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Vitamin A supplementation for preventing morbidity and mortality in children from six months to five years of age (Review)

Imdad A, Mayo-Wilson E, Haykal MR, Regan A, Sidhu J, Smith A, Bhutta ZA

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[Intervention Review]

Vitamin A supplementation for preventing morbidity and mortality in children from six months to five years of age

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ABSTRACT

Background

Vitamin A deficiency (VAD) is a major public health problem in low- and middle-income countries, affecting 190 million children under five years of age and leading to many adverse health consequences, including death. Based on prior evidence and a previous version of this review, the World Health Organization has continued to recommend vitamin A supplementation (VAS) for children aged 6 to 59 months. The last version of this review was published in 2017, and this is an updated version of that review.

Objectives

To assess the effects of vitamin A supplementation (VAS) for preventing morbidity and mortality in children aged six months to five years.

Search methods

We searched CENTRAL, MEDLINE, Embase, six other databases, and two trials registers up to March 2021. We also checked reference lists and contacted relevant organisations and researchers to identify additional studies.

Selection criteria

Randomised controlled trials (RCTs) and cluster-RCTs evaluating the effect of synthetic VAS in children aged six months to five years living in the community. We excluded studies involving children in hospital and children with disease or infection. We also excluded studies evaluating the effects of food fortification, consumption of vitamin A rich foods, or beta-carotene supplementation.

Data collection and analysis

For this update, two review authors independently assessed studies for inclusion resolving discrepancies by discussion. We performed meta-analyses for outcomes, including all-cause and cause-specific mortality, disease, vision, and side effects. We used the GRADE approach to assess the quality of the evidence.

Main results

The updated search identified no new RCTs.

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We identified 47 studies, involving approximately 1,223,856 children. Studies were set in 19 countries: 30 (63%) in Asia, 16 of these in India; 8 (17%) in Africa; 7 (15%) in Latin America, and 2 (4%) in Australia. About one-third of the studies were in urban/periurban settings, and half were in rural settings; the remaining studies did not clearly report settings. Most studies included equal numbers of girls and boys and lasted about one year. The mean age of the children was about 33 months. The included studies were at variable overall risk of bias; however, evidence for the primary outcome was at low risk of bias.

A meta-analysis for all-cause mortality included 19 trials (1,202,382 children). At longest follow-up, there was a 12% observed reduction in the risk of all-cause mortality for VAS compared with control using a fixed-effect model (risk ratio (RR) 0.88, 95% confidence interval (CI) 0.83 to 0.93; high-certainty evidence).

Nine trials reported mortality due to diarrhoea and showed a 12% overall reduction for VAS (RR 0.88, 95% CI 0.79 to 0.98; 1,098,538 children; high-certainty evidence). There was no evidence of a difference for VAS on mortality due to measles (RR 0.88, 95% CI 0.69 to 1.11; 6 studies, 1,088,261 children; low-certainty evidence), respiratory disease (RR 0.98, 95% CI 0.86 to 1.12; 9 studies, 1,098,538 children; low-certainty evidence), and meningitis. VAS reduced the incidence of diarrhoea (RR 0.85, 95% CI 0.82 to 0.87; 15 studies, 77,946 children; low-certainty evidence), measles (RR 0.50, 95% CI 0.37 to 0.67; 6 studies, 19,566 children; moderate-certainty evidence), Bitot's spots (RR 0.42, 95% CI 0.33 to 0.53; 5 studies, 1,063,278 children; moderate-certainty evidence), night blindness (RR 0.32, 95% CI 0.21 to 0.50; 2 studies, 22,972 children; moderate-certainty evidence), and VAD (RR 0.71, 95% CI 0.65 to 0.78; 4 studies, 2262 children, moderate-certainty evidence). However, there was no evidence of a difference on incidence of respiratory disease (RR 0.99, 95% CI 0.92 to 1.06; 11 studies, 27,540 children; low-certainty evidence) or hospitalisations due to diarrhoea or pneumonia. There was an increased risk of vomiting within the first 48 hours of VAS (RR 1.97, 95% CI 1.44 to 2.69; 4 studies, 10,541 children; moderate-certainty evidence).

Authors' conclusions

This update identified no new eligible studies and the conclusions remain the same. VAS is associated with a clinically meaningful reduction in morbidity and mortality in children. Further placebo-controlled trials of VAS in children between six months and five years of age would not change the conclusions of this review, although studies that compare different doses and delivery mechanisms are needed. In populations with documented VAD, it would be unethical to conduct placebo-controlled trials.

PLAIN LANGUAGE SUMMARY

Vitamin A supplementation for preventing disease and death in children aged six months to five years

Background

Vitamin A deficiency (VAD) is a major public health problem in low- and middle-income countries, affecting 190 million children under five years of age. VAD predisposes children to increased risk of a range of problems, including respiratory diseases, diarrhoea, measles, and vision problems, and it can lead to death. Previous studies show that giving synthetic vitamin A supplementation (VAS) to children aged six months to five years who are at risk of VAD can reduce the risk of death and some diseases. This is an update of the previous review.

Review question

This review evaluated the effect of synthetic VAS compared to placebo (dummy tablet) or no intervention for preventing illness and death in children aged six months to five years.

Review methods

We searched different databases that contain both published and unpublished results of medical studies. The literature search was updated in March 2021. We included only randomised control trials (RCTs: a study in which participants are randomly allocated to one or more treatments); these are considered the best form of experimental studies in research literature. We combined the results mathematically to obtain overall estimates of effectiveness of VAS against illness and death.

Study characteristics

The update identified no new studies. The review includes 47 RCTs representing 1,223,856 children. Studies took place in 19 countries: 30 (63%) in Asia, 16 of which were in India; 8 (17%) in Africa; 7 (15%) in Latin America, and 2 (4%) in Australia. About one-third of the studies were in urban/periurban settings, and half were in rural settings; the remaining studies did not clearly report settings. The average age of the children was about 33 months. Most studies included equal numbers of boys and girls and lasted about one year. The quality of the included studies was variable; however, it was unlikely that death rates were influenced by potential errors in the conduct of the studies.

Key results

The data on the effect of VAS for the prevention of death were available from 19 of the included studies, and the combined results indicate that VAS reduces overall risk of death and death due to diarrhoea by 12%. VAS does not specifically reduce death due to measles, respiratory infections, or meningitis, but it can reduce new occurrences of diarrhoea and measles. There was no effect on incidence of respiratory disease or admissions to hospital due to diarrhoea or pneumonia. Giving oral synthetic vitamin A to children at risk of VAD reduces the risk of

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night blindness and tiny flakes of protein in the eye called Bitot's spots. It also improves levels of vitamin A in their blood. The only reported side effect was risk of vomiting within 48 hours of taking vitamin A in large doses, as recommended by the World Health Organization.

Certainty of evidence

We rated the overall certainty of evidence using the GRADE approach, which considers methodological flaws within studies, consistency in reporting of results across studies, extent to which results apply to other settings, and effectiveness of treatments. Based on these criteria, we judged the overall certainty of evidence to be high for benefits of VAS against overall risk of death and death due to diarrhoea. For the other outcomes, we rated the evidence as low or moderate. One large, recently conducted study, which included about one million children, did not show any effect of VAS; however, when this study was combined with other, well-conducted studies, VAS still had beneficial effects for the prevention of death and illness. In summary, VAS can reduce risk of illness and death in children aged 6 to 59 months of age who are at risk of VAD. This update did not identify and new eligible studies and the conclusions remain the same.

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Summary of findings 1. Vitamin A supplementation versus placebo or usual care for preventing morbidity and mortality in children from 6 months to 5 years of age

Vitamin A supplementation for preventing morbidity and mortality in children from 6 months to 5 years of age

Patient or population: children aged between 6 months and 5 years

Intervention: vitamin A supplementation

Comparison: placebo or usual care

Setting: low- and middle-income countries

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	VAS				
All-cause mortality Follow-up: 12–96 weeks	**Study population**		**RR 0.88** (0.83 to 0.93)	1,202,382 (19 studies)	⊕⊕⊕⊕ **High**[b]	Random-effects RR 0.76 (95% CI 0.66 to 0.88)
	26 per 1000 [a]	**23 per 1000** (22 to 24)				
Mortality due to diarrhoea Follow-up: 48–104 weeks	**Study population**		**RR 0.88** (0.79 to 0.98)	1,098,538 (9 studies)	⊕⊕⊕⊕ **High**[b]	Total number of participants reflects number randomised to studies. The analysis combined cumulative risk and risk per 1000 years' follow-up.
	8 per 1000 [a]	**7 per 1000** (6 to 8)				
Mortality due to measles Follow-up: 52–104 weeks	**Study population**		**RR 0.88** (0.69 to 1.11)	1,088,261 (6 studies)	⊕⊕⊖⊖ **Low** [c,d]	Total number of participants reflects number randomised to studies. The analysis combined cumulative risk and risk per 1000 years' follow-up.
	2 per 10,000 [a]	**2 per 1000** (1 to 2)				
Mortality due to LRTI	**Study population**		**RR 0.98** (0.86 to 1.12)	1,098,538 (9 studies)	⊕⊕⊖⊖ **Low**[c,d]	Total number of participants reflects num-

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Follow-up: 48–104 weeks	**4 per 10,000** [a]	**4 per 1000** (3 to 5)				ber randomised to studies. The analysis combined cumulative risk and risk per 1000 years' follow-up.
Diarrhoea incidence Mean episodes per child per year Follow-up: 24–60 weeks	**Study population**		**RR 0.85** (95% CI 0.82 to 0.87)	77,946 (15 studies)	⊕⊕⊖⊖ **Low**[c,f]	—
	Mean episodes of diarrhoea in control group: **4.0 per child per year**[e]	VAS led to **3 fewer episodes** of diarrhoea per child per year **(3 to 4 fewer episodes)**				
Measles incidence Mean episodes of measles per child per year Follow-up: mean 52 weeks	**Study population**		**RR 0.50** (95% CI 0.37 to 0.67)	19,566 (6 studies)	⊕⊕⊕⊖ **Moderate** [c]	—
	Mean episodes of measles in control group: **0.2 per child per year**[e]	VAS led to **0.015 fewer episodes** per child per year (**0.019 events fewer per child to 0.01 events fewer per child**)				
LRTI incidence Mean episodes per child per year Follow-up: mean 52 weeks	**Study population**		**RR 0.99** (95% CI 0.92 to 1.06)	27,540 (11 studies)	⊕⊕⊖⊖ **Low** [c,d]	—
	Mean episodes of LRTI in control group: **0.1 episodes per child per year**[e]	VAS led to **0.1 more episodes** of LRTI per child per year **(0.1 fewer episodes to 0.1 more episodes)**				
Bitot's spots incidence Follow-up: mean 80.72 weeks	**Study population**		**RR 0.42** (95% CI 0.33 to 0.53)	1,063,278 (5 studies)	⊕⊕⊕⊖ **Moderate** [c]	—
	35 per 1000 [a]	**15 per 1000** (12 to 19)				
Night blindness incidence Follow-up: 52 to 68 weeks	**Study population**		**RR 0.32** (95% CI 0.21 to 0.50)	22,972 (2 studies)	⊕⊕⊕⊖ **Moderate** [c]	—
	4 per 1000 [g]	**1 per 1000** (1 to 2)				
Vomiting Follow-up: 0.14–52 weeks	**Study population**		**RR 1.97** (95% CI 1.44 to 2.69)	10,541 (4 studies)	⊕⊕⊕⊖ **Moderate**[c]	—
	31 per 1000 [g]	**61 per 1000** (45 to 83)				

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Vitamin A deficiency Follow-up: mean 54.5 weeks	**Study population**		**RR 0.71** (95% CI 0.65 to 0.78)	2262 (4 studies)	⊕⊕⊕⊖ **Moderate**[c]	—
	509 per 1000 [g]	**361 per 1000** (331 to 397)				

*The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **DEVTA:** deworming and enhanced vitamin A; **LRTI:** lower respiratory tract infection; **RR:** risk ratio; **VAS:** vitamin A supplementation.

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

[a]Based on control group mortality risk in DEVTA trial 2013.
[b]We acknowledge that the addition of DEVTA trial 2013 results decreased the overall effect size for this outcome compared to previous analysis for this review. However, we consider that vitamin A has robust effects on mortality as the direction of effect is in favour of intervention in most of the studies and summary estimate remains statistically significant irrespective of the use of random- or fixed-effect models for meta-analysis.
[c]Downgraded one level due to serious risk of bias of included studies in analysis (concerns with randomisation procedures, completeness, and reporting of outcome data in the included studies).
[d]Downgraded one level due to serious imprecision (wide CIs around the pooled effect estimate suggest both appreciable benefit and harm with vitamin A).
[e]Based on control event rate in Chowdhury 2002.
[f]Downgraded one level due to serious inconsistency (I^2 = 94%, and the results of Herrera 1992; Lie 1993; and Chowdhury 2002 demonstrated clear evidence of benefit and were discordant with the results of the other studies).
[g]Risk based on control event rates from the included studies.

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BACKGROUND

Description of the condition

Vitamin A is required for normal functioning of the visual system, maintenance of cell function for growth, epithelial integrity, red blood cell production, immunity, and reproduction (Sommer 1996). Vitamin A deficiency (VAD) impairs body functions and may cause death. Adverse health consequences may also include xerophthalmia (dry eyes), susceptibility to infection, stunting, and anaemia (Sommer 1996; Rice 2004). Chronic VAD may develop when animal sources and fortified foods are limited, for example in diets that rely heavily on vegetables and fruits (Ramakrishnan 2002). In poor societies, especially in low-income countries, dietary deficiency can begin very early in life, when colostrum is discarded or when breastfeeding is inadequate (Haskell 1999).

VAD is interconnected with a deprived ecological, social, and economic environment. People with VAD may be exposed to measles, diarrhoea, and respiratory diseases (Sommer 2002; Rice 2004). When these problems are comorbid, depressed appetite and poor absorption may lower intake of vitamin A, while excessive metabolism and excretion may deplete body stores (Alvarez 1995; Mitra 1998). This combination of poor diet and infection leads to a vicious cycle that particularly affects young children and pregnant or lactating mothers (Sommer 2002; West 2003).

VAD is common in low- and middle-income countries. About 19.1 million pregnant women and 190 million children under five years of age have VAD (i.e. serum retinol less than 0.70 µmol/L), representing about 33% of children under five years of age in populations at risk of VAD (WHO 2009). Based on biochemical VAD in young children, 122 countries have a moderate-to-severe public health problem (WHO 2009).

Data on global trends in VAD suggest that it remains widely prevalent in South Asia and Sub-Saharan Africa, while rates have significantly fallen in Southeast Asia and Latin America (Stevens 2015). Deaths attributable to VAD have almost disappeared in many regions of the world, suggesting the need to revisit supplementation strategies according to population needs (Stevens 2015).

Description of the intervention

Vitamin A is a term used for a subclass of retinoic acids, a family of lipid-soluble compounds (Bates 1995). Vitamin A is found in two main forms: provitamin A carotenoids and preformed vitamin A. Provitamin A carotenoids are found in plants; beta-carotene is the only one that is metabolised by mammals into vitamin A. Though fruits and vegetables are nutritious in other ways, normal dietary intake of plants may not deliver adequate amounts of vitamin A because the intestinal carotenoid-to-retinol conversion ratio varies with type of food, ranging from 6:1 to 26:1 (US Institute of Medicine 2001; van Lieshout 2005). Consequently, VAD can exist in places with high vegetable and fruit consumption (West 2002). Preformed vitamin A (retinol, retinal, retinoic acid, and retinyl esters) is the most active form of vitamin A and is found in animal sources. Supplements usually use preformed vitamin A (Shenai 1993; Bates 1995).

How the intervention might work

Vitamin A is an essential nutrient; it cannot be synthesised by the human body and must therefore come from dietary sources (Bates 1995). Oral vitamin A supplementation (VAS) and food fortification are the most direct methods for providing vitamin A to people whose diets are deficient.

Vitamin A has been described as an anti-infectious vitamin because of its role in regulating human immune function (Green 1928). Early studies in animals and humans revealed an association between VAD and increased susceptibility to infections (Semba 1999). In addition to its preventive and therapeutic effect against xerophthalmia (Sommer 1996), prophylactic VAS in apparently healthy children (over six months of age) residing in low-income countries may reduce childhood mortality by as much as 30% (Beaton 1993; Fawzi 1993; Glasziou 1993), particularly by reducing diarrhoea and measles mortality.

Side effects of VAS are rare in children aged six months or older; however, vitamin A toxicity can develop if large amounts of vitamin A are used over a prolonged period of time. Symptoms of toxicity include liver damage, headaches, vomiting, skin desquamation, bone abnormalities, joint pain, and alopecia (Smith 1976). A very high single dose can also cause transient acute toxic symptoms that may include a bulging fontanelle in children under one year of age, headaches, vomiting, diarrhoea, loss of appetite, and irritability. Toxicity from ingestion of food sources with preformed vitamin A is rare (Hathcock 1997).

Why it is important to do this review

The last version of this review was published in 2017 (Imdad 2017), and an update is needed to assess for any additional evidence that may have been published. The update considers whether new, potentially eligible evidence has become available since the publication of the original review (Imdad 2010a). A separate Cochrane Review has evaluated the therapeutic role of vitamin A for measles (Huiming 2005), while another has focused on non-measles pneumonia (Ni 2005). Different Cochrane Reviews in a variety of subpopulations of children and mothers are also evaluating the prophylactic role of vitamin A (Chen 2008; Darlow 2011; Gogia 2011; Wiysonge 2011; McCauley 2015; Bello 2016; Imdad 2016; Haider 2017; Hombali 2019).

OBJECTIVES

To assess the effects of vitamin A supplementation (VAS) for preventing morbidity and mortality in children aged six months to five years.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and cluster-RCTs evaluating the effect of synthetic VAS in children aged six months to five years. We included data from the first period of cross-over studies only. We considered studies for inclusion irrespective of publication status or language of publication.

We excluded quasi-RCTs, with the exception of two studies (see Differences between protocol and review).

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Types of participants

Children living in the community and aged six months to five years at the time of recruitment were eligible for inclusion. We excluded children in hospital and children with disease or infection.

We contacted trial authors to determine if the study population included some participants who were not eligible for this review (e.g. children over five years of age) and requested disaggregated data. If such data were not available, we included studies if most participants (51% or more) met the inclusion criteria. If this could not be determined and the participants met the inclusion criteria on average (e.g. the mean age was within the eligible range), we included these trials.

Types of interventions

Synthetic oral VAS compared to either placebo or treatment-as-usual control groups, including trials of various doses and frequencies. Co-interventions (e.g. multiple vitamin or mineral supplementation) must have been identical in both groups. We excluded studies evaluating the effects of food fortification, consumption of foods rich in vitamin A, and beta-carotene supplementation.

If a trial included more than one eligible intervention group (e.g. different doses), we combined the groups for the main analysis, although we treated the groups separately for subgroup analyses where appropriate. If a trial included multiple control groups (e.g. both placebo and treatment as usual), we selected the control group that most closely replicated the non-specific treatment of the intervention group (i.e. placebo).

Types of outcome measures

We extracted data on the outcomes listed below. In studies reporting more than one measure of an outcome, we combined measures for meta-analysis using the methods described in Data synthesis.

Primary outcomes

1. All-cause mortality.

Secondary outcomes

1. fCause-specific mortality due to:
   a. diarrhoea;
   b. measles;
   c. meningitis; and
   d. lower respiratory tract infection (LRTI).
2. Cause-specific morbidity (i.e. incidence and prevalence) due to:
   a. diarrhoea;
   b. measles;
   c. malaria;
   d. meningitis;
   e. LRTI;
   f. Bitot's spots;
   g. night blindness;
   h. xerophthalmia; and
   i. hospitalisation.
3. Side effects (e.g. vomiting or diarrhoea following supplementation).
4. Vitamin A deficiency (VAD) status (based on serum retinol level).

We combined pneumonia and LRTI outcomes post hoc. Pneumonia is a type of LRTI, and most of the studies did not test for pneumonia specifically (using specific clinical criteria). In the event a study reported both pneumonia and LRTI outcomes, we extracted the LRTI outcome data to combine with other studies.

Search methods for identification of studies

Electronic searches

For this update, we searched the databases and trials registers listed below in March 2021. Searches were limited to the period 2016 onwards, in order to identify new studies published since the previous version of the review Appendix 1. Details of the previous search strategies are available in Imdad 2010a and Imdad 2017.

1. Cochrane Central Register of Controlled Trials (CENTRAL; Issue 3, 2021) in the Cochrane Library (searched 5 March 2021).
2. MEDLINE Ovid (2016 to 8 March 2021).
3. Embase Elsevier (2016 to 8 March 2021).
4. Science Citation Index Web of Science (2016 to 8 March 2021).
5. Conference Proceedings Citation Index – Science Web of Science (2016 to 8 March 2021).
6. Cochrane Database of Systematic Reviews (CDSR; Issue 3, 2021) in the Cochrane Library (searched 5 March 2021).
7. ClinicalTrials.gov (clinicaltrials.gov; searched 8 March 2021).
8. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch; searched 8 March 2021).
9. Global Index Medicus (contains WPRIM, LILACS, IMSEAR, IMEMR, AIM; www.globalindexmedicus.net/; searched 8 March 2021).
10. Scopus Elsevier (1966 to 8 March 2021).

We applied no language limits to the searches.

Searching other resources

We checked the reference lists of reviews and included and excluded studies to identify additional citations. We also contacted organisations and researchers.

Data collection and analysis

Selection of studies

For this update, two review authors (from MH, AR, and JS) independently screened titles and abstracts through Covidence (Covidence) for inclusion in the review. They discarded clearly irrelevant records and obtained the full-text reports of those deemed potentially eligible or where more information was needed to determine eligibility. Two review authors (from MH, AR, and JS) then independently screened all full-text reports. At both stages, differences of opinions about suitability for inclusion were resolved by discussion and through consultation with a senior review author (AI).

For the previous version of the review (Imdad 2017), two people (AI (member of the review author team) and JD or RS (recruited to assist with data extraction)) independently screened titles and abstracts and full-text reports for inclusion in the review. We resolved differences of opinion about suitability for inclusion by

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discussion and through consultation with a third review author (EMW).

For both reviews, we recorded our final decisions in a PRISMA diagram (Moher 2009).

Data extraction and management

In the previous version of the review (Imdad 2017), two people (AI (member of the review author team) and JD or RS (recruited to assist with data extraction)) used a prepiloted data extraction sheet to independently extract the data below from each eligible study. Review authors resolved discrepancies through discussion.

1. General:
   a. year of study;
   b. location (country, urban/rural);
   c. method of recruitment;
   d. inclusion criteria;
   e. unit of analysis; and
   f. risk of bias (see Assessment of risk of bias in included studies).
2. Participants:
   a. sociodemographic characteristics (age, sex); and
   b. comorbidities.
3. For each intervention and comparison group of interest:
   a. dosage;
   b. duration;
   c. frequency; and
   d. co-intervention (if any).
4. For each outcome of interest:
   a. time points collected and reported;
   b. definition;
   c. validity;
   d. unit of measurement (if relevant); and
   e. loss to follow-up.

The main analyses included the longest reported follow-up in each study. We grouped outcomes according to follow-up period (0 to 12 months; 13 to 60 months, and greater than 60 months since randomisation); when trials reported multiple time points for a period, we extracted the longest outcome interval in a given period.

Assessment of risk of bias in included studies

In previous versions of the review (Imdad 2017), two people (AI (member of the review author team) and JD or RS (recruited to assist with data extraction)) independently assessed the risk of bias within each included study using the Cochrane risk of bias tool (Higgins 2011a). Discrepancies in assessment were resolved by discussion. For all studies, we assessed the following domains: sequence generation; allocation concealment; blinding of participants and providers; blinding of outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. We specifically looked for the possibility of performance bias (differential treatment of the intervention and control groups) and detection bias (e.g. differential effort to locate death records for the intervention and control groups). Findings are discussed in the Risk of bias in included studies section and included in the risk of bias tables of the Characteristics of included studies table. We considered an overall risk of bias assessment for GRADE analysis based on the nature of the outcome and how the risk of bias might change the direction of effect.

Measures of treatment effect

We measured morbidity in different ways, and we combined all available data whenever possible. For example, for diarrhoea, we included all types of diarrhoea (mild, moderate, and severe). In the case of pneumonia, we included lower (but not upper) respiratory tract infection.

To avoid review author bias, we predetermined the order of preference for extracting outcomes when data were available in several formats. For studies that randomised individuals, we gave preference to data that required the least manipulation by authors or inference by review authors. We extracted raw values (e.g. means and standard deviations) rather than calculated effect sizes (e.g. Cohen's d). For mortality data, we gave preference to denominators in the following order: number with definite outcome known (or imputed as described below), number randomised, and child-years. For other dichotomous outcomes to which both survivors and non-survivors may have contributed data (e.g. incidence of measles), we gave preference to child-years, number with definite outcome known, and number randomised.

In the case of cluster-RCTs, we used either adjusted estimates reported by the trial authors or raw data, and we inflated the standard error (SE) using the procedures described in the Unit of analysis issues section.

Unit of analysis issues

Cluster-randomised trials

In studies randomising units rather than the individual (i.e. clusters), trials should present results with controls for clustering (e.g. robust SEs or hierarchical linear models). We analysed clustered data using the procedures outlined in Higgins 2011b.

Where results did not control for clustering, we contacted trial authors to request an estimate of the intracluster correlation coefficient (ICC). If the trial authors were unable to provide an ICC, we calculated the ICC using design effects calculated previously (Beaton 1993), and we estimated the ICC for studies that did not publish a value (see section on 'Unit of randomisation' under Included studies). For estimated values, we conducted sensitivity analyses using larger and smaller design effects to determine if the results were robust (see Sensitivity analysis).

Multiple-arm trials

For multiple-arm trials, we grouped data so that the only difference between the groups was VAS. For example, if a trial had four arms (vitamin A plus zinc, zinc alone, vitamin A alone, and placebo), we included it as two comparisons: vitamin A plus zinc versus zinc alone and vitamin A alone versus placebo. In multiple-arm trials using two different doses of vitamin A, we combined the two groups to avoid double-counting the participants in the control group.

Cross-over trials

For cross-over trials, we included the data from the first phase of the trial only.

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Dealing with missing data

Differential dropout can lead to biased estimates of effect size, and bias may arise if reasons for dropout differ across groups.

We described missing data, including dropouts and reasons for dropout, when given. If data were missing for some cases, or if reasons for dropout were not reported, we contacted the trial authors. When analyses considered completers and controlled for dropout (e.g. imputed using regression methods), we extracted the latter.

Assessment of heterogeneity

We assessed included studies for clinical heterogeneity by comparing the distribution of important factors such as study participants, study setting, dose, and duration of intervention and co-interventions. We assessed methodological heterogeneity by comparing data included in the risk of bias tables (see Characteristics of included studies table). We assessed statistical heterogeneity by visual inspection of forest plots, the Chi^2 test (and P value), and the I^2 statistic. If the P value was less than 0.10 and the I^2 exceeded 50%, we considered heterogeneity to be substantial. We also reported Tau^2 – an estimate of between-study variance.

Assessment of reporting biases

To assess the possibility of small-study bias, we drew funnel plots for outcomes with 10 or more studies and compared random-effects estimates to fixed-effect estimates (see Sensitivity analysis).

Data synthesis

We performed meta-analysis using Review Manager 5 software (Review Manager 2014). When data were in several formats that we could not combine directly in Review Manager 5, we used the generic inverse variance (GIV) option. This was meant to handle the scenario when only summary estimates (such as the risk ratio (RR)) were available and no numbers for nominators and denominators were available to calculate the summary estimate. In this case, it would not be possible to pool that study with other studies using conventional methods. Hence, we used GIV, which does not require input of data in the form of nominators and denominators of intervention and control group, but the log of effect size (e.g. RR) and SE. We entered data into the built-in calculator in Review Manager 5 to calculate the log of RR and their SE.

We reported all outcomes with 95% confidence intervals (CIs) and weighted overall effects by the inverse of variance using a fixed-effect model. Although there might be some differences across trials (e.g. dose and population), the biological mechanism should be similar. We explored differences through analyses described elsewhere (Mayo-Wilson 2011).

For dichotomous outcomes, we calculated the overall RR. For incidence data, we combined RRs (events per child) and rate ratios (events per child-year) because these ratios use the same scale and can be interpreted in the same way for these studies (the duration of studies was relatively short, that is, median duration was one year or less).

In some cases, we estimated time at risk, as when trial authors reported incidence rate, duration of study, and number of children in each group.

We decided post hoc that we would pool incidence and prevalence data for morbidity separately. The primary difference between incidence and prevalence data is time at risk. Incidence data covers the time (prospectively) while prevalence data is a snapshot of a condition at one point in time. Therefore, we thought that combining incidence and prevalence data was not appropriate.

For continuous outcomes, we calculated Hedges *g*.

Subgroup analysis and investigation of heterogeneity

Effectiveness of the intervention may differ across members of populations (e.g. due to differences in baseline vitamin A status) and may be affected by other interventions (e.g. immunisation or deficiency of other micronutrients). For example, neonatal VAS is thought to have different effects in Asia compared with Africa (Klemm 2009). Unlike trial-level factors (such as dose), associations between individual-level moderators (such as VAS) and outcomes should be analysed using individual patient data from RCTs and observational studies. With two exceptions, we did not include subgroup analyses based on individual-level moderators in this review, as such analyses are at high risk of ecological fallacy (lack of variation between studies would not indicate there was no variation within them). We included subgroups of age and sex; trials commonly report separate effects for these groups. We performed subgroup analyses when disaggregated data were available for groups within studies or between studies.

We prespecified the following subgroup analyses, and explored differences using the Chi^2 test in Review Manager 5 (Review Manager 2014).

1. Dose: standard (up to 100,000 IU for children aged six to 11 months, and 200,000 IU for children aged 12 months to five years) versus high (greater than standard).
2. Frequency: high (doses more than once in six months) versus low (one dose every six months or six-plus-month interval).
3. Location: continent.
4. Age: six to 12 months versus one to five years.
5. Sex: boys versus girls.

Sensitivity analysis

We performed the following sensitivity analyses.

1. To test for bias, we repeated the primary analysis without studies at high risk of bias for sequence generation.
2. To test for small-study bias, we repeated the analysis using a random-effects model (as the assumption for this model is that effect is not identical across studies, and included studies are considered a 'random' sample of all the possible studies on the topic) and drew funnel plots for all outcomes with 10 or more studies.
3. To test the robustness of results when using imputed ICCs, we conducted sensitivity analyses using larger and smaller design effects (post hoc sensitivity analysis described under the 'Unit of randomisation' subheading in the Included studies section below).

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Summary of findings and assessment of the certainty of the evidence

In the previous version of this review, in collaboration with the Cochrane Editorial Unit, two review authors (AI and EMW) assessed the overall certainty of evidence using the GRADE approach (Guyatt 2011). Any discrepancies in assessment were resolved by discussion. The GRADE assessment was based on five criteria: limitations in the design and implementation of available studies, imprecision of results, inconsistency of results, indirectness of study results, and publication bias.

We assessed the certainty of evidence as 'high', 'moderate', 'low', or 'very low' for each of the following outcomes: all-cause mortality; mortality due to diarrhoea, measles, and LRTI; incidence of diarrhoea, measles, LRTI, Bitot's spots, and night blindness; vomiting; and VAD status. The main comparison was VAS versus placebo or usual care. We presented our certainty ratings and results in Summary of findings 1; our reasons for the certainty rating are available in footnotes of the table. We downgraded the certainty of evidence up to three levels. All the outcomes reported in summary of findings table were reported at longest follow-up.

RESULTS

Description of studies

Results of the search

For this update, electronic searches identified 3859 records; 3545 records remained after removal of duplicates. From these, we identified 39 potentially relevant citations and reviewed the full texts. We excluded all 39 reports; no new eligible studies were found in this update (Figure 1). For more information, see Excluded studies. One study is awaiting classification (Aklamati 2006); no additional details were available since the publication of the last review to facilitate a decision on the eligibility of this study for inclusion in the review. We found no new eligible studies for this update, so there are no changes to number of included studies (47 included studies (from 106 reports). The details of the searches for previous versions of this review are available elsewhere (Imdad 2010a; Imdad 2017).

