiency Expected infant mortality at 6 months of age: 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
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Rahmathullah 2003 (Continued)

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 was provided to allow judgement of allocation concealment for singleton births. However, for triplets (only 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 were 18.9%. Reasons and distributions in the 2 treatment groups were reported. Mortality in infants born alive but not enrolled was similar across 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 University and 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 were 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 month of age) and 30,000 RE (100,000 IU) in 6 drops of oil for infants 1-5 months 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 as follows: intervention = 791, control = 830
Outcomes	4-Month mortality, cause-specific mortality, adverse effects noted after 24 hours of dosing (vomiting, loose stools, fever, irritability, bulging fontanelles)
Notes	<ul style="list-style-type: none"> Conducted in district of Sarlahi, Nepal, between September 1989 and December 1991 Evaluated effect of VAS every 4 months on preschool child mortality No information about gestational age and birth weight recorded, and almost all neonates supplemented after the first week of life (Keith West, personnel communication, 2008) Treatment groups were comparable at baseline 4-Month mortality estimates 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 24-hour measurements from this trial

West 1995 (Continued)

in the analysis. This trial found no difference in the incidence of various adverse effects after 24 hours of supplementation in the 2 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 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"; "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 probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition among neonates was 1.04%; reasons were not provided. All analyses were performed on an intention-to-treat basis, that is, by randomised treatment group, irrespective of individual compliance with dosing regimen
Selective reporting (reporting bias)	Low risk	Comment: Published reports included all expected outcomes
Other bias	Unclear risk	Supported by a grant from Johns Hopkins University with assistance from Hoffmann-LaRoche industry (Basel, Switzerland). A protocol is described, but no details are provided

BCG: Bacille Calmette-Guérin

CRP: C-reactive protein

HIV: human immunodeficiency virus

MTCT: mother-to-child transmission

PPD: purified protein derivative

RBP: retinol binding protein

VAS: visual analogue scale

WHO: World Health Organization

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ahmad 2014	This study reported no relevant outcomes
Bezzera 2009	This study included supplementation of mothers only with vitamin A supplements during the immediate postpartum period and no vitamin A supplementation of neonates
Bhaskaram 1998	This study included supplementation of mothers only with vitamin A supplements within 24 hours of delivery; all neonates were given oral poliovirus vaccine (OPV) between 48 and 72 hours after birth

Study	Reason for exclusion
Mathew 2015	This paper was a commentary on an included study (Mazumder 2014)
Schmiedchen 2016	Study participants were infants with birth weight below 1500 grams and gestational age less than 33 weeks

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

[McDonald 2014](#)

Trial name or title	A Double Blind Randomized Controlled Trial in Neonates to Determine the Effect of Vitamin A Supplementation on Immune Responses
Methods	Double-blind, randomised, placebo-controlled trial in a peri-urban area of The Gambia
Participants	Two hundred mother-infant pairs were recruited at the Sukuta Health Centre, a government health clinic in the Western coastal region of The Gambia. Inclusion criteria: singleton birth, birth weight $\geq$ 1500 grams, mothers over 18 years of age, residency within the study area and administration of birth vaccinations and vitamin A supplementation within 48 hours of birth. Exclusion criteria: infants with a congenital disease, a serious infection at birth or inability to feed; mothers who were seriously ill at the time of enrolment, mothers participating in other studies and/or mothers who were HIV positive
Interventions	Within 48 hours of birth, neonates were randomised to receive an oral dose of 50,000 IU vitamin A or placebo
Outcomes	Primary outcome is the frequency of circulating T regulatory (Treg) cells expressing gut homing receptors in infants at 17 weeks post supplementation. Secondary outcomes are differences in thymus size (assessed at 1, 6, 12 and 17 weeks), differences in B cell immune responses after routine vaccination (assessed at 6 and 17 weeks) and improved mucosal barrier function (assessed at 6 and 17 weeks) in infant participants
Starting date	November 2011
Contact information	Suzanna McDonald Medical Research Council (MRC) International Nutrition Group (ING), London School of Hygiene & Tropical Medicine (LSHTM), Keppel Street, WC1E 7HT, United Kingdom & MRC Keneba, London, The Gambia Suzanna.McDonald@lshtm.ac.uk
Notes	<ul style="list-style-type: none"> Recruitment commenced in December 2011 and was completed in October 2012 The last study participant reached the 17th week of life in February 2013 and graduated from the trial in October 2013

