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

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

Imdad A, Herzer K, Mayo-Wilson E, Yakoob MY, Bhutta ZA

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

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A B S T R A C T

Background

Vitamin A deficiency (VAD) is a major public health problem in low and middle income countries affecting 190 million children under 5. VAD can lead to many adverse health consequences, including death.

Objectives

To evaluate the effect of vitamin A supplementation (VAS) for preventing morbidity and mortality in children aged 6 months to 5 years.

Search methods

We searched CENTRAL (*The Cochrane Library* 2010, Issue 2), MEDLINE (1950 to April Week 2 2010), EMBASE (1980 to 2010 Week 16), Global Health (1973 to March 2010), Latin American and Caribbean Health Sciences (LILACS), metaRegister of Controlled Trials and African Index Medicus (27 April 2010).

Selection criteria

Randomised controlled trials (RCTs) and cluster RCTs evaluating the effect of synthetic VAS in children aged 6 months to 5 years living in the community. We excluded studies of children in hospital and children with disease or infection. We excluded studies evaluating the effects of food fortification, consumption of vitamin A rich foods or beta-carotene supplementation.

Data collection and analysis

Two authors independently assessed studies for inclusion. Data were double abstracted and discrepancies resolved by discussion. Meta-analyses were performed for outcomes including all-cause and cause-specific mortality, disease, vision, and side-effects.

Main results

Forty-three trials involving 215,633 children were included. A meta-analysis for all-cause mortality included 17 trials (194,795 children). At follow-up, there was a 24% observed reduction in the risk of all-cause mortality for vitamin A compared with control (Relative risk (RR) = 0.76 (95% confidence interval (CI) 0.69 to 0.83). Seven trials reported diarrhoea mortality and showed a 28% overall reduction

for VAS (RR = 0.72 (95% CI 0.57 to 0.91)). There was no significant effect of VAS on cause specific mortality of measles, respiratory disease and meningitis. VAS reduced incidence of diarrhoea (RR = 0.85 (95% CI 0.82 to 0.87)) and measles morbidity (RR = 0.50 (95% CI 0.37 to 0.67)); however, there was no significant effect on incidence of respiratory disease or hospitalisations due to diarrhoea or pneumonia. There was an increased risk of vomiting within the first 48 hours of VAS (RR = 2.75 (95% CI 1.81 to 4.19)).

Authors' conclusions

VAS is effective in reducing all-cause mortality and we recommend universal supplementation for children under 5 in areas at risk of VAD. Further placebo-controlled trials of VAS in children between 6 months and 5 years of age are unnecessary, although studies that compare different doses and delivery mechanisms are needed.

PLAIN LANGUAGE SUMMARY

Vitamin A supplementation for preventing disease and death in children 6 months to five years of age

Vitamin A deficiency (VAD) is a major public health problem in low and middle income countries affecting 190 million children under 5 years of age. VAD pre-disposes children to increased risk of a range of problems, including respiratory diseases, diarrhoea, measles and vision problems, and can lead to death.

This review, including 43 randomised trials representing 215,633 children, shows that giving vitamin A capsules to children aged 6 months to 5 years can reduce death and some diseases. The results of 17 of the studies were summarised and indicate that vitamin A reduces the overall risk of death by 24%. Death due to measles, respiratory infections or meningitis was not specifically reduced, but vitamin A can reduce new occurrences of diarrhoea and measles. When people take very large doses of vitamin A, they may be more likely to vomit within two days of taking it.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

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

Patient or population: Children aged between 6 months and five years
Intervention: Vitamin A supplementation
Comparison: Placebo or usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	Control	**Vitamin A**				
All-cause mortality Follow-up: 12-96 weeks	**Low risk population**		RR 0.76; 95% CI 0.69 to 0.83	194,795 (17 studies)	++++ high	The inclusion of the DE-VTA trial reduced the effect size from 0.76 to 0.88 (Analysis 1.4). The impact on the absolute effect was to reduce the risk of mortality by 2 per 1000 in medium risk and 11 per 1000 in high risk populations
	0 per 1000[1]	0 per 1000 (0 to 0)				
	Medium risk population					
	11 per 1000[1]	8 per 1000 (7 to 9)				
	High risk population					
	90 per 1000[1]	68 per 1000 (62 to 75)				
Diarrhoea-related mortality Follow-up: 48-104 weeks	**Low risk population**		RR 0.72; 95% CI 0.57 to 0.91	90,951 (7 studies)	+++0 moderate[2]	Total number of participants reflects number randomised to studies. The analysis combined cumulative risk and risk per/1000 years follow-up

Outcomes	Illustrative comparative risks		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	3 per 1000[1]	2 per 1000 (2 to 3)				
	Medium risk population					
	4 per 1000[1]	3 per 1000 (2 to 4)				
	High risk population					
	9 per 1000[1]	6 per 1000 (5 to 8)				
Measles-related mortality Follow-up: 52-104 weeks	Low risk population		RR 0.80; 95% CI 0.51 to 1.24	88,261 (5 studies)	+++0 moderate[2]	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[1]	2 per 10,000 (1 to 3)				
	Medium risk population					
	16 per 10,000[1]	13 per 10,000 (8 to 20)				
	High risk population					
	44 per 10,000[1]	35 per 10,000 (22 to 55)				
LRTI-related mortality Follow-up: 48-104 weeks	Low risk population		RR 0.78; 95% CI 0.54 to 1.14	90,951 (7 studies)	++00 low[2,3]	Total number of participants reflects number randomised to studies. The analysis combined cumulative risk and risk per/1000 years follow-up

	4 per 10,000[1]	**3 per 10,000** (2 to 4)			
	Medium risk population				
	11 per 10,000[1]	**9 per 10,000** (6 to 13)			
	High risk population				
	219 per 10,000[1]	**171 per 10,000** (118 to 250)			
Diarrhoea incidence Mean episodes per child per year Follow-up: 24-60 weeks	Mean episodes of diarrhoea in control groups: 1.9/child/year in controls	VAS led to 0.29 episodes fewer per child per year (95% CI 0.34 episodes to 0.25 episodes fewer)	Rate ratio 0.85; 95% CI 0.82 to 0.87	69,972 (13 studies)	++00 low[4,5]
Measles-morbidity incidence Mean episodes of measles per child per year Follow-up: mean 52 weeks	Mean episodes in control groups: 0.028 event per child per year	VAS led to 0.015 fewer episodes per child per year (95% CI 0.019 events fewer per child to 0.01 events fewer per child)	Rate ratio 0.50; 95% CI 0.37 to 0.67	19,566 (6 studies)	++++ high
LRTI-morbidity incidence Mean episodes per child per year Follow-up: mean 52 weeks	Mean episodes in control groups: 0.7 episodes.	VAS led to 0.1 more episodes/child/year (95% CI 0.04 episodes fewer to 0.3 episodes more episodes per child per year	Rate ratio 1.14; 95% CI 0.95 to 1.37	19,566 (9 studies)	+000 very low[6,7,8]
Bitot's spots Follow-up: mean 80.72 weeks	**Low risk population**		RR 0.45; 95% CI 0.33 to 0.61	63,278 (4 studies)	+++0 moderate[9]

	4 per 1000[1]	2 per 1000 (1 to 2)		
	Medium risk population			
	14 per 1000[1]	6 per 1000 (5 to 9)		
	High risk population			
	203 per 1000[1]	91 per 1000 (67 to 124)		
Night blindness Follow-up: 52 to 68 weeks	**Low risk population**		RR 0.32; 95% CI 0.21 to 0.50	22,972 (2 studies)	+++0 moderate[11]
	4 per 1000[10]	1 per 1000 (1 to 2)		
	High risk population			
	7 per 1000[10]	2 per 1000 (2 to 4)		
Vitamin A deficiency Follow-up: mean 54.5 weeks	**Low risk population**		RR 0.71; 95% CI 0.65 to 0.78	2262 (4 studies)	++++ high
	93 per 1000[10]	66 per 1000 (60 to 72)		
	Medium risk population			
	286 per 1000[10]	203 per 1000 (186 to 223)		
	High risk population			

	588 per 1000[10]	**417 per 1000** (382 to 458)		
Vomiting Follow-up: 0.14 to 52 weeks	**Low risk population**		RR 2.75; 95% CI 1.81 to 4.19	2994 (3 studies)	++00 low [12,13]
	0 per 1000[10]	**0 per 1000** (0 to 0)		
	Medium risk population			
	22 per 1000[10]	**62 per 1000** (41 to 94)		
	High risk population			
	73 per 1000[10]	**200 per 1000** (132 to 305)		

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

CI: Confidence interval; RR: Risk Ratio

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

1. CERs identified from the studies for this outcome which report cumulative risk.
2. The wide confidence intervals around the pooled effect estimate included both a reduction and an increase in the risk of mortality with vitamin A.
3. The risk of bias assessments determined that Daulaire 1992 and Herrera 1992 were at high risk of selection bias. Inadequate blinding put the results of Daulaire 1992 at a high risk of detection bias. Incomplete data was considered to put the results of Chowdhury 2002 at a high risk of attrition bias. Baseline imbalance was noted for Agarwal 1995.
4. The risk of bias assessment determined that four studies contributing just over 25% weight of the estimated effect were at risk of selection or attrition bias.

5. The I square was 95%, and the results of Herrera 1992; Cheng 1993 and Chowdhury 2002 demonstrated clear evidence of benefit and were discordant with the results of the other studies.

6. The risk of bias assessment determined that Cheng 1993; Kartasasmita 1995 and Chowdhury 2002 were at high risk of attrition bias.

7. Diagnostic procedures were not consistent across the studies.

8. The CIs around the pooled effect included small benefit and a meaningful increase in the risk of RTIs.

9. The risk of bias assessment determined that there was a risk of attrition bias in Pant 1996, which was assigned 47% weight.

10. Risk based on CERs from the included studies.

11. The larger study was not well described and was of uncertain quality; this puts the results at a high risk of selection bias.

12. The follow-up was spread between 1 day and 52 weeks.

13. There was some evidence of under-reporting of adverse events in some of the studies, and the low number of trials giving data in relation to the large of studies included overall means that this selective reporting of adverse events cannot be excluded.

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, as in diets that rely heavily on vegetables and fruits (Ramakrishnan 2002). In poor societies, especially lower income countries, dietary deficiency can begin very early in life, as 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, intake of vitamin A may be lowered through depressed appetite and poor absorption, and body stores of vitamin A may be depleted through excessive metabolism and excretion (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 KP 2003).

VAD is common in the developing world. About 19.1 million pregnant women and 190 million children under 5 are vitamin A deficient (i.e. serum retinol < 0.70 μmol/l), representing about 33% of children under 5 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).

Africa and South-East Asia contain the highest proportions of pregnant females and children under 5 with biochemical VAD and night blindness (WHO 2009). Xerophthalmia is the world's leading preventable cause of blindness, and a cardinal indicator of VAD (Sommer 1996). Of the world's children with xerophthalmia, nearly half reside in South or South-East Asia, with more than 85% of these living in India (West 2002a).

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 is 12:

1 (US Institute of Medicine, Food and Nutrition Board). 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 therefore must be obtained through diet (Bates 1995). Oral 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 6 months of age) residing in developing 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 6 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 1 year, headaches, vomiting, diarrhoea, loss of appetite and irritability. Toxicity from ingestion of food sources of preformed vitamin A is rare (Hathcock 1997).

Why it is important to do this review

Prophylactic and therapeutic supplementation has been the subject of several reviews (Beaton 1993; Fawzi 1993; Glasziou 1993; Gogia 2008a). Three of these are 17 years old. The most recent one (Gogia 2008a) included studies of maternal VAS, neonatal VAS and childhood supplementation in a single meta-analysis. Direct supplementation of children and indirect methods through supplementation of breast-feeding mothers may have variable impacts on children, and supplementation may have different effects at these key developmental stages. These systematic reviews reported statistically significant reductions in all-cause child mortality. VAS appears to be a very cheap intervention that can be easily administered to children. In populations with low vitamin A status and where dietary intake of vitamin A is low, large-scale supplementation might lead to substantial public health benefits, including re-

duced childhood mortality, infections and blindness. On the basis of previous evidence, the WHO has long recommended VAS for young children and pregnant or breastfeeding mothers at a dose of 50,000 IU for infants under 6 months of age, 100,000 IU for infants 6 to 12 months of age and 200,000 IU for children over 12 months of age, every 4 to 6 months (WHO 1997).

Several studies have been conducted since these recommendations were made over a decade ago, and this review aims to provide an up-to-date assessment of the best available evidence for VAS, including subgroup analyses to identify populations most likely to benefit and the most effective doses. Gogia 2008a did not include several known studies of VAS, so there is a need for a systematic review with a highly sensitive search strategy. The therapeutic role of vitamin A has been evaluated for measles and non-measles pneumonia in two separate Cochrane reviews (Ni 2005; Yang 2009). The prophylactic role of vitamin A has also been or is being evaluated in different Cochrane reviews in different subpopulations of children and mothers (van den Broek 2002; Wiysonge 2005; Oliveira 2006; Darlow 2007; Chen 2008; Gogia 2008; Haider 2008; Bello 2009). However, no Cochrane review has addressed prophylactic VAS in children from 6 months to 5 years of age. Given some of the recent controversies raised on the efficacy/effectiveness of VAS in developing countries (Latham 2010), it is important to review the cumulative evidence to date on the impact on health outcomes of VAS in children aged 6 months to 5 years.

OBJECTIVES

To evaluate the effect of vitamin A supplementation (VAS) in children from 6 months to 5 years of age with respect to the prevention of mortality and morbidity.

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 6 months to 5 years. We included data from the first period only of cross-over studies. We considered studies for inclusion irrespective of publication status or language of publication. We excluded quasi-experimental studies, such as before-after designs and observational studies.

Post hoc, we included two studies in which participants were assigned using a quasi-random method (Herrera 1992; Stansfield 1993). In both cases, the authors and the editorial team agreed

that the methods of assignment (i) had the desirable characteristics of randomisation and (ii) were of no greater risk of bias than other included studies. For example, Stansfield 1993 used a random starting point and alternately assigned red or green pills. Participants received a single mega-dose of Vitamin A, so the people delivering the pills had no ongoing contact with participants; both selection bias and recruitment bias seem very unlikely.

Though the authors had access to the results of these studies, the decision to include them was made before data were extracted and before any analyses were undertaken. The search was comprehensive and we are not aware of any other studies similar to these two studies that could have been included in the review.

Types of participants

Children living in the community and aged 6 months to 5 years at the time of recruitment were eligible. Children in hospital and children with disease or infection were excluded.

We contacted trial authors if the study population included some participants who were not eligible for this review (for example, children over 5 years) and requested disaggregated data. If such data were not available, we included studies if the majority of participants (51%) met the inclusion criteria. If this could not be determined and the participants met the inclusion criteria on average (for example, the mean age was in the eligible range), then we included these trials.

Types of interventions

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

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

Types of outcome measures

The following outcomes were extracted. In studies reporting more than one measure of an outcome, measures were combined for meta-analysis using the methods described below (see Data synthesis).

Primary outcomes

All-cause mortality

Secondary outcomes

Cause-specific mortality due to:
- diarrhoea;
- measles;
- meningitis;
- lower respiratory tract infection (LRTI).

Cause-specific morbidity (i.e. incidence and prevalence):
- diarrhoea;
- measles;
- malaria;
- meningitis;
- lower respiratory tract infection (LRTI);
- Bitot's spots;
- night blindness;
- xerophthalmia.

Side effects (for example, vomiting or diarrhoea following supplementation).
Vitamin A deficiency status (serum retinol).

Search methods for identification of studies

Electronic searches

We searched CENTRAL (*The Cochrane Library* 2010, Issue 2), MEDLINE (1950 to April Week 2 2010), EMBASE (1980 to 2010 Week 16), Global Health (1973 to March 2010), Latin American Database (LILACS), metaRegister of Controlled Trials and African Index Medicus. All the searches were conducted on 27 April 2010.
The search strategies for each database are included in Appendix 1. Where possible, searches were limited to clinical trials involving human subjects, and were conducted without language restriction.

Searching other resources

To identify ongoing and unpublished trials, we used the World Health Organization International Clinical Trials Registry (IC-TRP), which searches multiple trial registries. Reference lists of reviews, included studies and excluded studies were searched for additional citations. We contacted organisations and researchers.

Data collection and analysis

Selection of studies

Two authors independently screened titles and abstracts for inclusion in the review (AI and KH). We resolved differences of opinion about suitability for inclusion by discussion and through consultation with a third author (EMW). Studies that met the screening criteria but did not meet the full inclusion criteria are listed in the Characteristics of excluded studies table with the reasons for exclusion.

Data extraction and management

We used a data extraction sheet to extract the following information from each study:
- year
- location (country, urban/rural);
- method of recruitment;
- inclusion criteria;
- unit of analysis; and
- risk of bias (see below).

Participants:
- socio-demographics (age, sex); and
- co-morbidities.

For each intervention and comparison group of interest:
- dosage;
- duration;
- frequency;
- co-intervention (if any).

For each outcome of interest:
- time points (i) collected and (ii) reported;
- definition;
- validity;
- unit of measurement (if relevant); and
- loss to follow-up.

Data from each eligible study were extracted independently by two people using Distiller software. Extraction was also done by a team at the Cochrane Editorial Unit (Toby Lasserson, Rachel Murphy and Karla Soares-Weiser), but there was always at least one extractor who was an author (AI, KH, YY, EMW). Discrepancies were resolved through discussion among the authors.
The main analyses included the longest reported follow-up in each study. Outcomes were also grouped by time (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

Two authors independently assessed the risk of bias associated with each included study using the Risk of Bias tool (Higgins 2008). For all studies, the following were assessed: sequence generation; allocation concealment; blinding of participants, providers and outcome assessors; incomplete outcome data; and selective outcome

reporting. We specifically looked for the possibility of performance bias (differential treatment of the intervention and control groups) and detection bias (for example, differential effort to locate death records for the intervention and control groups). Findings are discussed below and included in the Risk of Bias tables.

Measures of treatment effect

Morbidity was measured 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 respiratory tract infection (but not upper).

To avoid reviewer 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 reviewers. We extracted raw values (for example, means and standard deviations) rather than calculated effect sizes (for example, 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 contribute data (for example, incidence of measles), we gave preference to child-years, number with definite outcome known, and number randomised.

In the case of cluster RCTs, we (i) used adjusted estimates reported by the authors or (ii) used raw data and inflated the standard error (SE) using procedures described below.