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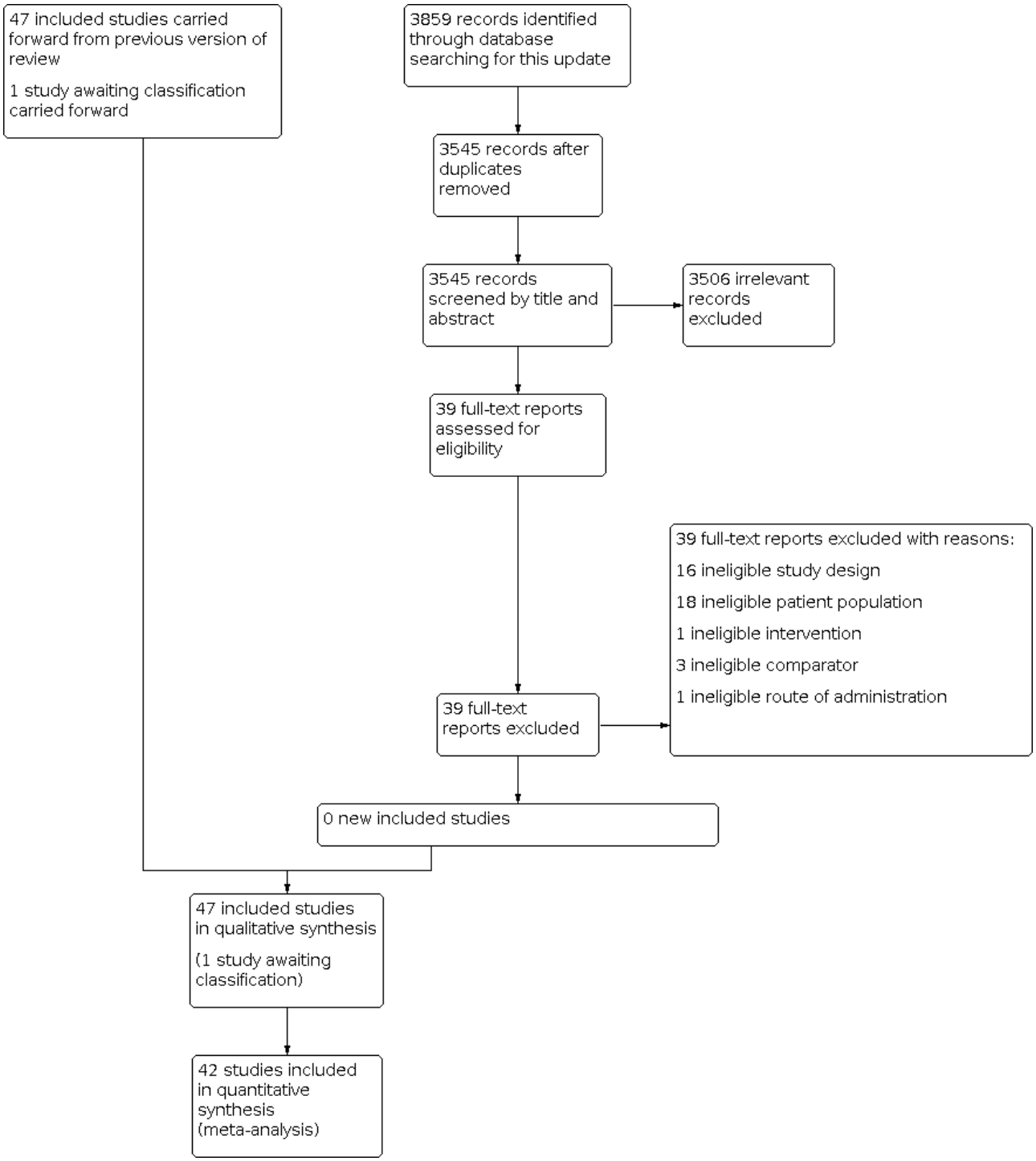
Figure 1. Study flow diagram.



Included studies

Study design

Three of the 47 included studies in this review were factorial design studies. Factorial design studies typically test more than one intervention in different combinations in a single study. For meta-analysis, we included each such study as two discrete data sets (with intervention and comparison group differentiated by VAS only) and counted them as one study overall (Reddy 1986a and Reddy 1986b; Long 2006a and Long 2006b; Chen 2013a and Chen 2013b). Further details are available below under the subheading 'Multiple-arms trials'. More than one report was available for 19 (40%) trials. Where multiple reports existed for an included trial, we extracted data from all reports in accordance with guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Further information about individual studies is available in the Characteristics of included studies table.

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Forty-two trials (89%) reported data that could be included in a meta-analysis; five trials reported outcomes that were not relevant to the review (Albert 2003; Cherian 2003), data that were not available by group (Lima 2014), or data that were incomplete (van Agtmaal 1988; Smith 1999).

We excluded quasi-RCTs with the exception of Herrera 1992 and Stansfield 1993; we made this decision post hoc (Differences between protocol and review). Given the design of the interventions and the placebos as well as steps to blind those administering the sequence, we do not think these studies are meaningfully different from RCTs. Herrera 1992 assigned participants alternately by household, while Stansfield 1993 used a random starting point and alternating distribution of red or green tablets. Lack of a truly random sequence was not related to other sources of bias (e.g. performance bias) because individuals delivering the capsules had no ongoing contact with participants, and the manufacturer (Roche) held the code until the study was completed. Though post hoc, we made the decision to include these studies before extracting data or conducting analyses; we conducted a sensitivity analysis to determine if the decision had any impact on the results, which it did not (see 'Sensitivity analysis' subheading, under 'Primary outcome: all-cause mortality' in Effects of interventions section).

Unit of randomisation

Cluster-randomised trials

Two studies randomised participants by household, and we treated participants as if they were individually randomised (Herrera 1992; Stansfield 1993). We conducted a sensitivity analysis for all-cause mortality using ICCs of 0 and 0.010 for studies estimating the mean design effect.

We used previously reported design effects from Beaton 1993 to calculate ICCs for clustered studies (Sommer 1986; Rahmathullah 1990; Vijayaraghavan 1990; West 1991; Daulaire 1992; Ross 1993 SURVIVAL). The ICCs were consistently around 0.002. We imputed an ICC value of 0.002 for the single study that did not account for clustering in the original analysis (DEVTA trial 2013).

Multiple-arm trials

Fifteen (31%) trials had multiple arms, nine of which were relevant to this review (Reddy 1986a; Florentino 1990; Benn 1997; Smith 1999; Rahman 2001; Long 2006a; Lin 2009; Chen 2013a; DEVTA trial 2013).

Seven trials used factorial designs, combining vitamin A with other treatments such as zinc (Smith 1999; Rahman 2001; Albert 2003; Long 2006a), deworming (Reddy 1986a; DEVTA trial 2013), or iron (Chen 2013a); we extracted data for comparisons that differed only in the provision of vitamin A (e.g. vitamin A versus placebo; and vitamin A plus zinc versus zinc alone). One trial provided no raw data, and we could not identify outcome data for an eligible comparison (Rahman 2001). One study combined different doses (Florentino 1990).

Location/setting

Studies were set in 19 countries: 30 (63%) in Asia, including 16 in India; eight (17%) in Africa (Herrera 1992; Ross 1993 HEALTH; Ross 1993 SURVIVAL; Stabell 1995; Benn 1997; Donnen 1998; Shankar 1999; Fisker 2014); seven (15%) in Latin America (Stansfield 1993; Barreto 1994; Sempértegui 1999; Smith 1999; Long 2006a; Long 2007; Lima 2014), and two (4%) in Australia (Pinnock 1986; Pinnock 1988). Eighteen (38%) studies were conducted in urban/periurban settings, and 26 (55%) were in rural settings. Three studies did not explicitly describe their urban or rural setting.

Time

Eleven studies continued for five years or more (Vijayaraghavan 1990; West 1991; Herrera 1992; Dibley 1996; Pant 1996; Shankar 1999; Chowdhury 2002; Long 2006a; Long 2007; DEVTA trial 2013; Ross 1993 SURVIVAL); the remainder of the studies had a duration of about one year or less. In the event that a single study reported data at more than one time point, we used the data from the longest interval in the overall analysis.

Sample size

Trials assigned approximately 1,223,856 participants, with sample sizes ranging between 35 participants in van Agtmaal 1988 to approximately 1 million participants in DEVTA trial 2013. The 42 trials that could be analysed included 1,223,607 participants (99.9% of children included in the review).

The 11 largest studies randomised about 1,200,214 children, 98.06% of participants in the review (Sommer 1986; Rahmathullah 1990; Vijayaraghavan 1990; West 1991; Daulaire 1992; Herrera 1992; Ross 1993 SURVIVAL; Stansfield 1993; Agarwal 1995; Pant 1996; DEVTA trial 2013).

Allocation ratio

Thirty-nine (83%) studies evenly allocated participants to the intervention and control groups. In eight (17%) studies, the number assigned to each group was unclear (Reddy 1986a; Ross 1993 HEALTH; Ross 1993 SURVIVAL; Stansfield 1993; Biswas 1994; Dibley 1996; Ramakrishnan 1995; Pant 1996).

Participants

Twenty studies categorically excluded children with clinical signs of VAD (such as xerophthalmia and Bitot's spots), while 23 studies did not clearly mention vitamin A. Four studies allowed children who had clinical signs of VAD (Rahmathullah 1990; West 1991; Daulaire 1992; DEVTA trial 2013). Only one trial mentioned biochemical VAD as an inclusion criterion (Albert 2003).

Age

Twenty-one (44%) studies reported mean age, which was 33 months across the studies.

Sex

Thirty-five (74%) studies reported sex. Most assigned approximately equal numbers of boys and girls. Three studies favoured boys by more than 10% (Semba 1991; Cherian 2001; Lin 2008). The median percentage of boys in the studies was 51%.

Comparisons

Seven (14%) studies compared VAS to treatment as usual (Sommer 1986; van Agtmaal 1988; West 1991; Daulaire 1992; Pant 1996; Donnen 1998; DEVTA trial 2013). Forty (85%) studies compared VAS to placebo. One large trial reported not using a placebo because it was forbidden by government (Sommer 1986).

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Dose

All studies used large doses of vitamin A in the range of 50,000 IU to 200,000 IU (one IU = 0.3 µg), depending on the age of participants, except for five studies that used small doses, that is, 3866 IU three times a week (Pinnock 1988), 8333 IU once a week (Rahmathullah 1990), 10,000 IU weekly (Sempértegui 1999; Smith 1999), or 25,000 IU every two weeks (Chen 2013a and Chen 2013b; considered as one study). Some studies had two different dosing regimens for younger children (50,000 IU or 100,000 IU for ages six to 11 months) and older children (100,000 IU or 200,000 IU for ages one year or older).

Frequency

Participants received the large doses (50,000 IU to 200,000 IU) every four to six months, either once or more, depending on the study duration. Studies that used smaller doses gave them more frequently (see under 'Dose' above).

Route

Retinol palmitate was the most commonly used compound to deliver vitamin A, and all studies used the oral route for supplementation.

Excluded studies

We excluded 57 studies from this review. We excluded 18 studies from previous versions of this review (Imdad 2010a; Imdad 2017), and 39 from this review. We list all excluded studies in the Characteristics of excluded studies table with reasons for exclusion. Of the 39 studies excluded from this version of the review, 16 were because of ineligible study design, 18 due to ineligible patient population, one due to ineligible intervention, three due to ineligible comparator, and one due to ineligible route of administration.

Studies awaiting assessment

We could not assess one trial reported in a conference abstract (Aklamati 2006). It appeared to meet the inclusion criteria but reported unclear results. For example, the study included 36 children and reported an outcome of 1.2% of 17; though one child out of 17 is nearly 6%. To the best of our knowledge, the complete results have not been published as yet. See Characteristics of studies awaiting classification table for more information.

Risk of bias in included studies

For each study, we assessed seven domains of methodological bias listed in the Assessment of risk of bias in included studies section and rated them at high, low, or unclear risk. See Figure 2.

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

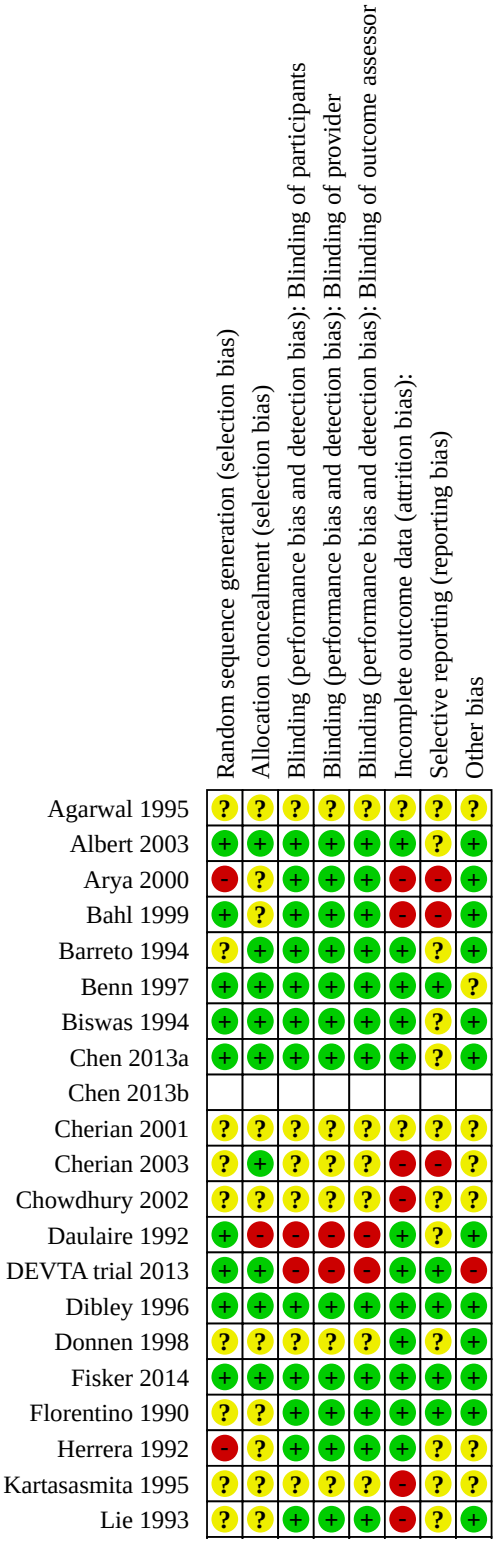

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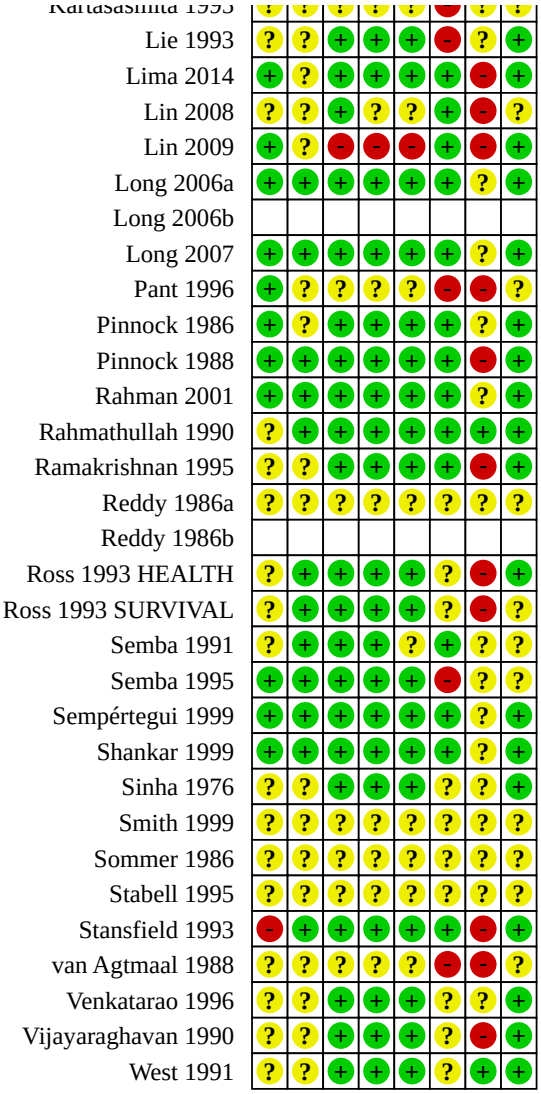
Figure 2. (Continued)



Allocation

Sequence generation

All included studies were RCTs or quasi-RCTs. Twenty (42%) studies specified the method of randomisation and were at low risk of bias for sequence generation. Twenty-four studies were at unclear risk. Three (6%) studies, including 42,660 participants (3% of those included in the review), were at high risk of bias in this domain (Herrera 1992; Stansfield 1993; Arya 2000). One of these studies described assignment as random (Arya 2000), but participants may have been assigned in order of arrival at hospital, which would not qualify as truly random.

Allocation concealment

We rated 21 studies at low risk of bias and 25 studies (53%) at unclear risk of bias. We judged one study to be at high risk of bias for allocation concealment (Daulaire 1992), as authors reported in correspondence that they had made no effort to conceal the allocation.

Blinding

Blinding of participants

Thirty-two (68%) studies described efforts to blind participants, and we considered them at low risk of bias for blinding of participants. We deemed 12 (25%) studies at unclear risk of bias (Reddy 1986a; Sommer 1986; van Agtmaal 1988; Agarwal 1995; Kartasasmita 1995; Stabell 1995; Pant 1996; Donnen 1998; Smith 1999; Cherian 2001; Chowdhury 2002; Cherian 2003). We judged three studies at high risk of bias (Daulaire 1992; Lin 2009; DEVTA trial 2013).

Blinding of providers

In some trials, staff delivering the intervention also conducted assessments. We considered 31 (65%) studies at low risk of bias for blinding of providers. The risk was unclear in 13 (27%) studies (Reddy 1986a; Sommer 1986; van Agtmaal 1988; Agarwal 1995; Kartasasmita 1995; Stabell 1995; Pant 1996; Donnen 1998; Smith 1999; Cherian 2001; Chowdhury 2002; Cherian 2003; Lin 2008). We

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considered three studies at high risk of bias (Daulaire 1992; Lin 2009; DEVTA trial 2013).

Blinding of outcome assessors

Thirty (63%) studies had low risk of bias. The risk was unclear in 14 (30%) studies (Reddy 1986a; Sommer 1986; van Agtmaal 1988; Semba 1991; Agarwal 1995; Kartasasmita 1995; Stabell 1995; Pant 1996; Donnen 1998; Smith 1999; Cherian 2001; Chowdhury 2002; Cherian 2003; Lin 2008). We assessed three (6%) studies at high risk of bias for blinding of outcome assessors (Daulaire 1992; Lin 2009; DEVTA trial 2013).

Incomplete outcome data

For incomplete outcome data, we judged 26 (55%) studies at low risk of bias. The risk was unclear in 12 (25%) studies (Sinha 1976; Reddy 1986a; Sommer 1986; Vijayaraghavan 1990; West 1991; Ross 1993 HEALTH; Ross 1993 SURVIVAL; Agarwal 1995; Stabell 1995; Venkatarao 1996; Smith 1999; Cherian 2001). We rated nine (19%) studies at high risk of bias (van Agtmaal 1988; Lie 1993; Kartasasmita 1995; Semba 1995; Pant 1996; Bahl 1999; Arya 2000; Chowdhury 2002; Cherian 2003). The primary reason for a high-risk rating was a lack of explanation for attrition in intervention and control group.

Selective reporting

Most of the trials in the review included multiple outcome measures, and positive results are more likely to be included in reports than negative results. Only seven (14%) studies appeared to be free of selective outcome reporting (Florentino 1990; Rahmathullah 1990; West 1991; Dibley 1996; Benn 1997; DEVTA trial 2013; Fisker 2014). We judged 26 (55%) studies at unclear risk of bias and 14 (29%) studies at high risk of bias (Pinnock 1988; van Agtmaal 1988; Vijayaraghavan 1990; Ross 1993 HEALTH; Ross 1993 SURVIVAL; Stansfield 1993; Ramakrishnan 1995; Pant 1996; Bahl 1999; Arya 2000; Cherian 2003; Lin 2008; Lin 2009; Lima 2014).

Most of the studies did not cite a published protocol, which is why we assessed a large proportion of studies at unclear risk of bias.

Other potential sources of bias

We extracted other potential sources of bias and noted them in the Characteristics of included studies table, but none were likely to influence the results of the review in a meaningful way.

Effects of interventions

See: **Summary of findings 1** Vitamin A supplementation versus placebo or usual care for preventing morbidity and mortality in children from 6 months to 5 years of age

We present the results for each outcome below, summarising the main outcomes in Summary of findings 1.

We did not conduct all of our planned subgroup analyses. For the primary outcome, only one study used a non-standard dose and frequency. Other analyses with more than 10 studies contained significantly fewer participants (e.g. the analysis of serum level included fewer than 7000 children). Consequently, we did not conduct subgroup analyses for dose and frequency because the analyses were clearly underpowered, and any effects would be attributable to chance. Results of the attempted subgroup analyses are listed in Table 1. We performed sensitivity analyses for all-cause mortality and incidence due to diarrhoea and vitamin A serum levels only, as most analyses contained a small number of studies.

Primary outcome

All-cause mortality

Nineteen trials involved 1,202,382 children (98.25% of the children included in the review) in an overall analysis (using data from the last follow-up for trials measuring outcomes multiple times) (Sommer 1986; Rahmathullah 1990; Vijayaraghavan 1990; West 1991; Daulaire 1992; Herrera 1992; Ross 1993 HEALTH; Ross 1993 SURVIVAL; Barreto 1994; Agarwal 1995; Dibley 1996; Pant 1996; Venkatarao 1996; Benn 1997; Donnen 1998; Chowdhury 2002; Lin 2008; DEVTA trial 2013; Fisker 2014). One trial reported no events (Lin 2008).

Vitamin A was associated with a 12% reduction in all-cause mortality (RR 0.88, 95% CI 0.83 to 0.93; Analysis 1.1; Figure 3), though there was moderate heterogeneity ($Chi^2 = 44.00$, degrees of freedom (df) = 17; $P < 0.001$; $I^2 = 61\%$). We judged the certainty of evidence to be high (see Summary of findings 1).

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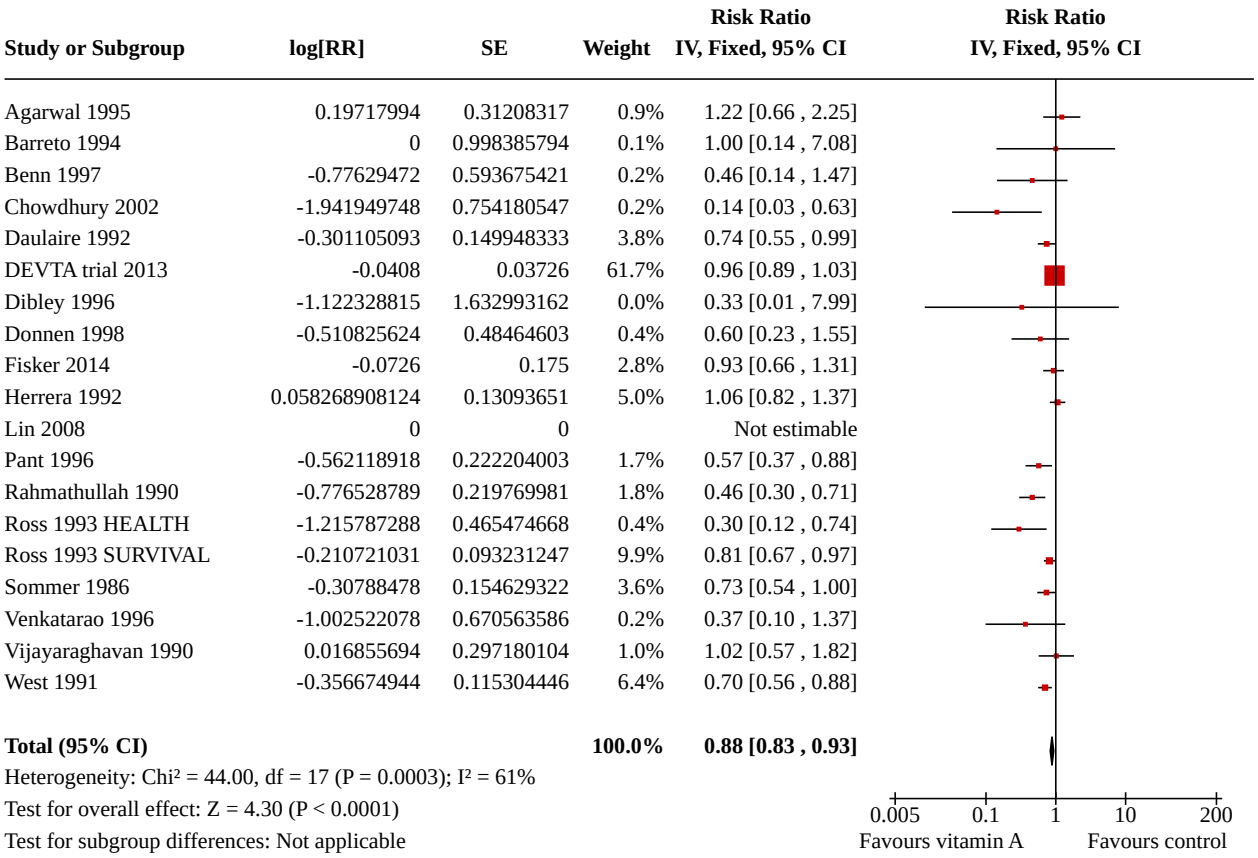
Figure 3. Forest plot of comparison: 1 Vitamin A versus control, outcome: 1.1 All-cause mortality at longest follow-up.



The effect during the first year postrandomisation was similar based on data available from 13 studies (RR 0.83, 95% CI 0.75 to 0.92), and the statistical heterogeneity was similar (Chi^2 = 34.29, df = 12; P < 0.001; I^2 = 65%). Only six (12%) studies measured mortality between 13 and 59 months, and the effect was similar (RR 0.88, 95% CI 0.81 to 0.97, 6 studies), with moderate and significant statistical heterogeneity (Chi^2 = 15.75, df = 5; P = 0.008; I^2 = 68%). See Table 1.

Subgroup analyses

Dose and frequency

Only one study reporting all-cause mortality did not use the standard dose and frequency recommended by WHO: Rahmathullah 1990 used a weekly dose for 52 weeks. We did not conduct the planned subgroup analyses.

Location

Twelve studies were set in Asia (RR 0.90, 95% CI 0.84 to 0.96), six in Africa (RR 0.86, 95% CI 0.75 to 0.98), and one in Latin America (RR 1.00, 95% CI 0.14 to 7.08). These results were not different based on location (P = 0.83). See Table 1.

Age

Five studies reported separate effects for children aged six to 12 months (RR 0.59, 95% CI 0.43 to 0.82; Analysis 1.2.1) and children aged one to five years (RR 0.68, 95% CI 0.57 to 0.81; Analysis 1.2.2) (Sommer 1986; Rahmathullah 1990; West 1991; Daulaire 1992; Benn 1997). The subgroups did not differ from each other (P = 0.46). Notably, both effect estimates were larger than the overall result from 19 trials reporting mortality.

Sex

Seven studies reported separate effects for boys (RR 0.96, 95% CI 0.89 to 1.04; Analysis 1.3.1) and girls (RR 0.90, 95% CI 0.84 to 0.97; Analysis 1.3.2). The effects were not different based on sex (P = 0.22) (Sommer 1986; West 1991; Daulaire 1992; Herrera 1992; Lin 2008; DEVTA trial 2013; Fisker 2014).

Child mortality

Seventeen studies from countries with high child mortality showed a similar effect as the overall estimate (RR 0.89, 95% CI 0.84 to 0.94), and two studies from countries with low child mortality showed no combined effect for VAS (RR 1.00, 95% CI 0.14 to 7.08). See Table 1.

Sensitivity analyses

Bias

Of the studies at high risk of bias due to sequence generation, only Herrera 1992 contributed to the main mortality analysis and reported no effect (RR 1.06, 95% CI 0.82 to 1.37), indicating that this study was not likely to influence the results in a positive direction.

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To test for small-study bias, we repeated the analysis using a random-effects model. The overall estimate was larger than the fixed-effect estimate (RR 0.76, 95% CI 0.66 to 0.88, 19 studies; heterogeneity: Tau^2 = 0.04; Chi^2 = 44.00, df = 17; P < 0.001; I^2 = 61%); however, CIs overlapped with estimates from the fixed-effect model. The apparent increase in effect size suggests that heterogeneity might be explained by relatively small studies compared to larger studies, as exclusion of the DEVTA trial 2013 reduced the heterogeneity (from Chi^2 = 44.00, df = 17; P < 0.001; I^2 = 61% to Chi^2 = 30.38, df = 16; P = 0.02; I^2 = 47%). See Table 1.

Design effects in cluster trials

Known ICCs were consistent. For three studies for which the ICC was not known, we estimated the ICC as 0.002 and adjusted SEs using this value and the mean cluster size. To determine if this decision had any impact on the results, we repeated the primary analysis using a much larger and much smaller ICC estimate. The size of the effect was slightly smaller when these trials were treated as if they had randomised individuals (RR 0.89, 95% CI 0.84 to 0.94, 19 studies). The effect was virtually unchanged when we increased the ICC to 0.01 (RR 0.89, 95% CI 0.84 to 0.94, 19 studies). See Table 1. These results indicate that over-weighting these three studies in the analysis would not impact the conclusions of this review; further inflating their SEs would increase the size of the effect estimate.

Secondary outcomes

Cause-specific mortality

Diarrhoea

Nine studies reported a combined 12% reduction in mortality due to diarrhoea (RR 0.88, 95% CI 0.79 to 0.98; 1,098,538 children; Analysis 1.4; Rahmathullah 1990; Daulaire 1992; Herrera 1992; Ross 1993 SURVIVAL; Agarwal 1995; Venkatarao 1996; Chowdhury 2002; DEVTA trial 2013; Fisker 2014), with no important heterogeneity (Chi^2 = 10.15, df = 8; P = 0.25; I^2 = 21%). We judged the certainty of this evidence to be high (Summary of findings 1). Results for diarrhoea mortality reported within one year of randomisation showed similar results (0.76, 95% CI 0.61 to 0.95; 6 studies; Table 1).

Measles

Six studies reported a lower risk of mortality due to measles (RR 0.88, 95% CI 0.69 to 1.11; 1,088,261 children; low-certainty evidence; Analysis 1.5; Rahmathullah 1990; Daulaire 1992; Herrera 1992; Ross 1993 SURVIVAL; Agarwal 1995; DEVTA trial 2013). There was no important heterogeneity (Chi^2 = 0.66, df = 5; P = 0.99; I^2 = 0%). We judged the certainty of this evidence as low (Summary of findings 1). One-year postrandomisation results were similar (RR 0.85, 95% CI 0.52 to 1.37; 4 studies; Table 1).

Meningitis

Three studies reported a lower risk of mortality due to meningitis, but the CI around the summary estimate was imprecise and included a null effect (RR 0.57, 95% CI 0.17 to 1.88; Analysis 1.6; Ross 1993 SURVIVAL; Agarwal 1995; Chowdhury 2002). There was no important heterogeneity (Chi^2 = 0.75, df = 2; P = 0.69; I^2 = 0%). Only one study reported data within one-year postrandomisation, with results that were imprecise and the CI included a null effect (RR 5.79, 95% CI 0.22 to 153.24; Table 1).

Lower respiratory tract infection

Nine studies found no evidence of a difference between the intervention and placebo group (RR 0.98, 95% CI 0.86 to 1.12; 1,098,538 children; Analysis 1.7; Rahmathullah 1990; Daulaire 1992; Herrera 1992; Ross 1993 SURVIVAL; Agarwal 1995; Venkatarao 1996; Chowdhury 2002; DEVTA trial 2013; Fisker 2014). There was no important heterogeneity (Chi^2 = 9.70, df = 8; P = 0.29; I^2 = 18%). We judged the certainty of evidence as low (Summary of findings 1). A combined result for one-year postrandomisation showed imprecise results and the CI included a null effect (RR 0.66, 95% CI 0.40 to 1.10; 6 studies; Table 1).

Cause-specific morbidity

Diarrhoea

Meta-analyses

Fifteen studies reported a 15% decrease in diarrhoea incidence (RR 0.85, 95% CI 0.82 to 0.87; 77,946 children; Analysis 1.8; Figure 4; Florentino 1990; Herrera 1992; Lie 1993; Barreto 1994; Biswas 1994; Ramakrishnan 1995; Dibley 1996; Venkatarao 1996; Sempértegui 1999; Shankar 1999; Arya 2000; Chowdhury 2002; Long 2007; Chen 2013a and Chen 2013b (counted as one study); Fisker 2014), though statistical heterogeneity was substantial (Chi^2 = 219.04, df = 14; P < 0.001; I^2 = 94%). We judged this evidence to be of low certainty (Summary of findings 1).