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)	11		Risk Ratio (Random, 95% CI)	Subtotals only
1.1 Term infants	3	22721	Risk Ratio (Random, 95% CI)	0.80 [0.54, 1.18]
1.2 All infants	11	154634	Risk Ratio (Random, 95% CI)	0.98 [0.89, 1.07]
1.3 All infants - male	5	65017	Risk Ratio (Random, 95% CI)	1.01 [0.92, 1.12]
1.4 All infants - female	5	60518	Risk Ratio (Random, 95% CI)	0.95 [0.84, 1.08]
1.5 All infants - Asia	6	86391	Risk Ratio (Random, 95% CI)	0.89 [0.80, 0.99]
1.6 All infants - Africa	5	68243	Risk Ratio (Random, 95% CI)	1.10 [1.00, 1.21]
2 All-cause infant mortality at 6 months: rate ratios (per years of follow-up)	5		Rate Ratio (Random, 95% CI)	Subtotals only
2.1 Term infants	2		Rate Ratio (Random, 95% CI)	0.93 [0.67, 1.30]
2.2 All infants	5		Rate Ratio (Random, 95% CI)	0.99 [0.84, 1.17]
2.3 All infants - male	2		Rate Ratio (Random, 95% CI)	0.88 [0.58, 1.35]
2.4 All infants - female	2		Rate Ratio (Random, 95% CI)	1.01 [0.79, 1.30]
2.5 All infants - Asia	2		Rate Ratio (Random, 95% CI)	0.85 [0.64, 1.13]
2.6 All infants - Africa	3		Rate Ratio (Random, 95% CI)	1.09 [0.96, 1.23]
3 All-cause infant mortality at 12 months: risk ratios based on cumulative risk (%)	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 All infants	8	118376	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.94, 1.15]
3.2 All infants - male	3	50164	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.14]
3.3 All infants - female	3	46542	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.90, 1.20]
3.4 All infants - Asia	2	46823	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.26, 1.60]
3.5 All infants - Africa	6	71553	Risk Ratio (M-H, Random, 95% CI)	1.08 [1.00, 1.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 All-cause infant mortality at 12 months: rate ratios (per years of follow-up)	6		Rate Ratio (Random, 95% CI)	Subtotals only
4.1 Term infants	3		Rate Ratio (Random, 95% CI)	0.94 [0.59, 1.50]
4.2 All infants	6		Rate Ratio (Random, 95% CI)	1.06 [0.92, 1.22]
4.3 All infants - male	5		Rate Ratio (Random, 95% CI)	0.89 [0.66, 1.19]
4.4 All infants - female	5		Rate Ratio (Random, 95% CI)	1.21 [1.05, 1.41]
4.5 All infants - Asia	3		Rate Ratio (Random, 95% CI)	0.94 [0.69, 1.29]
4.6 All infants - Africa	3		Rate Ratio (Random, 95% CI)	1.13 [0.94, 1.36]
5 Cause-specific infant mortality at 6 months (all infants): diarrhoea	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 infection	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-specific infant mortality at 12 months (all infants): respiratory infection	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	3		Rate ratio (Random, 95% CI)	0.89 [0.69, 1.14]
9.1 All Diarrhoea	3		Rate ratio (Random, 95% CI)	0.89 [0.69, 1.14]
10 Infant morbidity at 6 months (rate ratio): respiratory infection	2		Rate ratio (Random, 95% CI)	1.05 [0.91, 1.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11 Vitamin A deficiency (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 deficiency (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 < 105 g/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	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 Bulging fontanelle	5	100256	Risk Ratio (M-H, Random, 95% CI)	1.53 [1.11, 2.11]
14.2 Diarrhoea	5	102638	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.81, 1.13]
14.3 Vomiting	5	99582	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.93, 1.07]
14.4 Fever	3	96865	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.98, 1.09]
14.5 Inability to suck or feed	3	96598	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.81, 1.23]
14.6 Convulsions	3	96853	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.66, 1.88]
14.7 Excessive crying	1	44961	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.93, 1.05]
14.8 Jaundice	1	44961	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.96, 1.19]
14.9 Eye infection	1	44961	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.88, 1.12]
14.10 Skin infection	1	44961	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.09]
14.11 Umbilical infection	1	44961	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.81, 1.15]
14.12 Respiratory infection	1	44961	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.94, 1.24]
14.13 Feeding problems	1	44961	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.88, 1.16]
14.14 Others	1	44961	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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]
16 All-cause neonatal mortality: risk ratios based on cumulative risk (%), adjusted for clustering)	5		Risk Ratio (Fixed, 95% CI)	Subtotals only
16.1 All infants	5	126242	Risk Ratio (Fixed, 95% CI)	0.99 [0.90, 1.08]
16.2 All infants - male	4	57254	Risk Ratio (Fixed, 95% CI)	1.01 [0.87, 1.17]
16.3 All infants - female	4	53047	Risk Ratio (Fixed, 95% CI)	1.03 [0.89, 1.19]
17 All-cause neonatal mortality: rate ratios (person-years of follow-up)	1		Rate Ratio (Fixed, 95% CI)	Subtotals only
17.1 All infants	1		Rate Ratio (Fixed, 95% CI)	1.04 [0.86, 1.25]
17.2 All male infants	1		Rate Ratio (Fixed, 95% CI)	0.99 [0.77, 1.27]
17.3 All female infants	1		Rate Ratio (Fixed, 95% CI)	1.10 [0.82, 1.49]