Unit of analysis issues

In studies randomising units other than the individual (i.e. clusters), results should be presented with controls for clustering (for example, robust SEs or hierarchical linear models). We analysed clustered data using procedures outlined in Higgins 2008.

Where results did not control for clustering, we contacted authors to request an estimate of the intra-cluster correlation coefficient (ICC). If the authors were unable to provide an ICC, we used design effects calculated previously (Beaton 1993) to calculate the ICC, and we estimated the ICC for studies that did not publish a value (see below). For estimated values, we conducted sensitivity analyses using larger and smaller design effects to determine if the results were robust.

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.

Missing data are described, including dropouts and reasons for dropout where given. If data were missing for some cases, or if reasons for dropout were not reported, we contacted the authors. When analyses were reported for completers as well as controlling

for dropout (for example, imputed using regression methods), we extracted the latter.

Assessment of heterogeneity

Included studies were assessed for clinical heterogeneity by comparing the distribution of important factors, such as study participants, study setting, dose and duration of intervention and co-interventions. Methodological heterogeneity was assessed by comparing data included in the Risk of Bias tables. Statistical heterogeneity was assessed by visual inspection of forest plots, by performing the Chi^2 test (assessing the P value) and by calculating the I^2 statistic. If the P value was less than 0.10 and I^2 exceeded 50%, we considered heterogeneity to be substantial.

Assessment of reporting biases

To assess the possibility of small study bias, funnel plots were drawn for outcomes with 10 or more studies and random effects estimates were compared to the fixed effect estimate (see below).

Data synthesis

We performed meta-analysis using Review Manager Software Version 5 (RevMan 2008). When data were extracted in several formats that could not be combined directly in RevMan, we used the generic inverse variance option; data were entered into Comprehensive Meta-Analysis Version 2 and the log RR and SE were entered into RevMan.

All outcomes are reported with 95% confidence intervals (CI), and overall effects are weighted by the inverse of variance using a fixed-effect model; although there may be some differences across trials (for example, dose and population), the biological mechanism should be similar across trials and we will explore differences through analyses described elsewhere.

For dichotomous outcomes, we calculated the overall Risk Ratio (RR). For incidence data, Risk Ratio (events per child) and Rate Ratio (events per child-year) were combined because these ratios use the same scale and can be interpreted in the same way for these studies (the duration of studies was short, there was no interaction between the intervention and time at risk). In some cases, we estimated time at risk, as when authors reported incidence rate, duration of the study and number of children in the group.

For continuous outcomes we calculated Hedges *g*.

Subgroup analysis and investigation of heterogeneity

Effectiveness may differ across members of populations (for example, due to differences in baseline vitamin A status) and may be affected by other interventions (for example, immunisation or deficiency of other micronutrients). For example, neonatal VAS is thought to have different effects in Asia versus Africa (Klemm 2009). Unlike trial-level factors (such as dose), associations between individual-level moderators (such as vitamin A status) 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 the ecological fallacy (for example, lack of variation between studies would *not* indicate there was no variation within them). We included subgroups of age and gender; trials commonly report separate effects for these groups.

The following subgroup analyses were prespecified, and differences were tested using the Chi^2 test in RevMan:

1. Dose: Standard (up to 100,000 IU for children 6 to 11 months of age, and 200,000 IU for children 12 months to 5 years of age) versus High (greater than standard).

2. Frequency: High (doses within 6 months) versus Low (1 dose or 6+ month interval).

3. Location: Continent.

4. Age: 6 to 12 months versus 1 to 5 years.

5. Sex: males versus females.

Sensitivity analysis

Sensitivity analyses were performed as follows:

1) To test for bias, the primary analysis was repeated without studies at high risk of bias for sequence generation. To test for small study bias, the analysis was repeated using a random-effects model and funnel plots were drawn for all outcomes with 10 or more studies.

2) Imputed ICC (a post-hoc analysis described below).

3) Studies awaiting assessment (a post-hoc analysis described below).

R E S U L T S

Description of studies

Results of the search

Electronic searches identified 6683 citations; 4600 citations remained after duplicates were removed.

Additionally, we reviewed 129 studies from reference lists. There were 371 relevant citations, and all full texts were reviewed, see Figure 1.

Figure 1. Flow diagram for selection of studies
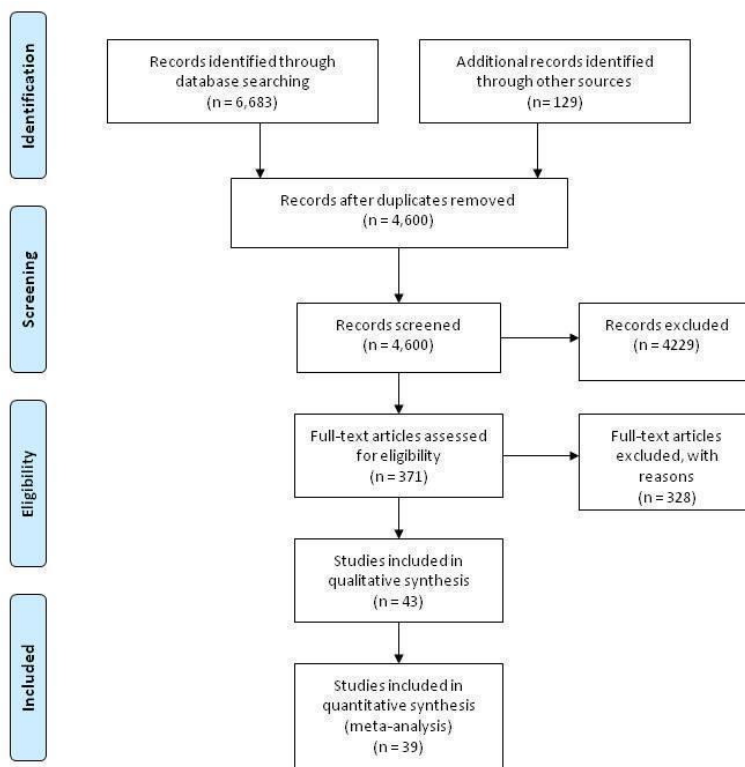
Included studies

Forty-three trials reported in 90 papers met the inclusion criteria, including factorial studies that were treated as two trials for meta-analysis (described below). More than one report was available for 16 (37%) trials. Where multiple reports existed for an included trial, we extracted data from all reports. Further information about individual studies is included in the Characteristics of included studies tables.

Thirty-nine trials (91%) reported data that could be included in a meta-analysis; four trials reported either outcomes that were not relevant to the review (Cherian 2003), or data that were not available by group (Lima 2010) or were incomplete (van Agtmaal 1988; Smith 1999).

Sample size

Trials assigned approximately 215,633 participants, with sample sizes ranging between 35 (van Agtmaal 1988) and approximately 29,236 (Sommer 1986), and a median sample size of 480. The 39

trials that could be analysed included 215,043 participants (99.7% of children included in the review).

The ten largest studies randomised about 200,214 children, 93% 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).

Comparisons

Six (14%) studies compared VAS to treatment-as-usual; 37 (86%) compared VAS to placebo. One large trial reported they did not use a placebo because it was forbidden by government (Sommer 1986).

Multiple trial arms

Twelve trials (28%) had multiple arms, 7 of which were relevant to the review (Reddy 1986; Florentino 1990; Benn 1997; Smith 1999; Rahman 2001; Long 2006; Lin 2009).

Four trials used factorial designs, combining vitamin A with other treatments such as zinc (Smith 1999; Rahman 2001; Long 2006) or deworming (Reddy 1986); data were extracted for comparisons that differed only in the provision of vitamin A (for example, vitamin A versus placebo; and vitamin A plus zinc versus zinc only). In one trial (Rahman 2001), raw data were not available and we could not identify outcome data for an eligible comparison. Different doses were combined in one study (Florentino 1990).

Unit of randomisation

Two studies (Herrera 1992; Stansfield 1993) randomised by household and we treated participants as if they were individually randomised. A sensitivity analysis was conducted for all-cause mortality, using ICCs of 0 and 0.01 for those studies in which the mean design effect was estimated.

Previously reported design effects from Beaton 1993 were used to calculate ICCs for clustered studies (Sommer 1986; Rahmathullah 1990; Vijayaraghavan 1990; West 1991; Daulaire 1992; Ross 1993 SURVIVAL). The ICCs were consistent around a value of 0.002. We imputed an ICC value of 0.002 for all studies in which clustering was not accounted for in the original analysis.

Allocation ratio

Participants were evenly allocated to the intervention and control groups in 35 studies (81%) and the number assigned to each group was unclear in 8 trials (19%) (Reddy 1986; Ross 1993 HEALTH; Ross 1993 SURVIVAL; Stansfield 1993; Biswas 1994; Dibley 1994; Ramakrishnan 1995; Pant 1996).

Location/setting

Trials were conducted in 19 countries: 27 (63%) in Asia, 15 of these in India; 7 (16%) in Africa; 7 (16%) in Latin America, and 2 (5%) in Australia. Sixteen (37%) of the studies were conducted in urban/peri-urban settings and 24 (56%) in rural settings, while three studies did not explicitly described their urban/rural setting.

Age

Average age was reported in 19 trials (44%). The median of the mean ages was 30.5 months.

Sex

Sex was reported in 32 trials (72%). The majority assigned approximately equal numbers of males and females. Three studies (Semba 1992; Ranjini 2001; Lin 2008) favoured males by more than 10%. The median study included 51% males.

Time

Outcomes measured at different times (0 to 12 months, 13 to 60 months, and 60 or more months) were collapsed for one overall analysis. Most studies lasted about a year, and dividing studies of similar length created potentially confusing/misleading subgroups. In the event that a single study reported data in more than one time point interval, the data from the longest interval was used in the overall analysis.

Excluded studies

After reviewing articles, 328 papers were excluded; eight nearly met the inclusion criteria, and reasons for exclusion are provided in Characteristics of excluded studies.

Studies awaiting assessment

Two trials could not be assessed at this time.

One trial (Aklamati 2006) was reported in a conference abstract. It appeared to meet the inclusion criteria, but reported impossible results. For example, the study included 36 children and reported an outcome of 1.2% of 17; though 1 child out of 17 is nearly 6%. We have contacted the authors for clarification and the study may be included in future versions of this review.

Importantly, one completed trial appears likely to meet the eligibility criteria and may be included in further updates of this review (DEVTA trial 2007). DEVTA is the largest randomised controlled trial ever conducted, including approximately one million children. That is, the trial included four times the combined participants of all included studies in this review. We contacted the authors of this trial several times prior to the completion of this review for information required to evaluate the conduct of the study and its outcomes. They provided an early analysis of the primary outcome, mortality, as well as cause-specific mortality and vitamin A serum level.

To assess how the results of DEVTA might impact the conclusions of this review, a sensitivity analysis was conducted. Due to lack of additional information, reasons for differences between this trial and other trials in the review could not be assessed.

Risk of bias in included studies

The risk of bias in each of the five domains was assessed for each study as High, Low or Unclear, see Figure 2.

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

Allocation

Sequence generation

All included studies were randomised or quasi-randomised controlled trials: 19 (44%) specified the method of randomisation and 16 (37%) were at Low risk of bias for sequence generation.

Three trials (7%) were at High risk of bias for sequence generation (Herrera 1992; Stansfield 1993; Arya 2000). These included 41,139 participants (19% of those included in the review).

One described assignment as random, but participants may have been assigned in order of arrival at hospital (Arya 2000).

Though technically quasi-random, we included two trials post hoc (Herrera 1992; Stansfield 1993) because the generation of the allocation sequence was not likely to result in systematically different groups. Given the design of the interventions and the placebos and steps to blind those administering the sequence, the reviewers do not think these studies are meaningfully different from randomised trials. In the first, participants were assigned alternately by household (Herrera 1992). The second used a random starting point and alternating distribution of red or green pills (Stansfield 1993). Lack of a truly random sequence was not related to other sources of bias (for example, performance bias) as 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, the decision to include these studies was made before data were extracted and before any analyses had been conducted; a sensitivity analysis was conducted (below) to determine if the decision had any impact on the results and it did not.

Allocation concealment

Allocation concealment is adequate when (i) trial staff and potential participants are unaware of assignments at the time of recruitment into the trial and (ii) the generation of the allocation sequence is protected from the influence of anyone aware of the participants' characteristics. Allocation concealment was coded as High risk of bias for only one study (Daulaire 1992) and Unclear for 27 studies (63%). In most 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.

Blinding

The intervention was conducive to blinding. Though there is some evidence that very large doses of vitamin A can lead to short-term side effects, participants and providers would not normally become aware of assignment after delivery of vitamin A in the form of pills, capsules or liquid solution. Efforts to blind participants and providers were described in 29 of the studies (67%), which were at Low risk of bias. In some trials, staff delivering the intervention also conducted assessments. Blinding of assessors was at High risk of bias in two studies (Daulaire 1992; Lin 2009) and Unclear in 14 (Reddy 1986; Sommer 1986; van Agtmaal 1988; Semba 1992; Agarwal 1995; Kartasasmita 1995; Stabell 1995; Pant 1996; Donnen 1998; Smith 1999; Ranjini 2001; Chowdhury 2002; Cherian 2003; Lin 2008).

In some trials, children interacted with researchers or clinicians who were aware of their assignment. Two studies (5%) were at High risk of performance bias, mostly because of failure to adequately blind staff, whereas 28 (65%) were at Low risk of performance bias. The reviewers 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 placebo rather than the reverse.

The review authors consider the primary outcome, mortality, is very unlikely to have been influenced by lack of blinding.

Incomplete outcome data

For incomplete outcome data, 23 trials (53%) were at Low risk of bias; 8 (17%) were at High risk of bias (van Agtmaal 1988; Kartasasmita 1995; Semba 1995; Pant 1996; Bahl 1999; Arya 2000; Chowdhury 2002; Cherian 2003) and 12 (28%) were Unclear (Sinha 1976; Reddy 1986; Sommer 1986; Vijayaraghavan 1990; West 1991; Ross 1993 HEALTH; Ross 1993 SURVIVAL; Agarwal 1995; Stabell 1995; Venkatarao 1996; Smith 1999; Ranjini 2001).

Missing data are much more likely to influence secondary analyses than the primary outcome. Results for all-cause mortality are known for 91% of randomised participants. Of the 17 studies (40%) that reported this outcome, 7 were Unclear, but 4 of these had minimal attrition (Vijayaraghavan 1990; Ross 1993 HEALTH; Ross 1993 SURVIVAL; Venkatarao 1996) and the others failed to report reasons for dropout. In 2 studies, missing data were not adequately handled (Pant 1996; Chowdhury 2002), but together these studies contributed only 5% to the pooled estimate.

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 5 (12%) trials appeared to be free of selective outcome reporting (Florentino 1990; Rahmathullah 1990; West 1991; Dibley 1994; Benn 1997). Twenty four (56%) were Unclear, while 14 (33%) were at High risk of bias (Pinnock 1988; van Agtmaal 1988; Vijayaraghavan 1990; Ross 1993 HEALTH;

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Ross 1993 SURVIVAL; Stansfield 1993; Ramakrishnan 1995; Pant 1996; Bahl 1999; Arya 2000; Cherian 2003; Lin 2008; Lin 2009; Lima 2010).

For the primary outcome, there is no meaningful risk of bias; the outcome was reported for large trials. Data were missing in small studies of short duration, which likely observed few deaths. For many of the secondary analyses, which included only a few trials representing a small proportion of the overall sample, adding unreported data might influence the observed effects.

Other potential sources of bias

Other potential sources of bias were extracted and are noted in the Characteristics of included studies tables, but none were likely to meaningfully influence the results of the review.

Effects of interventions

See: **Summary of findings for the main comparison**
Results for each outcome are presented below, the most important of which are described in Summary of findings for the main comparison.

Because most analyses contained a small number of studies, sensitivity analyses were restricted to the primary outcome.

Pneumonia and lower respiratory tract infection (LRTI) outcomes were combined post hoc. Pneumonia is a type of LRTI, and most of the studies did not test for pneumonia specifically (with a specific clinical criteria). In the event a study reported both pneumonia and LRTI outcomes, the LRTI outcome data were extracted for combination with other studies.

Not all subgroup analyses were conducted. For the primary outcome, only one study used a non-standard dose and this study also used a different frequency. Other analyses with more than 10 studies contained significantly fewer participants (for example, the analysis of serum level included less than 7000) and subgroup analyses for dose and frequency were not conducted because the analyses were clearly underpowered and any effects would be attributable to chance. Results of some of the attempted subgroup analyses are listed in Table 1.

1.0 All-cause mortality

Seventeen trials (Sommer 1986; Rahmathullah 1990; Vijayaraghavan 1990; West 1991; Daulaire 1992; Herrera 1992; Ross 1993 HEALTH; Ross 1993 SURVIVAL; Barreto 1994; Dibley 1994; Agarwal 1995; Pant 1996; Venkatarao 1996; Benn 1997; Donnen 1998; Chowdhury 2002; Lin 2008) contributed 194,795 children (90% of the children included in the review) in an overall analysis (using data from the last follow up for trials measuring outcomes multiple times). One reported no events (Lin 2008).

Vitamin A was associated with a 24% reduction in all-cause mortality (RR = 0.76 (95% CI 0.69 to 0.83)), though there was moderate heterogeneity (Chi² = 29.10, df = 15 (P = 0.02); I² = 48%) Figure 3.