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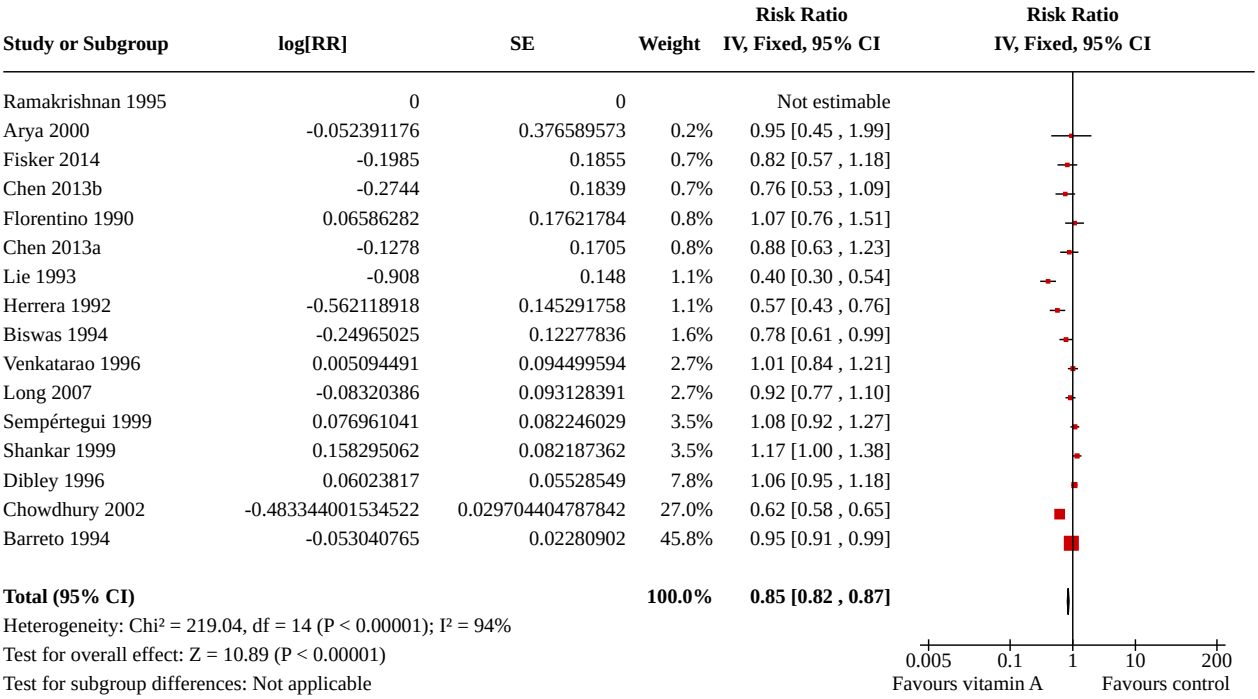
Figure 4. Forest plot of comparison: 1 Vitamin A versus control, outcome: 1.8 Diarrhoea incidence at longest follow-up.



Two studies were responsible for most of the heterogeneity and accounted for most of the overall effect (Lie 1993; Chowdhury 2002). Exclusion of these studies reduced the I^2 statistic from 94% to 61%, and the overall effect almost disappeared (RR 0.96, 95% CI 0.93 to 1.00; see Table 1). The observed heterogeneity may be due to measurement error or differences in the effects of VAS across populations and settings. For example, VAS may reduce susceptibility to particular infections that are prevalent in some places but not others.

Thirteen studies that reported data for within one-year postrandomisation showed a small effect (RR 0.93, 95% CI 0.89 to 0.96; Table 1).

Three studies reported no protective effect on diarrhoea prevalence (RR 1.06, 95% CI 1.03 to 1.10; Analysis 1.9; Stansfield 1993; Long 2006a and Long 2006b (counted as one study); DEVTA trial 2013), though statistical heterogeneity was substantial (Chi^2 = 28.91, df = 3; P < 0.001; I^2 = 90%).

Sensitivity analysis

To test for small-study bias, we repeated the analysis using a random-effects model. The overall estimate was identical to the fixed-effect estimate, though the CI widened compared to the fixed-effect model, suggesting that heterogeneity is not explained by small studies reporting larger effects (RR 0.84, 95% CI 0.73 to 0.98; 15 studies; Table 1). The funnel plot we produced was dominated by two studies accounting for 74% of the overall effect (Figure 5), and the plot was relatively flat.

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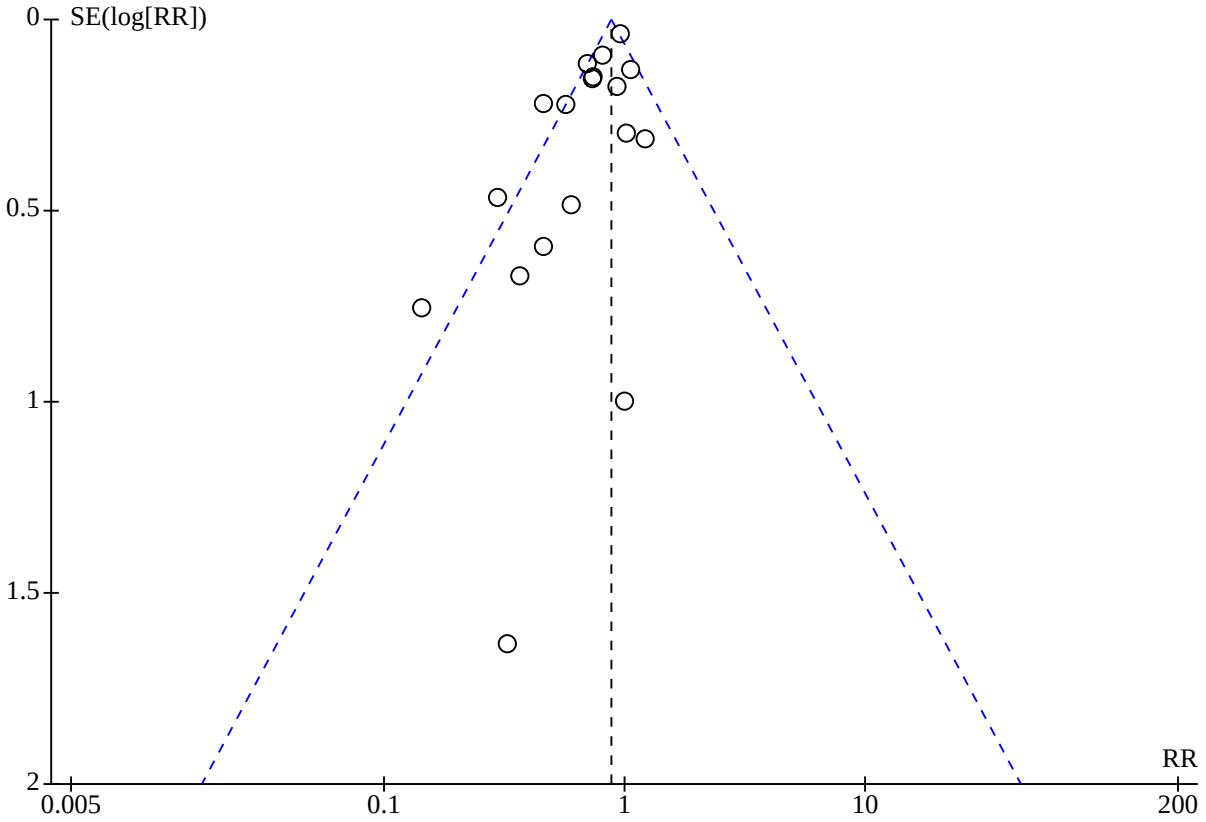
Figure 5. Funnel plot of comparison: 1 Vitamin A versus control, outcome: 1.1 All-cause mortality at longest follow-up.



With regard to the design effects in cluster trials, no ICCs were imputed, so a sensitivity analysis was not required.

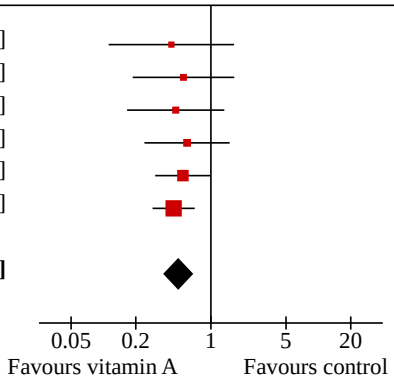
Measles

Six studies reported a 50% decrease in measles incidence (RR 0.50, 95% CI 0.37 to 0.67; 19,566 children; Analysis 1.10; Figure 6; Herrera 1992; Barreto 1994; Semba 1995; Benn 1997; Bahl 1999; Chowdhury 2002), with no important heterogeneity (Chi^2 = 0.55, df = 5; P = 0.99; I^2 = 0%). We judged this evidence to be of moderate certainty (Summary of findings 1).

Figure 6. Forest plot of comparison: 1 Vitamin A versus control, outcome: 1.12 Measles incidence at longest follow-up.

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Bahl 1999	-0.84729786	0.685359748	4.9%	0.43 [0.11 , 1.64]
Barreto 1994	-0.587786665	0.554874134	7.5%	0.56 [0.19 , 1.65]
Benn 1997	-0.753821864	0.531270633	8.2%	0.47 [0.17 , 1.33]
Herrera 1992	-0.510825624	0.465797456	10.7%	0.60 [0.24 , 1.49]
Semba 1995	-0.599691567	0.302982706	25.2%	0.55 [0.30 , 0.99]
Chowdhury 2002	-0.798386071	0.230353301	43.6%	0.45 [0.29 , 0.71]
Total (95% CI)			**100.0%**	**0.50 [0.37 , 0.67]**

Heterogeneity: Chi^2 = 0.55, df = 5 (P = 0.99); I^2 = 0%
Test for overall effect: Z = 4.61 (P < 0.00001)
Test for subgroup differences: Not applicable



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A combined effect from studies that reported measles incidence within one-year postrandomisation showed similar results (RR 0.54, 95% CI 0.36 to 0.80; 5 studies; Table 1).

There were no studies that reported data on prevalence of measles.

Malaria

One study reported a 27% reduction in malaria incidence at follow-up (RR 0.73, 95% CI 0.60 to 0.88; see the illustrative forest plot in Analysis 1.11 and Table 1; Shankar 1999).

Two studies reported data on malaria prevalence; the combined effect was imprecise and the CI around the summary estimate included a null effect (RR 0.73, 95% CI 0.41 to 1.28; Analysis 1.12; Ross 1993 HEALTH; Ross 1993 SURVIVAL), and there was no important heterogeneity (Chi^2 = 0.02, df = 1; P = 0.88; I^2 = 0%).

Meningitis

There were no studies that reported incidence or prevalence data for meningitis.

Lower respiratory tract infection

Eleven studies reported no combined effect for VAS on LRTI incidence (RR 0.99, 95% CI 0.92 to 1.06; 27,540 children; Analysis 1.13; Rahmathullah 1990; Lie 1993; Barreto 1994; Biswas 1994; Kartasasmita 1995; Venkatarao 1996; Sempértegui 1999; Chowdhury 2002; Long 2007; Chen 2013a and Chen 2013b (considered as one study); Fisker 2014), with no important heterogeneity (Chi^2 = 11.35, df = 9; P = 0.25; I^2 = 21%). We judged the certainty of evidence to be low (Summary of findings 1).

Eleven studies that reported data on LRTI incidence within one-year postrandomisation showed similar results (RR 0.96, 95% CI 0.89 to 1.04; Table 1).

Two trials with two relevant comparisons reported LRTI prevalence; the combined result suggests benefit for VAS (RR 0.60, 95% CI 0.45 to 0.81; Analysis 1.14; Long 2006a; DEVTA trial 2013).

Bitot's spots

Herrera 1992 reported no effect on Bitot's spots incidence (RR 0.93, 95% CI 0.76 to 1.14; Table 1).

Five trials reported a 58% reduction in Bitot's spots prevalence (RR 0.42, 95% CI 0.33 to 0.53; 1,063,278 children; Analysis 1.15; Sinha 1976; Sommer 1986; West 1991; Pant 1996; DEVTA trial 2013), with substantial heterogeneity (Chi^2 = 7.89, df = 4; P = 0.10; I^2 = 49%). We judged this evidence to be of moderate certainty (Summary of findings 1).

Three studies reported data within one-year postrandomisation, and combined results were similar (RR 0.43, 95% CI 0.33 to 0.56; Table 1).

Night blindness

Herrera 1992 reported a 47% reduction in night blindness incidence (RR 0.53, 95% CI 0.28 to 0.99), as shown in the illustrative forest plot in Analysis 1.16.

Sommer 1986 and West 1991 reported a 68% reduction in night blindness prevalence (RR 0.32, 95% CI 0.21 to 0.50; 22,972 children; Analysis 1.17), with no heterogeneity (Chi^2 = 0.19, df = 1; P = 0.66; I^2 = 0%). We judged the certainty of evidence to be moderate (Summary of findings 1).

One study reported prevalence within one-year postrandomisation, and results were similar (RR 0.30, 95% CI 0.17 to 0.52; Table 1).

Xerophthalmia

Three trials reported no combined effect on xerophthalmia incidence (RR 0.85, 95% CI 0.70 to 1.03; Analysis 1.18; West 1991; Herrera 1992; Barreto 1994), though statistical heterogeneity was substantial (Chi^2 = 2.69, df = 1; P = 0.10; I^2 = 63%).

Two studies reported data for one-year postrandomisation, and results were similar (RR 0.88, 95% CI 0.72 to 1.07; Table 1).

Sommer 1986 and West 1991 reported a 69% reduction in xerophthalmia prevalence (RR 0.31, 95% CI 0.22 to 0.45; Analysis 1.19), with no statistical heterogeneity (Chi^2 = 0.22, df = 1; P = 0.64; I^2 = 0%).

Hospitalisation

Ross 1993 HEALTH reported the likelihood of hospitalisations; however, results were imprecise and the CI around the summary estimate included a null effect (RR 0.64, 95% CI 0.40 to 1.02; see the illustrative forest plot in Analysis 1.20).

Lie 1993 reported inconclusive evidence on hospitalisation due to diarrhoea (RR 0.25, 95% CI 0.01 to 6.11; see the illustrative forest plot in Analysis 1.21) and hospitalisation due to LRTI (RR 0.11, 95% CI 0.01 to 2.06; see the illustrative forest plot in Analysis 1.22).

Side effects

We assessed two short-term side effects: vomiting (within 48 hours) and bulging fontanelle.

Four trials reported an increase in risk of vomiting (RR 1.97, 95% CI 1.44 to 2.69; 10,541 children; Analysis 1.23; Sinha 1976; Florentino 1990; Arya 2000; Fisker 2014), with substantial statistical heterogeneity (Chi^2 = 9.51, df = 3; P = 0.02; I^2 = 68%). We judged this evidence to be of moderate certainty (Summary of findings 1).

Four trials reported bulging fontanelle side effects, but the only two that had enough data to enable analysis reported no effect (RR 1.24, 95% CI 0.74 to 2.08; Analysis 1.24; Stabell 1995; Bahl 1999; Arya 2000; Fisker 2014). Most studies included children over one year of age and would not have assessed this side effect.

Vitamin A deficiency status

Meta-analyses

We assessed two indices of VAD: number deficient and serum retinol level.

Four trials reported a 29% reduction in the number of VAD children (RR 0.71, 95% CI 0.65 to 0.78; 2262 children; Analysis 1.25; Ross 1993 HEALTH; Dibley 1996; Shankar 1999; Cherian 2001); however, statistical heterogeneity was substantial (Chi^2 = 13.58, df = 3; P = 0.004; I^2 = 78%). We judged this evidence to be of moderate certainty (Summary of findings 1).

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Fourteen trials reported data on vitamin A serum retinol level at follow-up, including one factorial study contributing two comparisons (Pinnock 1986; Reddy 1986a and Reddy 1986b (considered as one study); Pinnock 1988; Semba 1991; Lie 1993; Ross 1993 HEALTH; Ross 1993 SURVIVAL; Kartasasmita 1995; Dibley 1996; Sempértegui 1999; Shankar 1999; Cherian 2001; Lin 2009; DEVTA trial 2013). Vitamin A serum levels were higher in the vitamin A group (standardised mean difference (SMD) 0.26, 95% CI 0.22 to 0.30; Analysis 1.26); however, statistical heterogeneity was substantial ($Chi^2 = 278.45$, df = 14; P < 0.001; $I^2 = 95\%$).

Eleven studies reported data within one-year postrandomisation and results showed a relatively modest effect (RR 0.45, 95% CI 0.37 to 0.53; Table 1).

Sensitivity analysis

No studies reporting VAD status were at high risk of bias for sequence generation.

To test for small-study bias, we repeated the analysis using a random-effects model. The overall estimate was considerably larger than the fixed-effect estimate, suggesting small studies report larger effects (SMD 0.50, 95% CI 0.30 to 0.70; 14 studies; Table 1).

The funnel plot that we produced was highly asymmetrical (data not shown).

With regard to the design effects in cluster trials, no ICCs were imputed, so a sensitivity analysis was not required.

DISCUSSION

Summary of main results

For this update, there were no new eligible RCTs.

In the previous version (Imdad 2017), despite the addition of newer studies, notably the large study from India (DEVTA trial 2013), VAS was still associated with a reduction in all-cause mortality of 12%. There was some statistical heterogeneity in the pooled data, and a sensitivity analysis using a random-effects model changed the effect size from 12% to 24%; however, the CIs overlapped with that of the fixed-effect model. Whatever method of analysis we used, vitamin A had a significant and clinically meaningful effect, so supplementation should be offered to children in populations at risk of VAD.

Even though the exact mechanism of vitamin A against mortality is unclear, at least some of its protective effect stems from reductions in death due to diarrhoea and measles. The overall effect for mortality due to measles was not significant, as not all the studies that reported all-cause mortality reported measles-specific mortality; however, the therapeutic effects of VAS in reducing measles-related mortality and morbidity are well established (Huiming 2005). Furthermore, VAS resulted in reduced incidence of diarrhoea and measles. Other reviews have shown that the therapeutic use of VAD may prevent acute diarrhoea from becoming chronic (Imdad 2010b). Together, these results suggest that reductions in diarrhoea and measles are potential pathways in the reduction of all-cause mortality.

In addition to reducing death and illness, VAS reduces night blindness and potential precursors to blindness, namely Bitot's spots and xerophthalmia.

Few studies reported data about side effects, including vomiting, bulging fontanelle, and diarrhoea soon after receiving the intervention. VAS may increase short-term vomiting almost two-fold.

Overall completeness and applicability of evidence

This review systematically assessed both mortality and morbidity associated with VAS. This update does not include any new eligible study, so the results are the same in terms of the effectiveness of VAS for reducing mortality, morbidity, and nutrition-related blindness.

All included studies reporting all-cause mortality were set in low- to middle-income countries. Given that a large proportion of the included studies (20/47) specifically excluded children with VAD, and vitamin A status was unclear in 23, it is likely that the effectiveness of VAS may be even more effective for children in low- and middle-income countries who are at risk of VAD. The primary analysis was based on 19 trials from different countries and locations. It included 1,202,382 children randomised. The risk of selective reporting for the primary outcome appeared minimal. Statistical heterogeneity suggested that the magnitude of the effect may differ across settings and populations, possibly due to the extent of VAD or the availability of other nutrients. For example, dietary intake of vitamin A will differ across locations, and the effects of supplementation may be smaller in places with greater access to foods rich in vitamin A. Concomitant nutrient deficiencies may also impair the bioavailability of the supplements, since some of these nutrients (including fat, protein, and zinc) could be limiting factors for the absorption and utilisation of vitamin A, which is lipid-soluble (Villamor 2000). Comorbid illnesses could also reduce absorption of vitamin A; that is, if vitamin A reduces mortality by reducing susceptibility to particular pathogens, differences in the prevalence of disease, sanitation, etc. might contribute to heterogeneity in outcomes across trials.

Analyses for many of the cause-specific mortality and morbidity outcomes were consistent in favour of VAS. A general weakness of many interventions is the under-reporting of implementation data, such as the core components of an intervention, the degree to which they are delivered in practice, and what aspects of the trial may have influenced implementation (Mayo-Wilson 2007). In theory, the putative effect of this intervention relies little on the relationship between the provider and participant, but it is essential that large-scale interventions effectively distribute capsules that have been stored properly and remain active. Additionally, the degree to which children were treated for morbidities across trials might influence incidence and prevalence data collected in various trials, and this could contribute to heterogeneity.

This review suggests some ways in which vitamin A might work, but it does not describe how the effects of vitamin A might differ across subpopulations. The included trials did not report the data required for such analyses, and we decided a priori not to include subgroup analyses based on individual-level moderators for reasons described in the section on Subgroup analysis and investigation of heterogeneity. A more detailed investigation

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of heterogeneity would require individual participant data and possibly information on vitamin A status at the individual or population level. Co-interventions, including other nutrients or vaccinations, might interact with vitamin A, but we were unable to review possible interaction effects. We were also unable to compare HIV-positive children to HIV-negative children, though there is a separate Cochrane Review that specifically considered the effectiveness of VAS in people infected with HIV, and the results were similar (Irlam 2010). Subgroup analyses by geographic region included few studies; some disaggregated data by sex and age, but these were not representative of the studies overall or the results. Subgroup results were neither significant nor meaningful, and they are vulnerable to reporting bias (i.e. differences are more likely to be reported than similarities). Though a review with individual participant data could be informative, systematic reviews are not the best method for answering all questions, and other studies might explain why results are sometimes different. In any case, the observed effects are so large that heterogeneity may be unimportant; vitamin A should be given to children whether it reduces childhood mortality by 7% or 17%.

Quality of the evidence

This update included no new eligible studies; however, previously, this review included 47 studies and an estimated 1,223,856 children. This is the largest review of VAS for children to date.

In certain studies, it was impossible to assess allocation concealment. Efforts to blind participants and providers suggest the overall risk of bias is minimal, and any impact on the primary outcome (all-cause mortality) is likely to be small.

In some trials, children interacted with researchers or clinicians who were aware of their assignment. We judged three studies at high risk of performance bias, mostly because of failure to adequately blind participants, providers, and outcome assessors (Daulaire 1992; Lin 2009; DEVTA trial 2013). We considered bias due to inadequate blinding to be low and, if anything, likely to underestimate effects; for example, a teacher would be more likely to give extra food to a child receiving the placebo rather than the reverse.

Missing data are much more likely to influence secondary analyses than the primary outcome. Results for all-cause mortality are known for over 98% of randomised participants. Of the 19 (40%) studies that reported this outcome, we judged seven at unclear risk of bias, but four of these had minimal attrition (Vijayaraghavan 1990; Ross 1993 HEALTH; Ross 1993 SURVIVAL; Venkatarao 1996. The others failed to report reasons for dropout. Two studies did not adequately manage missing data, but together these studies contributed only 5% to the pooled estimate (Pant 1996; Chowdhury 2002).

The DEVTA trial 2013, which included about one million children, found a small benefit for VAS. These findings generated controversy because many experts believe that the methods for the delivery of the intervention and the assessment of the primary outcome (i.e. all-cause mortality) were not rigorous (Habicht 2013; Mannar 2013; Mayo-Wilson 2013; Sloan 2013; Sommer 2013). For example, investigators did not count children at baseline or obtain informed consent, and methods of follow-up and data collection were not vigorous (Mannar 2013; Sommer 2013). In this cluster-RCT, vitamin A capsules were distributed by Anganwadi workers who had contact with only 26% of the children living in the study area (Sommer 2013). In reply to this extensive criticism, authors of DEVTA emphasised that results of this trial need to be interpreted alongside previously published studies (Peto 2013). In the updated analysis of 19 trials for all-cause mortality for this review, DEVTA accounted for 61.7% of the combined effect in a fixed-effect analysis. A sensitivity analysis using a random-effects model found a 24% reduction in mortality, essentially the same as our original estimate (RR 0.76, 95% CI 0.69 to 0.83), published previously (Imdad 2010a). Thus, VAS appears to have a robust effect on risk of death in children, which is clinically meaningful and important for policy. Unsurprisingly, the effect of VAS may be reduced when the intervention is not delivered with fidelity.

In summary, the primary outcome was at low risk of bias, and the size and the significance of the effect cannot be explained by bias. While there was some evidence of small-study bias for secondary outcomes, further research is unlikely to change the conclusion that VAS, delivered with high quality and coverage, prevents death among children aged six to 59 months in low- and middle-income countries. Despite sensitivity analyses and attempts to explain sources of heterogeneity by comparing the characteristics of the studies, we could not explain reasons for these differences across trials. Observational studies might investigate the mechanisms by which vitamin A reduces mortality.

Potential biases in the review process

This review used clearly specified inclusion and exclusion criteria, a comprehensive search strategy for the identification of relevant studies, and prespecified subgroup and sensitivity analyses to explore heterogeneity. We also described the post hoc decision to include two quasi-RCTs (Herrera 1992; Stansfield 1993). Only Herrera 1992 contributed data to the primary outcome of all-cause mortality, and sensitivity analyses demonstrated that exclusion of this study did not change the results significantly.

We combined RRs (events per child) and rate ratios (events per child-year) for incidence data. Strictly speaking these two ratios have different interpretations; however, we consider that the included studies used the same scale, and outcomes are less likely to be biased by use of denominator. For the primary outcome of all-cause mortality, there were three studies where the denominator was time at risk (Ross 1993 HEALTH; Dibley 1996; Fisker 2014), and exclusion of these studies did not change the results.

For three trials with multiple arms, we included each such study as two comparisons (Reddy 1986a and Reddy 1986b; Long 2006a and Long 2006b; Chen 2013a and Chen 2013b). We acknowledge that results for comparisons from the same study may be correlated; however, this is unlikely to affect the results of our analysis because each group was counted only once (i.e. we would have obtained the same overall result by combining the eligible treatment groups and the eligible control groups).

The comprehensive search strategy was devised to minimise publication bias by searching for both published and unpublished studies, though none of the included studies were unpublished. While studies with positive results are more likely to be published than studies with negative results, studies large enough to influence this review are very likely to be published. One study awaiting assessment was too small to affect any analysis (Aklamati 2006).

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Some secondary outcomes did not contain a majority of the children randomised in the review, and these results may be vulnerable to selective outcome reporting bias.

Agreements and disagreements with other studies or reviews

Our results are consistent with the results of other reviews assessing a similar question, though the magnitude of the reduction in risk of death was smaller. Glasziou 1993 reported a 30% reduction in all-cause mortality, and Beaton 1993 reported a 23% reduction. Fawzi 1993 used an odds ratio (OR) rather than RR as the measure of association, so the reported reduction is not directly comparable (OR 0.70, 95% CI 0.56 to 0.87).

AUTHORS' CONCLUSIONS

Implications for practice

Over the years, the prevalence of vitamin A deficiency (VAD) has decreased; however, it is still widely prevalent in Southeast Asia and Sub-Saharan Africa (Stevens 2015). Even though no new eligible study was included in this update, the previous versions of this review showed that synthetic vitamin A supplementation (VAS) reduced disease and death in children aged six to 59 months (Imdad 2010a; Imdad 2017). However, we acknowledge that synthetic VAS may not be the long-term solution to control VAD. Fortification, food distribution programmes, and horticultural developments may provide more permanent relief. For example, vitamin A could be added to rice or growers may aim to increase access to agricultural products such as orange-fleshed sweet potato (Klemm 2010; Klemm 2016). Furthermore, if vitamin A reduces mortality by preventing measles, widespread vaccination will reduce the relative contribution of VAS. Until such long-term solutions are in place, supplementation should continue. As access to vitamin A increases, it will be important to continue to identify at-risk groups and deliver supplements to them (Bhutta 2015).

The World Health Organization (WHO) currently recommends VAS to children between six and 59 months of age, in a dose of 100,000 IU for children aged six to 12 months and a dose of 200,000 IU for children aged one to five years, every six months. Based on existing literature, we suggest continuing this policy for children under five years of age in areas at risk of VAD. However, the global policy for universal VAS must be revisited for populations where VAD no longer remains a public health issue and VAD-associated deaths have markedly declined (Stevens 2015).

Implications for research

The effectiveness of VAS for preventing mortality is well established. The primary results in this review are robust and clinically meaningful. Further placebo-controlled studies would be unethical.

Nevertheless, this review does not answer a number of important questions. There was little variation in dosing among studies reporting the primary outcome. One trial used weekly doses and estimated a 54% reduction in all-cause mortality (Rahmathullah 1990). It would be ethical to conduct trials in which participants receive different doses of vitamin A that are likely to be beneficial, some of which could lead to larger benefits than those observed so far, and might lead to fewer side effects (e.g. vomiting).

Reductions in mortality are likely related to reduced incidence and severity of diarrhoea and measles. The effects of VAS on relevant pathogens and disease pathways are not well understood, and these could be examined in observational studies or in trials of other interventions for these problems.

Growth and other developmental outcomes are less important than mortality, and few studies have looked into these questions. These outcomes could be added to future versions of this review. Observational studies might elucidate the relationship (if any) between vitamin A and growth.

Despite the primary effect, observed increases in vitamin A serum levels were small. That said, serum level may be a poor indicator of status and may not be related to more meaningful outcomes such as mortality or blindness (WHO 2009). In addition, oral synthetic VAS supplementation may not be the best pathway for delivery. For example, absorption may be better in protein carriers compared to carbohydrate carriers. Further studies might compare synthetic supplementation to fortification or other delivery mechanisms.

Two additional Cochrane Reviews cover the preventive aspect of VAS for infants less than six months of age: one investigated the effects of vitamin A during the neonatal period (Haider 2017), while another focused on infants aged one to six months (Imdad 2016). Further reviews might investigate different delivery channels, including food supplementation and improved access to food or social programmes to increase uptake of vitamin A-rich foods. Several studies have investigated VAS for pregnant and lactating mothers; these and other efforts to promote delivery of vitamin A (e.g. by increased rates and duration of breastfeeding) may require further attention.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Agarwal 1995

Study characteristics	
Methods	Cluster-randomised trial conducted in Uttar Pradesh, India
Participants	**Eligibility**: children aged < 6 years **Excluded**: children with xerophthalmia **Sample**: 16 clusters (subcentres) were randomly selected and divided into 4 subdivisions (4 subcentres in each), with drugs A (vitamin A) and B (placebo) distributed in 2 each randomly. At the end of the study, investigators found that vitamin A was distributed in 3 subdivisions (12 subcentres) and placebo in 1 only (4 subcentres) by mistake. 17,778 children were approached but only 15,247 children were included in the final analysis based on the fact that they received ≥ 1 dose of vitamin A
Interventions	**Experimental group**: vitamin A 50,000 IU + vitamin E 10 IU for children aged 1–6 months and vitamin A 100,000 IU and vitamin E 20 IU for children aged 7–72 months

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Agarwal 1995 *(Continued)*

	Control group: placebo **Study duration**: intervention delivered every 4 months for 12 months
Outcomes	All-cause and cause-specific mortality due to diarrhoea, pneumonia, measles, and meningitis
Notes	The trial was conducted in 2 phases. The first phase consisted of 15 months (i.e. 3 months for registration and 12 months for intervention and measurement of relevant outcomes). In the second phase, mortality was measured in a subsample of initially included children, exactly 12 months after termination of first phase. The cause of death was assigned using a verbal autopsy tool. Baseline mortality rates for children < 6 years of age were 27.7 for the intervention group and 23.3 per 1000 for the control group, with significant differences in the 2 groups (P < 0.01). According to WHO, India is a country with a high child mortality rate (i.e. > 40/1000).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "Out of the total 43 subcentres, 16 were randomly selected, four subdivisions (4 subcentres in each) were made and drugs A and B distributed in two each randomly". **Comment**: authors did not specify the method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	**Comment**: insufficient information to permit judgement.
Blinding (performance bias and detection bias) Blinding of participants	Unclear risk	**Comment**: insufficient information to permit judgement.
Blinding (performance bias and detection bias) Blinding of provider	Unclear risk	**Comment**: insufficient information to permit judgement.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Unclear risk	**Comment**: insufficient information to permit judgement.
Incomplete outcome data (attrition bias)	Unclear risk	**Comment**: insufficient information to permit judgement.
Selective reporting (reporting bias)	Unclear risk	**Comment**: insufficient information to permit judgement.
Other bias	Unclear risk	**Comment**: insufficient information to permit judgement.