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).

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).

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

Study or subgroup	Vitamin A n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 1311 (Vitamin A), 1165 (Control)					
Heterogeneity: $\tau^2=0$; $\chi^2=1.84$, $df=5$ ($P=0.87$); $I^2=0\%$					
Test for overall effect: $Z=2.06$ ($P=0.04$)					
Test for subgroup differences: $\chi^2=2.33$, $df=1$ ($P=0.68$), $I^2=0\%$

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).

Study or subgroup	Vitamin A N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
1.4.1 Term infants						
Benn 2008	0	0	0.1 (0.152)		41.81%	1.07[0.79,1.44]
Benn 2014	0	0	0.2 (0.176)		39.55%	1.28[0.91,1.81]
Humphrey 1996	0	0	-1 (0.442)		18.63%	0.36[0.15,0.86]
Subtotal (95% CI)					100%	0.94[0.59,1.5]
Heterogeneity: $\tau^2=0.12$; $\chi^2=7.13$, $df=2$ ($P=0.03$); $I^2=71.95\%$						
Test for overall effect: $Z=0.26$ ($P=0.79$)						
1.4.2 All infants						
Benn 2008	0	0	0.1 (0.152)		15.59%	1.07[0.8,1.44]
Benn 2010	0	0	0.1 (0.158)		14.63%	1.08[0.79,1.47]
Benn 2014	0	0	0.2 (0.176)		12.5%	1.28[0.91,1.81]
Humphrey 1996	0	0	-1 (0.442)		2.44%	0.36[0.15,0.86]
Malaba 2005	0	0	0.1 (0.153)		15.32%	1.08[0.8,1.47]
Masanja 2015	0	0	0 (0.06)		39.53%	1.04[0.92,1.17]
Subtotal (95% CI)					100%	1.06[0.92,1.22]
Heterogeneity: $\tau^2=0.01$; $\chi^2=7.27$, $df=5$ ($P=0.2$); $I^2=31.24\%$						
Test for overall effect: $Z=0.8$ ($P=0.42$)						
1.4.3 All infants - male						
Benn 2008	0	0	-0.2 (0.212)		22.07%	0.84[0.56,1.28]
Benn 2010	0	0	-0.3 (0.245)		19.22%	0.73[0.45,1.19]
Benn 2014	0	0	0.3 (0.24)		19.65%	1.35[0.84,2.16]
Humphrey 1996	0	0	-1.9 (0.76)		3.56%	0.15[0.03,0.66]
Masanja 2015	0	0	-0 (0.079)		35.51%	0.95[0.82,1.12]
Subtotal (95% CI)					100%	0.89[0.66,1.19]
Heterogeneity: $\tau^2=0.06$; $\chi^2=9.47$, $df=4$ ($P=0.05$); $I^2=57.74\%$						
Test for overall effect: $Z=0.81$ ($P=0.42$)						
1.4.4 All infants - female						
Benn 2008	0	0	0.3 (0.221)		11.5%	1.39[0.9,2.14]
Benn 2010	0	0	0.4 (0.213)		12.38%	1.42[0.94,2.16]
Benn 2014	0	0	0.2 (0.259)		8.36%	1.21[0.73,2]
Humphrey 1996	0	0	-0.2 (0.606)		1.53%	0.84[0.25,2.74]
Masanja 2015	0	0	0.2 (0.092)		66.23%	1.16[0.97,1.39]
Subtotal (95% CI)					100%	1.21[1.05,1.41]
Heterogeneity: $\tau^2=0$; $\chi^2=1.55$, $df=4$ ($P=0.82$); $I^2=0\%$

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