Figure 3. Forest plot of comparison: 1 Vitamin A versus Control, outcome: 1.1 Mortality (all-cause) at Longest Follow-up.
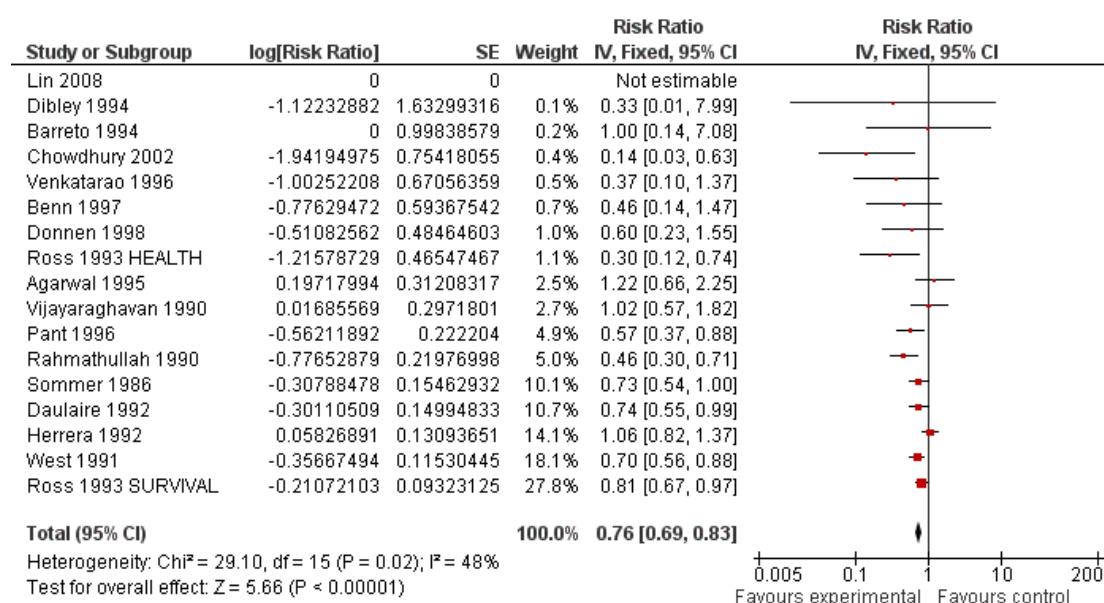
The effect during the first year of life was similar (RR = 0.82 (95% CI 0.74 to 0.91)), but the statistical heterogeneity was substantial (Chi² = 33.85, df = 11 (P = 0.0004); I² = 67%). Only 5 trials (7%) measured mortality between 13 and 60 months, and the effect was similar (RR = 0.75 (95% CI 0.64 to 0.88)) with moderate and significant statistical heterogeneity (Chi² = 9.29, df = 4 (P = 0.05); I² = 57%).

Subgroup analyses

1. Dose and frequency

Only one study reporting all-cause mortality did not use the standard dose recommended by WHO. Rahmathullah 1990 used weekly dose for 52 weeks. The planned subgroup analysis was not conducted.

2. Location

Eleven trials were conducted in Asia (RR = 0.69 (95% CI 0.61 to 0.79)), 5 in Africa (RR = 0.85 (0.73 to 0.98)), and 1 in Latin America (RR = 1.00 (0.14 to 7.08)). These were not significantly different (P = 0.12, see Table 1).

3. Age

Four trials (Rahmathullah 1990; West 1991; Daulaire 1992; Benn 1997) reported separate effects for children aged 6 to 12 months (RR = 0.59 (95% CI 0.43 to 0.82)) and children aged 1 to 5 years (RR = 0.68 (0.57 to 0.81)); the subgroups did not differ significantly (P = 0.46). Notably, both effect estimates are larger than the overall result from 17 trials reporting mortality.

4. Sex

Five trials (Sommer 1986; West 1991; Daulaire 1992; Herrera 1992; Lin 2008) reported separate effects for males (RR = 0.80 (95% CI 0.66 to 0.97)) and females (RR = 0.79 95% CI 0.65 to 0.95)), which were not significantly different (P = 0.89). Notably, both effect estimates are larger than the overall result from 17 trials reporting mortality.

Sensitivity analyses

1. Bias

Of the trials 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 these trials were not likely to influence the results in a positive direction.

To test for small study bias, we repeated the analysis using a random-effects model. The overall estimate was slightly larger than the fixed-effect estimate, suggesting that heterogeneity is partially explained by small studies reporting larger effects (RR = 0.71 (0.61 to 0.84)).

There was some evidence of visual asymmetry on the funnel plot we produced, but the overall effect was strongly influenced by five studies that accounted for over 80% of the weighted mean; even if the result was influenced by small study bias, the magnitude of the effect was small. To impact the results, missing studies would need to be very large and show no difference or harmful effects, as demonstrated in the third sensitivity analysis.

2. Design effects in cluster trials

Known ICCs were remarkably consistent. For three studies for which the ICC was not known, we estimated ICC = 0.002 and we adjusted SEs using this value and the average 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 = 0.81 (95% 0.75 to 0.89)). The effect was virtually unchanged when we increased the ICC to 0.01 (RR = 0.75 (95% CI 0.68 to 0.83)), 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.

3. Studies awaiting assessment

One study awaiting assessment was added to the analysis (DEVTA 2007). This trial found no significant effect of VAS on mortality (RR = 0.96 (95% CI 0.89 to 1.03)).

In our analysis of 18 trials, DEVTA 2007 accounted for 65.2% of the combined effect, which remained significant (RR = 0.88 (95% CI 0.84 to 0.94)) with substantial and significant heterogeneity (Chi² = 44.31, df = 16 (P = 0.0002); I² = 64%). (We assumed the study authors adjusted for clustering. As the results were not significant, inflating the SE would not change our interpretation of the trial's results, although it would decrease its weight in the analysis.)

Including DEVTA 2007 decreased the estimated benefit of Vitamin A by half (24% to 12%), but the result remained significant and clinically meaningful. As we were unable to assess the trial, we cannot explain this substantially different result.

2.0 Diarrhoea mortality

Seven trials (Rahmathullah 1990; Daulaire 1992; Herrera 1992; Ross 1993 SURVIVAL; Agarwal 1995; Venkatarao 1996; Chowdhury 2002) reported a combined 28% reduction in diarrhoea mortality (RR = 0.72 (95% CI 0.57 to 0.91)) with no important heterogeneity (Chi² = 6.12, df = 6 (P = 0.41); I² = 2%), Figure 4.

Figure 4. Forest plot of comparison: 1 Vitamin A versus Control, outcome: 1.5 Mortality due to Diarrhoea at Longest Follow-up.

3.0 Measles mortality

Five trials (Rahmathullah 1990; Daulaire 1992; Herrera 1992; Ross 1993 SURVIVAL; Agarwal 1995) reported a lower risk of measles mortality, but the effect was not statistically significant (RR = 0.80 (95% CI 0.51 to 1.24)). There was no important heterogeneity (Chi² = 0.40, df = 4 (P = 0.98); I² = 0%), Figure 5.

Figure 5. Forest plot of comparison: 1 Vitamin A versus Control, outcome: 1.6 Mortality due to Measles at Longest Follow-up.
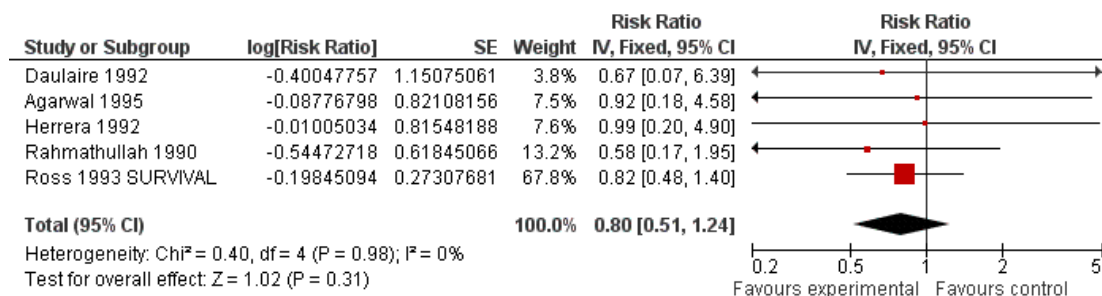
4.0 Meningitis mortality

Three trials (Ross 1993 SURVIVAL; Agarwal 1995; Chowdhury 2002) reported a lower risk of meningitis mortality, but the effect was not statistically significant (RR = 0.57 (95% CI 0.17 to 1.88)). There was no important heterogeneity (Chi² = 0.75, df = 2 (P = 0.69); I² = 0%).

5.0 Lower Respiratory Tract Infection (LRTI) mortality

Seven trials (Rahmathullah 1990; Daulaire 1992; Herrera 1992; Ross 1993 SURVIVAL; Agarwal 1995; Venkatarao 1996; Chowdhury 2002) reported a lower risk of LRTI mortality, but the effect was not statistically significant (RR = 0.78 (95% CI 0.54 to 1.14)). There was no important heterogeneity (Chi² = 7, df = 6 (P = 0.32); I² = 14%).

6.0 Diarrhoea

Thirteen trials (Florentino 1990; Herrera 1992; Cheng 1993; Barreto 1994; Biswas 1994; Dibley 1994; Ramakrishnan 1995; Venkatarao 1996; Sempertegui 1999; Shankar 1999; Arya 2000; Chowdhury 2002; Long 2007) reported an 18% decrease in diarrhoea incidence (RR = 0.85 (95% CI 0.82 to 0.87)), though statistical heterogeneity was substantial and highly significant (Chi² = 218.62, df = 11 (P < 0.00001); I² = 95%), Figure 6.

Figure 6. Forest plot of comparison: 1 Vitamin A versus Control, outcome: 1.9 Diarrhoea Incidence at Longest Follow-up.
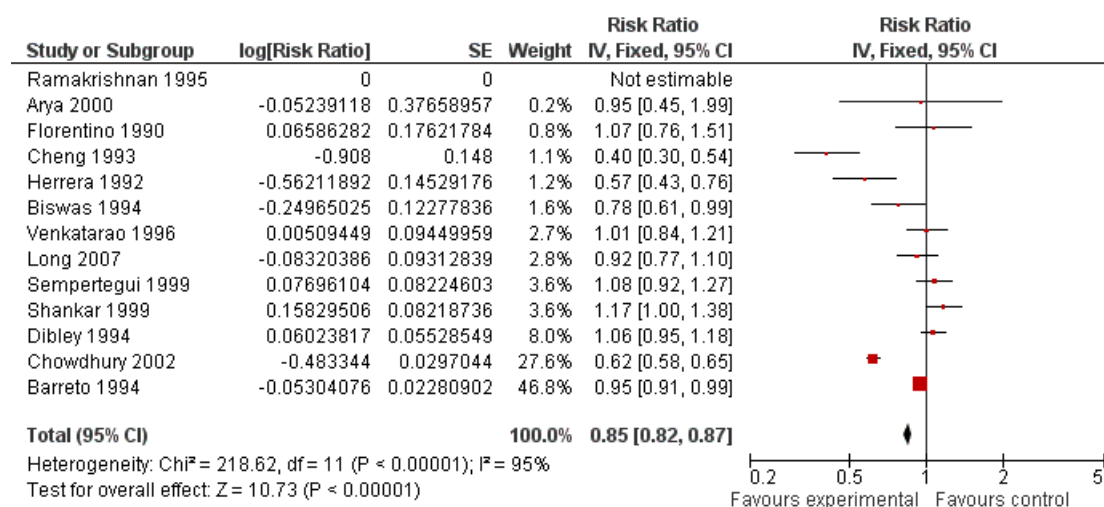
The results of this analysis were highly heterogenous and two studies account for the majority of the overall effect (Cheng 1993; Chowdhury 2002). The observed heterogeneity may be due to measurement error or differences in the effects of VAS across populations and settings. For example, it may reduce susceptibility to particular infections that are prevalent in some places but not others.

Two trials (Stansfield 1993 and Long 2006/Long 2006 (2)) reported no combined effect on diarrhoea prevalence (RR = 1.08 (95% CI 1.05 to 1.12)) though statistical heterogeneity was substantial and highly significant (Chi² = 15.76, df = 2 (P = 0.0004); I² = 87%).

Sensitivity analysis

1. Bias

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 result bordered on statistical significance, suggesting that heterogeneity is not explained by small studies reporting larger effects (RR = 0.85 (95% CI 0.72 to 1.00)).

The funnel plot we produced was dominated by two studies accounting for 74% of the overall effect, and the plot was relatively flat.

2. Design effects in cluster trials

No ICCs were imputed, so sensitivity analysis was not required.

7.0 Measles

Six trials (Herrera 1992; Barreto 1994; Semba 1995; Benn 1997; Bahl 1999; Chowdhury 2002) reported a 50% decrease in measles incidence (RR = 0.50 (95% CI 0.37 to 0.67)) with no important heterogeneity (Chi² = 0.55, df = 5 (P = 0.99); I² = 0%), Figure 7.

Figure 7.   Forest plot of comparison: 1 Vitamin A versus Control, outcome: 1.12 Measles Incidence at Longest Follow-up.
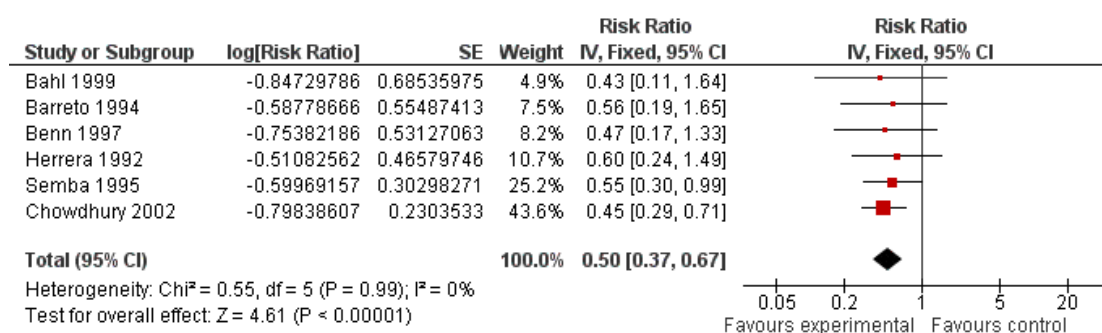
No trials reported data on measles prevalence that could be analysed at follow-up.

8.0 Malaria

One trial (Shankar 1999) reported a 27% reduction in malaria incidence (RR = 0.73 (95% CI 0.60 to 0.88)).
Two trials (Ross 1993 HEALTH; Ross 1993 SURVIVAL) reported data on malaria prevalence; the combined effect was not statistically significant (RR = 0.72 (0.42 to 1.23)) and there was no important heterogeneity (Chi² = 0.03, df = 1 (P = 0.87); I² = 0%). Only one study reported data on malaria prevalence that could be analysed at follow- up, the results of which were not significant (RR = 0.73 (0.41 to 1.28)).

9.0 Meningitis

No trials reported data on meningitis incidence or prevalence that could be analysed at follow-up.

10.0 Lower Respiratory Tract Infection

Nine trials (Rahmathullah 1990; Cheng 1993; Barreto 1994; Biswas 1994; Kartasasmita 1995; Venkatarao 1996; Sempertegui 1999; Chowdhury 2002; Long 2007) reported no combined effect on LRTI incidence (RR = 1.14 (0.95 to 1.37)) with no important heterogeneity (Chi² = 7.66, df = 6 (P = 0.26); I² = 22%). LRT prevalence was reported in a factorial trial (Long 2006) with two relevant comparisons; the combined result of which was inconclusive but suggests benefit (RR = 0.46 (95% CI 0.21 to 1.03)).

11.0 Vision

11.1 Bitot's spots

One trial (Herrera 1992) reported no effect on Bitot's spots incidence (RR = 0.93 (95% CI 0.76 to 1.14)).
Four trials (Sinha 1976; Sommer 1986; West 1991; Pant 1996) reported a 53% reduction in Bitot's spots prevalence (RR = 0.45 (95% CI 0.33 to 0.61)) with substantial and significant heterogeneity (Chi² = 8.25, df = 3 (P = 0.04); I² = 64%).

11.2 Night blindness

One trial (Herrera 1992) reported a 47% reduction in night blindness incidence (RR = 0.53 (95% CI 0.28 to 0.99)).

Two trials (Sommer 1986; West 1991) reported a 68% reduction night blindness prevalence (RR = 0.32 (95% CI 0.21 to 0.50)) with no heterogeneity (Chi² = 0.19, df = 1 (P = 0.66); I² = 0%).

11.3 Xerophthalmia

Three trials (West 1991; Herrera 1992; Barreto 1994) reported no combined effect on xerophthalmia incidence (RR = 0.85 (95% CI 0.70 to 1.03)), though statistical heterogeneity was substantial and significant (Chi² = 2.69, df = 1 (P = 0.10); I² = 63%).

Two trials (Sommer 1986; West 1991) reported a 69% reduction in xerophthalmia prevalence (RR = 0.31 (95% CI 0.22 to 0.45)) with no statistical heterogeneity (Chi² = 0.22, df = 1 (P = 0.64); I² = 0%).

12.0 Vitamin A deficiency

12.1 Number deficient

Four trials (Ross 1993 HEALTH; Dibley 1994; Shankar 1999; Ranjini 2001) reported a 29% reduction in the number of VAD children (RR = 0.71 (95% CI 0.65 to 0.78)); however, statistical heterogeneity was substantial and significant (Chi² = 13.58, df = 3 (P = 0.004); I² = 78%).

12.2 Serum level

Thirteen studies (Pinnock 1986; Reddy 1986; Pinnock 1988; Semba 1992; Cheng 1993; Ross 1993 HEALTH; Ross 1993 SURVIVAL; Dibley 1994; Kartasasmita 1995; Sempertegui 1999; Shankar 1999; Ranjini 2001; Lin 2009) reported vitamin A serum data at follow- up, including one factorial study contributing two comparisons. Vitamin A serum levels were higher in the Vitamin A group (SMD = 0.31 (95% CI 0.26 to 0.36)), however statistical heterogeneity was substantial and significant (Chi² = 270.23, df = 13 (P < 0.00001); I² = 95%).

Sensitivity analysis

1. Bias

No studies in this outcome 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 (RR = 0.53 (95% CI 0.27 to 0.79)).

The funnel plot that we produced was highly asymmetrical.

2. Design effects in cluster trials

No ICCs were imputed, so sensitivity analysis was not required.

13.0 Hospitalisation

One trial (Ross 1993 HEALTH) reported a reduction of the likelihood of hospitalisations that approached statistical significance (RR = 0.64 (95% CI 0.40 to 1.02)) and a 38% reduction in the number of hospitalisations (RR = 0.62 (95% CI 0.42 to 0.93)). One trial (Cheng 1993) reported inconclusive evidence on diarrhoea related hospitalisation (RR = 0.25 (95% CI 0.01 to 6.11)). One trial (Cheng 1993) reported inconclusive evidence on LRTI hospitalisation (RR = 0.11 (95% CI 0.01 to 2.06)).

14.0 Side effects

We assessed two short-term side effects:

14.1 Vomiting (within 48 hours)

Three trials (Sinha 1976; Florentino 1990; Arya 2000) reported a significant increase in risk of vomiting (RR = 2.75 (95% CI 1.81 to 4.19)) with statistical heterogeneity that was not important (Chi² = 2.53, df = 2 (P = 0.28); I² = 21%). Immediately following the intervention, the rate of vomiting increased from 2% to 6%.