Albert 2003

Study characteristics

Methods	Factorial design, individually randomised trial conducted in Dhaka, Bangladesh
Participants	**Eligibility**: children aged 2–5 years of either sex, VAD (serum retinol level < 20 mg/dL; and nutritional status corresponding to a weight-for-age score that was 61% of the median National Center for Health Standards standard

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Albert 2003 *(Continued)*

	Excluded: children who had received VAS during the preceding 6 months or with history of night blindness or sickness due to underlying illnesses such as diarrhoea or respiratory tract infections **Sample**: 256 children
Interventions	4 intervention groups **Experimental group I**: vitamin A. 5 mL vitamin A syrup 200,000 IU once a week before administration of the first dose of the vaccine and received 5 mL of a placebo syrup every day for 42 days starting 3 weeks before administration of the first dose of vaccine and ending 1 week after the second dose of vaccine **Experimental group II**: zinc. 5 mL zinc acetate syrup (containing 20 mg of elemental zinc) daily + single dose of a placebo syrup, according to the same schedule used for the children in the A group **Experimental group III**: vitamin A + zinc **Control group**: placebo
Outcomes	Vibriocidal antibody response to cholera vaccine
Notes	No clinical outcomes were available so no data were included in meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "Bottles of syrup were serially numbered according to the randomizations list". **Comment**: most likely done.
Allocation concealment (selection bias)	Low risk	**Quote**: "The randomizations code was broken after completion of the study".
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "The zinc syrup and its placebo syrup looked very similar, as did the vitamin A syrup and its placebo syrup".
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "The randomization code was broken after completion of the study".
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Quote**: "The randomization code was broken after completion of the study".
Incomplete outcome data (attrition bias)	Low risk	**Comment**: minimal attrition.
Selective reporting (reporting bias)	Unclear risk	**Comment**: no trial registration number was available.
Other bias	Low risk	**Comment**: study appeared free of other bias.

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Arya 2000

Study characteristics	
Methods	Individually randomised trial conducted in New Delhi, India
Participants	**Eligibility**: infants aged 9–12 months attending the immunisation clinic of Safdarjung hospital in New Delhi **Excluded**: sick infants requiring hospitalisation **Sample**: 256 infants; 128 in vitamin A group, 128 in placebo group. Mean age 9 months
Interventions	**Experimental group**: single-dose vitamin A 100,000 IU in arachis oil **Control group**: placebo in peanut oil Both vitamin A and placebo were administered at the time of measles vaccination. At end of study, vitamin A group received placebo, and placebo group received vitamin A.
Outcomes	Incidence of side effects in first 24 hours (vomiting, loose stools, fever, irritability, bulging fontanelle)
Notes	Study participants were not significantly different in sex, age, weight distribution, and nutritional status at the baseline. The baseline prevalence of vomiting, loose stools, fever, and irritability during the 24 hours prior to dosing was similar in both groups. 97.3% of the included infants had normal serum retinol level before the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	**Quote**: "The infants were randomised … according to the order of arrival at hospital. Randomisation was done by the nurse who gave measles vaccine to these children". **Comment**: probably not done.
Allocation concealment (selection bias)	Unclear risk	**Comment**: children were randomised according to their entry into hospital.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "This double-blind, randomised … supplied in small dark bottles marked '1' and '2' ".
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "This double-blind, randomised … supplied in small dark bottles marked '1' and '2' "
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Quote**: "This double-blind, randomised … supplied in small dark bottles marked '1' and '2' … Two clinicians examined each of the infants at both first and second visits. Neither clinician knew the bottle code".
Incomplete outcome data (attrition bias)	High risk	**Comment**: 39 (15.2%) infants were lost to follow-up with similar distribution in both the groups. Reasons for loss to follow-up not given.
Selective reporting (reporting bias)	High risk	**Comment**: methods described that the clinicians did physical examinations and recorded weight, nutritional status, any signs of VAD, heart rate, respiratory rate, temperature, and systemic examination, especially neurological examination including the state of the fontanelle, reflexes, motor and sensory func-

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Arya 2000 *(Continued)*

		tions, etc. But bulging fontanelle not reported as an outcome, or other variables mentioned in the results.
Other bias	Low risk	**Comment**: no other apparent bias.

Bahl 1999

Study characteristics	
Methods	Individually randomised study conducted in an urban slum of Delhi, India
Participants	**Eligibility**: infants aged 6–9 months enrolled into study when they turned 9 months old **Excluded**: infants with history of measles, contact with a case of measles or measles immunisation, or had received a dose of vitamin A in the previous 4 months; serious illness requiring hospitalisation or having clinical signs of VAD (i.e. xerophthalmia, Bitot's spots, etc.) **Sample**: 618 infants; 309 in vitamin A group, 309 in control group. 50% boys
Interventions	**Experimental group**: single-dose vitamin A 30 mg (100,000 IU) in the form of retinol palmitate **Control group**: soybean oil **Follow-up**: 4 months
Outcomes	Antibody response to measles vaccine, incidence of measles during study period, and side effects (e.g. vomiting, drowsiness, etc.) in first 48 hours
Notes	The primary objective of the study was to determine the response to measles vaccine when administered along with vitamin A at 9 months of age. The study found no significant difference in antibody titres between groups 3 months after the administration of intervention. The baseline prevalence of clinical VAD in children aged 1–5 years in the study area was 3.5% and that of biochemical VAD was 37%.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote**: "Infants were randomly assigned to receive vitamin A or a placebo by using a simple randomisation scheme with random permuted blocks of size eight, i.e. four infants each out of every eight infants enrolled were randomised to receive vitamin A or a placebo". **Comment**: probably done.
Allocation concealment (selection bias)	Unclear risk	**Comment**: insufficient information to permit judgement.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "This scheme ensured that all infants received 30 mg vitamin A by 12 mo [months] of age without interfering with the double-blind design of the study". **Comment**: probably done.
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Comment**: adequate masking of vitamin A and placebo should have meant that providers were adequately blinded.

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Bahl 1999 *(Continued)*

Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Comment**: adequate masking of vitamin A and placebo should have meant that outcome assessors were adequately blinded.
Incomplete outcome data (attrition bias)	High risk	**Comment**: losses to follow-up and exclusions described. Missing data excluded from the analysis. It is not possible to ascertain whether the exclusion of data from 17% of participants (equally distributed between treatment groups) would have impacted on the results. The investigators stated that the reason for their exclusion was that a follow-up serum sample could not be ascertained.
Selective reporting (reporting bias)	High risk	**Comment**: data on harms are incompletely disclosed in the study report.
Other bias	Low risk	**Comment**: study appeared free of other bias.

Barreto 1994

Study characteristics	
Methods	Individually randomised trial conducted in Serrinha, Brazil
Participants	**Eligibility**: children aged 6–48 months **Excluded**: presence of xerophthalmia or measles infection within the previous 30 days; children who received a high-dose VAS in previous 6 months or had weight-for-age < 60% of the statistical median **Sample**: 1240 children; 620 in vitamin A group, 620 in placebo group. Mean age 28 months. 52% boys
Interventions	**Experimental group**: vitamin A 100,000 IU for children aged < 12 months and 200,000 IU for children aged > 12 months **Control group**: placebo **Study duration**: intervention delivered every 4 months for 1 year
Outcomes	All-cause mortality, incidence and prevalence of diarrhoea and respiratory tract disease, incidence of measles and xerophthalmia
Notes	Study area had inadequate public health services. A previous survey in the area showed a biochemical deficiency (serum vitamin A concentration < 0.35 mmol/L) rate of 7.4% in children of this age group. According to WHO criteria, VAD should be considered a public health problem in this area. The surveillance for morbidity outcome was performed 3 times/week for 1 year, so the recall period was 48–72 hours. We used data for incidence of measles and xerophthalmia from account of attrition in study results section. According to WHO, Brazil does not have a high child mortality rate (i.e. < 40/1000).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "Children were randomly assigned to receive vitamin A or placebo four times-at the start of the trial and every 4 months thereafter". **Comment**: authors did not specify the method of sequence generation.

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Barreto 1994 *(Continued)*

Allocation concealment (selection bias)	Low risk	**Quote**: "… only an external investigator had the codes for the individually wrapped and numbered capsules". **Comment**: although specific details were not disclosed, the available information suggested that allocation was adequately concealed.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "The gelatinous capsules of vitamin A and placebo (supplied by Hoffman La Roche) were identical in appearance and were unwrapped just before administration". **Comment**: study was double-blind, with identical presentation and dosing of vitamin A and placebo.
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "The gelatinous capsules of vitamin A and placebo (supplied by Hoffman La Roche) were identical in appearance and were unwrapped just before administration". **Comment**: probably done.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Quote**: "The study was kept double-blind and only an external investigator had the codes for the individually wrapped and numbered capsules". **Comment**: if the assessors were not involved in the allocation process as suggested by the available information, outcome assessors were likely to have been blinded to treatment group assignment.
Incomplete outcome data (attrition bias)	Low risk	**Quote**: "The total loss in follow-up time was 10.3%, equally distributed between the study groups". **Comment**: the rate of attrition was balanced between groups and was primarily attributable to migration. On that basis, attrition bias is not likely to have impacted on the results of the review.
Selective reporting (reporting bias)	Unclear risk	**Comment**: protocol for the study was not available and, as such, this aspect of the reporting of the study could not be assessed.
Other bias	Low risk	**Comment**: study appeared free of other potential bias.

Benn 1997

Study characteristics	
Methods	Individually randomised trial conducted in Belem and Mindra, 2 districts in Bissau, Guinea-Bissau
Participants	**Eligibility**: infants aged 6–9 months **Excluded**: children with signs of xerophthalmia; history of previous VAS; history of measles infection before 9 months of age, or who had a positive haemagglutinin-inhibition assay titre at 9 months of age; infants reported to have had measles at 9–18 months of age **Sample**: 462 infants. Mean age 8.7 months. 51% boys
Interventions	3 intervention groups **Group I**: infants aged 6 months randomly allocated to receive either a dose of measles vaccine at 6 months and a dose of measles vaccine at 9 months together with vitamin A supplement or the same dosing of measles vaccine with placebo as the supplement

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Benn 1997 *(Continued)*

	Group II: infants randomly allocated either poliomyelitis vaccine at 6 months and a single dose of measles vaccine at 9 months with vitamin A supplement or the same vaccines with a placebo as the supplement **Group III**: infants aged > 7.5 months at the beginning of the study or who were not found at home until they reached the age of 7.5 months were included in the study at age 9 months and received a measles vaccine plus vitamin A or placebo supplement Vitamin A was in a single dose of 100,000 IU dissolved in 1 mL of vegetable oil along with 40 IU of vitamin E. Placebo was vitamin E 40 IU dissolved in 1 mL of vegetable oil
Outcomes	Antibody response to measles vaccine, all-cause mortality, incidence of measles
Notes	Primary objective of study was to calculate the antibody response to measles vaccine when given with vitamin A. The results for antibody response to measles vaccine showed no significant difference between the groups. The study concluded that simultaneous administration of measles vaccine and vitamin A had no negative effect on measles immunity. Similarly, VAS had no significant effect on immune response of CD4 and CD8 T-cells in children without clinical VAD. Vitamin A or placebo was given only at 9 months of age in all 3 study groups. The only difference among the groups was the frequency and type of vaccine administered. Therefore, we added the data for all 3 intervention and placebo groups to report the outcomes of interest to our review. We primarily took data from trial flow diagram and calculated the effect sizes accordingly.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "The allocation sequence was computer generated".
Allocation concealment (selection bias)	Low risk	**Quote**: "The allocation sequence was kept in sealed envelopes and only released when all clinical laboratory analyses were completed".
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "… because of the young age of the participants, any difference in taste was irrelevant …". **Comment**: identical presentation; probably adequate.
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "None of the staff involved knew whether the bottles contained vitamin A or placebo …".
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Quote**: "None of the staff involved knew whether the bottles contained vitamin A or placebo …". **Comment**: blinding of treatment group assignment and treatment to study personnel likely to have been maintained throughout.
Incomplete outcome data (attrition bias)	Low risk	**Comment**: number lost to follow-up and those excluded were explicitly described and equal in both the groups. Loss to follow-up exceeded the number of deaths and children with measles. Reasons for missing data (migration) probably unrelated to treatment.
Selective reporting (reporting bias)	Low risk	**Comment**: some evidence of selective outcome reporting around malaria; however, deaths and prevalence of measles reported.

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Benn 1997 *(Continued)*

Other bias	Unclear risk	**Comment**: authors reported imbalance in self-reported disease in the children aged 6 months at baseline. It is unclear how big an impact this will have had as the variable is not specific.

Biswas 1994

Study characteristics	
Methods	Individually randomised, placebo-controlled trial conducted in Gobinda-Khatick slum area of eastern Kolkata (formerly Calcutta), India
Participants	**Eligibility**: children aged 12–71 months **Excluded**: children with signs of VAD (e.g. xerophthalmia) **Sample**: 180 children. Mean age and proportions of boys not specified
Interventions	**Experimental group**: single-dose vitamin A 200,000 IU in form of retinyl palmitate **Control group**: placebo **Follow-up**: 6 months
Outcomes	Incidence of diarrhoea and acute respiratory tract infection
Notes	The baseline age and nutritional characteristics were similar in both the groups. The surveillance for morbidity outcomes was performed twice monthly. For respiratory disease morbidity, we used data for LRTI only.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote**: "For each strata, a restricted randomisation list was prepared … a random permutated block of block length 6 was used". **Comment**: block randomisation by age and weight; probably done.
Allocation concealment (selection bias)	Low risk	**Quote**: "… randomisation was done by a pharmacist of the drug manufacturing company". **Comment**: assuming that the pharmacist was independent of the study team, this was probably adequate.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "… identical (colour and taste) placebo. Both drug and placebo were prepared and dispensed in a single dose amber coloured glass ampoule by a local pharmaceutical company".
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "For keeping the trial totally blinded to all participants (for example, patients, investigators, surveyor), randomisation was done by a pharmacist of the drug manufacturing company. Samples of drug (or placebo) were identified by the code number of the respective child".
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Quote**: "For keeping the trial totally blinded to all participants (for example, patients, investigators, surveyor), randomisation was done by a pharmacist of the drug manufacturing company. Samples of drug (or placebo) were identified by the code number of the respective child".

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Biswas 1994 *(Continued)*

Incomplete outcome data (attrition bias)	Low risk	**Quote**: "… data was analysed for 174 children due to attrition of 6 children for various reasons (for example, 5 children were hospitalised due to illnesses unrelated to the study objectives and the death of 1 child due post-measles bronchopneumonia)". **Comment**: attrition was low and reported as unrelated to treatment.
Selective reporting (reporting bias)	Unclear risk	**Comment**: study protocol was not available to permit a clear judgement. Study aims were to measure diarrhoea and respiratory infection; both outcomes were reported in full in the study report. 1 child died and the treatment group assignment was not disclosed.
Other bias	Low risk	**Comment**: study appeared free of other bias.

Chen 2013a

Study characteristics	
Methods	Factorial design, individually randomised trial conducted in Chengdu City, China
Participants	**Eligibility**: children aged 3–6 years, apparently good health, haemoglobin concentration > 60 g/L, serum C-reactive protein < 10 mg/L, parental or guardian's approval for participation and parental or guardian's agreement to avoid additional use of vitamin A and iron supplements during the investigation **Excluded**: children with evidence of recent acute or chronic illnesses or haemoglobin < 60 g/L (or both) **Sample**: 387 children
Interventions	4 intervention groups **Experimental group I**: vitamin A 200,000 IU capsule (as retinol) just once initially **Experimental group II**: ferrous sulphate (elemental iron 1–2 mg/kg) once daily for 6 months **Experimental group III**: vitamin A 200,000 IU capsule once initially and ferrous sulphate (elemental iron 1–2 mg/kg) once daily for 6 months **Control group**: neither vitamin A nor ferrous sulphate
Outcomes	Incidence of diarrhoea and LRTI
Notes	Study setting was a periurban area in Huayuan Town, Pixian County of Chengdu City, Sichuan Province, western China, from March to September 2011. Supplementation was given in schools. The paper did not have a study flow diagram. The data from the factorial design were included in 2 data sets. The first data set is the comparison between vitamin A and placebo (Chen 2013a), while the second data set is the comparison between vitamin A + iron vs iron only (Chen 2013b). The data for meta-analysis was taken from table 2 and we calculated the rate ratio based on the number of events in the experimental and control groups with the denominator as person-days at risk.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote**: "The RAND function of Excel (Microsoft, Redmond, WA, USA) was used to generate computer randomly permutated codes".

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Chen 2013a *(Continued)*

Allocation concealment (selection bias)	Low risk	**Quote**: "The health care workers, outcome assessors, data analyst and children were not made aware of the intervention assignment until the completion of data analysis". **Comment**: probably done.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "Children were not made aware of the intervention".
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "The health care workers, outcome assessors, data analyst and children were not made aware of the intervention …".
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Quote**: "… outcome assessors, data analyst and children were not made aware of the intervention …"
Incomplete outcome data (attrition bias)	Low risk	**Comment**: loss to follow-up was 13% and balanced in each group with similar reasons for attrition.
Selective reporting (reporting bias)	Unclear risk	**Comment**: the trial registration number was not given. Authors did mention that they could not report some of the a priori mentioned serum biochemical markers, as they could not collect enough blood samples.
Other bias	Low risk	**Comment**: study appeared free of other bias.

Chen 2013b

Study characteristics	
Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	Same as Chen 2013a above.

Cherian 2001

Study characteristics	
Methods	Individually randomised trial conducted in India
Participants	**Eligibility**: children aged 12–60 months with recurrent respiratory tract infections **Excluded**: children with mild or moderate asthma; who were receiving vitamin supplements or who had received a massive dose of vitamin A in the previous 6 months; with pre-existing congenital heart disease, chronic lung disease, pulmonary tuberculosis or immunodeficiency disorders; receiving immunosuppressive drugs; with clinically apparent VAD

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Cherian 2001 *(Continued)*

	Sample: 61 children; 30 in vitamin A group, 31 in placebo group. Mean age 35.7 months. 60.7% boys
Interventions	**Experimental group**: single-dose vitamin A 200,000 IU **Control group**: placebo in arachis oil **Follow-up**: 6 months
Outcomes	Incidence of respiratory disease, mean vitamin A serum levels
Notes	Definition of respiratory illness used was not specific enough.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "Eligible children were randomly allocated to receive either 200,000 IU of vitamin A in arachis oil or a placebo containing arachis oil without vitamin A". **Comment**: details of sequence generation not specified.
Allocation concealment (selection bias)	Unclear risk	**Comment**: insufficient information to permit judgement.
Blinding (performance bias and detection bias) Blinding of participants	Unclear risk	**Quote**: "Eligible children were randomly allocated to receive either 200,000 IU of vitamin A in arachis oil or a placebo containing arachis oil without vitamin A".
Blinding (performance bias and detection bias) Blinding of provider	Unclear risk	**Comment**: not mentioned.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Unclear risk	**Comment**: not mentioned.
Incomplete outcome data (attrition bias)	Unclear risk	**Quote**: "Of the 61 included children, seven (3 in the placebo group and four in vitamin A group) did not return for follow-up" (second page). **Comment**: authors did not address the reasons for losses to follow-up, and given the small size of this trial, bias may or may not be introduced depending on why the losses occurred by group. Given this lack of discussion, it is difficult to judge whether there is a low or high risk of bias, but it is likely to be high.
Selective reporting (reporting bias)	Unclear risk	**Quote**: "Details of doctor or outpatient visits and hospital cough, wheezy breathing, shortness of breath and fever. Details of doctor or outpatient visits and hospital admissions during the study period were also recorded. During each monthly follow-up visit, the entries in the monthly calendar were reviewed with the parent". **Comment**: hospitalisation data were not reported though they were collected.
Other bias	Unclear risk	**Comment**: very little information provided in the paper; difficult to assess.

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Cherian 2003

Study characteristics	
Methods	Individually randomised trial conducted in Vellor, India
Participants	**Eligibility**: infants aged 9–12 months **Excluded**: children with history of measles vaccination or an exanthematous illness; with moderate or severe malnutrition; clinical signs of VAD; known immune deficiency or receiving immunosuppressive therapy; received blood or blood products in the previous 6 months **Sample**: 395 infants; 198 in vitamin A group, 197 in placebo group. Mean age 9.8 months. 52% boys
Interventions	**Experimental group**: single-dose vitamin A 100,000 IU **Control group**: placebo Interventions provided at time of measles vaccination
Outcomes	Antibody response to measles vaccine
Notes	Primary objective of study was to measure the antibody response to measles vaccine when given with and without vitamin A. Study found no significant inhibitory or enhancing influence on antibody response to measles vaccine when administered concomitantly with vitamin A.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "The infants who were immunized with monovalent measles vaccine were randomly assigned, in blocks of eight, to concomitantly receive 100,000 IU of vitamin A in arachis oil or a placebo containing carboxymethylcellulose prepared in the hospital pharmacy". **Comment**: authors did not specify the method of sequence generation.
Allocation concealment (selection bias)	Low risk	**Quote**: "… arachis oil or a placebo containing carboxymethylcellulose prepared in the hospital pharmacy". **Comment**: probably done since hospital pharmacy was responsible for preparing the order of vitamin A and placebo, and unlikely to have been internal to the study team.
Blinding (performance bias and detection bias) Blinding of participants	Unclear risk	**Quote**: "… Vitamin A in arachis oil or a placebo containing carboxymethylcellulose …" **Comment**: insufficient information to permit judgement.
Blinding (performance bias and detection bias) Blinding of provider	Unclear risk	**Comment**: insufficient information to permit judgement.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Unclear risk	**Comment**: insufficient information to permit judgement.
Incomplete outcome data (attrition bias)	High risk	**Comment**: the proportion of children providing adequate samples was low at 6 months, and there was insufficient detail about the reasons for missing data.

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Cherian 2003 *(Continued)*

Selective reporting (reporting bias)	High risk	**Comment**: there was no mention of mortality or any morbidity of measles or diarrhoea.
Other bias	Unclear risk	**Comment**: insufficient information to permit judgement.

Chowdhury 2002

Study characteristics	
Methods	Individually randomised trial conducted in urban slums of Chandigarh, India
Participants	**Eligibility**: children aged < 10 years **Excluded**: children with xerophthalmia and history of VAS **Sample**: 1520 children; 756 to vitamin A group, 759 to placebo group. Mean age 51 months. 50% boys
Interventions	**Experimental group**: vitamin A 50,000 IU for children aged < 6 months; 100,000 IU for children aged 6–12 months and 200,000 IU for children aged > 1 year **Control group**: placebo **Study duration**: intervention given every 4 months for 15 months
Outcomes	All-cause mortality; cause-specific mortality due to diarrhoea, pneumonia, and meningitis; incidence of diarrhoea, pneumonia, and measles. Measurement of subclinical VAD status was by conjunctival impression cytology
Notes	Baseline sociodemographic and anthropometric characteristics were similar in both the groups. Study population had a high prevalence of VAD. Children were contacted every 15 days by home visits to obtain information on morbidity and mortality. Study included children aged < 10 years; however, the mean age of the children was 51 months. Study methods were not explicitly described. According to WHO, India is a country with a high child mortality rate (i.e. > 40/1000).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote**: "From three slums of Chandigarh, 1520 non-xerophthalmic children of less than 10 years of age were individually randomised in equal number to receive vitamin A or placebo".
Allocation concealment (selection bias)	Unclear risk	**Comment**: insufficient information to permit judgement.
Blinding (performance bias and detection bias) Blinding of participants	Unclear risk	**Quote**: "An equivalent volume of arachis oil was given as placebo". **Comment**: insufficient information to permit judgement.
Blinding (performance bias and detection bias) Blinding of provider	Unclear risk	**Comment**: insufficient information to permit judgement.
Blinding (performance bias and detection bias)	Unclear risk	**Comment**: insufficient information to permit judgement.

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Chowdhury 2002 *(Continued)*

Blinding of outcome assessor		
Incomplete outcome data (attrition bias)	High risk	**Comment**: although attrition rates were balanced, the rates of mortality were lower than the rate of withdrawal. This could impact on the reliability of the results.
Selective reporting (reporting bias)	Unclear risk	**Comment**: insufficient information to permit judgement.
Other bias	Unclear risk	**Comment**: study not sufficiently reported in order to assess this item fully.

Daulaire 1992

Study characteristics	
Methods	Cluster-randomised, non-placebo-controlled trial conducted in Jumla district, Nepal
Participants	**Eligibility**: children aged 1–59 months **Sample**: 16 clusters randomly assigned. 7197 children; 3786 in vitamin A group, 3411 in control group. 51% boys
Interventions	**Experimental group**: single-dose vitamin A 200,000 IU for children aged 12–59 months; 100,000 IU for children aged 6–12 months; and 50,000 IU for children aged < 6 months **Control group**: treatment as usual **Follow-up**: 5 months
Outcomes	All-cause mortality and cause-specific mortality due to diarrhoea, pneumonia, and measles
Notes	Study site was a remote, mountainous region of northwestern Nepal with a total population of about 80,000, with 12,000 children under 5 years of age. This area was considered as 1 of the poorest and most medically underserved areas of the country. Infant mortality rate was 189 deaths per 1000 live births and child (1–4 years) mortality rate was 52 per 1000 per year. Malnutrition was prevalent in the study area, and 26% of children aged 1–4 years were experiencing substantial malnutrition. A survey of 3651 children aged < 5 years showed active xerophthalmia in 1.3–2% of population and 1–5% among infants, which is high for this age group. Disaggregated data on mortality were available according to different age groups. We used data for children aged 6–59 months according to the objectives of our review. According to WHO, Nepal is a country with a high child mortality rate (i.e. > 40/1000).

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote**: "We randomly selected by card eight of the 16 sub-districts for vitamin A supplementation". **Comment**: probably done.
Allocation concealment (selection bias)	High risk	**Comment**: author contacted and replied. **Quote from author**: "No effort was made to conceal the allocation sequence".
Blinding (performance bias and detection bias)	High risk	**Quote**: "There was no placebo or blinding".

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Daulaire 1992 *(Continued)*

Blinding of participants		
Blinding (performance bias and detection bias) Blinding of provider	High risk	**Quote**: "There was no placebo or blinding".
Blinding (performance bias and detection bias) Blinding of outcome assessor	High risk	**Quote**: "There was no placebo or blinding".
Incomplete outcome data (attrition bias)	Low risk	**Comment**: there was no loss to follow-up; coverage of intervention described in detail.
Selective reporting (reporting bias)	Unclear risk	**Comment**: insufficient information to permit judgement.
Other bias	Low risk	**Comment**: study appeared free of other bias.

DEVTA trial 2013

Study characteristics	
Methods	Factorial design, cluster-randomised trial conducted in Northern India
Participants	**Eligibility**: children aged 1–6 years **Sample**: total clusters were 72; 36 clusters in vitamin A group, 36 in control group. Authors claimed to include 1 million children in the trial
Interventions	**Experimental group**: vitamin A 200,000 IU every 6 months for 5 years. Vitamin A was supplemented on mass treatment days by village childcare workers. Capsules were open and poured into child's mouth **Control group**: no intervention Factorial design was: 1. group I: usual care 2. group II: 6-monthly vitamin A 3. group III: 6-monthly albendazole 4. group IV: 6-monthly vitamin A plus albendazole
Outcomes	All-cause mortality; cause-specific mortality due to diarrhoea, pneumonia, measles, and malnutrition; mean vitamin A serum levels; prevalence of Bitot's spots, and measles and pneumonia morbidity
Notes	Study was conducted in Uttar Pradesh, India. Study utilised the infrastructure of the Integrated Child Development Services, which maintains childcare centres called Anganwadi childcare centres across the state. The other intervention as part of the factorial design was albendazole for deworming. Study was approved by King George's Medical University. Surveillance for disease outcomes was performed every 6 months, and children were not selected randomly for that but chosen from Anganwadi childcare lists. Deaths were recorded by 18 full-time, motorcycle village-to-village monitors.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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DEVTA trial 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	**Quote**: "Neighbouring blocks (clusters), in groups of four (where possible in the same district), were randomly allocated in Oxford, UK", and "[a]part from the district each block was in, no relevant details of it were known to those generating the random allocation". **Comment**: most likely done.
Allocation concealment (selection bias)	Low risk	**Quote**: "Apart from the district each block was in, no relevant details of it were known to those generating the random allocation".
Blinding (performance bias and detection bias) Blinding of participants	High risk	**Comment**: intervention was given on mass treatment days, and used no placebo tablets. So participants most likely were not blinded to treatment allocation.
Blinding (performance bias and detection bias) Blinding of provider	High risk	**Comment**: again, intervention was delivered on mass treatment days by AWC and treatment was known to Anganwadi childcare centres.
Blinding (performance bias and detection bias) Blinding of outcome assessor	High risk	**Comment**: outcomes assessors seemed aware of the treatment allocation and control, as parents were asked if their children received intervention on mass treatment days.
Incomplete outcome data (attrition bias)	Low risk	**Comment**: loss to follow-up was 2%.
Selective reporting (reporting bias)	Low risk	**Comment**: the trial was registered as NCT00222547, and prespecified outcomes were mentioned in protocol and analysed accordingly.
Other bias	High risk	**Comment**: there were concerns that surveillance for implementation of intervention and assessment of outcomes were not rigorous.

Dibley 1996

Study characteristics	
Methods	Individually randomised trial conducted in 34 rural villages located on the southern coast of Central Java in Indonesia
Participants	**Eligibility**: children aged 6–47 months Excluded: children with cerebral palsy, epilepsy, flaccid paralysis, mental retardation, congenital or rheumatic heart disease were permanently excluded; those with weight-for-height > 3 standard deviations below the WHO growth reference mean or acute xerophthalmia were excluded for 1 cycle and treated with high-dose vitamin A and then included **Sample**: 1405 children; 50.9% boys
Interventions	**Experimental group**: vitamin A 206,000 IU in form of retinyl ester + vitamin E 37 IU for children aged > 12 months or 103,000 IU in form of retinyl ester + vitamin E 17 IU for children aged < 12 months of age **Control group**: placebo containing vitamin E 17 IU or 37 IU according to the age of the participant **Study duration**: intervention given every 4 months for 24 months Mean of 89% of the children received a treatment (vitamin A or placebo)

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Dibley 1996 *(Continued)*

Outcomes	All-cause mortality, incidence of diarrhoea and respiratory disease, mean vitamin A serum level, proportion of vitamin A deficient, growth
Notes	Baseline demographic, clinical, and nutritional characteristics of the participants were the same, and the groups remained balanced at the start of each of the other 5 cycles. Children were visited every other day for 6 cycles. The longest recall period allowed was 4 days. Observed child-days of ALRI of the vitamin A group was 280,186 and the control group was 273,630. According to WHO, Indonesia is a country with a high child mortality rate (i.e. > 40/1000).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "Randomization of the treatments was done with a 1:1 allocation ratio in blocks of eight, based on a table of random permutations of integers". **Comment**: likely to be adequate.
Allocation concealment (selection bias)	Low risk	**Quote**: "All investigators, field and laboratory staff, and participants were masked to the treatment code". **Quote**: "The capsules were packaged in opaque blister packs with a unique treatment code".
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "The oily contents of the vitamin A and placebo capsules were of similar taste and colour".
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "All investigators, field and laboratory staff, and participants were masked to the treatment code". **Comment**: adequate allocation concealment and the identical presentation of placebo and vitamin A should have prevented providers becoming unblinded to treatment group assignment. Low risk of performance bias.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Quote**: "All investigators, field and laboratory staff, and participants were masked to the treatment code". **Comment**: adequate allocation concealment and the identical presentation of placebo and vitamin A should have prevented outcome assessors becoming unblinded to treatment group assignment.
Incomplete outcome data (attrition bias)	Low risk	**Comment**: complete details of those excluded and lost to follow-up with reason were described. There was a low and balanced number of withdrawals between groups. The analytical method account for the time on treatment (i.e. follow-up time for each cycle), and this may have been adequate.
Selective reporting (reporting bias)	Low risk	**Comment**: lack of trial protocol hindered full assessment of this item. However, data on outcomes of relevance to the review were reported.
Other bias	Low risk	**Comment**: study appeared free of other bias.

Donnen 1998

Study characteristics

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Donnen 1998 *(Continued)*

Methods	Individually randomised, non-placebo-controlled trial conducted in South Kivu province of Congo
Participants	**Eligibility**: children aged 0–72 months. Children were recruited as soon they were discharged from Kotive Children's Hospital **Excluded**: none described **Sample**: 358 children; 118 in vitamin A group, 123 in mebendazole group, 117 in control group
Interventions	3 intervention groups **Experimental group I**: vitamin A 100,000 IU as retinol palmitate for children aged < 1 year and 200,000 IU for children aged > 1 year **Experimental group II**: mebendazole for deworming **Control group**: observation **Study duration**: supplementation was repeated after 6 months and continued for 12 months
Outcomes	All-cause mortality, growth, and incidence of diarrhoea and respiratory disease morbidity
Notes	Morbidity surveillance was performed every 2 weeks for the first 3 months, then every 3 months until 12 months. Data on morbidity outcomes were presented as odds ratios based on generalised estimating equation models. As we were using the data as RRs, and no nominators were given in this study, we could not pool the data for diarrhoea and respiratory morbidity from this study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "As soon as the children were discharged from the hospital, they were randomly assigned to one of the three groups". **Comment**: probably not done.
Allocation concealment (selection bias)	Unclear risk	**Comment**: insufficient details available to make a judgement.
Blinding (performance bias and detection bias) Blinding of participants	Unclear risk	**Comment**: insufficient details available to make a judgement.
Blinding (performance bias and detection bias) Blinding of provider	Unclear risk	**Comment**: insufficient details available to make a judgement.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Unclear risk	**Comment**: insufficient details available to make a judgement.
Incomplete outcome data (attrition bias)	Low risk	**Comment**: overall, 6% of the children were lost to follow-up, with approximately equal proportions in each group. Some had died but it was not indicated how or from which group.
Selective reporting (reporting bias)	Unclear risk	**Comment**: insufficient details available to make a judgement.