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

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

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

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

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

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

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

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

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

Analysis 1.14. 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, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.14.1 Bulging fontanelle					
Benn 2008	60/551	56/599		22.62%	1.16[0.82,1.65]
Edmond 2015	32/11421	21/11430		16.16%	1.53[0.88,2.64]
Humphrey 1996	46/1007	25/1001		18.23%	1.83[1.13,2.95]
Masanja 2015	21/15000	20/14286		14.52%	1[0.54,1.84]
Mazumder 2015	466/22480	220/22481		28.46%	2.12[1.81,2.48]
Subtotal (95% CI)	50459	49797		100%	1.53[1.11,2.11]
Total events: 625 (Intervention), 342 (Control)					
Heterogeneity: Tau ² =0.09; Chi ² =14.01, df=4(P=0.01); I ² =71.45%					
Test for overall effect: Z=2.6(P=0.01)					
1.14.2 Diarrhoea					
Benn 2008	103/551	146/599		23.23%	0.77[0.61,0.96]
Edmond 2015	80/11421	92/11430		17.48%	0.87[0.65,1.17]
Humphrey 1996	104/1008	90/1001		19.62%	1.15[0.88,1.5]
Masanja 2015	3/15000	5/16667		1.3%	0.67[0.16,2.79]
Mazumder 2015	2021/22480	1911/22481		38.39%	1.06[1,1.12]
Subtotal (95% CI)	50460	52178		100%	0.96[0.81,1.13]
Total events: 2311 (Intervention), 2244 (Control)					
Heterogeneity: Tau ² =0.02; Chi ² =9.6, df=4(P=0.05); I ² =58.34%					
Test for overall effect: Z=0.51(P=0.61)					
1.14.3 Vomiting					
Benn 2008	104/551	123/599		8.25%	0.92[0.73,1.16]
Edmond 2015	254/11421	248/11430		15.01%	1.03[0.86,1.22]
Humphrey 1996	92/1008	109/1001		6.53%	0.84[0.64,1.09]
Masanja 2015	26/14444	17/14167		1.22%	1.5[0.81,2.76]
Mazumder 2015	1183/22480	1172/22481		68.99%	1.01[0.93,1.09]
Subtotal (95% CI)	49904	49678		100%	1[0.93,1.07]
Total events: 1659 (Intervention), 1669 (Control)					
Heterogeneity: Tau ² =0; Chi ² =4.05, df=4(P=0.4); I ² =1.14%					
Test for overall effect: Z=0.1(P=0.92)					
1.14.4 Fever					
Edmond 2015	278/11421	263/11430		9.56%	1.06[0.9,1.25]
Masanja 2015	174/14500	179/14553		6.17%	0.98[0.79,1.2]
Mazumder 2015	2242/22480	2161/22481		84.27%	1.04[0.98,1.1]
Subtotal (95% CI)	48401	48464		100%	1.04[0.98,1.09]
Total events: 2694 (Intervention), 2603 (Control)