14.2 Fontanelle

Three trials (Stabell 1995; Bahl 1999; Arya 2000) reported fontanelle side effects, but only one could be analysed because the others reported insufficient data, which reported no effect (RR = 5.00 (95% CI 0.24 to 103.72)). Most studies included children over 1 year old and would not have assessed this side effect.

Results not contained in the Data and Analyses section are listed below in Table 1.

DISCUSSION

Summary of main results

Vitamin A supplementation appeared to reduce all-cause mortality by 24%. There was some statistical heterogeneity in the pooled data.

Much of the reduction in all-cause mortality is explained by reductions in death due to diarrhoea and measles, although many of the cause-specific mortality and morbidity outcomes were characterised by uncertainty. The overall effect for measles mortality was not significant, but the trend was consistent with the overall results and the therapeutic effects of VAS in reducing measles related mortality and morbidity are well established (Yang 2009).

Furthermore, VAS resulted in a reduced incidence of diarrhoea and measles. Other reviews have shown that the therapeutic use of VAD may prevent acute diarrhoea from becoming chronic (Imdad 2010). 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.

Some authors hypothesise that the preventive effect of VAS against infections is related to increased responsiveness to vaccines given around these times, especially in infants (Benn 2003). This has been recently challenged (Kirkwood 2010) and a meta-regression of studies does support the direction of overall effect (Rotondi 2010). A more detailed discussion about this hypothesis is available in the review on neonatal VAS by our group (Haider 2008).

The current review did not locate any trials that compare different co-interventions; policy makers and practitioners should use other types of studies to assess how the delivery and responsiveness to vitamin A might relate to other nutritional and health interventions.

Few studies reported data about side effects, including vomiting, bulging fontanelle and diarrhoea soon after receiving the intervention. VAS may increase short-term vomiting by 4%.

Overall completeness and applicability of evidence

This is the first published review to assess systematically both mortality and morbidity associated with VAS. Other outcomes relevant to VAS, including stunting, could be added to future versions, but few studies have measured these effects. Nonetheless, observed effects on morbidity suggest that vitamin A may improve overall health, and observational studies might examine the nature of this relationship.

All included studies reporting all-cause mortality were conducted in developing countries. The results appear applicable to developing countries with chronic VAD. The primary analysis is based on many large trials from several countries and locations. It included 90% of the children randomised in this review; risk of selective outcome reporting appears minimal. Statistical heterogeneity suggests 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 vitamin A rich food. 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. Future versions of this review might investigate if VAS reduces both mild and severe episodes of diarrhoea, as the latter are more closely linked to mortality. A few trials have measured malaria mortality, which was not included in the review protocol; this outcome should be added to future versions of the review.

All included studies reporting all-cause mortality were conducted in low- and middle-income countries. The results appear applicable to all such countries with chronic VAD.

Analyses for many of the cause-specific mortality and morbidity outcomes were consistent. A general weakness of many interventions is the underreporting 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 (discussed previously in the context of performance bias), 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.

Some readers will undoubtedly find these results unsatisfying, particularly because the review does not explain heterogeneity in the results. This review suggests some ways in which vitamin A might work, but it does not describe how effects of vitamin A might differ across subpopulations because trials did not report the data required for such analyses. We decided a priori not to include subgroup analyses based on individual-level moderators for reasons described above; we could not have done much more using study-level data. 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. Subgroup analyses by geographical region include few studies; a few studies disaggregated data by gender and age, but these were not representative of the studies overall and 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 patient 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. Furthermore, the observed effects are so large that heterogeneity may be considered unimportant; vitamin A should be given to children whether it reduces childhood mortality by 5% or 25%.

Quality of the evidence

The review included 43 studies and an estimated 215,633 children. This is the largest review of VAS for children to date.

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 6 to 59 months in the developing world. 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.

The DEVTA trial 2007, which includes more than four times the number of children in this review, found no benefit for vitamin A supplementation. However, details that might explain this difference were not available. It is possible that these relatively smaller studies were more prone to bias, but the reviewers find this explanation unlikely to explain the effect in its entirety. When the mortality data for DEVTA trial 2007 are included in the main analysis of this review, a statistically significant benefit for vitamin A is still observed, and that effect remains clinically meaningful.

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 subgroup and sensitivity analyses to explore heterogeneity that were specified a priori. Post-hoc decisions to include quasi-randomised trials and post-hoc analyses are noted, and sensitivity analyses demonstrate that these did not change the results. 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 make a difference in this review are very likely to be published. One study awaiting assessment is likely to be published soon (DEVTA trial 2007), and another was too small to affect any analysis (Aklamati 2006). The inclusion of DEVTA in a sensitivity analysis reduces the threat of publication bias and provides evidence that the main finding is robust.

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

These 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; Beaton 1993, a 23% reduction, and Fawzi 1993 used an odds ratio rather than risk ratio as the effect statistic so the reported reduction is not directly comparable.

This review contributes a timely update to the status of the evidence; most previous meta-analyses were conducted before publication of the trials contributing 30% of randomised children in the primary analysis. This effect was explored in a post-hoc cumulative meta-analysis which sorted the included trials by year. As reported in Beaton 1993, there was a 23% reduction in all-cause mortality by 1993 (RR = 0.77 (95% CI 0.70 to 0.85)). The trials that occurred after 1993 change the effect by only 1%.

AUTHORS' CONCLUSIONS

Implications for practice

National and regional programmes of VAS are in place in over 70 countries worldwide and may be among the most cost-effective public health interventions (Fawzi 2006). Worldwide, more than 190 million children are vitamin A deficient; reducing their risk of mortality by 24% could save almost 1 million lives per year. These interventions respond to an immediate need for adequate nutrition, but they are not ideal long-term solutions to the underlying problem.

Fortification, food distribution programs 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 the orange-fleshed sweet potato (Klemm 2010). Furthermore, if vitamin A reduces mortality by preventing measles, widespread vaccination will reduce the relative contribution of vitamin A supplementation. 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.

We strongly recommend vitamin A supplementation to children under 5 in areas at risk of VAD. The exact nature of how these programs should be structured and administered - the dose, frequency, and duration of intervention - are less certain. As discussed above, data on implementation for the trials included in this review (and more generally) are lacking. In the absence of this information, concrete recommendations for practice would be speculative at best. Comparative trials may be informative and policymakers should consider including such trials in plans for vitamin A distribution.

Implications for research

The effectiveness of VAS for preventing mortality is well-established. The primary result in this review is not meaningfully dif-

ferent from the results of reviews conducted in 1993. Not all studies conducted in the interim were required, and 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 (for example, vomiting).

Reductions in mortality are likely related to reduced incidence and severity of diarrhoea. 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 have been studied rarely. 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, and serum results are more vulnerable to bias than the overall results. Serum level may be a poor indicator of status, and may not be related to more meaningful outcomes like mortality and blindness. On the other hand, oral 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 have recently investigated the effects of vitamin A during the neonatal period (Haider 2008) and for infants 1 to 6 months of age (Gogia 2008) and will be available shortly. Further reviews might investigate different delivery channels, including food supplementation, 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 (for example, 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

Methods	Cluster randomised trial conducted in Uttar Pradesh, India, Asia
Participants	All children below 6 years of age were eligible for inclusion in the trial. Children with xerophthalmia were excluded A total of 16 clusters (subcentres) were randomly selected. Four subdivisions (4 subcentres in each) were made and drugs A (vitamin A) and B (placebo) distributed in two each randomly. It was found at the end of the study that by mistake vitamin 'A' was distributed in 3 subdivisions (12 subcentres) and placebo in 1 only (4 subcentres). A total of 17,778 children were approached but only 15,247 children were included in the final analysis based on the fact that they received at least 1 dose of vitamin A
Interventions	Children in experimental group received vitamin A along with small amounts of vitamin E. The dosages were 50,000 IU of vitamin A and 10 IU of vitamin E for children 1-6 months and 100,000 IU of vitamin A and 20 IU of vitamin E for children 7-72 months. The intervention was delivered every 4 months and continued for 12 months
Outcomes	All-cause and cause specific mortality of diarrhoea, pneumonia, measles and meningitis
Notes	The trial was conducted in two phases. First phase consisted of 15 months i.e. 3 months for registration and 12 months for intervention and measurement of relevant outcomes. In second phase, mortality was measured in a sub-sample of initially included children exactly after 12 months of termination of first phase. The cause of death was assigned by using a verbal autopsy tool. Baseline mortality rates for children below 6 years of age were 27. 7 and 23.3 per 1000 for intervention and control group respectively and was significantly different in two 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
Adequate sequence generation?	Unclear risk	"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" Authors do not specify the method of sequence generation.
Allocation concealment?	Unclear risk	Insufficient information to permit judgment.
Blinding? Blinding of Participants	Unclear risk	Insufficient information to permit judgment.

Agarwal 1995 *(Continued)*

Blinding? Blinding of provider	Unclear risk	Insufficent information to permit judgment.
Blinding? Blinding of outcome assessor	Unclear risk	Insufficent information to permit judgment.
Incomplete outcome data addressed?	Unclear risk	Insufficent information to permit judgment.
Free of selective reporting?	Unclear risk	Insufficent information to permit judgment.
Free of other bias?	Unclear risk	Insufficent information to permit judgment.

Arya 2000

Methods	Individually randomised trial conducted in New Delhi, India, Asia
Participants	Infants age 9-12 months attending immunisation clinic of Safdurjung hospital in New Delhi were eligible for inclusion in the trial. Sick infants requiring hospitalisation were excluded A total of 256 infants were enrolled in the study with equal numbers (i.e. 128) in vitamin A and placebo group. Mean age of participants was 9 months
Interventions	The experimental group received a single dose of 100 000 IU of vitamin A in Archis oil. The control group received placebo in peanut oil. Both vitamin A and placebo were administered at the time of measles vaccination. At the 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 motions, fever, irritability, bulging fontanelle
Notes	Study participants were not significantly different in sex, age and weight distribution and nutritional status at the baseline. The baseline prevalence of vomiting, loose stools, fever and irritability during 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
Adequate sequence generation?	High risk	"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." Probably not done.

Arya 2000 (*Continued*)

Allocation concealment?	Unclear risk	Children were randomised according to their entry into hospital
Blinding? Blinding of Participants	Low risk	"This double-blind, randomised, ... supplied in small dark bottles marked '1' and '2'."
Blinding? Blinding of provider	Low risk	"This double-blind, randomised, ... supplied in small dark bottles marked '1' and '2'."
Blinding? Blinding of outcome assessor	Low risk	"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 addressed?	High risk	A total of 39 (15.2%) infants were lost to follow-up with similar distribution in both the groups. Reasons for loss to follow-up not given
Free of selective reporting?	High risk	Methods describe that the clinicians did physical examinations and recorded weight, nutritional status, any signs of vitamin A deficiency, heart rate, respiratory rate, temperature and systemic examination especially neurological examination including the state of the fontanelle, reflexes, motor and sensory functions, etc. But bulging fontanelle not reported as an outcome, neither other variables mentioned in the results
Free of other bias?	Low risk	No other apparent bias was noted in the study.

Bahl 1999

Methods	This individually randomised study was conducted in an urban slum of Delhi, India, Asia
Participants	Infants aged 6-9 months were identified and enrolled into study when they became 9 months old. Those infants were excluded who had a previous history of measles, contact with a case of measles or measles immunisation, or if they had received a dose of vitamin A in the previous 4 months. Participants with serious illness requiring hospitalisation or having clinical signs of vitamin A deficiency (i.e. xerophthalmia, Bitot's spots etc.) were also excluded A total of 618 infants were enrolled and randomised either to vitamin A (309) or placebo group (309). 50% of study population consisted of male infants

Bahl 1999 (*Continued*)

Interventions	Participants in intervention group were given a single dose of 30 mg (100 000 IU) of vitamin A in the form of retinol palmitate and control group received soybean oil as placebo. Children were followed for four months
Outcomes	Antibody response to measles vaccine. Incidence of measles during study period and side effects like vomiting, drowsiness etc in first 48 hours were also reported
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 titers between the two groups at three months after the administration of intervention. The baseline prevalence of clinical vitamin A deficiency in children 1-5 years in study area was 3.5% and that of biochemical vitamin A deficiency of 37%

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	"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." Probably done.
Allocation concealment?	Unclear risk	Insuffcent information to permit judgment.
Blinding? Blinding of Participants	Low risk	"This scheme ensured that all infants received 30 mg vitamin A by 12 mo of age without interfering with the double-blind design of the study." Probably done.
Blinding? Blinding of provider	Low risk	Adequate masking of vitamin A and placebo should have meant that providers were adequately blinded
Blinding? Blinding of outcome assessor	Low risk	Adequate masking of vitamin A and placebo should have meant that outcome assessors were adequately blinded
Incomplete outcome data addressed?	High risk	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

Bahl 1999 (*Continued*)

		the results. The investigators state that the reason for their exclusion is that a follow-up serum sample could not be ascertained
Free of selective reporting?	High risk	Data on harms are incompletely disclosed in the study report
Free of other bias?	Low risk	This study appears to be free of other bias.

Barreto 1994

Methods	Individually randomised trial conducted in Serrinha, Brazil, Latin America
Participants	Children aged 6 to 48 months were eligible for inclusion in the trial. Exclusion criteria was presence of xerophthalmia or measles infection within the previous 30 days. Children who received a high dose of vitamin A supplementation in the previous 6 months or had weight-for-age less than 60% of the statistical median were also excluded A total of 1240 children were included, 620 in vitamin A group and 620 in placebo. Mean age of participants was 28 months and the proportion of males was 52%
Interventions	The experimental group received vitamin A in a dose of 100,000 IU for children younger than 12 months and 200,000 IU for the older. The control group received placebo only. The intervention was 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	The study area had inadequate pubic health services. A previous survey in the area showed biochemical deficiency (serum vitamin A concentration < 0.35 mmol/L) rate of 7.4% in children of this age group. According to WHO criteria, vitamin A deficiency should be considered a pubic health problem in this area. The surveillance for morbidity outcome was done 3 times per week for 1 year, so the recall period was 48 to 72 hours. We took data for incidence of measles and xerophthalmia from account of attrition in 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
Adequate sequence generation?	Unclear risk	"Children were randomly assigned to receive vitamin A or placebo four times-at the start of the trial and every 4 months thereafter." Authors do not specify the method of sequence generation.
Allocation concealment?	Low risk	"...only an external investigator had the codes for the individually wrapped and numbered capsules."

Barreto 1994   (*Continued*)

		Although specific details were not disclosed, the available information suggests that allocation was adequately concealed
Blinding? Blinding of Participants	Low risk	"The gelatinous capsules of vitamin A and placebo (supplied by Hoffman La Roche) were identical in appearance and were unwrapped just before administration." The study was double-blind, with identical presentation and dosing of vitamin A and placebo
Blinding? Blinding of provider	Low risk	"The gelatinous capsules of vitamin A and placebo (supplied by Hoffman La Roche) were identical in appearance and were unwrapped just before administration." Probably done.
Blinding? Blinding of outcome assessor	Low risk	"The study was kept double-blind and only an external investigator had the codes for the individually wrapped and numbered capsules." 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 addressed?	Low risk	"The total loss in follow-up time was 10. 3%, equally distributed between the study groups." The rate of attrition was balanced between the two treatment groups, and was primarily attributable to migration. On that basis, attrition bias is not likely to have impacted on the results of the review
Free of selective reporting?	Unclear risk	The protocol for the study was not available and as such, this aspect of the reporting of the study could not be assessed
Free of other bias?	Low risk	This study appears to be free of other potential bias.

Benn 1997

Methods	Individualy randomised trial conducted in Belem and Mindra, two districts in Bissau, the capital of Guinea-Bissau, Africa
Participants	Infants aged 6-9 months were eligible for inclusion in the trial. Those with signs of xerophthalmia, history of previous vitamin A supplementation, history of measles infection before age 9 months or who had a positive haemagglutinin-inhibition assay (HIA) titre at age 9 months, were excluded. All infants reported to have had measles between 9 to 18 months of age were also excluded A total of 462 infants were randomised to either intervention or control group. The mean age of participants was 8.7 months and proportion of males was 51%
Interventions	There were three study groups: Group 1: included "infants aged 6 months and were 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" Group 2: consisted of "infants who were 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 vaccine doings with a placebo as the supplement" Group 3: included "Infants who were older than 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. They were included in the study at age 9 months and received a measles vaccine plus vitamin A or placebo supplement at that age Vitamin A was supplemented in a single dose of 100 000 IU dissolved in 1 ml of vegetable oil along with 40 IU of vitamin E. The placebo group received 40 IU of vitamin E dissolved in vegetable oil
Outcomes	Antibody response to measles vaccine, all-cause mortality, incidence of measles
Notes	The primary objective of the 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. It was concluded from the study that simultaneous administration of measles vaccine and vitamin A has no negative effect on measles immunity. Similarly vitamin A supplementation was shown to have no significant effect on immune response of CD4 and CD8 T-cell in children without clinical vitamin A deficiency. Please note that vitamin A or placebo was given only at 9 months of age in all three study groups. The only difference among the groups was the frequency and type of vaccine administered. We therefore added all the numbers for all three 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
Adequate sequence generation?	Low risk	"The allocation sequence was computer generated."

Benn 1997 *(Continued)*

Allocation concealment?	Low risk	"The allocation sequence was kept in sealed envelopes and only released when all clinical laboratory analyses were completed."
Blinding? Blinding of Participants	Low risk	Identical presentation: "...because of the young age of the participants, any difference in taste was irrelevant..." Probably adequate.
Blinding? Blinding of provider	Low risk	"None of the staff involved knew whether the bottles contained vitamin A or placebo. .."
Blinding? Blinding of outcome assessor	Low risk	"None of the staff involved knew whether the bottles contained vitamin A or placebo. .." Masking of treatment group assignment and treatment to study personnel likely to have been maintained throughout
Incomplete outcome data addressed?	Low risk	Number lost to follow-up and those excluded were explicitly described and was 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
Free of selective reporting?	Low risk	Some evidence of selective outcome reporting around malaria; however, deaths and prevalence of measles reported
Free of other bias?	Unclear risk	Authors report 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

Methods	This study was an individual randomised, placebo-controlled trial conducted in Gobinda-Khatick slum area of eastern Calcutta, India, Asia
Participants	Children aged 12-71 months were eligible for inclusion in the study. Participants with signs of vitamin A deficiency (for example, xeropthalmia) were excluded A total of 180 children were randomised either to vitamin A or placebo group. Mean age of children and proportion of males were not specified in the study

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Biswas 1994   *(Continued)*

Interventions	The experimental group received 200 000 IU of vitamin A in the form of retinyl palmitate. The control group received placebo. Only a single dose of intervention was administered and children were followed for 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 done fortnightly. For respiratory disease morbidity, we took data for lower respiratory tract infection only

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Block randomisation by age and weight: "For each strata, a restricted randomisation list was prepared (...) a random permutated block of block length 6 was used." Probably done.
Allocation concealment?	Low risk	"...randomisation was done by a pharmacist of the drug manufacturing company." Assuming that the pharmacist was independent of the study team this was probably adequate
Blinding? Blinding of Participants	Low risk	"...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? Blinding of provider	Low risk	"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? Blinding of outcome assessor	Low risk	"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."