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Donnen 1998 *(Continued)*

Other bias	Low risk	**Comment**: study appeared free of other bias.

Fisker 2014

Study characteristics	
Methods	Individually randomised, double-blind trial conducted in Guinea-Bissau
Participants	**Eligibility**: children aged 6–23 months **Excluded**: VAS within the preceding month; participation in another trial **Sample**: 7587 children
Interventions	**Experimental group**: vitamin A 100,000 IU for children aged 6–11 months and 200,000 IU for children aged 12–23 months. Vitamin A bottles contained vegetable oil with vitamin A 200,000 IU as retinyl palmitate and vitamin E 40 IU per mL oil **Control group**: placebo in same liquid volume as the intervention group. Placebo bottles contained vitamin E 40 IU per mL oil. Supplementation given at time of vaccination.
Outcomes	All-cause mortality, sex-specific mortality, diarrhoea incidence, respiratory infection, adverse events
Notes	Children who died because of accident were censored from mortality data analysis. We used the raw data to calculate the mortality and morbidity estimates (i.e. number of events in intervention group compared to control group, with denominators as time of follow-up).

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote**: "The mother then drew a lot from an envelope prepared by the study supervisor". **Comment**: probably done.
Allocation concealment (selection bias)	Low risk	**Quote**: "Coded vitamin A and placebo supplements were prepared by Skanderborg Pharmacy, Denmark".
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "The dark brown bottles contained 10 ml". **Comment**: probably done.
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Comment**: both the interventions were placed in a similar bottle, so it was less likely that those provided knew the allocation.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Comment**: study investigators were unaware of allocation.
Incomplete outcome data (attrition bias)	Low risk	**Comment**: 27 loss to follow-up in vitamin A group and 21 in placebo group. Reason for attrition were given, and they were similar in both groups.

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Fisker 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	**Comment**: the trial was registered (NCT00514891). All a priori outcomes were reported.
Other bias	Low risk	**Comment**: study appeared free of other bias.

Florentino 1990

Study characteristics	
Methods	Individually randomised trial conducted in the municipalities of Pililla and Binangonan in the province of Rizal, Philippines
Participants	**Eligibility**: children aged 1–6 years **Excluded**: any child with clinical signs of VAD **Sample**: 2471 children. Mean age 3.4 years. 49.5% boys
Interventions	3 intervention groups **Experimental group I**: single high-dose vitamin A (200,000 IU) **Experimental group II**: single medium-dose vitamin A (100,000 IU) **Control group**: placebo **Follow-up**: 1 week.
Outcomes	Incidence of side effects within 1 week (nausea or vomiting (or both), headache, diarrhoea and fever)
Notes	The study area had a high prevalence of malnutrition, and therefore VAD was likely to be prevalent. The study reported outcomes for the first 48 hours and within 1 week. We pooled the data for the first week.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "By use of a double-blind study design, children were randomly assigned to three treatment groups". **Comment**: no qualifying information on what 'randomly assigned' means. Difficult to assess sequence generation.
Allocation concealment (selection bias)	Unclear risk	**Comment**: insufficient details available to make a judgement.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "Neither the researchers and field workers nor the subjects knew the contents of the preparations; the code was kept confidential by Hoffman La Roche until after the analysis of the results was completed".
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "Neither the researchers and field workers nor the subjects knew the contents of the preparations; the code was kept confidential by Hoffman La Roche until after the analysis of the results was completed". **Comment**: blinding adequate and performance bias unlikely to have influenced results.

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Florentino 1990 *(Continued)*

Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Quote**: "Neither the researchers and field workers nor the subjects knew the contents of the preparations; the code was kept confidential by Hoffman La Roche until after the analysis of the results was completed".
Incomplete outcome data (attrition bias)	Low risk	**Comment**: complete details of those excluded and lost to follow-up were provided. Only 76 children lost; differences slight between groups.
Selective reporting (reporting bias)	Low risk	**Comment**: though not explicitly stated, all reported measured outcomes have data reported in results with sufficient clarity and explanation.
Other bias	Low risk	**Comment**: no other apparent bias was noted.

Herrera 1992

Study characteristics	
Methods	Cluster-randomised trial conducted in 5 rural councils in northern Sudan
Participants	**Eligibility**: children aged 9–72 months **Excluded**: children with xerophthalmia **Sample**: randomisation by households. 28,753 children; 14,455 in vitamin A group, 14,298 in placebo group. 50.7% boys
Interventions	**Experimental group**: vitamin A 200,000 IU of retinol palmitate + vitamin E 40 IU **Control group**: vitamin E 40 IU **Study duration**: intervention given every 6 months for 18 months.
Outcomes	All-cause mortality; cause-specific mortality due to diarrhoea, measles, respiratory disease; incidence of diarrhoea, respiratory disease, and measles; incidence of xerophthalmia, Bitot's spots, and night blindness
Notes	Authors used non-specific terms for describing cause of death (in table 4) such as "shortness of breath", "convulsions", and "fever", etc. We pooled data for "shortness of breath" under the heading of mortality due to LRTI. This is because it is highly unlikely that a child will die of an upper respiratory tract infection, and LRTI is a more general term than pneumonia to cover this, as it includes pneumonia as well. According to WHO, Sudan is a country with a high child mortality rate (i.e. > 40/1000).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	**Quote**: "Randomisation was done by household … Assignment to treatment group was achieved by the two interviewers visiting alternate households throughout the village. All eligible children in alternate households were assigned to receive, every 6 months, either a capsule of 60 mg (200 000 IU) of vitamin A and 40 mg (40 IU) of vitamin E or a capsule of 40 mg of vitamin E without vitamin A". **Comment**: did not appear to be randomised.
Allocation concealment (selection bias)	Unclear risk	**Comment**: insufficient details available to make a judgement.

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Herrera 1992 *(Continued)*

Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "The capsules were colour-coded to avoid the possibility of mix ups, but none of the study team members was aware which was the experimental capsule and which was the placebo until the end of data collection. All eligible children in a household received capsules of the same colour".
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "The capsules were colour-coded to avoid the possibility of mix ups, but none of the study team members was aware which was the experimental capsule and which was the placebo until the end of data collection. All eligible children in a household received capsules of the same colour". **Comment**: performance bias unlikely given that trialists and staff were blinded during the intervention.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Quote**: "Only the manufacturer knew the contents of the capsules until after data collection and preliminary analysis of the results". **Comment**: probably done.
Incomplete outcome data (attrition bias)	Low risk	**Comment**: 3320 children did not receive 1 or 2 of the 3 vitamin A or placebo capsules. Most of this non-compliant group consisted of children absent from the household at the time of follow-up, whereas others had moved away or refused to take part further. As a group, the non-compliant children tended to be from poorer households than those who continued in the study. However, there were no significant differences between vitamin A and placebo groups in the number of non-compliant children or in their ages, sex or nutritional status. With respect to the variables relevant to the intervention, the losses to follow-up were not significantly different from those who remained in the study.
Selective reporting (reporting bias)	Unclear risk	**Comment**: did not reference a protocol or trial registration number and did not state that all measured outcomes were reported.
Other bias	Unclear risk	**Comment**: insufficient details available to make a judgement.

Kartasasmita 1995

Study characteristics	
Methods	Individually randomised trial conducted in a suburban community of city Bandung, Indonesia
Participants	**Eligibility**: children aged 12–54 months **Excluded**: not specified **Sample**: 269 children; 126 children in vitamin A group, 141 children in control group. Mean age 33 months. 51% boys
Interventions	**Experimental group**: vitamin A 200,000 IU once every 6 months for 12 months **Control group**: placebo
Outcomes	Incidence of respiratory disease, mean serum retinol levels
Notes	Authors presented data on respiratory outcomes according to severity of disease. We included data for "severe respiratory disease" only.

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Kartasasmita 1995 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "The children were selected by randomised stratified sampling from the almost 2000 under-fives residing in Cikutra". **Comment**: insufficient details available to make a judgement.
Allocation concealment (selection bias)	Unclear risk	**Comment**: insufficient details provided to make a judgement.
Blinding (performance bias and detection bias) Blinding of participants	Unclear risk	**Quote**: "All children participated in an age- and sex-matched randomised, double blind vitamin A supplementation programme by receiving vitamin A 200,000 IU or placebo capsules orally, at the start and at the 6th month of the study".
Blinding (performance bias and detection bias) Blinding of provider	Unclear risk	**Comment**: insufficient detail provided to make a judgement.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Unclear risk	**Comment**: insufficient detail provided to make a judgement.
Incomplete outcome data (attrition bias)	High risk	**Comment**: insufficient reporting of attrition/exclusions to permit judgement.
Selective reporting (reporting bias)	Unclear risk	**Comment**: insufficient detail provided to make a judgement.
Other bias	Unclear risk	**Comment**: methods of study were not described very clearly.

Lie 1993

Study characteristics	
Methods	Randomised trial conducted in a rural area of China
Participants	**Eligibility**: children aged 6 months to 3 years **Sample**: 198 children; 105 in vitamin A group, 81 in the placebo group. Mean age and proportion of boys not specified
Interventions	**Experimental group**: vitamin A 200,000 IU for children aged > 12 months and 100,000 IU for children aged < 12 months **Control group**: placebo (vegetable oil) **Study duration**: interventions given every 4 months for 12 months
Outcomes	Incidence of diarrhoea and respiratory disease, all-cause hospitalisations, diarrhoea-specific hospitalisations, pneumonia-specific hospitalisations, mean vitamin A serum levels

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Lie 1993 *(Continued)*

Notes	Baseline serum levels of retinol were similar in both groups. Measurement of biochemical vitamin A levels in the study area fulfilled the WHO criterion for an action to be triggered at a public health level. Morbidity surveillance was performed twice a month

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "198 children who were randomly assigned on a 3:2 allocation to treatment (105) and control (81) groups". **Comment**: no more information provided about sequence generation.
Allocation concealment (selection bias)	Unclear risk	**Comment**: insufficient information to permit judgement.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "Administration was double blind: neither parents nor doctors knew whether the child was in a treatment or control group". **Comment**: placebo capsules contained vegetable oil and were likely to have been indistinguishable from intervention.
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "Placebo capsules contained vegetable oil and were likely to have been indistinguishable from intervention". **Comment**: in view of the adequate blinding procedures, performance bias was unlikely to have influenced the results.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Quote**: "Data collected by doctors who were already blind to treatment group assignment".
Incomplete outcome data (attrition bias)	High risk	**Comment**: reasons for loss to follow-up were not provided. The number randomised and those reported after loss to follow-up did not match.
Selective reporting (reporting bias)	Unclear risk	**Comment**: protocol of study was not available to permit a clear judgement.
Other bias	Low risk	**Comment**: study appeared free of other bias.

Lima 2014

Study characteristics

Methods	Individually randomised trial conducted in Fortaleza, the capital of the Ceara state in northeastern Brazil
Participants	**Eligibility**: children aged 2 months to 9 years Excluded: children with fever > 38 °C or exclusively breastfed **Sample**: 79 children; 39 in vitamin A group, 40 in control group. Mean age 43.3 months. 57% boys
Interventions	**Experimental group**: vitamin A 100,000 IU in form of retinol palmitate for children aged < 12 months and 200,000 IU for children aged > 12 months

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Lima 2014 *(Continued)*

	Control group: vitamin E Supplements given at enrolment, 4 months and 8 months
Outcomes	Mean serum retinol levels, growth and adverse reactions to vitamin A
Notes	Infant mortality rate in study area was 35/1000 live births. Primary objective of study was to measure the effect of vitamin A on barrier function of gastrointestinal tract. Study concluded that the prevalence of new parasitic infection, especially with Giardia species, was significantly decreased with vitamin A intervention, suggesting an immune regulatory modulation of this nutrient on parasitic intestinal infections.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment**: 79 children were randomly selected (using computer-generated random numbers).
Allocation concealment (selection bias)	Unclear risk	**Comment**: insufficient detail provided to make a judgement.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Comment**: the parent or guardian of the children, field study team and investigators were blinded to treatment agent.
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Comment**: the parent or guardian of the children, field study team and investigators were blinded to treatment agent
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Comment**: the parent or guardian of the children, field study team and investigators were blinded to treatment agent. Indication that blinded field study teams assessed outcomes.
Incomplete outcome data (attrition bias)	Low risk	**Comment**: after 12-month follow-up, 22 children were withdrawn from the study due to: change of address (16), parents or guardians did not co-operate with the study (5), and had above the median z score for length or height at the time of the study initiation (1). The percentage of participants completing the study at 12 months was 72.2%.
Selective reporting (reporting bias)	High risk	**Comment**: the objective of study also included reporting of diarrhoea. Authors had reported the overall incidence of diarrhoea in the whole population but the figures were presented in a way that they could not be used in the meta-analysis.
Other bias	Low risk	**Comment**: no other apparent bias observed.

Lin 2008

Study characteristics

Methods	Randomised, placebo-controlled trial conducted in Wuhan, an industrial centre in central region of China
Participants	**Eligibility**: children aged 2–7 years. Children were recruited from kindergarten in the area

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Lin 2008 *(Continued)*

	Excluded: children with fever, diarrhoea or a recent preventive injection; underweight children with BMI age- and sex-specific 5th percentile of the first US National Health and Nutrition Examination Survey data; children whose protein or energy intake met Chinese RDA **Sample**: 105 children. Mean age 55 months. 61% boys
Interventions	3 intervention groups. 2 consisted of children who were vitamin A deficient and 1 with children who were vitamin A sufficient. **Experimental group I** (vitamin A deficient): vitamin A 100,000 IU every month for 3 months **Control group I** (vitamin A deficient): placebo **Control group II** (vitamin A sufficient): placebo
Outcomes	All-cause mortality, mean serum vitamin A levels
Notes	We included data for vitamin A deficient children who were either supplemented with vitamin A or placebo. According to WHO, China does not have a high child mortality rate (i.e. < 40/1000).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "The remaining 70 vitamin A-deficient children were randomly and equally divided into vitamin A deficient-supplemented group and vitamin A-deficient placebo group". **Comment**: the term 'randomised' is also used to describe a third group that is clearly matched. This may not be a randomised controlled trial.
Allocation concealment (selection bias)	Unclear risk	**Comment**: insufficient detail provided to make a judgement.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "Children of vitamin A-deficient-supplemented group were given 100 000 IU (retinol equivalent) vitamin A capsules every 2 weeks for 3 months (Grubesic, 2004). Children of vitamin A-sufficient placebo group and vitamin A-deficient placebo group received placebo capsules in the same way".
Blinding (performance bias and detection bias) Blinding of provider	Unclear risk	**Comment**: although study was double randomised trial, no details of how blinding was achieved was described in the district.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Unclear risk	**Comment**: insufficient detail provided to make a judgement.
Incomplete outcome data (attrition bias)	Low risk	**Comment**: no attrition reported.
Selective reporting (reporting bias)	High risk	**Comment**: main outcome data not reported in a manner that could be analysed.
Other bias	Unclear risk	**Comment**: as blinding was not described, potential performance bias and other sources of bias could not be assessed.

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Lin 2009

Study characteristics	
Methods	Individually randomised trial conducted in rural China
Participants	**Eligibility**: children aged 6 months to 7 years **Excluded**: children without informed consent or with acute and chronic diseases **Sample**: 132 children. Mean age 36.5 months. 50% boys
Interventions	3 intervention groups **Experimental group I**: vitamin A 100,000 IU every month for 3 months **Experimental group II**: beta-carotene **Control group**: placebo (biscuits)
Outcomes	Mean vitamin A serum levels
Notes	We included the results for vitamin A group versus placebo only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "The 50 severe vitamin A deficient children and 82 marginal vitamin A deficient children were randomly divided into three groups respectively by using a table with randomly assorted digits". **Comment**: probably done.
Allocation concealment (selection bias)	Unclear risk	**Comment**: no methods of allocation concealment are described in the text.
Blinding (performance bias and detection bias) Blinding of participants	High risk	**Quote**: "Vitamin A intervening group were administered 100,000 IU vitamin A capsules … the beta-carotene intervening group … was administered 4 mg purified beta-carotene … dissolved in vegetable oil and dropped into a general little biscuit … the placebo group were just administered a general little biscuit". **Comment**: vitamin A and placebo were administered in 2 different forms. Vitamin A in capsule form while placebo was in the form of biscuits.
Blinding (performance bias and detection bias) Blinding of provider	High risk	**Comment**: vitamin A and placebo were administered in 2 different forms. Vitamin A in capsule form while placebo was in the form of biscuits.
Blinding (performance bias and detection bias) Blinding of outcome assessor	High risk	**Comment**: vitamin A and placebo were administered in 2 different forms. Vitamin A in capsule form while placebo was in the form of biscuits.
Incomplete outcome data (attrition bias)	Low risk	**Comment**: no dropouts reported, and numbers at baseline and follow-up appeared to be the same.
Selective reporting (reporting bias)	High risk	**Comment**: use of clinic services, hospitalisation, cause-specific morbidity not reported.

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Lin 2009 *(Continued)*

Other bias	Low risk	**Comment**: study appeared free of other bias.

Long 2006a

Study characteristics	
Methods	Factorial design, individually randomised trial conducted in La Magdalena Atlicpac, Mexico
Participants	**Eligibility**: children aged 6–15 months **Excluded**: children with diseases causing immunosuppression and any congenital or acquired alteration of the digestive tract that could alter the absorption of micronutrients; children taking vitamin supplements **Sample**: 786 children. Mean age 9.8 months. 51.7% boys
Interventions	4 intervention groups **Experimental group I**: vitamin A 20,000 IU retinol every 2 months for children aged < 1 year or 45,000 IU for children aged > 1 year **Experimental group II**: daily dose equivalent to 20 mg elemental zinc as zinc methionine **Experimental group III**: zinc supplement + vitamin A as above **Control group**: placebo **Study duration**: interventions delivered every 2 months for 12 months
Outcomes	Diarrhoea and respiratory disease morbidity
Notes	We included data of this factorial design trial in 2 sets. The first data set compared vitamin A vs placebo, and second set compared vitamin A + zinc vs zinc only. Data on respiratory morbidity were given with 3 definitions. We pooled the data for "cough + difficulty breathing" under the heading of LRTI.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "The randomisation sequence was generated by using a random-number table by project personnel from CENSIA, a division of the Mexican Ministry of Health".
Allocation concealment (selection bias)	Low risk	**Quote**: "These solutions were packaged in consecutively numbered, colour-coded, opaque plastic droplet bottles to ensure that field personnel and the principal investigator were blinded".
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "The vitamin A, zinc, and vitamin A + zinc supplements were prepared by personnel at the National Institute of Nutrition in 5-mL solutions that were similar in taste and appearance".
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "This double-blind randomised trial … These solutions were packaged in consecutively numbered, color-coded, opaque plastic droplet bottles to ensure that field personnel and the principal investigator were blinded".

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Long 2006a *(Continued)*

Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Quote**: "This double-blind randomised trial … These solutions were packaged in consecutively numbered, color-coded, opaque plastic droplet bottles to ensure that field personnel and the principal investigator were blinded". **Comment**: probably done.
Incomplete outcome data (attrition bias)	Low risk	**Comment**: lost to follow-up data given along with reasons for lost to follow-up. 93 children were lost to follow-up or excluded.
Selective reporting (reporting bias)	Unclear risk	**Comment**: study protocol not available so could not assess or make a judgement.
Other bias	Low risk	**Comment**: study appeared free of other bias.

Long 2006b

Study characteristics	
Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	As above (Long 2006a).

Long 2007

Study characteristics	
Methods	Individually randomised trial conducted in Mexico
Participants	**Eligibility**: children aged 5–15 months **Excluded**: children who were immunosuppressed; had any congenital abnormality or chronic diarrhoea; history of VAS **Sample**: 195 children; 97 in vitamin A group, 98 in placebo group. 49.7% boys
Interventions	**Experimental group**: vitamin A 20,000 IU for children aged < 12 months and 45,000 IU for children aged > 12 months **Control group**: placebo **Study duration**: intervention repeated every 2 months for 12 months
Outcomes	Incidence of diarrhoea and respiratory disease
Notes	Baseline sociodemographic characteristics of study children and households were similar between groups. Children received monthly visits and referrals to the doctor, which appeared to exceed normal treatment.

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Long 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "The randomisation sequence was generated by project personnel based at the National Institute of Public Health". **Comment**: probably done.
Allocation concealment (selection bias)	Low risk	**Comment**: personnel at the National Institute of Nutrition prepared the supplements to assure that field personnel and the principal investigator were unaware of treatment regimen. Children in the vitamin A and placebo groups received a 5 mL solution, from identical opaque plastic droplet bottles numbered consecutively, administered by the field team.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "Testing had been carried out at the National Institute of Nutrition to assure that the placebo and vitamin A water miscible solution were similar in taste, viscosity and colour".
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "Personnel at the National Institute of Nutrition carried out the preparation of the supplements to assure that field personnel and the principal investigator were unaware of treatment regimen".
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Quote**: "Personnel at the National Institute of Nutrition carried out the preparation of the supplements to assure that field personnel and the principal investigator were unaware of treatment regimen".
Incomplete outcome data (attrition bias)	Low risk	**Comment**: unclear what was done with data for 7 missing children, but dropout was small and similar between groups (4 in vitamin A group, 3 in control group).
Selective reporting (reporting bias)	Unclear risk	**Comment**: protocol not referenced, though the grant applications may be available.
Other bias	Low risk	**Comment**: study appeared free of other bias.

Pant 1996

Study characteristics

Methods	Cluster-randomised trial in rural Nepal
Participants	**Eligibility**: children aged 6 months to 10 years **Sample**: from 100 potentially eligible cluster sites, 75 were randomised (approximately 25,301 children). Baseline data on the number in each treatment group, proportion of boys and mean age not provided
Interventions	3 intervention groups **Experimental group I**: single-dose vitamin A 100,000 IU for children aged 6–12 months and 200,000 IU for children aged 1–10 years via a capsule **Control group I**: control (not adequately described) **Control group II**: nutritional education

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Pant 1996 *(Continued)*

	Study duration: 24 months
Outcomes	All-cause mortality and Bitot's spots
Notes	No details on loss to follow-up were given. Inclusion/exclusion criteria were inadequately described. No nominators/denominators were available for Bitot's spots.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "Using random number tables and the reference number for each block …".
Allocation concealment (selection bias)	Unclear risk	**Comment**: insufficient detail provided to make a judgement.
Blinding (performance bias and detection bias) Blinding of participants	Unclear risk	**Comment**: insufficient detail provided to make a judgement.
Blinding (performance bias and detection bias) Blinding of provider	Unclear risk	**Comment**: insufficient detail provided to make a judgement.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Unclear risk	**Comment**: insufficient detail provided to make a judgement.
Incomplete outcome data (attrition bias)	High risk	**Comment**: no information given as regards how incomplete outcome data were addressed.
Selective reporting (reporting bias)	High risk	**Comment**: very specific outcomes reported. 5 types of examinations were administered to the children: ophthalmic, physical, anthropometric, blood and faecal; however, data in results were given only for prevalence of Bitot's spots and all-cause mortality
Other bias	Unclear risk	**Comment**: insufficient detail provided to make a judgement.

Pinnock 1986

Study characteristics	
Methods	Individually randomised study in urban area of Australia
Participants	**Eligibility**: children aged 1–4 years of age in 3 general practices from Adelaide. Children with > 15 days of cough or 3 separate episodes of respiratory illness during the preceding 3 months were eligible **Sample**: 147 children. Mean age 39.3 months. 50% boys
Interventions	**Experimental group**: vitamin 1160 µg as retinyl palmitate 3 times per week for 20 weeks **Control group**: placebo
Outcomes	Acute respiratory infections, pneumonia, mean serum vitamin A

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Pinnock 1986 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "Randomization of treatment was achieved by combining active and placebo bottles in a sequence, which was determined by consulting a table of random numbers, and numbering the bottles accordingly". **Comment**: probably done.
Allocation concealment (selection bias)	Unclear risk	**Comment**: insufficient information to permit judgement.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "The placebo was a similarly constituted syrup omitting retinyl palmitate and labelled and bottled identically".
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "All staff connected with the study remained blind to the identity of the child's medication".
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Quote**: "All staff connected with the study remained blind to the identity of the child's medication".
Incomplete outcome data (attrition bias)	Low risk	**Comment**: a high rate of attrition, but reasons for withdrawal given and that there were no significant changes in the distribution of major potential confounding factors between the 2 groups.
Selective reporting (reporting bias)	Unclear risk	**Comment**: protocol not available.
Other bias	Low risk	**Comment**: no other apparent bias observed.

Pinnock 1988

Study characteristics

Methods	Individually randomised study in urban area of Australia
Participants	**Eligibility**: children aged 0–2 years with history of bronchiolitis and nasal culture positive for RSV **Excluded**: children taking vitamin A; children with cystic fibrosis, cardiopulmonary difficulties, major brain dysfunctions **Sample**: 206 children. Mean age 58 months. 60% boys
Interventions	**Experimental group**: vitamin 4.2 mg per week as retinyl palmitate for 12 months **Control group**: placebo
Outcomes	Diarrhoea, diarrhoea-related hospitalisation, acute respiratory infections, pneumonia, pneumonia-related hospitalisation, mean serum vitamin A

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Pinnock 1988 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "Randomization was achieved by randomly allocating four of eight batch numbers to vitamin A supplement and the remaining four to placebo". **Quote**: "the batch number code was retained by the manufacturer".
Allocation concealment (selection bias)	Low risk	**Quote**: "The batch number code was retained by the manufacturer. The bottles were then distributed sequentially according to batch number as children presented …". **Comment**: probably done.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "The placebo had an identical appearance and formulation except for the active ingredient". **Comment**: probably done.
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "Both investigators and parents were blind as to the treatment status of the child".
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Quote**: "Both investigators and parents were blind as to the treatment status of the child … The batch number code was retained by the manufacturer".
Incomplete outcome data (attrition bias)	Low risk	**Comment**: complete details of those excluded and lost to follow-up were provided.
Selective reporting (reporting bias)	High risk	**Comment**: outcomes mentioned in methods not reported in results.
Other bias	Low risk	**Comment**: study appeared free of other bias.

Rahman 2001

Study characteristics

Methods	Individually randomised study conducted in an urban area of Bangladesh
Participants	**Eligibility**: children aged 12–35 months **Excluded**: children who had received vitamin A within previous 4 months; had severe malnutrition, with signs or symptoms of vitamin A or zinc deficiency; or with any systemic illness such as diarrhoea, respiratory infection, fever or any other illness that warranted medical intervention at the time of enrolment **Sample**: 800 children; 200 in each of 4 treatment groups. Mean age 23.5–24.2 months across treatment groups. 56% boys
Interventions	4 intervention groups

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Rahman 2001 *(Continued)*

	Group I: vitamin A 200,000 IU (60 mg) given as a single capsule at day 14 + placebo syrup daily for 14 days **Group II**: placebo capsule at day 14 + placebo syrup for 14 days **Group III**: vitamin A 200,000 IU (60 mg) given as a single capsule at day 14 + zinc syrup daily for 14 days **Group IV**: zinc syrup daily for 14 days + placebo capsule at day 14 **Study duration**: 6 months
Outcomes	Diarrhoea, acute respiratory infections, serum vitamin A levels and vitamin deficiency
Notes	Data on treatment analysis were not presented. We have written to authors to request data on each treatment arm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "The children were randomly assigned by a person not involved in the study who used permuted blocks of random numbers". **Comment**: probably done.
Allocation concealment (selection bias)	Low risk	**Quote**: "Sets of 2 bottles and 1 capsule for each child were serially numbered … A local pharmaceutical company prepared the study syrups (zinc and placebo) which were supplied in identical 50-mL bottles … The vitamin A and placebo capsules looked identical". **Comment**: probably done.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "The zinc and placebo syrups were supplied in bottles that looked identical, and the appearance and consistency of the syrups were similar. Vitamin A and placebo capsules were identical in appearance". **Comment**: probably done.
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "The randomisation code was kept sealed until the completion of the study". **Comment**: identical presentation; probably done.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Quote**: "The treatment allocations were disclosed after the final analysis".
Incomplete outcome data (attrition bias)	Low risk	**Comment**: data on loss to follow-up given and also stated that the baseline characteristics of children who were excluded or lost to follow-up were comparable to those of the children who continued in the study.
Selective reporting (reporting bias)	Unclear risk	**Comment**: protocol not available.
Other bias	Low risk	**Comment**: no other apparent bias.

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Rahmathullah 1990

Study characteristics	
Methods	Cluster-randomised trial conducted in Trichy district of Tamil Nadu in southern India
Participants	**Eligibility**: children aged 6–60 months **Sample**: clustering unit was 'panchyat' (local government areas). 206 clusters were formed, and most consisted of 50–100 children. The included clusters had 15,419 children; 7764 in vitamin A group, 7655 in placebo group
Interventions	**Experimental group**: weekly doses vitamin A 8333 IU + vitamin E 20 mg **Control group**: vitamin E 20 IU in peanut oil Any children diagnosed with xerophthalmia at baseline, mid-term or final examination were given a high-dose vitamin A (200,000 IU) and continued in study. **Study duration**: supplementations given for 52 weeks Children who missed 7 consecutive dosages were excluded from the analysis.
Outcomes	All-cause mortality; cause-specific mortality due to diarrhoea, measles, and respiratory disease; incidence of diarrhoea and respiratory disease morbidity
Notes	Baseline characteristics of groups were similar in terms of age and sex, 1-month history of diarrhoea and respiratory disease, anthropometric indexes of nutritional status, xerophthalmia status, 5-year retrospective history of mortality of children aged < 5 years, household economic, household hygienic status and serum retinol levels. On average, > 90% of children were contacted each week, and the lowest coverage in any single week was 88%. 11% had clinical evidence of xerophthalmia, while about 38% had serum retinol concentrations < 0.35 mmol/L at baseline.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote**: "The clusters were arranged according to population size; after a random start, they were assigned alternately to the treated or control groups". **Comment**: exact method of sequence generation was not provided.
Allocation concealment (selection bias)	Low risk	**Quote**: "… no one associated with the study was aware of the colour code, which was held by the Hoffmann-LaRoche until the study ended".
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "The appearance and taste of the solutions were identical … no one associated with the study was aware of the colour code, which was held by the Hoffmann-LaRoche until the study ended". **Comment**: probably done.
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "The appearance and taste of the solutions were identical … no one associated with the study was aware of the colour code, which was held by the Hoffmann-LaRoche until the study ended … masked controlled …". **Comment**: probably done.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Quote**: "The appearance and taste of the solutions were identical … no one associated with the study was aware of the colour code, which was held by the Hoffmann-LaRoche until the study ended … masked controlled …".

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Rahmathullah 1990 *(Continued)*

Incomplete outcome data (attrition bias)	Low risk	**Quote**: "There was no difference in rates of contact between the treated and control groups. The reasons for lack of contact included moving from the study area …". **Comment**: reasons for loss to follow-up given with a note that there was no difference in contact rates between the 2 groups.
Selective reporting (reporting bias)	Low risk	**Comment**: all important outcomes given in results as mentioned in the methods section.
Other bias	Low risk	**Comment**: no other apparent bias.

Ramakrishnan 1995

Study characteristics	
Methods	Individually randomised trial conducted in rural India
Participants	**Eligibility**: children aged 6–36 months **Excluded**: children with ophthalmic signs of xerophthalmia, serious diseases, or severe malnutrition (< 60% of weight-for-age or < 85% of height-for-age of the National Center for Health Statistics median), who received appropriate treatment, including vitamin A **Sample**: 583 children; 309 in vitamin A group, 274 in placebo group. Mean age 18.6 months. 49.9% boys
Interventions	**Experimental group**: vitamin A 100,000 IU for children aged < 1 year and 200,000 IU for children aged > 1 year **Control group**: placebo **Study duration**: interventions given every 4 months for 12 months
Outcomes	Incidence of diarrhoea and respiratory disease
Notes	Definition used for respiratory disease was too generalised to be included under LRTI. It mainly covered upper respiratory tract infections.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote**: "The study design was a randomised, double-blind, placebo controlled intervention trial in which every 4 mo [months] the treatment group received a high-dose vitamin A supplement and the control group received a placebo". **Comment**: insufficient detail provided.
Allocation concealment (selection bias)	Unclear risk	**Comment**: insufficient information to permit judgement.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "The study design was a randomised, double-blind, placebo controlled intervention trial in which every 4 mo the treatment group received a high-dose vitamin A supplement and the control group received a placebo". **Comment**: statement that blinding occurred, no further details provided.