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

Analysis 1.16. Comparison 1 Neonatal vitamin A supplementation versus control, Outcome 16 All-cause neonatal mortality: risk ratios based on cumulative risk (%), adjusted for clustering).

Analysis 1.17. Comparison 1 Neonatal vitamin A supplementation versus control, Outcome 17 All-cause neonatal mortality: rate ratios (person-years of follow-up).

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/risk ratio	Correspondence with study investigators; published paper	All infants	55	964	2106	50	1003	2169
Benn 2010	Rate ratio/risk ratio	Correspondence with study investigators; published paper	All infants	62	393	854	62	397	863
Benn 2014	-	-	-	-	-	-	-	-	-
Bhutta 2016 ^a	Risk ratio	Soofi et al (unpublished data)	All infants	128	-	5648	115	-	5380
			All infants - male	58	-	2966	49	-	2774
			All infants - female	70	-	2682	66	-	2606
Edmond 2015	Risk ratio	Edmond et al (Lancet 2015;385:1315-23)	All infants	278	-	11,345	248	-	11,353
			All infants - male	150	-	5802	124	-	5715
			All infants - female	128	-	5543	124	-	5638
Humphrey 1996	Risk ratio	Correspondence with study investigators (denominators are numbers of neonates randomised)	All infants	7	-	1034	18	-	1033
			Term infants	6	-	1011	15	-	1007
Klemm 2008 ^b	Risk ratio	Klemm et al (Pediatrics 2008;122:e242-50)	All infants	306	-	7953	360	-	7984
			Term infants	129	-	6109	171	-	6061
			All infants - male	169	-	4117	185	-	4020

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

			All infants - fe- male	137	-	3836	175	-	3964
Malaba 2005	Risk ratio	Correspondence with study investigators. Data aggregated for the 4 treatment groups: maternal vitamin A and infant vitamin A + maternal placebo and infant vitamin A vs maternal placebo and infant placebo + maternal vitamin A and infant placebo (for term infants, denominators are numbers of HIV-negative mothers with term deliveries)	All infants	73	-	4309	66	-	4352
			Term infants	62	-	4253	57	-	4280
Masanja 2015	Rate ratio/ risk ratio	Masanja et al (Lancet 2015;385:1324-32)	All infants	407	7521	15,428	372	7542	15,464
			All infants - male	233	3960	8135	215	3927	8070
			All infants - fe- male	174	3559	7291	157	3614	7392
Mazumder 2015	Risk ratio	Muzumder et al (Lancet 2015;385:1333-42)	All infants	656	-	22,493	726	-	22,491
			All infants - male	293	-	11,689	310	-	11,729
			All infants - fe- male	363	-	10,804	416	-	10,762
Rahmath- ullah 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	-
		Rahmathullah et al (BMJ 2003;327(7409):254)	All infants - male	68	1378.2	-	100	1412.3	-
		Rahmathullah et al (BMJ 2003;327(7409):254)	All infants - fe- male	78	1334.8	-	88	1306.7	-
West 1995 c	Rate ratio/ risk ratio	West et al (American Journal of Clinical Nutrition 1995;62:143-8). Data were ex-	All infants	38	268.4	819	34	256.9	785