Biswas 1994 (*Continued*)

Incomplete outcome data addressed?	Low risk	"....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)." Attrition was low and reported not to relate to treatment.
Free of selective reporting?	Unclear risk	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. One child died and the treatment group assignment was not disclosed
Free of other bias?	Low risk	This study appears to be free of other bias.

Cheng 1993

Methods	This randomised trial was conducted in a rural area of China, Asia
Participants	Children aged 6 months to 3 years were eligible for inclusion in the trial A total of 198 children were randomised either to vitamin A or placebo group. There were 105 children in vitamin A and 81 in placebo group. Mean age of children and proportion of males were not specified in the study
Interventions	Vitamin A was supplemented in a dose of 200 000 IU for children > 12 months and 100 000 IU for < 12 months of age. Control group received placebo in the form of vegetable oil. Interventions were 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
Notes	Baseline serum levels of retinol were similar in both the groups. Measurement of biochemical vitamin A levels in the study area fulfilled the WHO criteria for an action to be triggered at a pubic health level. The morbidity surveillance was done twice a month

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	"198 children who were randomly assigned on a 3:2 allocation to treatment (105) and control (81) groups." No more information was provided about sequence generation.

Cheng 1993 *(Continued)*

Allocation concealment?	Unclear risk	Insufficent information to permit judgment.
Blinding? Blinding of Participants	Low risk	"Administration was double blind: neither parents nor doctors knew whether the child was in a treatment or control group." Placebo capsules contained vegetable oil and were likely to have been indistinguishable from intervention
Blinding? Blinding of provider	Low risk	"Placebo capsules contained vegetable oil and were likely to have been indistinguishable from intervention." In view of the adequate blinding procedures, performance bias was unlikely to have influenced the results
Blinding? Blinding of outcome assessor	Low risk	"Data collected by doctors who were already blind to treatment group assignment."
Incomplete outcome data addressed?	High risk	Reasons for loss to follow-up were not provided. The number randomised and those reported after loss to follow-up do not match
Free of selective reporting?	Unclear risk	Protocol of study was not available to permit a clear judgement
Free of other bias?	Low risk	This study appears to be free of other bias.

Cherian 2003

Methods	Individually randomised trial conducted in Vellor, India, Asia
Participants	Infants aged 9-12 months were eligible for inclusion in the study. Participants with previous history of measles vaccination or an exanthematous illness, with moderate or severe malnutrition, clinical signs of vitamin A deficiency, known immune deficiency or on immunosuppressive therapy and those who had received blood or blood products in the previous 6 months were excluded A total of 395 infants were randomised to either vitamin A or placebo group. There were 198 infants in vitamin A group and 197 in placebo. Mean age of participants was 9.8 months and proportion of males was 52%
Interventions	Infants in experimental group received a single dose of vitamin A in a dose of 100 000 IU. The control group received placebo only. Interventions were given out at the time of measles vaccination
Outcomes	Antibody response to measles vaccine.

Cherian 2003 *(Continued)*

Notes	The primary objective of the study was to measure the antibody response to measles vaccine when given with and without vitamin A. This 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
Adequate sequence generation?	Unclear risk	"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." Authors do not specify the method of sequence generation.
Allocation concealment?	Low risk	"...arachis oil or a placebo containing carboxymethylcellulose prepared in the hospital pharmacy." Probably done since hospital pharmacy was responsible for preparing the order of vitamin A and placebo and not likely to have been internal to the study team
Blinding? Blinding of Participants	Unclear risk	"...Vitamin A in arachis oil or a placebo containing carboxymethylcellulose..." Insufficient information to permit judgment.
Blinding? Blinding of provider	Unclear risk	Insufficient information to permit judgment.
Blinding? Blinding of outcome assessor	Unclear risk	Insufficient information to permit judgment.
Incomplete outcome data addressed?	High risk	The proportion of children providing adequate samples is low at 6 months, and there is insufficient detail about the reasons for missing data
Free of selective reporting?	High risk	There is no mention of mortality or any morbidity of measles or diarrhoea
Free of other bias?	Unclear risk	Insufficient information to permit judgment.

Chowdhury 2002

Methods	Individually randomised trial conducted in urban slums of Chandigarh, India, Asia
Participants	Children aged less than 10 years were eligible for inclusion in the study. Children with xerophthalmia and previous history of vitamin A supplementation were excluded A total of 1520 children were randomised either to vitamin A or placebo group. There were 756 children in vitamin A group and 759 in placebo group. Mean age of participants was 51 months and proportion of males in study sample was 50%
Interventions	The experimental group received vitamin A in a of 50 000 IU for children aged < 6 months, 100 000 IU for 6-12 months and 200 000 for > 1 year. The control group received placebo. The intervention was given every 4 months for 15 months
Outcomes	All-cause mortality, cause specific mortality of diarrhoea, pneumonia and meningitis. Incidence of diarrhoea, pneumonia and measles. Measuerement of sub-clinical vitamin A deficiency status by conjunctival impression cytology
Notes	Baseline socio-demographic and anthropometric characteristics were similar in both the groups. Study population had high prevalence of vitamin A deficiency. Children were contacted every 15 days by home visits to obtain information on morbidity and mortality. The study included children less than ten of years of age; however, the mean age of 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
Adequate sequence generation?	Unclear risk	"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?	Unclear risk	Insufficent information to permit judgment.
Blinding? Blinding of Participants	Unclear risk	"An equivalent volume of arachis oil was given as placebo." Insufficient information to permit judgment.
Blinding? Blinding of provider	Unclear risk	Insufficient information to permit judgment.
Blinding? Blinding of outcome assessor	Unclear risk	Insufficent information to permit judgment.

Chowdhury 2002 (*Continued*)

Incomplete outcome data addressed?	High risk	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
Free of selective reporting?	Unclear risk	Insuffcient information to permit judgment.
Free of other bias?	Unclear risk	Study not sufficiently reported in order to assess this item fully

Daulaire 1992

Methods	A cluster randomised, non-placebo controlled trial conducted in Jumla district, Nepal, Asia
Participants	Children 1-59 months were eligible for inclusion in the trial A total of 16 clusters were randomly assigned either to vitamin A or control group. These include a total of 7197 children in which 3786 children were in vitamin A group and 3411 in control group. Proportion of male participants was 51%
Interventions	Children in experimental group received vitamin A in a dose of 200 000 IU for children aged 12-59 months, 100 000 IU for those of 6-12 months and 50 000 IU for < 6 months old. Vitamin A was supplemented once only and children were followed for 5 months
Outcomes	All-cause mortality and cause specific mortality for diarrhoea, pneumonia and measles
Notes	The 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 one 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 suffering from substantial malnutrition. A survey of 3651 children in children under 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 was available according to different age groups. We have used data for children 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
Adequate sequence generation?	Low risk	"We randomly selected by card eight of the 16 sub-districts for vitamin A supplementation." Probably done.

Daulaire 1992   (*Continued*)

Allocation concealment?	High risk	Author contacted and replied, "No effort was made to conceal the allocation sequence."
Blinding? Blinding of Participants	High risk	"There was no placebo or blinding."
Blinding? Blinding of provider	High risk	"There was no placebo or blinding."
Blinding? Blinding of outcome assessor	High risk	"There was no placebo or blinding."
Incomplete outcome data addressed?	Low risk	There was no loss to follow- up. Coverage of intervention was described in detail
Free of selective reporting?	Unclear risk	Insufficent information to permit judgment.
Free of other bias?	Low risk	This study appears to be free of other bias.

DEVTA 2007

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study was not included, but some available data was used in a sensitivity analysis. See Characteristics of studies awaiting classification

Dibley 1994

Methods	Individually randomised trial conducted in 34 rural villages located on the southern coast of Central Java in Indonesia, Asia
Participants	Children aged 6 to 47 months were eligible for inclusion in the review. Children with cerebral palsy, epilepsy, flaccid paralysis, mental retardation, congenital or rheumatic heart disease were permanently excluded. Those with weight-for-height more than 3.00 SD below the WHO growth reference mean or acute xerophthalmia were excluded for one cycle and treated with high dose vitamin A and then included
A total of 1405 children were randomised to either vitamin A or placebo group. Proportion of male participants was 50.9%

Dibley 1994 (*Continued*)

Interventions	Intervention group received 206,000 IU of vitamin A in the form of retinyl ester plus 37 IU vitamin E for children > 12 months or 103,000 IU retinyl ester plus 17 IU vitamin E if less than 12 months of age. The control group received placebo that contained 17 or 37 IU vitamin E according to the age of the subject. The intervention was given every 4 months for 24 months. An average of 89% of the children received a treatment (vitamin A or placebo)
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 balance 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 vitamin A group and control group were 280,186 and 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
Adequate sequence generation?	Low risk	"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 (Cochrane and Cox 1950)." Likely to be adequate.
Allocation concealment?	Low risk	"All investigators, field and laboratory staff, and participants were masked to the treatment code." "The capsules were packaged in opaque blister packs with a unique treatment code."
Blinding? Blinding of Participants	Low risk	"The oily contents of the vitamin A and placebo capsules were of similar taste and colour."
Blinding? Blinding of provider	Low risk	"All investigators, field and laboratory staff, and participants were masked to the treatment code." 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? Blinding of outcome assessor	Low risk	"All investigators, field and laboratory staff, and participants were masked to the treat-

Dibley 1994   (*Continued*)

		ment code." 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 addressed?	Low risk	Complete details of those excluded and lost to follow-up with reason were described. There were a low and balanced number of withdrawals between the treatment groups. The analytical method took account of the time on treatment (i.e. follow-up time for each cycle) and this may have been adequate
Free of selective reporting?	Low risk	Lack of trial protocol hinders full assessment of this item. However, data on outcomes of relevance to the review were reported
Free of other bias?	Low risk	This study appears to be free of other bias.

Donnen 1998

Methods	Individually randomised, non-placebo controlled trial conducted in South Kivu province of Congo, Africa
Participants	Children 0-72 months were eligible for inclusion in the trial. Children were recruited as soon they were discharged from children hospital Kotive. No exclusion criteria was described A total of 358 children were randomly assigned to vitamin A, mebendazole, or control group. Vitamin A had 118 children and control group had 117
Interventions	There were three study groups. The first group was supplemented with vitamin A, second group received mebendazole for deworming and third group was simply observed as control. Children in vitamin A group received retinol palmitate in a dose of 100 000 IU for children aged < 1 year and 200 000 IU for those > 1 year. 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 done every 2 weeks during 3 months, then every 3 months until 12 months. Data on morbidity outcomes were presented in the form of odds ratios based on generalised estimating equation models. As we were using the data in the form of relative risk and no nominators were given in this study, we could not pool the data for diarrhoea and respiratory morbidity of this study

Risk of bias

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Donnen 1998 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	"As soon as the children were discharged from the hospital, they were randomly assigned to one of the three groups." Probably not done
Allocation concealment?	Unclear risk	Insufficient details available to make a judgment.
Blinding? Blinding of Participants	Unclear risk	Insufficient details available to make a judgment.
Blinding? Blinding of provider	Unclear risk	Insufficient details available to make a judgment.
Blinding? Blinding of outcome assessor	Unclear risk	Insufficient details available to make a judgment.
Incomplete outcome data addressed?	Low risk	Authors indicate that 6% were lost to follow-up, not discussed in detail. Number died but not indicated how or by group data. Overall, 6% of the children were lost to follow-up, with approximately equal proportions in each group
Free of selective reporting?	Unclear risk	Insufficient details available to make a judgment.
Free of other bias?	Low risk	This study appears to be free of other bias.

Florentino 1990

Methods	Individually randomised trial conducted in the municipalities of Pililla and Binangonan in the province of Rizal, Philippines, Asia
Participants	Children 1-6 years of age were eligible for inclusion in the study. Any child with clinical signs of vitamin A deficiency was excluded from the trial A total of 2471 children were randomised to three intervention groups. Mean age of children was 3.4 years and proportion of males in study population was 49.5%
Interventions	There were 3 study groups, 2 were supplemented with vitamin A and 1 with placebo. The first group in the experimental group received a high dose of vitamin A i.e. 200 000 IU and the second group received a medium dose of vitamin A i.e. 100 000 IU. The control group received placebo only. Children were supplemented only once and were followed for 1 week

Florentino 1990   (*Continued*)

Outcomes	Incidence of side effects within 1 week: nausea and/or vomiting, headache, diarrhoea and fever
Notes	The study area had a high prevalence of malnutrition, and therefore vitamin A deficiency was likely to be prevalent. Study reported outcome for first 48 hours and within a week. We have pooled the data for first week

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	"By use of a double-blind study design, children were randomly assigned to three treatment groups." No qualifying information on what 'randomly assigned' means is provided. Difficult to assess sequence generation
Allocation concealment?	Unclear risk	Insufficient details available to make a judgment.
Blinding? Blinding of Participants	Low risk	"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? Blinding of provider	Low risk	"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 adequate and performance bias unlikely to have influenced results
Blinding? Blinding of outcome assessor	Low risk	"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 addressed?	Low risk	Complete details of those excluded and lost to follow-up were provided. Only 76 children lost, differences slight between groups
Free of selective reporting?	Low risk	Though not explicitly stated all reported measured outcomes have data reported in results with sufficient clarity and explana-

Florentino 1990 *(Continued)*

		tion
Free of other bias?	Low risk	No other apparent bias was noted.

Herrera 1992

Methods	Cluster randomised trial was conducted in five rural councils in northern Sudan, Africa
Participants	Eligibily criteria was age 9-72 months. Children with xerophthalmia were excluded. Randomisation was done by households. Study included a total of 28,753 children of whom 14,343 were in vitamin A group and 14,149 were in placebo group. Proportion of male children in the study was 50.7%
Interventions	Children in vitamin A group received 200 000 IU of retinol palmitate along with 40 IU of vitamin E. The comparison group received 40 IU of vitamin E only. The intervention was given every six months for 18 months
Outcomes	All-cause mortality and cause specific mortality of diarrhoea, measles, respiratory disease. Incidence of diarrhoea, respiratory disease and measles. Incidence of xeropthalmia, Bitot's spots and night blindness
Notes	Authors used non- specific terms for describing cause of death (in table 4) like "shortness of breath" "convulsions" and "fever" etc. We have pooled data for "shortness of breath" under heading of lower respiratory tract infection mortality. This is because it is highly unlikely that a child will die of an upper respiratory tract infection and lower respiratory tract infection 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
Adequate sequence generation?	High risk	"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." Does not appear to be randomised.
Allocation concealment?	Unclear risk	Insufficient details available to make a judgment.

Herrera 1992 (*Continued*)

Blinding? Blinding of Participants	Low risk	"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? Blinding of provider	Low risk	"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." Performance bias unlikely given that trialists and staff were blinded during the intervention
Blinding? Blinding of outcome assessor	Low risk	"Only the manufacturer knew the contents of the capsules until after data collection and preliminary analysis of the results." Probably done.
Incomplete outcome data addressed?	Low risk	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 subjects 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 that remained in the study
Free of selective reporting?	Unclear risk	Does not reference a protocol or trial registration and does not state that all measured outcomes are reported
Free of other bias?	Unclear risk	Insufficient details available to make a judgment.

Kartasasmita 1995

Methods	Individually randomised trial conducted in a suburban community of city Bandung, Indonesia, Asia
Participants	Children aged 12-54 months were included in the study. No exclusion criteria was specified A total of 269 children were randomised either to vitamin A or placebo group. Vitamin A supplemented group had 126 children while placebo group had 141 children. Mean age of study participants was 33 months and proportion of males was 51%
Interventions	The experimental group received 200 000 IU of vitamin A once every 6 months for 12 months. The comparison group received placebo only
Outcomes	Incidence of respiratory disease. Mean serum retinol levels.
Notes	Authors presented data on respiratory outcomes according to severity of disease. We have included data for "severe respiratory disease" only

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	"The children were selected by randomised stratified sampling from the almost 2000 under-fives residing in Cikutra." Insufficient details available to make a judgment.
Allocation concealment?	Unclear risk	Insufficient detail provided to make judgement.
Blinding? Blinding of Participants	Unclear risk	"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? Blinding of provider	Unclear risk	Insufficient detail provided to make judgement.
Blinding? Blinding of outcome assessor	Unclear risk	Insufficient detail provided to make judgement.
Incomplete outcome data addressed?	High risk	Insufficient reporting of attrition/exclusions to permit judgement
Free of selective reporting?	Unclear risk	Insufficient detail provided to make judgement.

Kartasasmita 1995 *(Continued)*

Free of other bias?	Unclear risk	The methods of the study are not described very clearly.

Lima 2010

Methods	Individually randomised trial conducted in Fortaleza, the capital of the Ceara state in northeastern Brazil, Latin America
Participants	Children aged 2 months to 9 years were eligible for inclusion in the study. Those participants who had fever > 38 C or exclusively breastfed were excluded A total of 79 children were randomised either to vitamin A or placebo group. There were 39 participants in vitamin A group and 40 in placebo. Mean age of participants was 43.3 months and proportion of males was 57%
Interventions	Retinol palmitate was supplemented in a dose of 100 000 IU for children aged < 12 months and 200 000 IU > 12 months in experimental group. The comparison group received Tocopherol (vitamin E) as placebo. Supplements were given at enrolment, 4 and 8 months
Outcomes	Mean serum retinol levels, growth and adverse reactions to vitamin A
Notes	The infant mortality rate in study are was 35/1000 live births. The primary objective of the study was to measure the effect of vitamin A on barrier function of gastrointestinal tract. The 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
Adequate sequence generation?	Low risk	79 children were randomly selected (using computer-generated random numbers)
Allocation concealment?	Unclear risk	Insufficient detail provided to make judgement.
Blinding? Blinding of Participants	Low risk	The parent or guardian of the children, field study team, and investigators were blinded to treatment agent
Blinding? Blinding of provider	Low risk	The parent or guardian of the children, field study team, and investigators were blinded to treatment agent
Blinding? Blinding of outcome assessor	Low risk	The parent or guardian of the children, field study team, and investigators were blinded to treatment agent

Lima 2010 *(Continued)*

		Indication that field study teams assessed outcomes. They were blinded
Incomplete outcome data addressed?	Low risk	After 12-month follow-up, a total of 22 children were withdrawn from the study for the following reasons: change of address (16), parents or guardians did not co-operate with the study (5), and 1 had above the median z score for length or height at the time of the study initiation. The percentage of participants completing the study at 12 months was 72.2%
Free of selective reporting?	High risk	The objective of study also included reporting of diarrhoea. Authors had reported the overall incidence of diarrhoea in the whole population but the figures had been presented in a way that they can not be used in the meta-analysis
Free of other bias?	Low risk	No other apparent bias was observed.