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Ramakrishnan 1995 *(Continued)*

Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "The study design was a randomised, double-blind, placebo controlled intervention trial in which every 4 mo the treatment group received a high-dose vitamin A supplement and the control group received a placebo". **Comment**: statement that blinding occurred, no further details provided.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Quote**: "The study design was a randomised, double-blind, placebo controlled intervention trial in which every 4 mo the treatment group received a high-dose vitamin A supplement and the control group received a placebo". **Comment**: statement that blinding occurred, no further details provided.
Incomplete outcome data (attrition bias)	Low risk	**Quote**: "Out of the 660 children who were eligible, a final group of 592 children who had both pre- and post-anthropometric measurements were used in this analysis. The losses at follow-up due to migration (n = 50), death (n = 10) and incomplete measurements (n = 8) were similar for both groups". **Comment**: losses were not large and balanced between groups; unlikely to introduce substantial bias here. Clinically relevant impact unlikely.
Selective reporting (reporting bias)	High risk	**Quote**: "The examination for ophthalmic signs of vitamin A deficiency, using WHO criteria (27), was conducted by trained ophthalmologists from the Department of Ophthalmology, CMCH, at baseline and at the end of the 1-y follow-up period. Blood samples were also taken (from finger pricks) at the beginning and the end of the study by using 250-pt capillary tubes. Serum retinol concentrations were estimated by using reversed-phase HPLC at the Wellcome Research Laboratory, CMCH, Vellore, using retinyl acetate and all trans-retinol (Sigma Chemical Co, St Louis) as standards". **Comment**: though measured, serum retinol results were not reported.
Other bias	Low risk	**Comment**: no other apparent bias.

Reddy 1986a

Study characteristics	
Methods	Factorial design, individually randomised trial conducted in India
Participants	**Eligibility**: children aged 1–5 years **Excluded**: children without parental consent **Sample**: 487 children. Mean age and proportion of boys not reported
Interventions	4 intervention groups **Experimental group I**: oral administration of L-tetramisole 50 mg followed 3 days later by vitamin A 200,000 IU **Experimental group II**: vitamin A 200,000 IU **Experimental group III**: L-tetramisole 50 mg orally **Control group**: placebo
Outcomes	Mean vitamin A serum levels

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Reddy 1986a *(Continued)*

Notes	Data included in 2 sets

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "After the baseline survey, the children were assigned, randomly, into four groups, matched for age, anthropometry, serum vitamin A, and worm infestation and the following treatment was given". **Comment**: insufficient details provided to make a judgement.
Allocation concealment (selection bias)	Unclear risk	**Comment**: insufficient information to permit judgement.
Blinding (performance bias and detection bias) Blinding of participants	Unclear risk	**Comment**: insufficient information to permit judgement.
Blinding (performance bias and detection bias) Blinding of provider	Unclear risk	**Comment**: insufficient information to permit judgement.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Unclear risk	**Comment**: insufficient information to permit judgement.
Incomplete outcome data (attrition bias)	Unclear risk	**Comment**: insufficient information to permit judgement.
Selective reporting (reporting bias)	Unclear risk	**Quote**: "After 6 months and 12 months, heights and weights were measured, clinical status was assessed and morbidity for the preceding one month was recorded. Finger-prick blood samples were collected and serum vitamin A levels were estimated, stool samples were examined for the presence of ascaris ova and other parasites". **Comment**: authors did not report height or weights, or detailed data on clinical status or morbidity.
Other bias	Unclear risk	**Comment**: insufficient information to permit judgement.

Reddy 1986b

Study characteristics	
Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	As Reddy 1986a above.

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Ross 1993 HEALTH

Study characteristics	
Methods	Randomised, double-blind controlled trial conducted in Guinea savannah area of Ghana
Participants	**Eligibility**: children aged 6–59 months **Excluded**: children with active xerophthalmia or measles once they were confirmed **Sample**: 1455 children. 49.5% boys
Interventions	**Experimental group**: vitamin A 200,000 IU retinol equivalent for children aged > 12 months or 100,000 IU for children aged 6–12 months **Control group**: placebo **Study duration**: interventions given every 4 months for 12 months
Outcomes	All-cause mortality; mean daily prevalence of respiratory tract disease, diarrhoea, measles, malaria; mean vitamin A serum levels; all-cause hospitalisations
Notes	Study populations were rural and their main staple foods are deficient in carotenoids and vitamin A. VAD and xerophthalmia were recognised as problems locally. Children were visited weekly for 1 year. Children in the Health Study were followed up for 596 child-years for vitamin A group and 589 for control group. According to WHO, Ghana is a country with a high child mortality rate (i.e. > 40/1000).

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote**: "Randomisation was blocked in both studies to ensure similar numbers of children in each group in each part of the study area". **Comment**: explicit methods for generating allocation sequence not available.
Allocation concealment (selection bias)	Low risk	**Quote**: "Randomisation was carried out in London by an independent statistician, who held the randomisation code and who also did an interim analysis of the mortality results from the Survival Study for the trial's data-monitoring committee after a year of follow-up". **Comment**: code was protected for the duration of the trial.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "Vitamin A and placebo were supplied by Hoffmann-La-Roche's Sight and Life Programme, and were similar in taste and colour. In the Survival Study, liquid vitamin A or placebo was supplied in opaque 150 mL bottles containing 20 IU/mL vitamin E alone (placebo) or plus 100,000 IU/mL retinol equivalent as retinyl palmitate (vitamin A) in purified peanut oil. Each bottle had a unique number, and was labelled with a cluster code before despatch to Ghana".
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Comment**: as above; probably done.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Comment**: in view of the blinding procedures in place elsewhere in the study, this was probably adequate.

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Ross 1993 HEALTH *(Continued)*

Incomplete outcome data (attrition bias)	Unclear risk	**Comment**: morbidity information was missing for 5–7% of the weekly follow-up visits, owing to temporary absences of the study children or their mothers, but the missing data were equally distributed between groups.
Selective reporting (reporting bias)	High risk	**Comment**: there was an indication that xerophthalmia data were measured, but none were reported. No protocol available.
Other bias	Low risk	**Comment**: no other apparent bias.

Ross 1993 SURVIVAL

Study characteristics	
Methods	Cluster-randomised trial conducted in Ghana
Participants	**Eligibility**: children aged 6–90 months **Excluded**: children with xerophthalmia **Sample**: 185 clusters that included 21,906 children. 51.5% boys
Interventions	**Experimental group**: vitamin A 100,000 IU for children aged 6–11 months and 200,000 IU for older children + vitamin E 20 IU **Control group**: placebo + vitamin E 20 IU **Study duration**: intervention delivered every 4 months for 24 months
Outcomes	All-cause mortality and cause-specific mortality due to diarrhoea, respiratory disease, measles and meningitis; mean vitamin A serum levels; malaria prevalence
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "Randomisation was blocked in both studies to ensure similar numbers of children in each group in each part of the study area". **Comment**: explicit methods for generating allocation sequence not available.
Allocation concealment (selection bias)	Low risk	**Quote**: "Randomisation was carried out in London by an independent statistician, who held the randomisation code and who also did an interim analysis of the mortality results from the Survival Study for the trial's data-monitoring committee after a year of follow-up". **Comment**: code was protected for the duration of trial.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "Vitamin A and placebo were supplied by Hoffmann-La-Roche's Sight and Life Programme, and were similar in taste and colour. In the Survival Study, liquid vitamin A or placebo was supplied in opaque 150 mL bottles containing 20 IU/mL vitamin E alone (placebo) or plus 100,000 IU/mL retinol equivalent as retinyl palmitate (vitamin A) in purified peanut oil. Each bottle had a unique number, and was labelled with a cluster code before despatch to Ghana".

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Ross 1993 SURVIVAL *(Continued)*

		Comment: probably done.
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Comment**: as above; probably done.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Comment**: in view of the blinding procedures in place elsewhere in the study, this was probably adequate.
Incomplete outcome data (attrition bias)	Unclear risk	**Comment**: 8.4% (1847) children lost to follow-up and similar between groups. The reasons for losses to follow-up were not provided.
Selective reporting (reporting bias)	High risk	**Comment**: authors collected data on night blindness, Bitot's spots and xerophthalmia, but did not report them.
Other bias	Unclear risk	**Comment**: the method for inflating the CIs was not well-described. No ICC reported

Semba 1991

Study characteristics	
Methods	Individually randomised trial conducted in Indonesia
Participants	**Eligibility**: children aged 3–6 years **Excluded**: children with median weight for age < 80% of the National Center for Health Statistics; children with serious illness were excluded from the study and treated appropriately **Sample**: 236 children. Mean age 58.9 months. 71.6% boys
Interventions	4 intervention groups. 2 groups (vitamin A and placebo) had clinical signs of VAD, while 2 groups were clinically normal. **Experimental groups**: single-dose vitamin A 60,000 µg of retinol equivalent **Control groups**: placebo **Follow-up**: 1 month
Outcomes	Mean vitamin A serum levels
Notes	The 2 vitamin A and 2 placebo groups were combined, respectively, for meta-analysis.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote**: "A double-masked, randomised, placebo-controlled, clinical trial involving 236 preschool children, age 3–6 years, was carried out at the outpatient clinic of the Cicendo Eye Hospital in Bandung, West Java, Indonesia". **Comment**: details of sequence generation not provided.
Allocation concealment (selection bias)	Low risk	**Quote**: "The treatment code was broken after the conclusion of the study".

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Semba 1991 *(Continued)*

		Comment: allocation sequence appeared to have been protected.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "A double-masked, randomised, placebo-controlled, clinical trial involving 236 preschool children". **Quote**: "The vitamin A and placebo solutions were supplied in coded containers, and the identity of the solutions was known only to the manufacturer … The solutions were identical in colour, taste, smell and consistency".
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Comment**: as above; providers likely to have been adequately blinded.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Unclear risk	**Comment**: the provider administering vitamin A and the outcome assessor appear to be different individuals, and it is not clearly stated if the outcome assessors were also blinded to group assignment.
Incomplete outcome data (attrition bias)	Low risk	**Comment**: 232/236 children enrolled at baseline completed the study protocol (p. 102).
Selective reporting (reporting bias)	Unclear risk	**Comment**: did not reference a protocol or trial registration number and did not state that all measured outcomes were reported.
Other bias	Unclear risk	**Comment**: insufficient information to permit judgement.

Semba 1995

Study characteristics	
Methods	Individually randomised study in rural Indonesia
Participants	**Eligibility**: children aged 6 months at vaccination against measles **Excluded**: children who had measles previously **Sample**: 336 children. Baseline details on age and sex not provided
Interventions	**Experimental group**: single-dose vitamin A 100,000 IU **Control group**: placebo Vitamin A or placebo given with measles vaccine **Study duration**: 6 months
Outcomes	Measles
Notes	Primary objective of study was to measure the antibody response to measles vaccine when given with vitamin A or placebo. Trialists found a significant decrease in seroconversion of measles vaccine in the vitamin A group compared to placebo.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote**: "Treatment was assigned by random number table in blocks of ten".

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Semba 1995 *(Continued)*

		Comment: probably done.
Allocation concealment (selection bias)	Low risk	**Quote**: "Infants received identification numbers as they were enrolled in the study, and each identification number had an envelope with an identical capsule containing either vitamin A or placebo". **Comment**: probably done.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "Vitamin A, 100,000 IU, or placebo in identical capsules". **Comment**: probably done.
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "Infants received identification numbers as they were enrolled in the study, and each identification number had an envelope with an identical capsule containing either vitamin A or placebo". **Comment**: probably done.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Comment**: as above; probably done.
Incomplete outcome data (attrition bias)	High risk	**Quote**: "Follow-up rates were 93% and 90% at one and six months post immunisation, respectively". **Comment**: the reasons for lost to follow-up not given; only available-case data given.
Selective reporting (reporting bias)	Unclear risk	**Comment**: study protocol not available.
Other bias	Unclear risk	**Comment**: inadequate information presented to assess this formally.

Sempértegui 1999

Study characteristics	
Methods	Individually randomised trial conducted in the northwestern region of the Quito, Ecuador
Participants	**Eligibility**: children aged 6–36 months **Excluded**: children with clinical VAD, who did not reliably stay at home or at day care centres during weekdays or who had been given multivitamins in last 3 months **Sample**: 400 children; 200 in vitamin A group, 200 in placebo group. Mean age 21.1 months. 50% boys
Interventions	**Experimental group**: weekly dose vitamin A 10,000 IU for 40 weeks **Control group**: weekly placebo for 40 weeks
Outcomes	Incidence of diarrhoea and respiratory disease morbidity, mean vitamin A serum levels
Notes	The baseline study characteristics were comparable between groups. The study was conducted in a slum with substantial rates of malnutrition and subclinical VAD. Morbidity surveillance was done weekly.

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Sempértegui 1999 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "For random allocation of each child to treatment or placebo group the following procedure was performed. Identical flasks containing vitamin A or placebo were numbered from 1 to 400 by members of the study team in Boston, Massachusetts. The local Ethical Committee of the Ecuadorian Biotechnology Corporation in Quito did not know the identity of the active or placebo flasks, because they did not have the code. Then, this committee assigned each flask to a specific child from a random list by using a table of random numbers. After randomisation, the ethical committee received the confidential code from Boston".
Allocation concealment (selection bias)	Low risk	**Quote**: "After randomisation, the ethical committee received the confidential code from Boston and kept it for the remainder of the study, when it was revealed".
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "Identical flasks containing vitamin A or placebo were numbered from 1 to 400 by members of the study team in Boston, Massachusetts". **Comment**: trial described as double-blind; given procedures used for ensuring that intervention and placebo were identical, it is very likely that blinding of children was maintained.
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "The syrups were administered at home and at day care centres by study researchers who were blinded to the presence or absence of active drug".
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Comment**: outcome assessors were the same as the providers, therefore blinded.
Incomplete outcome data (attrition bias)	Low risk	**Quote**: "A total of 306 children finished the study, because 50 children from the supplement-treated group and 44 from the non-supplemented group were lost to follow-up when their families moved to other neighbourhoods. Of all children, 70%, including those lost to follow-up, accumulated > 30 weeks of observation … Children with incomplete follow-up were distributed evenly in relation to the baseline variables". **Comment**: loss to follow-up similar in magnitude in both groups and for similar reasons. Some lost still contributed data.
Selective reporting (reporting bias)	Unclear risk	**Comment**: protocol referred to but not referenced. Not explicitly stated if all measured outcomes were reported.
Other bias	Low risk	**Comment**: no other apparent bias was noted.

Shankar 1999

Study characteristics	
Methods	Individually randomised trial conducted in Guinea Bissau
Participants	**Eligibility**: children aged 6–60 months who planned to reside within the study area for ≥ 1 year

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Shankar 1999 *(Continued)*

	Excluded: children with ocular signs of VAD or history of night blindness **Sample**: 480 children; 239 in vitamin A group, 241 in control group. 51% boys
Interventions	**Experimental group**: vitamin A 100,000 IU for children aged < 1 year and 200,000 IU for older children + vitamin E 20 IU **Control group**: placebo + vitamin E 20 IU **Study duration**: intervention given every 4 months for 13 months
Outcomes	Incidence of diarrhoea and malaria morbidity, mean vitamin A serum levels
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "Within these strata, children were individually allocated vitamin A or placebo in blocks of four (two vitamin A, two placebo) by computer generated randomly permutated codes".
Allocation concealment (selection bias)	Low risk	**Quote**: "Capsules were encoded into four groups; two placebo and two vitamin A, and the code was kept offsite by personnel who were not involved in the study".
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Comment**: identical capsules, and allocation was concealed and code kept off site; described as double-blind.
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Comment**: as above; probably done.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Comment**: unlikely that the trained village-based morbidity worker knew the assignments, however, this is never stated explicitly. Probably done.
Incomplete outcome data (attrition bias)	Low risk	**Quote**: "Cross sectional follow-up rates for mid-study and end of study were 428 of 480 (89%) and 410 of 480 (85%), respectively, and similar for vitamin A and placebo groups. During the trial two children dropped out, 66 moved out of the study area, and two died". **Comment**: intention-to-treat used. Missing outcome data balanced in numbers across groups.
Selective reporting (reporting bias)	Unclear risk	**Comment**: protocol not referenced and not stated that all measured outcomes were reported. Data at 7 months not completely reported.
Other bias	Low risk	**Comment**: no other apparent bias.

Sinha 1976

Study characteristics

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Sinha 1976 *(Continued)*

Methods	Individually randomised trial conducted in India
Participants	**Eligibility**: children aged 2 months to 4.5 years **Excluded**: not described **Sample**: 306 children; 153 in vitamin A group, 153 in control group
Interventions	**Experimental group**: vitamin A 200,000 IU every 4 months for 12 months **Control group**: placebo
Outcomes	Bitot's spots, side effects (vomiting)
Notes	The people in the study population were extremely poor.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "The children were divided in two groups of 153 each (two of the children died in the 1st year and two left the village) and were matched for age, sex, socioeconomic status, and playmate contacts. One of the children of each matched pair was selected randomly for receiving vitamin A and the other child received a placebo". **Comment**: no detail about randomisation method provided.
Allocation concealment (selection bias)	Unclear risk	**Quote**: "In a separate laboratory, the designated 2-ml dose of vitamin A or placebo for each child was put into a vial labelled with the child's number and the vials were then shipped to the field station for distribution. Neither the clinician nor the paramedical workers, who personally fed vitamin A and placebo or examined the children for the signs and symptoms of vitamin A deficiency, knew which children received vitamin A". **Comment**: insufficient details provided.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "Neither the clinician nor the paramedical workers, who personally fed vitamin A and placebo or examined the children for the signs and symptoms of vitamin A deficiency, knew which children received vitamin A". **Comment**: probably done.
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "Neither the clinician nor the paramedical workers, who personally fed vitamin A and placebo or examined the children for the signs and symptoms of vitamin A deficiency, knew which children received vitamin A". **Quote**: "The placebo consisted of deodorized arachis oil which was coloured and favoured with orange to match exactly the vitamin A preparation". **Comment**: provider blinded.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Quote**: "Neither the clinician nor the paramedical workers, who personally fed vitamin A and placebo or examined the children for the signs and symptoms of vitamin A deficiency, knew which children received vitamin A".
Incomplete outcome data (attrition bias)	Unclear risk	**Comment**: based on the outcome data reported, it seems that no children dropped out (i.e. there were no losses); however, this could be because the authors were conducting an intention-to-treat analysis but never reported this.

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Sinha 1976 *(Continued)*

		They were not explicit in this regard, as such the risk of bias due to incomplete outcome data was unclear.
Selective reporting (reporting bias)	Unclear risk	**Comment**: did not reference a protocol or trial registration number and did not state that all measured outcomes were reported.
Other bias	Low risk	**Comment**: no other apparent bias.

Smith 1999

Study characteristics	
Methods	Factorial design, individually randomised trial conducted in Belize
Participants	**Eligibility**: children aged 2.2–5.5 years Excluded: children with fever or serious respiratory illness **Sample**: 51 children. Mean age 46.3 months
Interventions	4 intervention groups **Experimental group I**: vitamin A 10,000 IU **Experimental group II**: zinc 70 mg **Experimental group III**: vitamin A 10,000 IU + zinc 70 mg **Control group**: placebo **Study duration**: 6 months
Outcomes	Vitamin A serum level
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote**: "The children selected were randomly assigned to receive one of the following supplements once per week: placebo; Zn, 70 mg as Zn gluconate; vitamin A, 3030 RE as retinyl palmitate; or a combination of vitamin A and Zn". **Comment**: stated to be randomised, but no further data reported.
Allocation concealment (selection bias)	Unclear risk	**Comment**: insufficient details provided.
Blinding (performance bias and detection bias) Blinding of participants	Unclear risk	**Quote**: "Supplements were ingested orally in an orange flavoured powder (10 g), Tangt (Kraft General Foods Inc, White Plains, NY 10625) prepared as a beverage dissolved in approximately 120 mL of water". **Comment**: stated to be "double-blind" in the article keywords, but there appeared to be no details about blinding methods in the text. The intervention (or no intervention in the placebo group) were diluted in the same solution, so presumably all groups were identical.

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Smith 1999 *(Continued)*

Blinding (performance bias and detection bias) Blinding of provider	Unclear risk	**Comment**: not adequately reported.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Unclear risk	**Comment**: not adequately reported.
Incomplete outcome data (attrition bias)	Unclear risk	**Comment**: insufficient details provided; losses not accounted for by group and small sample size made this especially relevant.
Selective reporting (reporting bias)	Unclear risk	**Comment**: did not reference a protocol or trial registration number and did not state that all measured outcomes were reported.
Other bias	Unclear risk	**Comment**: insufficient details provided.

Sommer 1986

Study characteristics	
Methods	Cluster-randomised trial conducted in a rural area of Indonesia
Participants	**Eligibility**: children aged 0–5 years Excluded: children with active xerophthalmia **Sample**: 29,236 children from 450 villages (cluster sites) in Java. 50% boys
Interventions	**Experimental group**: vitamin A 200,000 IU capsules administered twice over the course of the study + vitamin E 40 IU **Control group**: no treatment (served as a waiting list control) **Study duration**: 9–13 months
Outcomes	Mortality, diarrhoea, Bitot's spots, night blindness, xerophthalmia
Notes	ICC not reported (CIs from analyses reported to have been adjusted for design effect). TJL back-calculated an ICC of 0.008307 from effect estimate provided in paper. Vitamin A was not intended to have been distributed to children aged < 12 months, but it would appear that some children aged 0–12 months received the vitamin A capsule. Outcome data were reported on a cohort of 0- to 12-month-old children.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote**: "From a random start, 450 villages were systematically selected for the study; these were then randomised for capsule distribution after the baseline examination …". **Comment**: inadequate information provided.
Allocation concealment (selection bias)	Unclear risk	**Comment**: inadequate information was presented to assess this item in relation to timing of recruitment into the study.

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Sommer 1986 *(Continued)*

Blinding (performance bias and detection bias) Blinding of participants	Unclear risk	**Quote**: "The Government of Indonesia would not condone the use of placebos but field-workers collecting demographic data were unaware that mortality was a research issue". **Comment**: described as a controlled study, without adequate description of what the control group received.
Blinding (performance bias and detection bias) Blinding of provider	Unclear risk	**Quote**: "The Government of Indonesia would not condone the use of placebos but field-workers collecting demographic data were unaware that mortality was a research issue". **Comment**: described as a controlled study, without adequate description of what the control group received.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Unclear risk	**Quote**: "The Government of Indonesia would not condone the use of placebos but field-workers collecting demographic data were unaware that mortality was a research issue". **Comment**: described as a controlled study, without adequate description of what the control group received.
Incomplete outcome data (attrition bias)	Unclear risk	**Quote**: "Follow-up information was available on 89% of the programme children and 88.4% of the controls". **Comment**: authors indicated percentage remaining per group at follow-up, but nothing more detailed.
Selective reporting (reporting bias)	Unclear risk	**Comment**: trial protocol not available.
Other bias	Unclear risk	**Comment**: insufficient information to permit judgement.

Stabell 1995

Study characteristics	
Methods	Individually randomised trial conducted in Guinea Bissau
Participants	**Eligibility**: children aged 6 months of age **Sample**: 68 children; 32 in vitamin A group and 36 in placebo group
Interventions	**Experimental group**: vitamin A 100,000 IU at the time of measles vaccination at 6 and 9 months of age **Control group**: placebo
Outcomes	Side effects (bulging fontanelle)
Notes	Denominator data not entirely clear in Table 1 of the study.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote**: "Carrying out a double-blinded, randomised, placebo-controlled trial". **Comment**: sequence generation not mentioned in the paper.

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Stabell 1995 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	**Comment**: nothing mentioned regarding allocation concealment.
Blinding (performance bias and detection bias) Blinding of participants	Unclear risk	**Comment**: claimed it was blinded but no details provided.
Blinding (performance bias and detection bias) Blinding of provider	Unclear risk	**Comment**: claimed it was blinded but no details provided.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Unclear risk	**Quote from author**: "Children were examined by one of us (CS) to see if their fontanelle was normal, sunken or bulging". **Comment**: appeared outcome assessors were the same people as the investigators.
Incomplete outcome data (attrition bias)	Unclear risk	**Comment**: losses to follow-up by group indicated but no detail provided. Unclear what losses actually occurred in Table 1.
Selective reporting (reporting bias)	Unclear risk	**Comment**: no protocol referenced or statement that all measured outcomes were reported.
Other bias	Unclear risk	**Comment**: short communication, insufficient detail to make an informed judgement.

Stansfield 1993

Study characteristics	
Methods	Randomised, placebo-controlled trial conducted in northwest of Haiti
Participants	**Eligibility**: children aged 6–83 months **Excluded**: children with corneal changes consistent with VAD; with measles; those who had received vitamin A within the past 4 months **Sample**: 13,651 children. 49% boys
Interventions	**Experimental group**: vitamin A 100,000 IU every 4 months for 3 distribution cycles for children aged 6–11 months and 200,000 IU for the older children **Control group**: placebo
Outcomes	2-week prevalence of signs of respiratory tract infections (cold, cough and rapid breathing, and diarrhoea)
Notes	A slightly larger number of children (55%) were assigned to vitamin A group. There was a significant difference between groups with respect to age. Study area had a high prevalence of malnutrition and xerophthalmia in the study population. Children were visited every 2 weeks for 12 months. The respiratory disease morbidity was reported with respect to cold, cough and rapid breathing, which were too non-specific for inclusion under umbrella of pneumonia or LRTI morbidity in our review.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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Stansfield 1993 *(Continued)*

Random sequence generation (selection bias)	High risk	**Quote from the author**: "A random number generator was used to number the first household and the households were numbered sequentially thereafter. Every other household was given a green capsule, while the rest were given red capsules". **Comment**: alternate allocation.
Allocation concealment (selection bias)	Low risk	**Quote from the author**: "The manufacturer (Roche) held the code until the study was completed".
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "The colour code was held only by the manufacturer until the study was completed". **Comment**: probably done.
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Quote**: "Before the study inquiries among health workers and community members had indicated no symbolism associated with or preference for either green or red". **Comment**: highly unlikely that providers would be biased about a single intervention.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Quote**: "The colour code was held only by the manufacturer until the study was completed". **Comment**: probably done.
Incomplete outcome data (attrition bias)	Low risk	**Quote**: "The frequency of non-participation was essentially identical among children from even and odd-numbered households". **Comment**: probably done.
Selective reporting (reporting bias)	High risk	**Quote**: "We did not collect data on the impact of supplementation on vitamin A status, or on the incidence, duration, or severity of symptoms of infection". **Comment**: only mortality and morbidity outcomes given. Protocol not available.
Other bias	Low risk	**Comment**: study appeared free of other bias.

van Agtmaal 1988

Study characteristics	
Methods	Individually randomised, non-placebo trial conducted in Thailand
Participants	**Eligibility**: not described **Excluded**: not described **Sample**: 30 children; 14 in vitamin A group, 21 in control group. Mean age 3.1 years
Interventions	**Experimental group**: single-dose vitamin A 200,000 IU **Control group**: no supplement **Follow-up**: 4 months

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van Agtmaal 1988 *(Continued)*

Outcomes	Mean vitamin A serum levels
Notes	Children were recruited from 3 rural day care centres

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "After selection, 14 children were randomly supplemented with a single, oral dose of vitamin A (110 mg retinyl palmitate, 200,000 IU),according to WHO recommendations (9), and 21 children served as a control group". **Comment**: inadequate information provided.
Allocation concealment (selection bias)	Unclear risk	**Comment**: inadequate information provided.
Blinding (performance bias and detection bias) Blinding of participants	Unclear risk	**Comment**: inadequate information provided.
Blinding (performance bias and detection bias) Blinding of provider	Unclear risk	**Comment**: inadequate information provided.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Unclear risk	**Comment**: inadequate information provided.
Incomplete outcome data (attrition bias)	High risk	**Quote**: "Due to the absence of some children at the different time points the number of data available for statistical analysis was less than the total number of children involved in this study … the number of children from whom complete data sets could be collected was rather low". **Comment**: no comprehensive data given on lost to follow-up nor reasons for loss.
Selective reporting (reporting bias)	High risk	**Comment**: did not report data on serum retinol levels, which were collected/measured.
Other bias	Unclear risk	**Comment**: inadequate information provided.

Venkatarao 1996

Study characteristics	
Methods	Individually randomised trial conducted in India
Participants	**Eligibility**: infants aged 6 months **Sample**: 909 infants. 50% boys
Interventions	3 intervention groups **Group I**: mother and infants both received vitamin A

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Venkatarao 1996 *(Continued)*

	Group II: mother received vitamin A while infant received placebo **Group III**: both mother and infant received placebo Dose of vitamin A for infant was 200,000 IU
Outcomes	All-cause mortality and cause-specific mortality due to diarrhoea and respiratory disease; incidence of diarrhoea and respiratory disease morbidity
Notes	We included the data for groups I vs II.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "Each pair of subjects enrolled for the study was randomly allocated to one of the following three groups: (i) AA-Both mother and infant received vitamin A, the former soon after delivery and the latter at 6 months; (ii) AP: mother received vitamin A but her infant received a placebo (Sesame oil); and (iii) PP: both mother and infant received placebo, the former Vitamin E and the latter Sesame oil". **Comment**: insufficient detail to form a judgement.
Allocation concealment (selection bias)	Unclear risk	**Comment**: insufficient detail to form a judgement.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "At the age of 6 to 6Vi months, the infant was weighed again and given the appropriate syrup by the Medical Officer from coded bottles, supplied again by the Statistical Section at the Camp Office". **Comment**: probably done.
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Comment**: as above; probably done.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Comment**: as above; probably done.
Incomplete outcome data (attrition bias)	Unclear risk	**Quote**: "4 each in the AA and AP groups and 5 in the PP group were withdrawn from the trial on medical grounds such as congenital abnormalities, epileptic fits or jaundice. Migration accounted for the loss of 34 infants in the AA group, 25 in the AP group and 20 in the PP group while 7, 9 and 7 were excluded due to other miscellaneous reasons. Of the remaining 263, 255 and 256 infants in the three group, 233 in the AA and 228 each in the AP and PP groups were followed-up very regularly and form the basis for analyses in this report". **Comment**: they provided specific information about losses by group. However, it is unclear why 263 (group I), 255 (group II) and 256 infants (group III) that remain after attrition is described in the results as only 233 in the group I and 228 each in group II and III being used as the basis for analysis.
Selective reporting (reporting bias)	Unclear risk	**Comment**: did not reference a protocol or trial registration number and did not state that all measured outcomes were reported.
Other bias	Low risk	**Quote**: "Quality control of the morbidity data collected by the field investigators was undertaken throughout. As long recall periods pose problems, the

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Venkatarao 1996 *(Continued)*

	collection of morbidity data was intensified from once a fortnight to once a week when the study had been in progress for 9 months". **Comment**: authors attempted to minimise other biases such as recall bias, though specific details of "quality control" were not provided.

Vijayaraghavan 1990

Study characteristics		
Methods	Cluster-randomised study in rural India	
Participants	**Eligibility**: children aged 1–5 years **Excluded**: children with corneal involvement **Sample**: 15,775 children in 84 clusters. 50.4% boys	
Interventions	**Experimental group**: vitamin A 200,000 IU given twice **Control group**: placebo (arachis oil) **Study duration**: unclear	
Outcomes	Mortality, diarrhoea, acute respiratory infections, measles	
Notes	Respiratory infection has non-specific definition of "clinically significant cough".	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	**Quote**: "The villages were allocated randomly into two groups-treatment and control". **Comment**: insufficient detail to form a judgement.
Allocation concealment (selection bias)	Unclear risk	**Comment**: insufficient detail provided.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "The trial was double blind: the investigators and medical officers did not know which were the treatment and which were the control areas. They were not aware whether the dose they were distributing was vitamin A or placebo. Decoding was done only after data had been collected".
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Comment**: as above; probably done.
Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Comment**: as above; probably done.
Incomplete outcome data (attrition bias)	Unclear risk	**Comment**: insufficient detail provided.