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

^a [Bhutta 2016](#) was a cluster-randomised study. Study investigators reported that observed design effect and intracluster coefficient (ICC) for infant mortality at 6 months were 1.26666 and 0.00978

^b [Klemm 2008](#) was a cluster-randomised study. Study authors reported that observed design effect was 0.9%

^c [West 1995](#) was a cluster-randomised study. Study authors reported that 95% confidence intervals of effect estimates were inflated by 10% to account for the impact of the design on the study. We estimated that the 10% increase in 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 ra- tio	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 ra- tio/risk ratio	Benn et al (BMJ 2008;336(7658):1416-20)	All infants	88	1795	2106	86	1884	2169
Benn 2010	Rate ra- tio/risk ratio	Benn et al (BMJ 2010;340:c1101)	All infants	83	757	701	78	762	710
Benn 2014	Rate ra- tio/risk ratio	Benn et al (Journal of Nutrition 2014;144:1474-9)	All infants	115	2744	3948	45	1377	1987
			All infants - male	63	1406	-	24	724	-
			All infants - female	52	1339	-	21	653	-
Bhutta 2016	-	-	-	-	-	-	-	-	-
Edmond 2015	Risk ratio	Edmond et al (Lancet 2015;385:1315-23)	All infants	371	-	11,133	328	-	11,158
			All infants - male	199	-	5676	166	-	5612
			All infants - female	172	-	5457	162	-	5546
Humphrey 1996	Rate ra- tio/risk ratio	Humphrey et al (Journal of Pedi- atrics 1996;128:489-96)	All infants (include 6% preterms)	7	969.6	925	19	957.1	914

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

			All infants - male	2	505.8	-	13	492.1	-
			All infants - female	5	463.9	-	6	465	-
Klemm 2008	-	-	-	-	-	-	-	-	-
Malaba 2005	Rate ratio/ Risk ratio	Malaba et al (American Journal of Clinical Nutrition 2005;81:454-60). Data aggregated for the 4 treatment groups: maternal vitamin A and infant vitamin A + maternal placebo and infant vitamin A vs maternal placebo and infant placebo + maternal vitamin A and infant placebo	All infants	88	4195	4079	82	4239	4127
Masanja 2015	Rate ratio/ Risk ratio	Masanja et al (Lancet 2015;385:1324-32)	All infants	566	15,010	14,686	546	15,059	14,749
			All infants - male	312	7899	7745	324	7833	7713
			All infants - female	254	7108	6939	222	7223	7034
Mazumder 2015	Risk ratio	Muzumder et al (Lancet 2015;385:1333-42)	All infants	879	-	22,493	939	-	22,491
			All infants - male	371	-	11,689	396	-	11,729
			All infants - female	508	-	10,804	543	-	10,762
Rahmath-ullah 2003	-	-	-	-	-	-	-	-	-
West 1995	-	-	-	-	-	-	-	-	-

Table 3. Data type and source: all-cause neonatal mortality

Study ID	Analyzed as rate/ risk ratio	Data source	Infants	Vitamin A group: deaths	Vitamin A group: n	Vitamin A group: n	Control group: deaths	Control group: n	Control group: n
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Table 3. Data type and source: all-cause neonatal mortality (Continued)