Lin 2008

Methods	This study was described as randomised, placebo-controlled trial conducted in Wuhan, an industrial centre in central region of China, Asia
Participants	Inlcusion criteria was age 2 to 7 years. children were recruited from kindergarten in the area. Those who had fever, diarrhoea or a recent preventive injection were excluded from the study. Underweight children with BMI age- and sex- specific 5th percentile of the first US National Health and Nutrition Examination Survey data were excluded. Children whose protein or energy intake of Chinese RDA were also excluded A total of 105 children were randomised to three intervention groups (described below) . Mean age of study participants was 55 months and proportion of male participants was 61%
Interventions	There were 3 study groups. Two of these consisted of children who were vitamin A deficient and 1 with children who were vitamin A sufficient. Vitamin A was given only to 1 of the group of vitamin A deficient children in a dose of 100 000 IU every month for three months. The rest of two groups received placebo
Outcomes	All-cause mortality, mean serum vitamin A levels.
Notes	In this review we have 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	

Lin 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	"The remaining 70 vitamin A-deficient children were randomly and equally divided into vitamin A deficient-supplemented group and vitamin A-deficient placebo group." The term 'randomised' is also used to describe a 3rd group that is clearly matched. This may not be a RCT
Allocation concealment?	Unclear risk	Insufficient detail provided to make judgement.
Blinding? Blinding of Participants	Low risk	"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? Blinding of provider	Unclear risk	Although study was double randomised trial but no details of how blinding was achieved was described in the district
Blinding? Blinding of outcome assessor	Unclear risk	Insufficient detail provided to make judgement.
Incomplete outcome data addressed?	Low risk	No attrition reported.
Free of selective reporting?	High risk	Main outcome data are not reported in a manner that can be analysed
Free of other bias?	Unclear risk	As blinding is not described, potential performance bias and other sources of bias cannot be assessed

Lin 2009

Methods	Individual randomised trial conducted in rural China, Asia.
Participants	Children age 6 months to 7 years were included in the study. Those without informed consent or with acute and chronic diseases were excluded. A total of 132 children were randomly allocated to three intervention groups. Mean age of children was 36.5 months and proportion of males was 50%

Lin 2009 *(Continued)*

Interventions	The three intervention groups included vitamin A, beta-carotene and placebo. The experimental group received 100 000 IU of vitamin A every month for 3 months. Placebo group received biscuits
Outcomes	Mean vitamin A serum levels
Notes	We have included the results for vitamin A group versus placebo only

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	"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." Probably done.
Allocation concealment?	Unclear risk	No methods of allocation concealment are described in the text
Blinding? Blinding of Participants	High risk	"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." Vitamin A and placebo were administered in two different forms. Vitamin A was administered in capsule form while placebo was given in the form of biscuits
Blinding? Blinding of provider	High risk	Vitamin A and placebo were administered in two different forms. Vitamin A was administered in capsule form while placebo was given in the form of biscuits
Blinding? Blinding of outcome assessor	High risk	Vitamin A and placebo were administered in two different forms. Vitamin A was administered in capsule form while placebo was given in the form of biscuits
Incomplete outcome data addressed?	Low risk	No dropouts reported, and numbers at baseline and follow-up appear to be the same

Lin 2009 *(Continued)*

Free of selective reporting?	High risk	Use of clinic services, hospitalisation, cause specific morbidity not reported
Free of other bias?	Low risk	This study appears to be free of other bias.

Long 2006

Methods	Factorial design, individually randomised trial conducted in La Magdalena Atlicpac, Mexico, North America
Participants	Children aged 6 to 15 months were eligible for inclusion in the review. Children who were suffering from diseases causing immunosuppression and any congenital or acquired alteration of the digestive tract that could alter the absorption of micronutrients, were excluded. Children who were taking vitamin supplements were also excluded from the study. A total of 786 children were randomised to four intervention groups. Mean age of participants was 9.8 months. The proportion of males in study population was 51.7%
Interventions	The four intervention groups were as follows: 1) Vitamin A group that received 20,000 IU retinol every 2 months for children aged < 1 year or 45,000 IU for children aged > 1 year. 2) Zn group that received a daily dose equivalent to 20 mg elemental Zn as zinc methionine 3) A group that received both the zinc supplement and the vitamin A as above 4) A placebo group Interventions were delivered every 2 months for 12 months.
Outcomes	Diarrhoea and respiratory disease morbidity.
Notes	We have included data of this factorial design trial in two sets. First data set give comparisons for vitamin A vs. placebo and the second set includes data for vitamin A + Zinc vs. zinc only. Data on respiratory morbidity was given with three definitions. We have pooled the data for "cough + difficulty breathing" under the heading of lower respiratory tract infection

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	"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?	Low risk	"These solutions were packaged in consecutively numbered, colour-coded, opaque plastic droplet bottles to ensure that field personnel and the principal investigator

Long 2006 *(Continued)*

		were blinded."
Blinding? Blinding of Participants	Low risk	"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? Blinding of provider	Low risk	"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."
Blinding? Blinding of outcome assessor	Low risk	"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." Probably done.
Incomplete outcome data addressed?	Low risk	Lost to follow-up data given along with reasons for lost to follow-up. Ninety-three children were lost to follow-up or were excluded
Free of selective reporting?	Unclear risk	Study protocol not available so can not assess or make any judgement
Free of other bias?	Low risk	This study appears to be free of other bias.

Long 2006 (2)

Methods	
Participants	
Interventions	
Outcomes	
Notes	As Long 2006 above.

Long 2007

Methods	Individually randomised trial conducted in Mexico, North America
Participants	Children 5-15 months were eligible for inclusion in the trial. Those who were immuno-suppressed, had any congenital abnormality or chronic diarrhoea were excluded. Those who had a history of vitamin A supplementation were also excluded A total of 195 children were randomised in which 97 were in vitamin A group and 98 in placebo group. The proportion of males study population was 49.7%
Interventions	The experimental group received vitamin A in a dose of 20,000 IU for those aged < 12 months and 45,000 IU for those > 12 months. Intervention was repeated every 2 months for 12 months
Outcomes	Incidence of diarrhoea and respiratory disease.
Notes	The baseline socio-demographic characteristics of study children and households were similar between children who received vitamin A and those who were given the placebo. Children received monthly visits and referrals to the doctor, which appeared to exceed normal treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	"The randomisation sequence was generated by project personnel based at the National Institute of Public Health." Probably done.
Allocation concealment?	Low risk	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. Children in the vitamin A and placebo groups received a 5ml solution, from identical opaque plastic droplet bottles numbered consecutively, administered by the field team
Blinding? Blinding of Participants	Low risk	"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? Blinding of provider	Low risk	"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."

Long 2007 *(Continued)*

Blinding? Blinding of outcome assessor	Low risk	"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 addressed?	Low risk	Unclear what was done with data for 7 missing children, but dropout was small and similar between groups (4 intervention, 3 control)
Free of selective reporting?	Unclear risk	Protocol not referenced, though the grant applications may be available
Free of other bias?	Low risk	This study appears to be free of other bias.

Pant 1996

Methods	Cluster randomised trial in rural Nepal, Asia.
Participants	Children aged between 6 months and 10 years were eligible to participate in the study From 100 potentially eligible cluster sites, 75 were randomised (approximately 25,301 children). Baseline data on the number in each treatment group, proportion of male participants and mean age were not provided
Interventions	The intervention groups were: 1. Vitamin A given as a single dose via a capsule (100,000 IU for children aged 6 to 12 months and 200,000 IU for children aged 1 to 10 years) 2. Control (not adequately described) 3. Nutritional education 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
Adequate sequence generation?	Low risk	"Using random number tables and the reference number for each block …"
Allocation concealment?	Unclear risk	Insufficient detail provided to make judgment.

Pant 1996 (*Continued*)

Blinding? Blinding of Participants	Unclear risk	Insufficient detail provided to make judgment.
Blinding? Blinding of provider	Unclear risk	Insufficient detail provided to make judgment.
Blinding? Blinding of outcome assessor	Unclear risk	Insufficient detail provided to make judgment.
Incomplete outcome data addressed?	High risk	No information regarding incomplete outcome data addressed given
Free of selective reporting?	High risk	Very specific outcomes reported. Five types of examinations were administered to the study children: ophthalmic, physical, anthropometric, blood, and faecal; while data in results is given only for prevalence of Bitot's spots and all-cause mortality
Free of other bias?	Unclear risk	Insufficient detail provided to make judgment.

Pinnock 1986

Methods	Individually randomised study in urban area of Australia.
Participants	Children aged between 1 and 4 years of age in three general practices from Adelaide. Children with more than 15 days of cough or three separate episodes of respiratory illness during the preceding 3 months were eligible 147 children were randomised to the treatment groups. Mean age was 39.3 months. 50% of the sample was male
Interventions	Vitamin A administered orally as retinyl palmitate (1160mcg) three times per week for 20 weeks versus placebo
Outcomes	Acute respiratory infections, pneumonia, mean serum vitamin A
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	"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 num-

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Pinnock 1986 (*Continued*)

		bering the bottles accordingly." Probably done.
Allocation concealment?	Unclear risk	Insuffcent information to permit judgment.
Blinding? Blinding of Participants	Low risk	"The placebo was a similarly constituted syrup omitting retinyl palmitate and labelled and bottled identically."
Blinding? Blinding of provider	Low risk	"All staff connected with the study remained blind to the identity of the child's medication."
Blinding? Blinding of outcome assessor	Low risk	"All staff connected with the study remained blind to the identity of the child's medication."
Incomplete outcome data addressed?	Low risk	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 two groups
Free of selective reporting?	Unclear risk	The protocol of the study not available.
Free of other bias?	Low risk	No other apparent bias was observed.

Pinnock 1988

Methods	Individually randomised study in urban area of Australia.
Participants	Children aged between 0 and 2 years with previous history of bronchiolitis and nasal culture positive for HSV were included Children taking vitamin A, and those with cystic fibrosis, cardiopulmonary difficulties, major brain dysfunctions were excluded 206 children were randomised to the treatment groups. Mean age was 58 months. 60% sample was male
Interventions	Vitamin A administered as retinyl palmitate 4.2mg per week for 12 months versus placebo
Outcomes	Diarrhoea, diarrhoea-related hospitalisation, acute respiratory infections, pneumonia, pneumonia-related hospitalisation, mean serum vitamin A
Notes	
Risk of bias	

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	"Randomization was achieved by randomly allocating four of eight batch numbers to Vitamin A supplement and the remaining four to placebo. The batch number code was retained by the manufacturer."
Allocation concealment?	Low risk	"The batch number code was retained by the manufacturer. The bottles were then distributed sequentially according to batch number as children presented..." Probably done.
Blinding? Blinding of Participants	Low risk	"The placebo had an identical appearance and formulation except for the active ingredient." Probably done.
Blinding? Blinding of provider	Low risk	"Both investigators and parents were blind as to the treatment status of the child."
Blinding? Blinding of outcome assessor	Low risk	"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 addressed?	Low risk	Complete details of those excluded and lost to follow-up were provided
Free of selective reporting?	High risk	Outcomes mentioned in methods not reported in results.
Free of other bias?	Low risk	This study appears to be free of other bias.

Rahman 2001

Methods	Individually randomised study conducted in an urban area of Bangladesh, Asia
Participants	Children aged between 12 and 35 months were eligible for inclusion in the study Children who had received Vitamin A within the 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 were excluded 800 children were enrolled (200 in each of the four treatment groups). Mean age of participants was between 23.5 and 24.2 months across the treatment groups. 56% of the participants were male

Rahman 2001 (*Continued*)

Interventions	There were four treatment groups: 1. Vitamin A 200,000 IU (60 mg) given as a single capsule at day 14, with placebo syrup daily for 14 days 2. Placebo capsule at day 14 and placebo syrup for 14 days. 3. Vitamin A 200,000 IU (60 mg) given as a single capsule at day 14, with zinc syrup daily for 14 days 4. Zinc syrup daily for 14 days, placebo capsule at day 14. Duration of study: 6 months.
Outcomes	Diarrhoea, acute respiratory infections, serum vitamin A levels and vitamin deficiency
Notes	Data on treatment analysis was not presented. We have written to authors for data on each treatment arm

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	"The children were randomly assigned by a person not involved in the study who used permuted blocks of random numbers." Probably done.
Allocation concealment?	Low risk	"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." Probably done.
Blinding? Blinding of Participants	Low risk	"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." Probably done.
Blinding? Blinding of provider	Low risk	Identical presentation and: 'The randomisation code was kept sealed until the completion of the study.' Probably done.
Blinding? Blinding of outcome assessor	Low risk	"The treatment allocations were disclosed after the final analysis."

Rahman 2001   *(Continued)*

Incomplete outcome data addressed?	Low risk	Data on lost 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
Free of selective reporting?	Unclear risk	Protocol not available.
Free of other bias?	Low risk	No other bias was noticed.

Rahmathullah 1990

Methods	Cluster-randomised trial conducted in Trichy district of Tamil Nadu in southern India, Asia
Participants	Children aged 6 to 60 months were included in the study. Clustering unit was "panchyat" (local-government areas). A total of 206 clusters were formed, and the majority of them consisted of 50 to 100 children. The included clusters had a total of 15,419 children of whom 7764 were in vitamin A group and 7655 in placebo group
Interventions	Children in experimental group received weekly doses of 8333 IU vitamin A and 20 mg vitamin E. The control group received 20 IU of vitamin E only in peanut oil. Any children diagnosed with xerophthalmia at baseline, midterm, or final examination was given a high-dose (200 000 IU) supplement of vitamin A and continued in the study. Supplementations were given for 52 weeks. Children who missed 7 consecutive dosages were excluded from the analysis
Outcomes	All-cause mortality, cause specific mortality of diarrhoea, measles and respiratory disease. Incidence of diarrhoea and respiratory disease morbidity
Notes	The baseline characteristics of the two groups were similar in terms of age and sex, one-month history of diarrhoea and respiratory disease, anthropometric indexes of nutritional status, xerophthalmia status, five-year retrospective history of mortality of children under five, household economic, household hygienic status, and serum retinol levels. On average > 90% of the 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
Adequate sequence generation?	Unclear risk	"The clusters were arranged according to population size; after a random start, they were assigned alternately to the treated or control groups." Exact method of sequence generation was

Rahmathullah 1990 (*Continued*)

		not provided.
Allocation concealment?	Low risk	"...no one associated with the study was aware of the colour code, which was held by the Hoffmann-LaRoche until the study ended."
Blinding? Blinding of Participants	Low risk	"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." Probably done.
Blinding? Blinding of provider	Low risk	"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..." Probably done.
Blinding? Blinding of outcome assessor	Low risk	"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..."
Incomplete outcome data addressed?	Low risk	"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 ..." Reasons for lost to follow-up given with a note that there was no difference in contact rates between the two groups
Free of selective reporting?	Low risk	All important outcomes given in results as mentioned in the methods section
Free of other bias?	Low risk	No other apparent bias was noticed.

Ramakrishnan 1995

Methods	Individually randomised trial conducted in rural India, Asia
Participants	Children aged 6-36 months were eligible for inclusion in the trial. Those 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) were excluded and received appropriate treatment including vitamin A

Ramakrishnan 1995   (*Continued*)

	A total of 538 children were included, 309 in vitamin A group and 274 in placebo group. Mean age of children was 18.6 months and proportion males was 49.9%
Interventions	Children in experimental group received vitamin A in a dose of 100,000 IU for children aged < 1 year and 200,000 IU for children aged > 1 year. The comparison group received only placebo. The interventions were 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 lower respiratory tract infection. It mainly covered upper respiratory tract infections

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	"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." Insufficient detail provided.
Allocation concealment?	Unclear risk	Insufficent information to permit judgment.
Blinding? Blinding of Participants	Low risk	"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." Statement that blinding occurred, no further details provided
Blinding? Blinding of provider	Low risk	"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." Statement that blinding occurred, no further details provided
Blinding? Blinding of outcome assessor	Low risk	"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 sup-

Ramakrishnan 1995   *(Continued)*

		plement and the control group received a placebo." Statement that blinding occurred, no further details provided
Incomplete outcome data addressed?	Low risk	"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." Losses were not large and balanced between groups; unlikely to introduce substantial bias here. Clinically relevant impact unlikely
Free of selective reporting?	High risk	"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." Though measured, serum retinol results are never reported.
Free of other bias?	Low risk	This study appears to be free of other bias.