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Vijayaraghavan 1990 *(Continued)*

Selective reporting (reporting bias)	High risk	**Comment**: incidence of infections outcome not given with respect to vitamin A and control groups. Given according to the clinical vitamin A status of all the study children.
Other bias	Low risk	**Comment**: study appeared free of other bias.

West 1991

Study characteristics	
Methods	Cluster-randomised study in rural Nepal
Participants	**Eligibility**: children aged 0–5 years; children with xerophthalmia **Excluded**: children who had recently participated in a vitamin A programme **Sample**: 28,630 children in 261 clusters. 51.3% boys
Interventions	**Experimental group I**: vitamin A 100,000 IU for children aged 6–11 months and 200,000 IU for children aged ≥ 12 months administered 1–3 times + vitamin E 40 IU **Experimental group II**: very low dose vitamin A (1000 IU) + vitamin E 40 IU **Study duration**: 16 months
Outcomes	Mortality, cause-specific mortality, Bitot's spots, night blindness, xerophthalmia
Notes	ICC not disclosed, although study estimates reported to have been adjusted for the unit of allocation. Study had additional recruitment phases in second and third treatment cycles. 1807 children at 4 months and 2018 children at 8 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "After blocking on the local development area, the 261 wards were randomly assigned to receive vitamin A supplementation or placebos at 4-month intervals". **Comment**: inadequately described to permit judgement.
Allocation concealment (selection bias)	Unclear risk	**Quote**: "Both the investigators and communities were masked to the random assignment". **Comment**: study was a cluster-designed trial and there was insufficient information to determine whether allocation occurred before or after treatment group assignment was known.
Blinding (performance bias and detection bias) Blinding of participants	Low risk	**Quote**: "The supplements were given as single-dose gelatin capsules of identical taste and appearance".
Blinding (performance bias and detection bias) Blinding of provider	Low risk	**Comment**: as above; probably done.

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West 1991 *(Continued)*

Blinding (performance bias and detection bias) Blinding of outcome assessor	Low risk	**Comment**: as above; probably done.
Incomplete outcome data (attrition bias)	Unclear risk	**Quote**: "All analyses were carried out on an intention-to-treat basis. Computed mortality rates were based on child-years of observation". **Quote**: " … all children living in wards which received high dose vitamin A every 4 months were considered to have been treated with vitamin A, and all children living in wards which received placebo were considered 'untreated' ". **Comment**: the rates of withdrawal were balanced between groups and the data were analysed based on patient-years of observation. The unclear reasons for withdrawals, variable duration of follow-up due to more than recruitment cycle and the low rate of mortality in relation to the withdrawal rates mean that it is uncertain whether the study was at risk of attrition bias.
Selective reporting (reporting bias)	Low risk	**Comment**: complete data for all time points were available for the review. The last available observation reported in a follow-up article gave an RR for mortality slightly higher than that for the 12-month data given in the primary study report (0.74 versus 0.7).
Other bias	Low risk	**Comment**: a method for estimating the ICCs was reported in Katz 1995.

ALRI: acute lower respiratory illness; BMI: body mass index; CENSIA: Centro Nacional para la Salud de la Infancia y la Adolescencia; CI: confidence interval; CMCH: Christian Medication College & Hospital; HPLC: high-performance liquid chromatography; ICC: intracluster correlation coefficient; LRTI: lower respiratory tract infection; RAND: a function in Excel, which is used to generate a random number; RDA: recommended dietary allowance; RR: risk ratio; RSV: respiratory syncytial virus; VAD: vitamin A deficiency; VAS: vitamin A supplementation; WHO: World Health Organization.

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

Study	Reason for exclusion
Ahmad 2020	Ineligible patient population
Ali 2017	Ineligible patient population
Al-Mekhlafi 2013	Ineligible patient population (included children aged 7–12 years)
Bahl 1997	Ineligible patient population (included children currently with diarrhoea)
Basu 2019	Study included only very-low birth weight infants
Benn 2017	Ineligible study design
Berde 2019	Ineligible study design
Bhaskaram 1997	Ineligible study design (not a randomised controlled trial)
Bhattacharya 2017	Ineligible study design
Bloem 1990	Ineligible study design (not a randomised controlled trial); ineligible patient population (mean age of children was 6.6 years (range 3–9 years))
Changezi 2017	Ineligible study design

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Study	Reason for exclusion
Chen 2012	Ineligible comparator (all groups received vitamin A supplementation)
Chen 2016	Ineligible patient population
Chhagan 2009	Ineligible comparator (all groups received vitamin A supplementation)
Clermont 2017	Ineligible study design
Edmond 2012	Ineligible patient population (maternal vitamin A supplementation)
Fahmida 2007	Ineligible patient population (included children aged 3–6 months)
Gannon 2014	Ineligible intervention (vitamin A given with maize)
Guevara 2016	Ineligible patient population
Handjieva-Darlenska 2014	Ineligible intervention
Handjieva-Darlenska 2016	Ineligible study design
Healy 2018	Ineligible study design
Hoang 2021	Ineligible patient population
Horton 2018	Ineligible study design
Kahbazi 2019	Ineligible patient population
Kartasurya 2012	Ineligible comparator (vitamin A given to both groups)
Kartasurya 2020	Ineligible comparator
Khan 2020	Ineligible study design
Kheirkhah 2016	Ineligible patient population
Koroma 2020	Ineligible study design
Kothari 1991	Ineligible study design (not a randomised controlled trial)
Kranz 2017	Ineligible study design
Laillou 2021	Ineligible study design
Lakshman 2011	Ineligible study design
Liben 2019	Ineligible study design
Longardt 2014	Ineligible patient population
Murray 2016	Ineligible study design
Nankabirwa 2011	Ineligible study design (vitamin A supplementation not randomised)
NCT03383744	Ineligible comparator

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Study	Reason for exclusion
NCT04137354	Comparison between high- and low-dose vitamin A and iron. No placebo group without vitamin A
Oiye 2019	Ineligible study design
Oliveira 2016	Ineligible route of administration
Owusu-Agyei 2013	Ineligible comparator (vitamin A given to both groups)
Pacifici 2016	Ineligible patient population
Patel 2019	Ineligible patient population
Pimpin 2016	Ineligible study design
Semba 1990	Ineligible intervention (vitamin A given as a therapeutic intervention for Bitot's spots)
Semba 2005	Ineligible patient population (study population consisted of children infected with HIV)
Smith 2016	Ineligible patient population
Srinivasan 2016	Ineligible study design
Sukmawati 2020	Ineligible intervention
Tomiya 2017	Ineligible patient population
Wu 2007	Ineligible study design (not a randomised controlled trial)
Yakymenko 2011	Ineligible comparator (vitamin A given to both groups)
Yang 2002	Ineligible intervention (other micronutrients were supplemented with vitamin A and these supplements were not balanced out in the control group). It was difficult to disaggregate the effect of vitamin A.
Zhang 2016	Ineligible patient population
Zhang 2018	Ineligible study design

Characteristics of studies awaiting classification *[ordered by study ID]*

Aklamati 2006

Methods	Individually randomised, placebo-controlled trial conducted in Zambia, Africa
Participants	Boys aged 3–4 years 36 children; 19 in vitamin A group, 17 in placebo group
Interventions	Experimental group: single-dose vitamin A 60 mg Control group: placebo
Outcomes	Mean plasma retinol levels, prevalence of fever, diarrhoea, rhinorrhoea, cough and malaria

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Aklamati 2006 *(Continued)*

Notes	Data were available only in the form of abstract, and the numbers did not match those given in the results section of abstract. We decided to wait for publication of this study before we include it in the review.

DATA AND ANALYSES

Comparison 1. Vitamin A versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality at longest follow-up	19		Risk Ratio (IV, Fixed, 95% CI)	0.88 [0.83, 0.93]
1.2 All-cause mortality at longest follow-up (subgroup analysis): age	5		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
1.2.1 Aged 6–12 months	4		Risk Ratio (IV, Fixed, 95% CI)	0.59 [0.43, 0.82]
1.2.2 Aged 1–5 years	4		Risk Ratio (IV, Fixed, 95% CI)	0.68 [0.57, 0.81]
1.3 All-cause mortality at longest follow-up (subgroup analysis): sex	7		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
1.3.1 Boys	7		Risk Ratio (IV, Fixed, 95% CI)	0.96 [0.89, 1.04]
1.3.2 Girls	7		Risk Ratio (IV, Fixed, 95% CI)	0.90 [0.84, 0.97]
1.4 Mortality due to diarrhoea at longest follow-up	9		Risk Ratio (IV, Fixed, 95% CI)	0.88 [0.79, 0.98]
1.5 Mortality due to measles at longest follow-up	6		Risk Ratio (IV, Fixed, 95% CI)	0.88 [0.69, 1.11]
1.6 Mortality due to meningitis at longest follow-up	3		Risk Ratio (IV, Random, 95% CI)	0.57 [0.17, 1.88]
1.7 Mortality due to lower respiratory tract infection (LRTI) at longest follow-up	9		Risk Ratio (IV, Fixed, 95% CI)	0.98 [0.86, 1.12]
1.8 Diarrhoea incidence at longest follow-up	16		Risk Ratio (IV, Fixed, 95% CI)	0.85 [0.82, 0.87]
1.9 Diarrhoea prevalence at longest follow-up	4		Risk Ratio (IV, Fixed, 95% CI)	1.06 [1.03, 1.10]
1.10 Measles incidence at longest follow-up	6		Risk Ratio (IV, Fixed, 95% CI)	0.50 [0.37, 0.67]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.11 Malaria incidence at longest follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.12 Malaria prevalence at longest follow-up	2		Risk Ratio (IV, Fixed, 95% CI)	0.73 [0.41, 1.28]
1.13 LRTI incidence at longest follow-up	12		Risk Ratio (IV, Fixed, 95% CI)	0.99 [0.92, 1.06]
1.14 LRTI prevalence at longest follow-up	2		Risk Ratio (IV, Fixed, 95% CI)	0.60 [0.45, 0.81]
1.15 Bitot's spots prevalence at longest follow-up	5		Risk Ratio (IV, Fixed, 95% CI)	0.42 [0.33, 0.53]
1.16 Night blindness incidence at longest follow-up	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
1.17 Night blindness prevalence at longest follow-up	2		Risk Ratio (IV, Fixed, 95% CI)	0.32 [0.21, 0.50]
1.18 Xerophthalmia incidence at longest follow-up	3		Risk Ratio (IV, Fixed, 95% CI)	0.85 [0.70, 1.03]
1.19 Xerophthalmia prevalence at longest follow-up	2		Risk Ratio (IV, Fixed, 95% CI)	0.31 [0.22, 0.45]
1.20 Hospitalisation: number of children hospitalised once or more at longest follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.21 Hospitalisation due to diarrhoea at longest follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.22 Hospitalisation due to LRTI at longest follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.23 Side effect: vomiting	4	4427	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [1.44, 2.69]
1.24 Side effect: bulging fontanelle	4	2318	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.74, 2.08]
1.25 Vitamin A deficiency status: number deficient at longest follow-up	4	2262	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.65, 0.78]
1.26 Vitamin A deficiency status: vitamin A serum retinol level at longest follow-up	15	11788	Std. Mean Difference (IV, Fixed, 95% CI)	0.26 [0.22, 0.30]

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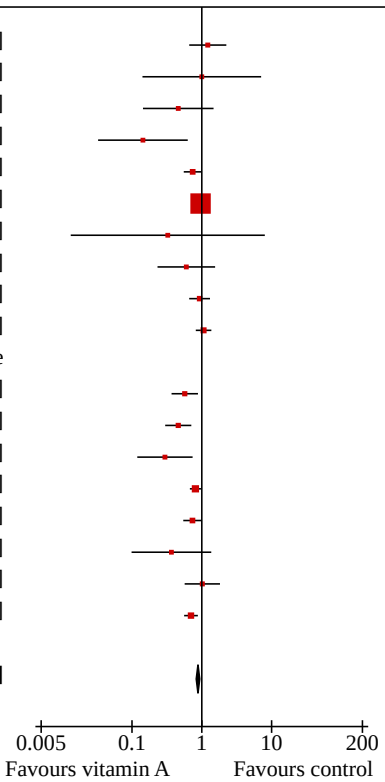
Analysis 1.1. Comparison 1: Vitamin A versus control, Outcome 1: All-cause mortality at longest follow-up

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Agarwal 1995	0.19717994	0.31208317	0.9%	1.22 [0.66 , 2.25]
Barreto 1994	0	0.998385794	0.1%	1.00 [0.14 , 7.08]
Benn 1997	-0.77629472	0.593675421	0.2%	0.46 [0.14 , 1.47]
Chowdhury 2002	-1.941949748	0.754180547	0.2%	0.14 [0.03 , 0.63]
Daulaire 1992	-0.301105093	0.149948333	3.8%	0.74 [0.55 , 0.99]
DEVTA trial 2013	-0.0408	0.03726	61.7%	0.96 [0.89 , 1.03]
Dibley 1996	-1.122328815	1.632993162	0.0%	0.33 [0.01 , 7.99]
Donnen 1998	-0.510825624	0.48464603	0.4%	0.60 [0.23 , 1.55]
Fisker 2014	-0.0726	0.175	2.8%	0.93 [0.66 , 1.31]
Herrera 1992	0.058268908124	0.13093651	5.0%	1.06 [0.82 , 1.37]
Lin 2008	0	0		Not estimable
Pant 1996	-0.562118918	0.222204003	1.7%	0.57 [0.37 , 0.88]
Rahmathullah 1990	-0.776528789	0.219769981	1.8%	0.46 [0.30 , 0.71]
Ross 1993 HEALTH	-1.215787288	0.465474668	0.4%	0.30 [0.12 , 0.74]
Ross 1993 SURVIVAL	-0.210721031	0.093231247	9.9%	0.81 [0.67 , 0.97]
Sommer 1986	-0.30788478	0.154629322	3.6%	0.73 [0.54 , 1.00]
Venkatarao 1996	-1.002522078	0.670563586	0.2%	0.37 [0.10 , 1.37]
Vijayaraghavan 1990	0.016855694	0.297180104	1.0%	1.02 [0.57 , 1.82]
West 1991	-0.356674944	0.115304446	6.4%	0.70 [0.56 , 0.88]
Total (95% CI)			**100.0%**	**0.88 [0.83 , 0.93]**

Heterogeneity: Chi² = 44.00, df = 17 (P = 0.0003); I² = 61%
Test for overall effect: Z = 4.30 (P < 0.0001)
Test for subgroup differences: Not applicable



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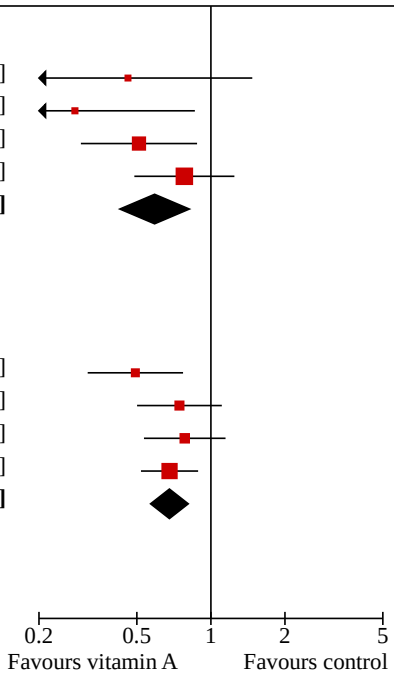
Analysis 1.2. Comparison 1: Vitamin A versus control, Outcome 2: All-cause mortality at longest follow-up (subgroup analysis): age

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
1.2.1 Aged 6–12 months				
Benn 1997	-0.77629472	0.593675421	7.8%	0.46 [0.14 , 1.47]
Rahmathullah 1990	-1.272965676	0.572823454	8.4%	0.28 [0.09 , 0.86]
Daulaire 1992	-0.673344553	0.277413003	35.7%	0.51 [0.30 , 0.88]
West 1991	-0.248461359	0.238905777	48.1%	0.78 [0.49 , 1.25]
Subtotal (95% CI)			**100.0%**	**0.59 [0.43 , 0.82]**
Heterogeneity: Chi² = 3.51, df = 3 (P = 0.32); I² = 15%				
Test for overall effect: Z = 3.18 (P = 0.001)				
1.2.2 Aged 1–5 years				
Rahmathullah 1990	-0.707095599	0.227716965	15.6%	0.49 [0.32 , 0.77]
Sommer 1986	-0.294534092	0.202314948	19.7%	0.74 [0.50 , 1.11]
Daulaire 1992	-0.244863722	0.194755763	21.3%	0.78 [0.53 , 1.15]
West 1991	-0.387206937	0.136447983	43.4%	0.68 [0.52 , 0.89]
Subtotal (95% CI)			**100.0%**	**0.68 [0.57 , 0.81]**
Heterogeneity: Chi² = 2.72, df = 3 (P = 0.44); I² = 0%				
Test for overall effect: Z = 4.32 (P < 0.0001)				
Test for subgroup differences: Chi² = 0.54, df = 1 (P = 0.46), I² = 0%				



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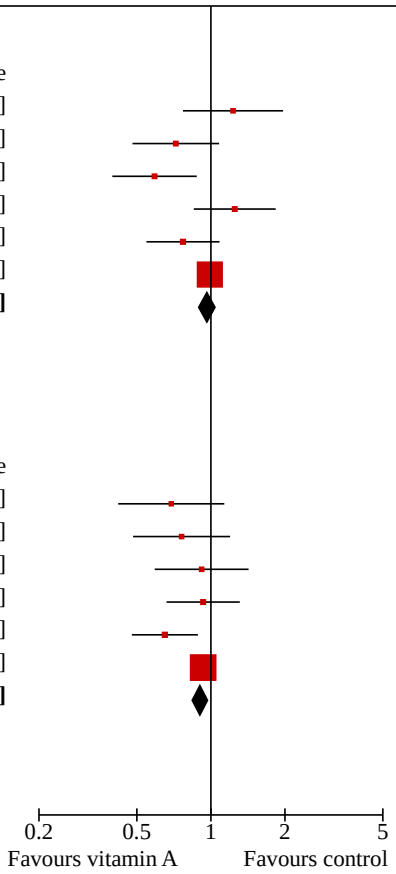
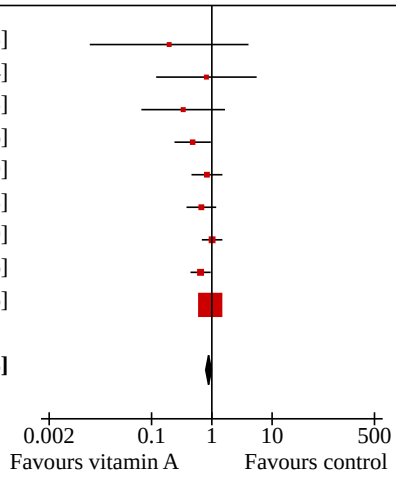
Analysis 1.3. Comparison 1: Vitamin A versus control, Outcome 3: All-cause mortality at longest follow-up (subgroup analysis): sex

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
1.3.1 Boys				
Lin 2008	0	0		Not estimable
Fisker 2014	0.207	0.239	2.6%	1.23 [0.77 , 1.96]
Daulaire 1992	-0.328504067	0.206873754	3.5%	0.72 [0.48 , 1.08]
Sommer 1986	-0.527632742	0.201548343	3.7%	0.59 [0.40 , 0.88]
Herrera 1992	0.223143551	0.195624742	3.9%	1.25 [0.85 , 1.83]
West 1991	-0.261364764	0.174496752	4.9%	0.77 [0.55 , 1.08]
DEVTA trial 2013	-0.0101	0.043	81.3%	0.99 [0.91 , 1.08]
Subtotal (95% CI)			**100.0%**	**0.96 [0.89 , 1.04]**
Heterogeneity: Chi² = 12.77, df = 5 (P = 0.03); I² = 61%				
Test for overall effect: Z = 0.98 (P = 0.33)				
1.3.2 Girls				
Lin 2008	0	0		Not estimable
Fisker 2014	-0.3711	0.2533	2.1%	0.69 [0.42 , 1.13]
Daulaire 1992	-0.274436846	0.231617134	2.5%	0.76 [0.48 , 1.20]
Sommer 1986	-0.08664781	0.224063732	2.6%	0.92 [0.59 , 1.42]
Herrera 1992	-0.07257069	0.174886525	4.3%	0.93 [0.66 , 1.31]
West 1991	-0.430782916	0.157511914	5.4%	0.65 [0.48 , 0.89]
DEVTA trial 2013	-0.0726	0.04	83.1%	0.93 [0.86 , 1.01]
Subtotal (95% CI)			**100.0%**	**0.90 [0.84 , 0.97]**
Heterogeneity: Chi² = 6.61, df = 5 (P = 0.25); I² = 24%				
Test for overall effect: Z = 2.83 (P = 0.005)				
Test for subgroup differences: Chi² = 1.51, df = 1 (P = 0.22), I² = 33.8%				



Analysis 1.4. Comparison 1: Vitamin A versus control, Outcome 4: Mortality due to diarrhoea at longest follow-up

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Venkatarao 1996	-1.631037024	1.546402174	0.1%	0.20 [0.01 , 4.05]
Agarwal 1995	-0.20721746	0.979274639	0.3%	0.81 [0.12 , 5.54]
Chowdhury 2002	-1.094651887	0.814878146	0.5%	0.33 [0.07 , 1.65]
Rahmathullah 1990	-0.733969175	0.353653019	2.4%	0.48 [0.24 , 0.96]
Fisker 2014	-0.1863	0.3011	3.3%	0.83 [0.46 , 1.50]
Ross 1993 SURVIVAL	-0.400477567	0.289061042	3.6%	0.67 [0.38 , 1.18]
Herrera 1992	0.00995033	0.200115565	7.5%	1.01 [0.68 , 1.50]
Daulaire 1992	-0.430782916	0.196352398	7.8%	0.65 [0.44 , 0.96]
DEVTA trial 2013	-0.0619	0.0635	74.5%	0.94 [0.83 , 1.06]
Total (95% CI)			**100.0%**	**0.88 [0.79 , 0.98]**
Heterogeneity: Chi² = 10.15, df = 8 (P = 0.25); I² = 21%				
Test for overall effect: Z = 2.28 (P = 0.02)				
Test for subgroup differences: Not applicable				



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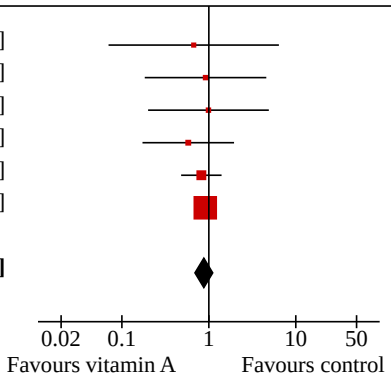
Analysis 1.5. Comparison 1: Vitamin A versus control, Outcome 5: Mortality due to measles at longest follow-up

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Daulaire 1992	-0.400477567	1.150750611	1.1%	0.67 [0.07 , 6.39]
Agarwal 1995	-0.087767982	0.821081555	2.1%	0.92 [0.18 , 4.58]
Herrera 1992	-0.01005034	0.815481876	2.2%	0.99 [0.20 , 4.90]
Rahmathullah 1990	-0.544727175	0.618450657	3.7%	0.58 [0.17 , 1.95]
Ross 1993 SURVIVAL	-0.198450939	0.273076807	19.2%	0.82 [0.48 , 1.40]
DEVTA trial 2013	-0.0943	0.1412	71.7%	0.91 [0.69 , 1.20]
Total (95% CI)			**100.0%**	**0.88 [0.69 , 1.11]**

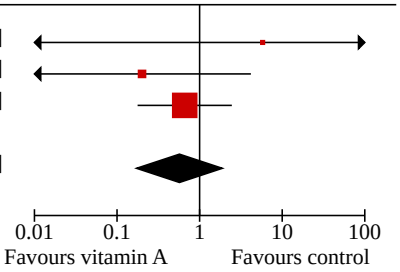
Heterogeneity: Chi² = 0.66, df = 5 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Vitamin A versus control, Outcome 6: Mortality due to meningitis at longest follow-up

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
Agarwal 1995	1.756832023	4.644218683	1.7%	5.79 [0.00 , 52017.39]
Chowdhury 2002	-1.605482733	1.54834208	15.5%	0.20 [0.01 , 4.18]
Ross 1993 SURVIVAL	-0.415515444	0.670186075	82.8%	0.66 [0.18 , 2.45]
Total (95% CI)			**100.0%**	**0.57 [0.17 , 1.88]**

Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.92 (P = 0.36)
Test for subgroup differences: Not applicable



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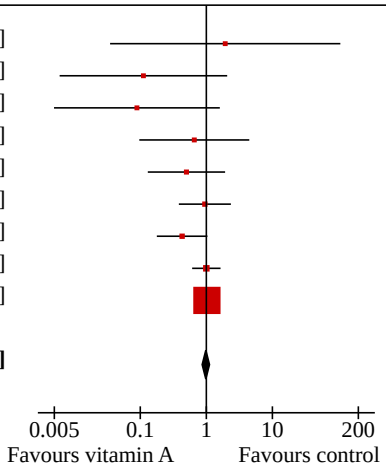
Analysis 1.7. Comparison 1: Vitamin A versus control, Outcome 7: Mortality due to lower respiratory tract infection (LRTI) at longest follow-up

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Agarwal 1995	0.658129764	2.04734345	0.1%	1.93 [0.03 , 106.79]
Chowdhury 2002	-2.193269397	1.489827315	0.2%	0.11 [0.01 , 2.07]
Venkatarao 1996	-2.419494385	1.474170229	0.2%	0.09 [0.00 , 1.60]
Rahmathullah 1990	-0.419603744	0.977941122	0.4%	0.66 [0.10 , 4.47]
Fisker 2014	-0.6931	0.6873	0.9%	0.50 [0.13 , 1.92]
Daulaire 1992	-0.0512933	0.462623882	2.0%	0.95 [0.38 , 2.35]
Herrera 1992	-0.84397007	0.449903316	2.1%	0.43 [0.18 , 1.04]
Ross 1993 SURVIVAL	0	0.252298657	6.7%	1.00 [0.61 , 1.64]
DEVTA trial 2013	0.0198	0.0696	87.4%	1.02 [0.89 , 1.17]
Total (95% CI)			**100.0%**	**0.98 [0.86 , 1.12]**

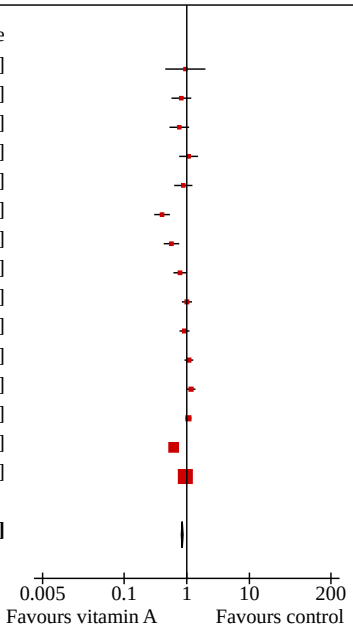
Heterogeneity: Chi² = 9.70, df = 8 (P = 0.29); I² = 18%
Test for overall effect: Z = 0.27 (P = 0.79)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Vitamin A versus control, Outcome 8: Diarrhoea incidence at longest follow-up

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Ramakrishnan 1995	0	0		Not estimable
Arya 2000	-0.052391176	0.376589573	0.2%	0.95 [0.45 , 1.99]
Fisker 2014	-0.1985	0.1855	0.7%	0.82 [0.57 , 1.18]
Chen 2013b	-0.2744	0.1839	0.7%	0.76 [0.53 , 1.09]
Florentino 1990	0.06586282	0.17621784	0.8%	1.07 [0.76 , 1.51]
Chen 2013a	-0.1278	0.1705	0.8%	0.88 [0.63 , 1.23]
Lie 1993	-0.908	0.148	1.1%	0.40 [0.30 , 0.54]
Herrera 1992	-0.562118918	0.145291758	1.1%	0.57 [0.43 , 0.76]
Biswas 1994	-0.24965025	0.12277836	1.6%	0.78 [0.61 , 0.99]
Venkatarao 1996	0.005094491	0.094499594	2.7%	1.01 [0.84 , 1.21]
Long 2007	-0.08320386	0.093128391	2.7%	0.92 [0.77 , 1.10]
Sempértegui 1999	0.076961041	0.082246029	3.5%	1.08 [0.92 , 1.27]
Shankar 1999	0.158295062	0.082187362	3.5%	1.17 [1.00 , 1.38]
Dibley 1996	0.06023817	0.05528549	7.8%	1.06 [0.95 , 1.18]
Chowdhury 2002	-0.483344001534522	0.029704404787842	27.0%	0.62 [0.58 , 0.65]
Barreto 1994	-0.053040765	0.02280902	45.8%	0.95 [0.91 , 0.99]
Total (95% CI)			**100.0%**	**0.85 [0.82 , 0.87]**

Heterogeneity: Chi² = 219.04, df = 14 (P < 0.00001); I² = 94%
Test for overall effect: Z = 10.89 (P < 0.00001)
Test for subgroup differences: Not applicable



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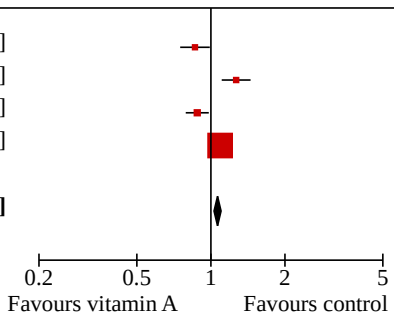
Analysis 1.9. Comparison 1: Vitamin A versus control, Outcome 9: Diarrhoea prevalence at longest follow-up

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Long 2006b	-0.149120034	0.07061765	5.6%	0.86 [0.75 , 0.99]
Long 2006a	0.236298851	0.068888814	5.9%	1.27 [1.11 , 1.45]
DEVTA trial 2013	-0.1278	0.055	9.2%	0.88 [0.79 , 0.98]
Stansfield 1993	0.086177696	0.018731841	79.3%	1.09 [1.05 , 1.13]
Total (95% CI)			**100.0%**	**1.06 [1.03 , 1.10]**

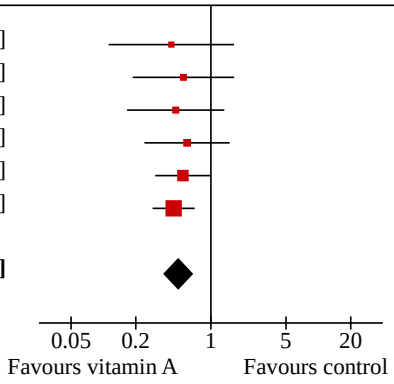
Heterogeneity: Chi² = 28.91, df = 3 (P < 0.00001); I² = 90%
Test for overall effect: Z = 3.73 (P = 0.0002)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Vitamin A versus control, Outcome 10: Measles incidence at longest follow-up

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Bahl 1999	-0.84729786	0.685359748	4.9%	0.43 [0.11 , 1.64]
Barreto 1994	-0.587786665	0.554874134	7.5%	0.56 [0.19 , 1.65]
Benn 1997	-0.753821864	0.531270633	8.2%	0.47 [0.17 , 1.33]
Herrera 1992	-0.510825624	0.465797456	10.7%	0.60 [0.24 , 1.49]
Semba 1995	-0.599691567	0.302982706	25.2%	0.55 [0.30 , 0.99]
Chowdhury 2002	-0.798386071	0.230353301	43.6%	0.45 [0.29 , 0.71]
Total (95% CI)			**100.0%**	**0.50 [0.37 , 0.67]**

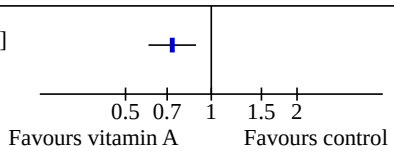
Heterogeneity: Chi² = 0.55, df = 5 (P = 0.99); I² = 0%
Test for overall effect: Z = 4.61 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Vitamin A versus control, Outcome 11: Malaria incidence at longest follow-up

Study or Subgroup	Vitamin A Events	Vitamin A Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
Shankar 1999	178	86184	249	87948	0.73 [0.60 , 0.88]

Test for subgroup differences: Not applicable



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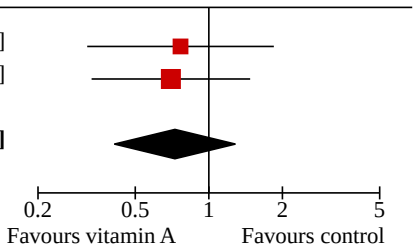
Analysis 1.12. Comparison 1: Vitamin A versus control, Outcome 12: Malaria prevalence at longest follow-up