					child- years of follow-up			child- years of follow-up	
Benn 2008	-	-	-	-	-	-	-	-	-
Benn 2010	-	-	-	-	-	-	-	-	-
Benn 2014	-	-	-	-	-	-	-	-	-
Bhutta 2016	Risk ratio	Soofi et al (unpublished data)	All infants	57	-	5648	48	-	5380
			All infants - male	26	-	2966	21	-	2774
			All infants - female	31	-	2682	27	-	2606
Edmond 2015	Risk ratio	Edmond et al (Lancet 2015;385:1315–23)	All infants	147	-	11,447	130	-	11,459
			All infants - male	79	-	5857	69	-	5768
			All infants - female	68	-	5590	61	-	5691
Humphrey 1996	-	-	-	-	-	-	-	-	-
Klemm 2008	Risk ratio	Klemm et al (Pediatrics 2008;122:e242-50)	All infants	222	-	7953	250	-	7984
Malaba 2005	-	-	-	-	-	-	-	-	-
Masanja 2015	Rate ratio/risk ratio	Masanja et al (Lancet 2015;385:1324-32)	All infants	213	1192	15,677	206	1194	15,710
			All infants - male	124	628	8273	124	622	8198
			All infants - female	89	563	7402	82	572	7510
Mazumder 2015	Risk ratio	Mazumder et al (Lancet 2015;385:1333–42)	All infants	281	-	22,493	298	-	22,491
			All infants - male	124	-	11,689	132	-	11,729

Table 3. Data type and source: all-cause neonatal mortality *(Continued)*

			All infants - female	157	-	10,804	166	-	10,762
Rahmathullah 2003	-	-	-	-	-	-	-	-	-
West 1995	-	-	-	-	-	-	-	-	-

APPENDICES

Appendix 1. Standard search methods

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

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

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

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

Appendix 2. Risk of bias tool

The following issues were evaluated and entered into the risk of bias table:

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorised the method used to generate the allocation sequence as:

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

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorised the method used to conceal the allocation sequence as:

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

3. Blinding (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study? At study entry? At the time of outcome assessment?

For each included study, we categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or classes of outcomes. We categorised the methods as:

- a. low risk, high risk or unclear risk for participants;
- b. low risk, high risk or unclear risk for personnel;
- c. low risk, high risk or unclear risk for outcome assessors.

4. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion, when reported, and whether missing data were balanced across groups or were related to outcomes. When sufficient information was reported or supplied by trial authors, we re-included missing data in analyses.

We categorised the methods as:

- a. low risk (< 20% missing data);
- b. high risk (≥ 20% missing data);
- c. unclear risk.

5. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

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

- a. low risk (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);

- b. high risk (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- c. unclear risk.

6. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we described any important concerns we had about other possible sources of bias (e.g. whether a potential source of bias was related to the specific study design, whether the trial was stopped early owing to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

- a. low risk;
b. high risk;
c. unclear risk.

If needed, we planned to explore the impact of the level of bias by undertaking sensitivity analyses.

WHAT'S NEW

Date	Event	Description
18 July 2016	New citation required and conclusions have changed	We added to this update new outcomes and new studies that have altered conclusions.
18 July 2016	New search has been performed	We found 5 new studies during the updated literature search in March 2016. We added a new subgroup for sex of the neonate, along with a new outcome of all-cause neonatal mortality.

HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 10, 2011

Date	Event	Description
13 March 2012	Amended	We corrected a minor typographical error.
14 May 2008	Amended	We made a needed reference correction.
8 May 2008	Amended	We converted this review to new review format.
12 October 2007	New citation required and major changes	We made substantive amendments to this review.

CONTRIBUTIONS OF AUTHORS

Batool A Haider (BAH) wrote the review protocol under the guidance of Zulfiqar A Bhutta (ZAB). BAH and Renee Sharma (RS) extracted data. BAH and RS entered data, created comparisons, analysed data and wrote the text of the review. ZAB provided supervision and contributed to the writing process for the review. BAH was at the Harvard School of Public Health at the time of this review.

DECLARATIONS OF INTEREST

Zulfiqar A Bhutta is a principal investigator of a neonatal vitamin A supplementation trial in Pakistan ([Bhutta 2016](#)).

Batool A Haider: none.

Renee Sharma: none.

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Internal sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the 2017 update, we added neonatal mortality as a secondary outcome. We added the methods and the plan for 'Summary of findings' tables and GRADE recommendations, which we did not include in the original protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans; Infant; Infant, Newborn