Ranjini 2001

Methods	Individually randomised trial conducted in India, Asia.
Participants	Children aged 12-60 months and having recurrent respiratory tract infections were eligible for inclusion in the trial. Those with mild or moderate asthma; children who were on vitamin supplements or who had received a massive dose of vitamin A in the previous 6 months, those with pre-existing congenital heart disease, chronic lung disease, pulmonary tuberculosis or immunodeficiency disorders, those on immunosuppressive drugs and those with clinically apparent vitamin A deficiency were excluded A total of 61 children were randomised in which 30 were in vitamin A group and 31 in placebo group. The mean age of children was 35.7 months and proportion of males was

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Ranjini 2001 (*Continued*)

	60.7%
Interventions	Children in experimental group received a single dose of vitamin A in a dose of 200 000 IU. The comparison group was given placebo in archis oil. Follow- up period was 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
Adequate sequence generation?	Unclear risk	"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." Details of sequence generation not specified.
Allocation concealment?	Unclear risk	Insufficent information to permit judgment.
Blinding? Blinding of Participants	Unclear risk	"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? Blinding of provider	Unclear risk	Not mentioned.
Blinding? Blinding of outcome assessor	Unclear risk	Not mentioned.
Incomplete outcome data addressed?	Unclear risk	"Of the 61 included children, seven (three in the placebo group and four in vitamin A group) did not return for follow-up." (second page) Authors do 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 weather or not there is a low or high risk of bias, but it is likely to be high
Free of selective reporting?	Unclear risk	"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

Ranjini 2001   (*Continued*)

		the study period were also recorded. During each monthly follow-up visit, the entries in the monthly calendar were reviewed with the parent." (1st, 2nd page) Hospitalisation was not reported though it was collected.
Free of other bias?	Unclear risk	Very little information provided in the paper; difficult to assess

Reddy 1986

Methods	Factorial design individually randomised trial conducted in India, Asia
Participants	Children aged 1-5 years were included in the study. Those without parental consent were excluded A total of 487 children were randomised to four intervention groups. Mean age and proportion of males were not described
Interventions	The four intervention groups were as follows: Group A: oral administration of L-tetramisole (50 mg) followed 3 days later by a dose of 200 000 IU of vitamin A. Group B: massive dose of vitamin A of 200 000 IU Group C L-tetramisole (50 mg) orally. Group D placebo.
Outcomes	Mean vitamin A serum levels.
Notes	Data have been included in two sets.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	"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." Insufficient details provided to make judgement.
Allocation concealment?	Unclear risk	Insufficient information to permit judgment.
Blinding? Blinding of Participants	Unclear risk	Insufficient information to permit judgment

Reddy 1986 *(Continued)*

Blinding? Blinding of provider	Unclear risk	Insufficient information to permit judgment
Blinding? Blinding of outcome assessor	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data addressed?	Unclear risk	Insufficient information to permit judgment
Free of selective reporting?	Unclear risk	"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." Authors do not report height or weights, or detailed data on clinical status or morbidity
Free of other bias?	Unclear risk	Insufficient information to permit judgment.

Reddy 1986 (2)

Methods	
Participants	
Interventions	
Outcomes	
Notes	As Reddy 1986 above.

Ross 1993 HEALTH

Methods	Randomised double-blind controlled trial conducted in guinea savannah area of Ghana, Africa
Participants	Children aged 6 to 59 months were included. Those with active xerophthalmia or measles were excluded from the trial the moment them were confirmed A total of 1455 children were included. The proportion of male children was 49.5%
Interventions	Children in vitamin A group received either 200,000 IU retinol equivalent for participants aged > 12 months or 100,000 IU for aged 6-12 months. The control group received placebo. Interventions were given every 4 months for 12 months

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Outcomes	All-cause mortality. Mean daily prevalence of respiratory tract disease, diarrhoea, measles, malaria. Mean vitamin A serum levels, all-cause hospitalisations
Notes	The study populations were rural and their main staple foods are deficient in carotenoids and vitamin A. Vitamin A deficiency and xerophthalmia were recognised as problems locally. Children were visited weekly for 1 year. Children in the Health Study were followed up 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
Adequate sequence generation?	Unclear risk	"Randomisation was blocked in both studies to ensure similar numbers of children in each group in each part of the study area." Explicit methods for generating allocation sequence not available
Allocation concealment?	Low risk	"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." Code was protected for the duration of the trial.
Blinding? Blinding of Participants	Low risk	"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? Blinding of provider	Low risk	As above; probably done.
Blinding? Blinding of outcome assessor	Low risk	In view of the blinding procedures in place elsewhere in the study this was probably adequate

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Incomplete outcome data addressed?	Unclear risk	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 the treatment groups
Free of selective reporting?	High risk	There was an indication that xerophthalmia data were measured, but none are reported. No protocol is available
Free of other bias?	Low risk	No other apparent bias was noted.

Ross 1993 SURVIVAL

Methods	Cluster randomised trial conducted Ghana, Africa.
Participants	Children aged 6-90 months were eligible for inclusion in the trial. Xeropthalmic children were excluded Study involved 185 cluster that included 21906 children. Proprtion of male children was 51.5%
Interventions	The experimental group received vitamin A supplementation in a dose of 100 000 IU for children aged 6-11 months and 200,000 IU for older children. The comparison group received placebo. Vitamin E in a dose of 20 IU was given to both the groups. Intervention were delivered every 4 months for 24 months
Outcomes	All-cause mortality and cause specific mortality of diarrhoea, respiratory disease, measles and meningitis. Mean vitamin A serum levels. Malaria prevalence
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	"Randomisation was blocked in both studies to ensure similar numbers of children in each group in each part of the study area." Explicit methods for generating allocation sequence not available
Allocation concealment?	Low risk	"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."

Ross 1993 SURVIVAL (*Continued*)

		Code was protected for the duration of the trial.
Blinding? Blinding of Participants	Low risk	"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." Probably done.
Blinding? Blinding of provider	Low risk	As above; probably done.
Blinding? Blinding of outcome assessor	Low risk	In view of the blinding procedures in place elsewhere in the study this was probably adequate
Incomplete outcome data addressed?	Unclear risk	8.4% (1847) children lost to follow-up and similar between treatment groups The reasons for losses to follow-up are not provided.
Free of selective reporting?	High risk	Authors collected data on night blindness, Bitot's spots, and xerophthalmia but do not report it
Free of other bias?	Unclear risk	The method for inflating the CIs is not well-described. No ICC reported

Semba 1992

Methods	Individually randomised trial conducted in Indonesia, Asia.
Participants	Children aged 3-6 years were eligible for inclusion in the study. Those who had median weight for age <80% of the National Center for Health Statistics were excluded from the study. Children with serious illness were also excluded from the study and treated appropriately A total of 236 children were randomised to four intervention groups. Mean age of participants was 58.9 months and proportion of males was 71.6%

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Semba 1992 *(Continued)*

Interventions	There were 4 intervention groups. Two groups (vitamin A and placebo) had clinical signs of vitamin A deficiency while two groups were clinically normal Participants in vitamin A groups received a single dose of 60 000 microgram of retinol equivalent. Children were followed for one 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
Adequate sequence generation?	Unclear risk	"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." Details of sequence generation not provided.
Allocation concealment?	Low risk	"The treatment code was broken after the conclusion of the study." Allocation sequence appears to have been protected.
Blinding? Blinding of Participants	Low risk	"A double-masked, randomised, placebo-controlled, clinical trial involving 236 preschool children." "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? Blinding of provider	Low risk	As above; providers likely to have been adequately blinded.
Blinding? Blinding of outcome assessor	Unclear risk	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 addressed?	Low risk	232/236 children enrolled at baseline completed the study protocol. (page 102)

Semba 1992   (*Continued*)

Free of selective reporting?	Unclear risk	Does not reference a protocol or trial registration and does not state that all measured outcomes are reported
Free of other bias?	Unclear risk	Insufficient information to permit judgment.

Semba 1995

Methods	Individually randomised study in rural Indonesia, Asia.
Participants	Children aged 6 months at vaccination against measles were included Children who had measles previously were excluded. 336 children were randomised to the two treatment groups. Baseline details on age and gender were not provided
Interventions	Vitamin A given as a single dose (100,000 IU) versus placebo Vitamin A or placebo given with measles vaccine. Study duration: 6 months.
Outcomes	Measles.
Notes	The primary objective of the study was to measure the antibody response to measles vaccine when given along with vitamin A or placebo. Trialists found a significant decrease in seroconversion of measles vaccine in the intervention group compared to placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	"Treatment was assigned by random number table in blocks of ten." Probably done.
Allocation concealment?	Low risk	"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." Probably done.
Blinding? Blinding of Participants	Low risk	"Vitamin A, 100 000 IU, or placebo in identical capsules." Probably done.
Blinding? Blinding of provider	Low risk	"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." Probably done.
Blinding? Blinding of outcome assessor	Low risk	As above; probably done.
Incomplete outcome data addressed?	High risk	"Follow-up rates were 93% and 90% at one and six months post immunisation, respectively." The reasons for lost to follow-up not given; only available case data given
Free of selective reporting?	Unclear risk	Study protocol was not available.
Free of other bias?	Unclear risk	Inadequate information presented to assess this formally.

Sempertegui 1999

Methods	Indivdualy randomised trial conducted in the northwestern region of the Quito, Ecuador, South America
Participants	Children aged 6 to 36 months were eligible for inclusion in the review. Those children who had clinical vitamin A deficiency, who did not reliably stayed at home or at day care centres during weekdays or who had been given multivitamins in the last 3 months, were excluded A total of 400 children were randomised either to vitamin A or placebo group with equal (200 each) in both the groups. Mean age of participants was 21.1 months and half of the study population was male
Interventions	Children in the supplement-treated group received a weekly dose of 10,000 IU of vitamin A for 40 weeks, and children in the non-supplement group received a weekly placebo for the same period
Outcomes	Incidence of diarrhoea and respiratory disease morbidity. Mean vitamin A serum levels
Notes	The baseline study characteristics were comparable in both the groups. Study was conducted in a slum with substantial rates of malnutrition and subclinical vitamin A deficiency. Morbidity surveillance was done weekly

Risk of bias

Bias	Authors' judgement	Support for judgement

Adequate sequence generation?	Low risk	"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?	Low risk	"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? Blinding of Participants	Low risk	"Identical flasks containing vitamin A or placebo were numbered from 1 to 400 by members of the study team in Boston, Massachusetts." 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? Blinding of provider	Low risk	"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? Blinding of outcome assessor	Low risk	Outcome assessors were the same as the providers, therefore blinded
Incomplete outcome data addressed?	Low risk	"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 (Table 2)." Loss to follow-up similar in magnitude in

Sempertegui 1999 *(Continued)*

		both groups and for similar reasons. Some lost still contributed data
Free of selective reporting?	Unclear risk	Protocol referred to but not referenced. Not explicitly stated if all measured outcomes were reported
Free of other bias?	Low risk	No other apparent bias was noted

Shankar 1999

Methods	This study was an individually randomised trial conducted in Guinea Bissau, Africa
Participants	Children aged 6-60 months and those who plan to reside within the study area for at least 1 year were eligible for inclusion in the trial. Those with ocular signs of vitamin A deficiency or history of night blindness were excluded A total of 480 children were randomised either to vitamin A or placebo group. The vitamin A group had 239 participants whole placebo group 241. Proportion of males in the study population was 51%
Interventions	The experimental group received vitamin A supplementation in a dose of 100 000 IU for children aged < 1 year and 200,000 IU for older children. The comparison group received placebo. Both the groups received 20 IU of vitamin E. Intervention was 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
Adequate sequence generation?	Low risk	"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?	Low risk	"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? Blinding of Participants	Low risk	Identical capsules, and allocation was concealed and code kept off site. Described as double-blind

Shankar 1999 *(Continued)*

Blinding? Blinding of provider	Low risk	As above; probably done.
Blinding? Blinding of outcome assessor	Low risk	Unlikely that the trained village-based morbidity worker knew the assignments, however this is never stated explicitly Probably done.
Incomplete outcome data addressed?	Low risk	"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." Intention-to-treat used. Missing outcome data balanced in numbers across groups
Free of selective reporting?	Unclear risk	Protocol not referenced and not stated that all measured outcomes were reported. Data at 7 months not completely reported
Free of other bias?	Low risk	No other apparent bias was noted.

Sinha 1976

Methods	Individually randomised trial conducted in India, Asia.
Participants	Children aged 2 months to 4.5 years were eligible for inclusion in the trial. No exclusion criteria was described A total of 306 children were randomised either to vitamin A or placebo group in equal numbers (153 in each group)
Interventions	Children in experimental group received vitamin A in a dose of 200 000 IU every 4 months for 12 months. The comparison group received placebo only
Outcomes	Bitot spots. Side effects; vomiting.
Notes	The people in the study population were extremely poor.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	"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

Sinha 1976 (*Continued*)

		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." No detail about randomisation method provided.
Allocation concealment?	Unclear risk	"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." Insufficient details provided.
Blinding? Blinding of Participants	Low risk	"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." Probably done.
Blinding? Blinding of provider	Low risk	"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." "The placebo consisted of deodorized arachis oil which was coloured and favoured with orange to match exactly the vitamin A preparation." Provider blinded.
Blinding? Blinding of outcome assessor	Low risk	"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 addressed?	Unclear risk	Based on the outcome data reported it does not seem that any children dropped out (i. e., there were no losses); however, this could be because the authors are conducting an intent-to-treat analysis but never say so. They

Sinha 1976 *(Continued)*

		are not explicit in this regard, as such the risk of bias due to incomplete outcome data is unclear
Free of selective reporting?	Unclear risk	Does not reference a protocol or trial registration and does not state that all measured outcomes are reported
Free of other bias?	Low risk	No other apparent bias was noted.

Smith 1999

Methods	Factorial design, individually randomised trial conducted in Belize, Central America
Participants	Children aged 2.2 to 5.5 years were eligible for inclusion in the trial. Those with fever or serious respiratory illness were excluded A total of 51 children were randomised to four intervention groups. Mean age of children were 46.3 months
Interventions	The four intervention groups were as follow: Vitamin A only; received 10 000 IU vitamin A Zinc only; received 70 mg zinc Vitamin A + Zinc; received vitamin A and zinc in above mentioned dosage Placebo Duration of study was for 6 months.
Outcomes	Vitamin A serum level.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	"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." Stated to be randomised, but no further data reported.
Allocation concealment?	Unclear risk	Insufficient details provided.
Blinding? Blinding of Participants	Unclear risk	"Supplements were ingested orally in an orange flavoured powder (10 g), Tangt (Kraft General Foods Inc, White Plains, NY

Smith 1999   (*Continued*)

		10625) prepared as a beverage dissolved in approximately 120 mL of water." Stated to be "double-blind" in the article keywords, but there appear 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
Blinding? Blinding of provider	Unclear risk	Not adequately reported.
Blinding? Blinding of outcome assessor	Unclear risk	Not adequately reported.
Incomplete outcome data addressed?	Unclear risk	Insufficient details provided; losses not accounted for by group and small sample size makes this especially relevant
Free of selective reporting?	Unclear risk	Does not reference a protocol or trial registration and does not state that all measured outcomes are reported
Free of other bias?	Unclear risk	Insufficient details provided.

Sommer 1986

Methods	Cluster randomised trial conducted in a rural area of Indonesia, Asia
Participants	Children aged between 0 and 5 years were included. Children with active xerophthalmia were excluded from the study 29,236 children from 450 villages (cluster sites) in Java. 50% of the sample were male
Interventions	Vitamin A (capsules administered twice over the course of the study: 200,000 IU of Vitamin A) was compared with a no treatment control group that served as a waiting list control 40 IU of vitamin E was also administered with vitamin A. Duration of study: 9-13 months.
Outcomes	Mortality, diarrhoea, Bitot's spots, night blindness, xerophthalmia
Notes	ICC not reported (confidence intervals 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 under the age of 12 months, but it would appear that some 0 to 12 month old children received the vitamin A capsule. Outcome data were reported on a cohort of 0 to 12 month old children

Sommer 1986 *(Continued)*

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	"From a random start, 450 villages were systematically selected for the study; these were then randomised for capsule distribution after the baseline examination…" Inadequate information provided.
Allocation concealment?	Unclear risk	Inadequate information was presented in order to assess this item in relation to timing of recruitment into the study
Blinding? Blinding of Participants	Unclear risk	"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." Described as a controlled study, without adequate description of what control group received
Blinding? Blinding of provider	Unclear risk	"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." Described as a controlled study, without adequate description of what control group received
Blinding? Blinding of outcome assessor	Unclear risk	"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." Described as a controlled study, without adequate description of what control group received
Incomplete outcome data addressed?	Unclear risk	"Follow-up information was available on 89% of the programme children and 88.4% of the controls." Authors indicate percent remaining per group at follow-up, but nothing more detailed
Free of selective reporting?	Unclear risk	Trial protocol not available.

Sommer 1986 *(Continued)*

Free of other bias?	Unclear risk	Insuffcient information to permit judge-ment.

Stabell 1995

Methods	Individually randomised trial conducted in Guinea Bissau, Africa
Participants	Children aged 6 months of age years were eligible for inclusion in the trial A total of 68 children were included in which 32 were in vitamin A group and 36 in placebo
Interventions	Children in the intervention group received vitamin A in a dose of 100 000 IU at the time of measles vaccination at age of 6 and 9 months. The comparison group received placebo only
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
Adequate sequence generation?	Unclear risk	"Carrying out a double-blinded, ran-domised, placebo-controlled trial." Sequence generation not mentioned in the paper.
Allocation concealment?	Unclear risk	Nothing mentioned regarding allocation concealment.
Blinding? Blinding of Participants	Unclear risk	Claimed it was blinded but no detail pro-vided.
Blinding? Blinding of provider	Unclear risk	Claimed it was blinded but no detail pro-vided.
Blinding? Blinding of outcome assessor	Unclear risk	Children were examined by one of us (C.S.) to see if their fontanelle was normal, sunken or bulging Appears outcome assessors were the same in-dividuals as the investigators
Incomplete outcome data addressed?	Unclear risk	Losses to follow-up by group indicated but no detail provided. Unclear what losses ac-tually occurred in Table 1

Stabell 1995 (*Continued*)

Free of selective reporting?	Unclear risk	No protocol referenced, nor statement that all measured outcomes were reported
Free of other bias?	Unclear risk	Short communication, insufficient detail to make an informed judgment

Stansfield 1993

Methods	This randomised, placebo-controlled was conducted north west of Haiti, Latin America
Participants	Children aged 6 to 83 months were included in the study. Those with corneal changes consistent with vitamin A deficiency, with measles and those had received vitamin A within the past 4 months were excluded A total of 13651 children were found to be eligible for inclusion in the trial. The proportion of males in the study population was 49%
Interventions	The vitamin A group received 100,000 IU supplements every 4 months for 3 distribution cycle for those 6 to 11 months and 200,000 IU for the older, while the other group only received 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 2 study 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 lower respiratory tract infection morbidity in our review

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	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." Alternate allocation.
Allocation concealment?	Low risk	Quote from the author: "The manufacturer (Roche) held the code until the study was completed."