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Ross 1993 HEALTH	-0.266781721	0.448485327	41.9%	0.77 [0.32 , 1.84]
Ross 1993 SURVIVAL	-0.357623684	0.381068855	58.1%	0.70 [0.33 , 1.48]
Total (95% CI)			**100.0%**	**0.73 [0.41 , 1.28]**

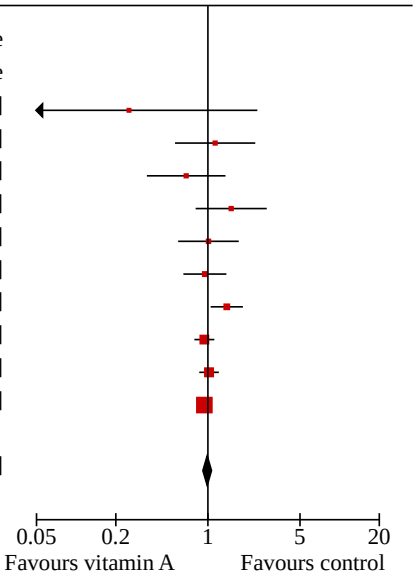
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1: Vitamin A versus control, Outcome 13: LRTI incidence at longest follow-up

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Barreto 1994	0	0		Not estimable
Venkatarao 1996	0	0		Not estimable
Lie 1993	-1.379514674	1.144384436	0.1%	0.25 [0.03 , 2.37]
Kartasasmita 1995	0.126562723	0.357669719	1.2%	1.13 [0.56 , 2.29]
Biswas 1994	-0.379700971	0.350422787	1.2%	0.68 [0.34 , 1.36]
Long 2007	0.406904196	0.317001887	1.5%	1.50 [0.81 , 2.80]
Rahmathullah 1990	0.00995033	0.270144513	2.0%	1.01 [0.59 , 1.72]
Sempértegui 1999	-0.05286182	0.191767121	4.0%	0.95 [0.65 , 1.38]
Chowdhury 2002	0.330214931	0.14380055	7.1%	1.39 [1.05 , 1.84]
Chen 2013b	-0.0619	0.0887	18.7%	0.94 [0.79 , 1.12]
Chen 2013a	0.0198	0.0871	19.4%	1.02 [0.86 , 1.21]
Fisker 2014	-0.0619	0.0574	44.7%	0.94 [0.84 , 1.05]
Total (95% CI)			**100.0%**	**0.99 [0.92 , 1.06]**

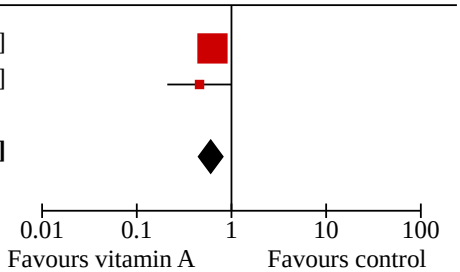
Heterogeneity: Chi² = 11.35, df = 9 (P = 0.25); I² = 21%
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1: Vitamin A versus control, Outcome 14: LRTI prevalence at longest follow-up

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
DEVTA trial 2013	-0.462	0.1605	86.1%	0.63 [0.46 , 0.86]
Long 2006a	-0.7765	0.4001	13.9%	0.46 [0.21 , 1.01]
Total (95% CI)			**100.0%**	**0.60 [0.45 , 0.81]**

Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 3.39 (P = 0.0007)
Test for subgroup differences: Not applicable



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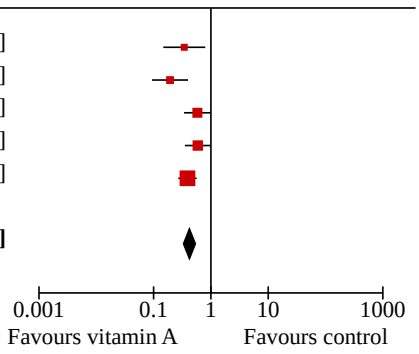
Analysis 1.15. Comparison 1: Vitamin A versus control, Outcome 15: Bitot's spots prevalence at longest follow-up

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
West 1991	-1.070224305	0.429614736	7.8%	0.34 [0.15 , 0.80]
Sommer 1986	-1.643090405	0.368222137	10.7%	0.19 [0.09 , 0.40]
Sinha 1976	-0.543615447	0.273389328	19.4%	0.58 [0.34 , 0.99]
Pant 1996	-0.527632742	0.26293555	20.9%	0.59 [0.35 , 0.99]
DEVTA trial 2013	-0.9416	0.1876	41.1%	0.39 [0.27 , 0.56]
Total (95% CI)			**100.0%**	**0.42 [0.33 , 0.53]**

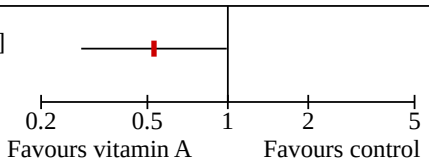
Heterogeneity: Chi² = 7.89, df = 4 (P = 0.10); I² = 49%
Test for overall effect: Z = 7.17 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.16. Comparison 1: Vitamin A versus control, Outcome 16: Night blindness incidence at longest follow-up

Study or Subgroup	log[RR]	SE	Risk Ratio IV, Fixed, 95% CI
Herrera 1992	-0.636388557	0.319970237	0.53 [0.28 , 0.99]

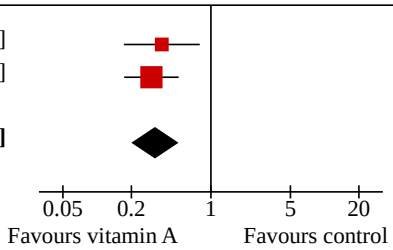
Test for subgroup differences: Not applicable



Analysis 1.17. Comparison 1: Vitamin A versus control, Outcome 17: Night blindness prevalence at longest follow-up

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
West 1991	-0.994252273	0.39190376	33.9%	0.37 [0.17 , 0.80]
Sommer 1986	-1.203972804	0.280748842	66.1%	0.30 [0.17 , 0.52]
Total (95% CI)			**100.0%**	**0.32 [0.21 , 0.50]**

Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 4.96 (P < 0.00001)
Test for subgroup differences: Not applicable



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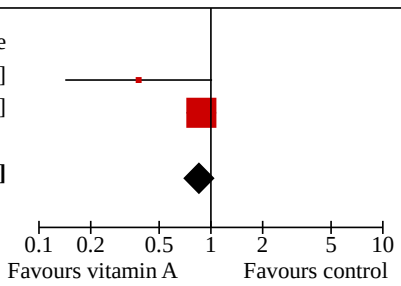
Analysis 1.18. Comparison 1: Vitamin A versus control, Outcome 18: Xerophthalmia incidence at longest follow-up

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Barreto 1994	0	0		Not estimable
West 1991	-0.967584026	0.501568619	3.9%	0.38 [0.14 , 1.02]
Herrera 1992	-0.127833372	0.101063774	96.1%	0.88 [0.72 , 1.07]
Total (95% CI)			**100.0%**	**0.85 [0.70 , 1.03]**

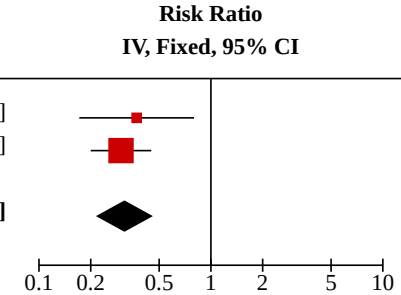
Heterogeneity: Chi² = 2.69, df = 1 (P = 0.10); I² = 63%
Test for overall effect: Z = 1.62 (P = 0.11)
Test for subgroup differences: Not applicable



Analysis 1.19. Comparison 1: Vitamin A versus control, Outcome 19: Xerophthalmia prevalence at longest follow-up

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
West 1991	-0.994252273	0.39190376	21.8%	0.37 [0.17 , 0.80]
Sommer 1986	-1.203972804	0.206873754	78.2%	0.30 [0.20 , 0.45]
Total (95% CI)			**100.0%**	**0.31 [0.22 , 0.45]**

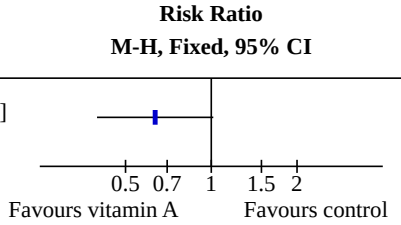
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 6.33 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1: Vitamin A versus control, Outcome 20: Hospitalisation: number of children hospitalised once or more at longest follow-up

Study or Subgroup	Vitamin A Events	Vitamin A Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
Ross 1993 HEALTH	27	596	42	589	0.64 [0.40 , 1.02]

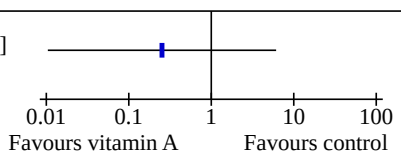
Test for subgroup differences: Not applicable



Analysis 1.21. Comparison 1: Vitamin A versus control, Outcome 21: Hospitalisation due to diarrhoea at longest follow-up

Study or Subgroup	Vitamin A Events	Vitamin A Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
Lie 1993	0	98	1	74	0.25 [0.01 , 6.11]

Test for subgroup differences: Not applicable



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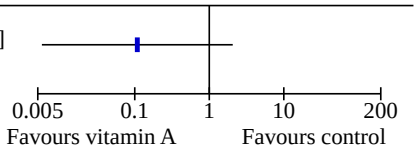
Analysis 1.22. Comparison 1: Vitamin A versus control, Outcome 22: Hospitalisation due to LRTI at longest follow-up

Study or Subgroup	Vitamin A Events	Vitamin A Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
Lie 1993	0	98	3	74	0.11 [0.01 , 2.06]

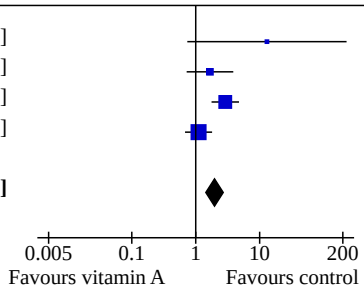
Test for subgroup differences: Not applicable



Analysis 1.23. Comparison 1: Vitamin A versus control, Outcome 23: Side effect: vomiting

Study or Subgroup	Vitamin A Events	Vitamin A Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sinha 1976	6	153	0	153	0.8%	13.00 [0.74 , 228.77]
Arya 2000	13	107	8	110	12.8%	1.67 [0.72 , 3.87]
Florentino 1990	102	1635	18	836	38.6%	2.90 [1.77 , 4.75]
Fisker 2014	32	703	30	730	47.7%	1.11 [0.68 , 1.80]
Total (95% CI)		**2598**		**1829**	**100.0%**	**1.97 [1.44 , 2.69]**
Total events:	153		56			

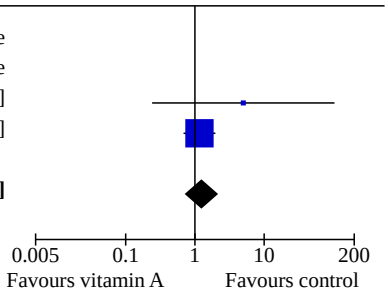
Heterogeneity: Chi² = 9.51, df = 3 (P = 0.02); I² = 68%
Test for overall effect: Z = 4.25 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.24. Comparison 1: Vitamin A versus control, Outcome 24: Side effect: bulging fontanelle

Study or Subgroup	Vitamin A Events	Vitamin A Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Arya 2000	0	107	0	110		Not estimable
Stabell 1995	0	30	0	20		Not estimable
Bahl 1999	2	309	0	309	2.0%	5.00 [0.24 , 103.72]
Fisker 2014	28	703	25	730	98.0%	1.16 [0.69 , 1.97]
Total (95% CI)		**1149**		**1169**	**100.0%**	**1.24 [0.74 , 2.08]**
Total events:	30		25			

Heterogeneity: Chi² = 0.87, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 0.81 (P = 0.42)
Test for subgroup differences: Not applicable



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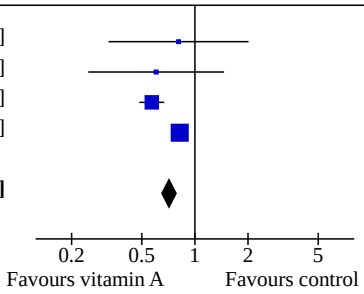
Analysis 1.25. Comparison 1: Vitamin A versus control, Outcome 25: Vitamin A deficiency status: number deficient at longest follow-up

Study or Subgroup	Vitamin A Events	Vitamin A Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cherian 2001	6	26	8	28	1.3%	0.81 [0.32 , 2.01]
Shankar 1999	7	125	13	140	2.1%	0.60 [0.25 , 1.46]
Dibley 1996	135	423	237	423	40.9%	0.57 [0.48 , 0.67]
Ross 1993 HEALTH	268	556	318	541	55.6%	0.82 [0.73 , 0.92]
Total (95% CI)		**1130**		**1132**	**100.0%**	**0.71 [0.65 , 0.78]**
Total events:	416		576			

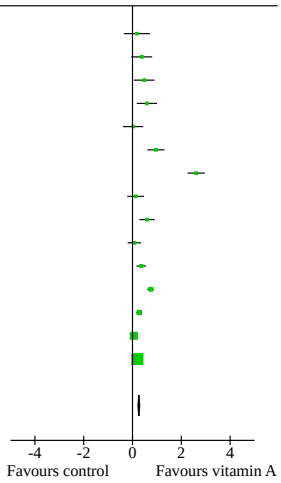
Heterogeneity: Chi² = 13.58, df = 3 (P = 0.004); I² = 78%
Test for overall effect: Z = 7.23 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.26. Comparison 1: Vitamin A versus control, Outcome 26: Vitamin A deficiency status: vitamin A serum retinol level at longest follow-up

Study or Subgroup	Vitamin A Mean	Vitamin A SD	Vitamin A Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Cherian 2001	33.9	10.5	26	32.3	7	28	0.5%	0.18 [-0.36 , 0.71]
Lin 2009	35.39772727	29.152	44	22.99761905	35.726	42	0.7%	0.38 [-0.05 , 0.80]
Sempértegui 1999	48.5	12.6	46	42.9	10.5	43	0.8%	0.48 [0.06 , 0.90]
Lie 1993	30.89	12.24	56	23.32	13.39	40	0.8%	0.59 [0.18 , 1.00]
Pinnock 1986	50.2	11.65	47	49.9	10.49	43	0.8%	0.03 [-0.39 , 0.44]
Reddy 1986b	31.6	9.44	98	23.6	5.53	53	1.1%	0.96 [0.61 , 1.31]
Semba 1991	1.7	0.5	117	0.7	0.2	115	1.1%	2.61 [2.26 , 2.96]
Pinnock 1988	36.5	8.246211251	68	35.5	7.0866	62	1.1%	0.13 [-0.22 , 0.47]
Reddy 1986a	30.1	10.83	110	24.5	6.31	66	1.4%	0.59 [0.28 , 0.90]
Kartasasmita 1995	26.6	9.4	103	25.9	9.1	101	1.8%	0.08 [-0.20 , 0.35]
Shankar 1999	21.9	7.2	201	19.2	7.8	209	3.6%	0.36 [0.16 , 0.55]
Dibley 1996	0.89	0.255	423	0.71	0.228	426	7.0%	0.74 [0.60 , 0.88]
Ross 1993 HEALTH	0.68	0.294746	556	0.6	0.290743	541	9.6%	0.27 [0.15 , 0.39]
Ross 1993 SURVIVAL	0.7	1.741068	1894	0.61	1.142576	1065	24.1%	0.06 [-0.02 , 0.13]
DEVTA trial 2013	0.72	0.5	2581	0.62	0.5	2584	45.5%	0.20 [0.15 , 0.25]
Total (95% CI)			**6370**			**5418**	**100.0%**	**0.26 [0.22 , 0.30]**

Heterogeneity: Chi² = 278.45, df = 14 (P < 0.00001); I² = 95%
Test for overall effect: Z = 13.76 (P < 0.00001)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Subgroup and sensitivity analyses

Outcome or subgroup	Studies	Heterogeneity	Statistical method	Effect estimate	Test for subgroup differences (P value)
All-cause mortality					
All-cause mortality, outcomes < 1 year since randomisation	13	Chi^2 = 34.29, df = 12; P < 0.001; I^2 = 65%	Risk ratio (GIV, fixed, 95% CI)	0.83 (0.75 to 0.92)	NA

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Table 1. Subgroup and sensitivity analyses *(Continued)*

All-cause mortality, outcomes 13–59 months since randomisation	6	Chi^2 = 15.75, df = 5; P < 0.001; I^2 = 68%	Risk ratio (GIV, fixed, 95% CI)	0.88 (0.81 to 0.97)	NA
All-cause mortality at longest follow-up (subgroup analysis): Asia	12	Chi^2 = 42.65, df = 10; P < 0.001; I^2 = 77%	Risk ratio (GIV, fixed, 95% CI)	0.90 (0.84 to 0.96)	0.83
All-cause mortality at longest follow-up (subgroup analysis): Africa	6	Chi^2 = 10.06, df = 5; P = 0.07; I^2 = 50%	Risk ratio (GIV, fixed, 95% CI)	0.86 (0.75 to 0.98)	
All-cause mortality at longest follow-up (subgroup analysis): Latin America	1	NA	Risk ratio (GIV, fixed, 95% CI)	1.00 (0.14 to 7.08)	
All-cause mortality at longest follow-up, by national child mortality rate (subgroup analysis): high (> 40/1000)	17	Chi^2 = 53.07, df = 16 (P < 0.001; I^2 = 70%	Risk ratio (GIV, fixed, 95% CI)	0.89 (0.84 to 0.94)	0.9
All-cause mortality at longest follow-up, by national child mortality rate (subgroup analysis): low (< 40/1000)	2	NA	Risk ratio (GIV, fixed, 95% CI)	1.00 (0.14 to 7.08)	
All-cause mortality at longest follow-up (sensitivity analysis): random-effects model	19	Tau^2 = 0.04; Chi^2 = 44.00, df = 17; P = 0.001; I^2 = 61%	Risk ratio (GIV, fixed, 95% CI)	0.76 (0.66 to 0.88)	NA
All-cause mortality at longest follow-up (sensitivity analysis): without DEVTA trial	18	Chi^2 = 30.38, df = 16; P = 0.02; I^2 = 47%	Risk ratio (GIV, fixed, 95% CI)	0.77 (0.70 to 0.84)	NA
All-cause mortality at longest follow-up (sensitivity analysis): ICC = 0.002 (assumes no impact of clustering for studies with unknown ICC)	19	Chi^2 = 57.02, df = 16; P < 0.001; I^2 = 72%	Risk ratio (GIV, fixed, 95% CI)	0.89 (0.84, 0.94)	NA
All-cause mortality at longest follow-up (sensitivity analysis): ICC = 0.010 (assumes high impact of clustering for studies with unknown ICC)	19	Chi^2 = 47.87, df = 16; P < 0.001; I^2 = 67%	Risk ratio (GIV, fixed, 95% CI)	0.89 (0.84 to 0.94)	NA
Cause-specific mortality					
Mortality due to diarrhoea, outcomes < 1 year since randomisation	6	Chi^2 = 5.23, df = 5; P = 0.39; I^2 = 4%	Risk ratio (GIV, fixed, 95% CI)	0.76 (0.61 to 0.95)	NA
Mortality due to measles, outcomes < 1 year since randomisation	4	Chi^2 = 0.52, df = 3; P = 0.91; I^2 = 0%	Risk ratio (GIV, fixed, 95% CI)	0.85 (0.52 to 1.37)	NA
Mortality due to meningitis, outcomes < 1 year since randomisation	1	NA	Risk ratio (GIV, fixed, 95% CI)	5.79 (0.22 to 153.24)	NA

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Table 1. Subgroup and sensitivity analyses *(Continued)*

Mortality due to LRTI, outcomes < 1 year since randomisation	6	Chi^2 = 5.66, df = 5; P = 0.34; I^2 = 12%	Risk ratio (GIV, fixed, 95% CI)	0.66 (0.40 to 1.10)	NA
Cause-specific morbidity					
Diarrhoea incidence at longest follow-up (sensitivity analysis): analysis without Lie 1993 and Chowdhury 2002	13	Heterogeneity: Chi^2 = 30.71, df = 12; P = 0.002; I^2 = 61%	Risk ratio (GIV, fixed, 95% CI)	0.96 (0.93 to 1.00)	NA
Diarrhoea incidence, outcomes < 1 year since randomisation	13	Chi^2 = 51.64, df = 11; P < 0.001; I^2 = 79%	Risk ratio (GIV, fixed, 95% CI)	0.93 (0.89 to 0.96)	NA
Diarrhoea incidence at longest follow-up (sensitivity analysis): random-effects model	15	Tau^2 = 0.07; Chi^2 = 219.04, df = 14; P < 0.001; I^2 = 94%	Risk ratio (GIV, random, 95% CI)	0.84 (0.73, 0.98)	NA
Measles incidence, outcomes < 1 year since randomisation	5	Chi^2 = 0.24, df = 4; P = 0.99; I^2 = 0%	Risk ratio (GIV, fixed, 95% CI)	0.54 (0.36 to 0.80)	NA
Malaria incidence, outcomes 1 + years since randomisation (subgroup analysis): age	1	NA	Risk ratio (M-H, fixed, 95% CI)	0.73 (0.60 to 0.88)	NA
LRTI Incidence, outcomes < 1 year since randomisation	11	Chi^2 = 5.23, df = 8; P = 0.73; I^2 = 0%	Risk ratio (GIV, fixed, 95% CI)	0.96 (0.89 to 1.04)	NA
Bitot's spots incidence, outcomes < 1 year since randomisation	1	NA	Risk ratio (GIV, fixed, 95% CI)	0.93 (0.76 to 1.14)	NA
Bitot's spots prevalence, outcomes < 1 year since randomisation	3	Chi^2 = 6.06, df = 2; P = 0.05; I^2 = 67%	Risk ratio (GIV, fixed, 95% CI)	0.43 (0.33 to 0.56)	NA
Night blindness prevalence, outcomes < 1 year since randomisation	1	NA	Risk ratio (GIV, fixed, 95% CI)	0.30 (0.17 to 0.52)	NA
Xerophthalmia incidence, outcomes < 1 year since randomisation	**2**	NA	Risk ratio (GIV, fixed, 95% CI)	0.88 (0.72 to 1.07)	NA
Vitamin A deficiency status					
Vitamin A serum retinol level, outcomes < 1 year since randomisation	11	Chi^2 = 178.42, df = 10; P < 0.001; I^2 = 94%	Standardised mean difference (GIV, fixed, 95% CI)	0.45 (0.37 to 0.53)	NA
Vitamin A serum retinol level at longest follow-up (sensitivity analysis): random-effects model	14	Tau^2 = 0.13; Chi^2 = 278.45, df = 14; P < 0.001; I^2 = 95%	Standardised mean difference (GIV, random, 95% CI)	0.50 (0.30 to 0.70)	NA

CI: confidence interval; df: degrees of freedom; GIV: generic inverse variance; LRTI: lower respiratory tract infection; M-H: mantel Haenszel method; NA: not applicable.

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APPENDICES

Appendix 1. Search strategies 2021

Cochrane CENTRAL

#1 MeSH descriptor: [Vitamin A] explode all trees
#2 "Vitamin A" or retinol* or "Aquasol A" or retinal
#3 #1 OR #2
#4 MeSH descriptor: [Child] explode all trees
#5 MeSH descriptor: [Infant] explode all trees
#6 (baby OR babies OR infant* OR toddler* OR child* OR (pre NEXT school*) OR preschool* OR pre-school* OR girl* OR boy*)
#7 #4 OR #5 OR #6
#8 #3 AND #7 Publication Date 2016 to 2021

MEDLINE Ovid (R)

1 exp Vitamin A/
2 (retinol$ or retinal$ or aquasol a or vitamin a).tw.
3 1 or 2
4 exp Infant/
5 exp Child/
6 (baby or babies or infant$ or toddler$ or child$ or girl$ or boy$ or pre school$ or pre-school$ or preschool$)
7 4 or 5 or 6
8 exp placebos/
9 randomized controlled trial.pt.
10 controlled clinical trial.pt.
11 randomi#ed.ab.
12 placebo$.ab.
13 drug therapy.fs.
14 randomly.ab.
15 random.ab.
16 trial.ab.
17 trials.ab.
18 group.ab.
19 groups.ab.
20 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21 3 and 7 and 20
22 exp animals/ not humans.sh.
23 21 not 22
24 limit 19 to yr="2016 -Current"

Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations

1 (retinol$ or retinal$ or aquasol a or vitamin a).tw.
2 (baby or babies or infant$ or toddler$ or child$ or girl$ or boy$ or pre school$ or pre-school$ or preschool$).tw.
3 1 and 2
4 random$.tw.
5 placebo$.tw.
6 trial.tw.
7 trials.tw.
8 group.tw.
9 groups.tw.
10 (crossover or cross-over).tw.
11 ((singl$ or doubl$ or tripl$ or trebl$) adj1 (blind$ or mask$)).tw.
12 prospective.tw.
13 factorial$.tw.
14 assign$.ab.
15 allocat$.ab.
16 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17 3 and 16
18 remove duplicates from 17
19 limit 16 to yr="2016 -Current"

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#1 'retinol'/exp
#2 retinol* OR retinal* OR 'aquasol a' OR 'vitamin a'
#3 #1 OR #2
#4 'child'/exp
#5 baby OR babies OR infant* OR toddler* OR child* OR girl* OR boy* OR 'pre school*' OR preschool*
#6 #4 OR #5
#7 'randomized controlled trial'/exp
#8 'controlled clinical trial'/exp
#9 'single blind procedure'/exp
#10 'double blind procedure'/exp
#11 'triple blind procedure'/exp
#12 'crossover procedure'/exp
#13 crossover OR 'cross over'
#14 (singl* OR doubl* OR tripl* OR trebl*) NEXT/1 (blind* OR mask*)
#15 'placebo'/exp
#16 placebo*
#17 prospective
#18 factorial*
#19 random*
#20 assign*:ab
#21 allocat*:ab
#22 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #3 AND #6 AND #22
#24 #23 NOT ([animals]/lim NOT [humans]/lim)
#25 #24 AND [2016-2021]/py
#26 #25 NOT [medline]/lim

Web of Science (Science Citation Index and Conference Proceedings Citation Index – Science)

#1 TS=(retinol OR "vitamin a")
#2 TS=(baby OR babies OR infant* OR toddler* OR child* OR girl* OR boy* OR "pre school*" OR pre-school* OR preschool*)
#3 #2 AND #1
#4 TS=(random* OR placebo* OR trial OR trials)
#5 #4 AND #3
#6 #5 Timespan=2016-2021

Cochrane Database of Systematic Reviews

#1 MeSH descriptor: [Vitamin A] explode all trees
#2 "Vitamin A" or retinol* or "Aquasol A" or retinal
#3 #1 OR #2
#4 MeSH descriptor: [Child] explode all trees
#5 MeSH descriptor: [Infant] explode all trees
#6 (baby OR babies OR infant* OR toddler* OR child* OR (pre NEXT school*) OR preschool* OR pre-school* OR girl* OR boy*)
#7 #4 OR #5 OR #6
#8 #3 AND #7 Publication Date 01/01/16 to 02/03/2021

ClinicalTrials.gov

Advanced search: Intervention: Vitamin A AND Age Group: child

World Health Organization International Clinical Trials Registry Platform

Searched from standard search page

(Vitamin A AND child) OR (Vitamin A AND babies) OR (Vitamin A AND infants)

Global Index Medicus (WPRIM, LILACS, IMSEAR, IMEMR, AIM)

(mh:(retinol)) OR (("vitamin a" OR retinol* OR "aquasol a" OR retinal*)) AND ((mh:(child)) OR ((mh:(infant))) OR ((baby OR babies OR child* OR infant* OR toddler* OR girl* OR boy* OR preschool* OR "pre school*" OR pre-school*))) AND ((mh:(placebos)) OR ((random* OR placebo* OR trial OR trials OR group OR groups OR crossover OR cross-over OR prospective OR factorial*) OR ((ab:(assign* OR allocat*))) OR ((singl* OR doubl* OR tripl* OR trebl*) AND ((blind* OR mask*))))) AND NOT ((mh:(animals)) AND NOT ((mh:(animals)) AND ((mh:(humans))))) AND (year_cluster:[2016 TO 2021])

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Scopus Elsevier

((TITLE-ABS-KEY (retinol* OR retinal* OR "aquasol a" OR "vitamin a")) AND (TITLE-ABS-KEY (baby OR babies OR infant* OR toddler* OR child* OR girl* OR boy* OR "pre school*" OR preschool* OR pre-school*))) AND ((TITLE-ABS-KEY (random* OR placebo* OR trial OR trials OR group OR groups OR crossover OR cross-over OR prospective OR factorial*)) OR (TITLE-ABS-KEY (singl* OR doubl* OR tripl* OR trebl*) PRE/1 TITLE-ABS-KEY (blind* OR mask*)) OR (ABS (assign* OR allocat*))) AND NOT INDEX (medline) AND (LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR, 2014))

WHAT'S NEW

Date	Event	Description
4 August 2021	New search has been performed	Review updated following a new search in March 2021
4 August 2021	New citation required but conclusions have not changed	No new studies found. Conclusions remain unchanged.

HISTORY

Protocol first published: Issue 5, 2010
Review first published: Issue 12, 2010

Date	Event	Description
23 November 2017	Amended	Added additional sentences to the Excluded studies section that further describe studies excluded from the review.
13 January 2017	New search has been performed	Updated following a new search in March 2016.
13 January 2017	New citation required but conclusions have not changed	We included four new studies.
7 December 2010	Amended	Edited to correct typographical errors and improve readability.

CONTRIBUTIONS OF AUTHORS

AI and EMW contributed to the background section.

EMW and AI were primarily responsible for the methods section.

AS conducted the literature search.

JS, MH and AR reviewed citations for inclusion and resolved disagreements through consultation.

EMW and ZAB contributed to writing the discussion.

ZAB provided supervision and contributed to the writing and analyses.

AI is the guarantor of the review.

DECLARATIONS OF INTEREST

AI: reported that he has no conflicts of interest.

EMW: reported that he has no conflicts of interest.

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MH: reported that she has no conflicts of interest.

AR: reported that she has no conflicts of interest.

JS: reported that she has no conflicts of interest.

AS: reported that she has no conflicts of interest.

ZB: reported that he has no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Aga Khan University, Karachi, Pakistan

  Zulfiqar A Bhutta - Faculty member

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The current version of the review is similar to the last version (Imdad 2017), except for minor changes and those that are mentioned in the sections below. Most of the changes mentioned below reflect differences between the protocol (Imdad 2010c), and the first version of the review (Imdad 2010a).

Differences between protocol and original review

Types of studies

We made a post hoc decision to include two studies in which participants were assigned using a quasi-random method (Herrera 1992; Stansfield 1993). Given the design of the interventions and the placebos as well as steps to blind those administering the sequence, we did not think these studies were meaningfully different from RCTs. For more information, see Included studies section.

Types of outcome measures > secondary outcomes

We made a post hoc decision to include two new outcomes.

1. Hospitalisation.
2. Vitamin A deficiency status based on serum retinol level.

See Secondary outcomes section.

Differences between original review and last update

Electronic searches

1. The Global Health database, which we searched in the previous version of this review (Imdad 2010a), was no longer available to us.
2. The metaRegister of Controlled Trials (mRCT) was under review and unavailable at the time of searching, so we searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) instead.
3. We searched four additional databases for this update.
   a. Science Citation Index.
   b. Conference Proceedings Citation Index – Science.
   c. *Cochrane Database of Systematic Reviews.*
   d. Database of Abstracts of Reviews of Effects (DARE).

Differences between last update of the review and this version

Data collection and analysis

Electronic searches

1. For this update, we did not search DARE, as it was no longer available.
2. In this update, LILACS and AIM were searched via Global Index Medicus. WPRIM (Western Pacific Region Index Medicus), IMSEAR (Index Medicus for the South-East Asia Region), and IMEMR (Index Medicus for the Eastern Mediterranean Region) were also searched as part

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of Global Index Medicus. Scopus was searched for this review. The 2021 Embase search was conducted in Embase Elsevier, not Embase Ovid.

Selection of studies

We used the software COVIDENCE for screening of titles for this update. This software was used to assist the team with double screening and management of citations.

INDEX TERMS

Medical Subject Headings (MeSH)

Diarrhea [chemically induced]; Dietary Supplements; *Measles [chemically induced] [complications]; Morbidity; *Respiration Disorders; Vitamin A [therapeutic use]; *Vitamin A Deficiency [epidemiology] [prevention & control]

MeSH check words

Child; Child, Preschool; Female; Humans; Male

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