Stansfield 1993   *(Continued)*

Blinding? Blinding of Participants	Low risk	"The colour code was held only by the man-ufacturer until the study was completed." Probably done.
Blinding? Blinding of provider	Low risk	"Before the study inquiries among health workers and community members had indi-cated no symbolism associated with or pref-erence for either green or red." Highly unlikely that providers would be bi-ased about a single intervention
Blinding? Blinding of outcome assessor	Low risk	"The colour code was held only by the man-ufacturer until the study was completed." Probably done.
Incomplete outcome data addressed?	Low risk	"The frequency of non-participation was es-sentially identical among children from even and odd-numbered households." Probably done.
Free of selective reporting?	High risk	"We did not collect data on the impact of supplementation on vitamin A status, or on the incidence, duration, or severity of symp-toms of infection." Only mortality and morbidity outcomes given. Protocol not available
Free of other bias?	Low risk	This study appears to be free of other bias.

van Agtmaal 1988

Methods	Individually randomised, non-placebo trial conducted in Thailand, Asia
Participants	Participants had a mean age of 3.1 years. No exclusion criteria was described Study included 30 children in which 14 were in vitamin A group and 21 in control group
Interventions	Children in experimental group received a single dose vitamin A in a dose of 200 000 IU. Study participants were followed for 4 months
Outcomes	Mean vitamin A serum levels.
Notes	Children were recruited from three rural day care centres.

Risk of bias

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

van Agtmaal 1988 *(Continued)*

Adequate sequence generation?	Unclear risk	"After selection, 14 children were randomly supplemented with a single, oral dose of vitamin A (110 mg retinylpalmitate, 200, 000 IU),according to WHO recommendations (9). and 21 children served as a control group." Inadequate information provided.
Allocation concealment?	Unclear risk	Inadequate information provided.
Blinding? Blinding of Participants	Unclear risk	Inadequate information provided.
Blinding? Blinding of provider	Unclear risk	Inadequate information provided.
Blinding? Blinding of outcome assessor	Unclear risk	Inadequate information provided.
Incomplete outcome data addressed?	High risk	"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." No comprehensive data given on lost to follow-up nor reasons for loss
Free of selective reporting?	High risk	Does not report data on serum retinol levels, which were collected/measured
Free of other bias?	Unclear risk	Inadequate information provided.

Venkatarao 1996

Methods	Individual randomised trial conducted in India, Asia.
Participants	Infants aged 6 months were included. Proportion of males in the study was 50% A total of 909 infants were randomised to three intervention groups
Interventions	The three intervention groups were as follows: Group AA: Mother received and infants both received vitamin A Group AP: Mother received vitamin A while infant received placebo Group PP: Both mother and infant received placebo. Dose of vitamin A for infant was 200 000 IU.

Venkatarao 1996 (*Continued*)

Outcomes	All-cause mortality and cause specific mortality of diarrhoea and respiratory disease. Incidence of diarrhoea and respiratory disease morbidity
Notes	We have included the data for groups AA vs. AP.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	"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." Insufficient detail to form judgment.
Allocation concealment?	Unclear risk	Insufficient detail to form judgment.
Blinding? Blinding of Participants	Low risk	"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." Probably done.
Blinding? Blinding of provider	Low risk	As above; probably done.
Blinding? Blinding of outcome assessor	Low risk	As above; probably done.
Incomplete outcome data addressed?	Unclear risk	"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 anal-

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Venkatarao 1996   (*Continued*)

		yses in this report." They provided specific information about losses by group. However, it is unclear why 263, 255 and 256 infants that remain in the three group after attrition is described results in only 233 in the AA and 228 each in the AP and PP groups being used as the basis for analysis
Free of selective reporting?	Low risk	Does not reference a protocol or trial registration and do not state that all measured outcomes are reported
Free of other bias?	Low risk	"Quality control of the morbidity data collected by the field investigators was undertaken throughout. As long recall periods pose problems, the collection of morbidity data was intensified from once a fortnight to once a week when the study had been in progress for 9 months." Authors attempted to minimise other biases such as recall bias, though specific details of "quality control" are not provided

Vijayaraghavan 1990

Methods	Cluster randomised study in rural India, Asia.
Participants	Children aged 1-5 years were eligible for entry in the study. Children with corneal involvement were excluded from the review 15,775 children in 84 clusters were randomised to the treatment groups. 50.4% participants were male
Interventions	Vitamin A given twice (200,000 IU) versus placebo (archis oil) Study duration: not clear.
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
Adequate sequence generation?	Unclear risk	"The villages were allocated randomly into two groups-treatment and control." Insufficient detail to form judgment.

Vijayaraghavan 1990 *(Continued)*

Allocation concealment?	Unclear risk	Insufficient detail provided.
Blinding? Blinding of Participants	Low risk	"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? Blinding of provider	Low risk	As above; probably done.
Blinding? Blinding of outcome assessor	Low risk	As above probably done.
Incomplete outcome data addressed?	Unclear risk	Insufficient detail provided.
Free of selective reporting?	High risk	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
Free of other bias?	Low risk	This study appears to be free of other bias.

West 1991

Methods	Cluster randomised study in rural Nepal, Asia.
Participants	Children aged between 0 and 5 years were eligible for the study. Children with xerophthalmia were included. Children who had recently participated in a Vitamin A programme were excluded from the study 28,630 children in 261 clusters were recruited. 51.3% sample was male
Interventions	Vitamin A (100,000 IU for 6-11 months and 200,000 IU for children 12 months and older) administered 1 to 3 times was compared with a very low dose of vitamin A (1000 IU). Both supplements contained 40 IU vitamin E 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 and 2018 children entered at 4 and 8 months

Risk of bias

West 1991 (*Continued*)

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	"After blocking on the local development area, the 261 wards were randomly assigned to receive vitamin A supplementation or placebos at 4-month intervals." Inadequately described to permit judgment.
Allocation concealment?	Unclear risk	"Both the investigators and communities were masked to the random assignment." The study was a cluster-designed trial and there was insufficient information to determine whether allocation took place before or after treatment group assignment was known
Blinding? Blinding of Participants	Low risk	"The supplements were given as single-dose gelatin capsules of identical taste and appearance."
Blinding? Blinding of provider	Low risk	As above; probably done.
Blinding? Blinding of outcome assessor	Low risk	As above; probably done.
Incomplete outcome data addressed?	Unclear risk	"All analyses were carried out on an intention-to-treat basis. Computed mortality rates were based on child-years of observation." "...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.'" The rates of withdrawal were balanced between the treatment 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 is at risk of attrition bias

West 1991   *(Continued)*

Free of selective reporting?	Low risk	Complete data for all time points were available for the review. The last available observation reported in a follow-up article gave a RR for mortality slightly higher than that for the 12 month data given in the primary study report (0.74 versus 0.7)
Free of other bias?	Low risk	A method for estimating the ICCs was reported in Katz 1988 (Journal of international epidemiology)

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

Study	Reason for exclusion
Bahl 1997	The study included children currently having diarrhoea.
Bhaskaram 1997	The study was not a randomised controlled trial.
Bloem 1990	The study was not a randomised controlled trial. The mean age of children was 6.6 years (range 3-9 years)
Kothari 1991	The study was not a randomised controlled trial.
Semba 1990	Vitamin A was given as a therapeutic intervention for Bitot's spots
Semba 2005	The study population consisted of children infected with HIV
Wu 2007	The study was not a randomised controlled trial.
Yang 2002	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

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

Aklamati 2006

Methods	Individually randomised, placebo-controlled trial conducted in Zambia, Africa
Participants	Boys 3-4 years old were eligible for inclusion in the trial. A total of 36 children were included in the trial in which 19 were in vitamin A and 17 in placebo group
Interventions	The intervention group received a single dose of 60 mg vitamin A and control group received the same amount of placebo

Aklamati 2006   (Continued)

Outcomes	Mean plasma retinol levels, prevalence of fever, diarrhoea, rhinorrhoea, cough and malaria
Notes	Data were available only in the form of abstract and the numbers do not match given in the results section of abstract. It was decided among the group to wait for publication of this study before we include it in the review

DEVTA trial 2007

Methods	Cluster-randomised trial conducted in Northern India, Asia.
Participants	Children aged 1-6 years were eligible for inclusion in the review. Total clusters were 72 in which 36 clusters received vitamin A supplementation while 36 acted as control. Authors claim to include a total of 1 million children in the trial
Interventions	Children in experimental group received 200,000 IU of vitamin A every 6-months for 5 years. Vitamin A was supplemented on mass treatment days by village child care workers
Outcomes	All-cause mortality, cause specific mortality of diarrhoea, pneumonia, measles and malnutrition. Mean vitamin A serum levels, incidence of Bitot's spots and prevalence of measles and pneumonia morbidity
Notes	This is the largest randomised controlled trial conducted on vitamin A but has not been published yet. The current data is based on the abstract presented in ILSI Micronutrient Forum, Istanbul, 16-18 April 2007. It does not contain detail information on conduct of trial neither it give details on attrition of the study. We contacted all the authors of the trial multiple times and asked for more details on methods and results but did not receive any positive response. As we did not have sufficient information on methods and outcome we decided to wait for publication of results of this large trial. We aim to include that in the next update of this 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 Mortality (all-cause) at Longest Follow-up	17		Risk Ratio (Fixed, 95% CI)	0.76 [0.69, 0.83]
2 Mortality (all-cause) at Longest Follow-up (by Age)	5		Risk Ratio (Fixed, 95% CI)	Subtotals only
2.1 6 to 12 months old	4		Risk Ratio (Fixed, 95% CI)	0.59 [0.43, 0.82]
2.2 1 to 5 years old	4		Risk Ratio (Fixed, 95% CI)	0.68 [0.57, 0.81]
3 Mortality (all-cause) at Longest Follow-up (by Sex)	5		Risk Ratio (Fixed, 95% CI)	Subtotals only
3.1 Males	5		Risk Ratio (Fixed, 95% CI)	0.80 [0.66, 0.97]
3.2 Females	5		Risk Ratio (Fixed, 95% CI)	0.79 [0.65, 0.95]
4 Mortality (all-cause) at Longest Follow-up (Sensitivity Analysis including DEVTA trial)	18		Risk Ratio (Fixed, 95% CI)	0.88 [0.84, 0.94]
5 Mortality due to Diarrhoea at Longest Follow-up	7		Risk Ratio (Fixed, 95% CI)	0.72 [0.57, 0.91]
6 Mortality due to Measles at Longest Follow-up	5		Risk Ratio (Fixed, 95% CI)	0.80 [0.51, 1.24]
7 Mortality due to Meningitis at Longest Follow-up	3		Risk Ratio (Fixed, 95% CI)	0.57 [0.17, 1.88]
8 Mortality due to LRTI at Longest Follow-up	7		Risk Ratio (Fixed, 95% CI)	0.78 [0.54, 1.14]
9 Diarrhoea Incidence at Longest Follow-up	13		Risk Ratio (Fixed, 95% CI)	0.85 [0.82, 0.87]
10 Diarrhoea Prevalence at Longest Follow-up	3		Risk Ratio (Fixed, 95% CI)	1.08 [1.05, 1.12]
11 Measles Incidence at Longest Follow-up	6		Risk Ratio (Fixed, 95% CI)	0.50 [0.37, 0.67]
12 Malaria Incidence at Longest Follow-up	1	174132	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.60, 0.88]
13 Malaria Prevalence at Longest Follow-up	2		Risk Ratio (Fixed, 95% CI)	0.73 [0.41, 1.28]
14 Lower Respiratory Tract Infection Incidence at Longest Follow-up	9		Risk Ratio (Fixed, 95% CI)	1.14 [0.95, 1.37]
15 Bitot's Spots Prevalence at Longest Follow-up	4		Risk Ratio (Fixed, 95% CI)	0.45 [0.33, 0.61]
16 Night Blindness Incidence at Longest Follow-up	1		Risk Ratio (Fixed, 95% CI)	0.53 [0.28, 0.99]
17 Night Blindness Prevalence at Longest Follow-up	2		Risk Ratio (Fixed, 95% CI)	0.32 [0.21, 0.50]
18 Xerophthalmia Incidence at Longest Follow-up	3		Risk Ratio (Fixed, 95% CI)	0.85 [0.70, 1.03]

19 Xerophthalmia Prevalence at Longest Follow-up	2	Risk Ratio (Fixed, 95% CI)	0.31 [0.22, 0.45]
20 Vitamin A Deficient at Longest Follow-up	4	2262	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.65, 0.78]
21 Vitamin A Serum Level at Longest Follow-up	14	6623	Std. Mean Difference (IV, Fixed, 95% CI)	0.31 [0.26, 0.36]
22 Hospitalisation, Number of Children Hospitalised Once or More at Longest Follow-up	1	1185	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.40, 1.02]
23 Hospitalisation due to Diarrhoea at Longest Follow-up	1	172	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.01, 6.11]
24 Hospitalisation due to Lower Respiratory Tract Infection at Longest Follow-up	1	172	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 2.06]
25 Side effect - Bulging Fontanelle	3	885	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.24, 103.72]
26 Side effect - Vomiting	3	2994	Risk Ratio (M-H, Fixed, 95% CI)	2.75 [1.81, 4.19]

Analysis 1.1. Comparison 1 Vitamin A versus Control, Outcome 1 Mortality (all-cause) at Longest Follow-up.

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

Comparison: 1 Vitamin A versus Control

Outcome: 1 Mortality (all-cause) at Longest Follow-up

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Lin 2008	0 (0)			Not estimable
Dibley 1994	-1.12232882 (1.63299316)		0.1 %	0.33 [0.01, 7.99]
Barreto 1994	0 (0.99838579)		0.2 %	1.00 [0.14, 7.08]
Chowdhury 2002	-1.94194975 (0.75418055)		0.4 %	0.14 [0.03, 0.63]
Venkatarao 1996	-1.00252208 (0.67056359)		0.5 %	0.37 [0.10, 1.37]
Benn 1997	-0.77629472 (0.59367542)		0.7 %	0.46 [0.14, 1.47]
Donnen 1998	-0.51082562 (0.48464603)		1.0 %	0.60 [0.23, 1.55]
Ross 1993 HEALTH	-1.21578729 (0.46547467)		1.1 %	0.30 [0.12, 0.74]
Agarwal 1995	0.19717994 (0.31208317)		2.5 %	1.22 [0.66, 2.25]
Vijayaraghavan 1990	0.01685569 (0.2971801)		2.7 %	1.02 [0.57, 1.82]
Pant 1996	-0.56211892 (0.222204)		4.9 %	0.57 [0.37, 0.88]
Rahmathullah 1990	-0.77652879 (0.21976998)		5.0 %	0.46 [0.30, 0.71]

0.005   0.1   1   10   200

Favours experimental   Favours control

(*Continued* . . .)

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Sommer 1986	-0.30788478 (0.15462932)		10.1 %	0.73 [0.54, 1.00]
Daulaire 1992	-0.30110509 (0.14994833)		10.7 %	0.74 [0.55, 0.99]
Herrera 1992	0.05826891 (0.13093651)		14.1 %	1.06 [0.82, 1.37]
West 1991	-0.35667494 (0.11530445)		18.1 %	0.70 [0.56, 0.88]
Ross 1993 SURVIVAL	-0.21072103 (0.09323125)		27.8 %	0.81 [0.67, 0.97]
Total (95% CI)			**100.0 %**	**0.76 [0.69, 0.83]**

Heterogeneity: Chi² = 29.10, df = 15 (P = 0.02); I² =48%

Test for overall effect: Z = 5.66 (P < 0.00001)

Test for subgroup differences: Not applicable

```
          0.005   0.1    1    10    200
```
Favours experimental   Favours control

Analysis 1.2.   Comparison 1 Vitamin A versus Control, Outcome 2 Mortality (all-cause) at Longest Follow-up (by Age).

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

Comparison: 1 Vitamin A versus Control

Outcome: 2 Mortality (all-cause) at Longest Follow-up (by Age)

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 6 to 12 months old				
Benn 1997	-0.77629472 (0.59367542)		7.8 %	0.46 [0.14, 1.47]
Rahmathullah 1990	-1.27296568 (0.57282345)		8.4 %	0.28 [0.09, 0.86]
Daulaire 1992	-0.67334455 (0.277413)		35.7 %	0.51 [0.30, 0.88]
West 1991	-0.24846136 (0.23890578)		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 = 0.0015)

2 1 to 5 years old

```
          0.2    0.5    1    2    5
```
Favours experimental   Favours control

(*Continued* . . .)

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Rahmathullah 1990	-0.7070956 (0.22771697)		15.6 %	0.49 [0.32, 0.77]
Sommer 1986	-0.29453409 (0.20231495)		19.7 %	0.74 [0.50, 1.11]
Daulaire 1992	-0.24486372 (0.19475576)		21.3 %	0.78 [0.53, 1.15]
West 1991	-0.38720694 (0.13644798)		43.4 %	0.68 [0.52, 0.89]
Subtotal (95% CI)			**100.0 %**	**0.68 [0.57, 0.81]**

Heterogeneity: Chi^2 = 2.72, df = 3 (P = 0.44); I^2 =0.0%

Test for overall effect: Z = 4.32 (P = 0.000015)

Test for subgroup differences: Chi^2 = 0.54, df = 1 (P = 0.46), I^2 =0.0%

```
              0.2   0.5    1    2     5

        Favours experimental    Favours control
```

Analysis 1.3. Comparison 1 Vitamin A versus Control, Outcome 3 Mortality (all-cause) at Longest Follow-up (by Sex).

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

Comparison: 1 Vitamin A versus Control

Outcome: 3 Mortality (all-cause) at Longest Follow-up (by Sex)

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Males				
Lin 2008	0 (0)			Not estimable
Daulaire 1992	-0.32850407 (0.20687375)		21.8 %	0.72 [0.48, 1.08]
Sommer 1986	-0.52763274 (0.20154834)		23.0 %	0.59 [0.40, 0.88]
Herrera 1992	0.22314355 (0.19562474)		24.4 %	1.25 [0.85, 1.83]
West 1991	-0.26136476 (0.17449675)		30.7 %	0.77 [0.55, 1.08]
Subtotal (95% CI)			**100.0 %**	**0.80 [0.66, 0.97]**

Heterogeneity: Chi^2 = 7.79, df = 3 (P = 0.05); I^2 =62%

Test for overall effect: Z = 2.26 (P = 0.024)

2 Females

```
              0.2   0.5    1    2     5

        Favours Vitamin A    Favours control
```

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Lin 2008	0 (0)			Not estimable
Daulaire 1992	-0.27443685 (0.23161713)		16.7 %	0.76 [0.48, 1.20]
Sommer 1986	-0.08664781 (0.22406373)		17.9 %	0.92 [0.59, 1.42]
Herrera 1992	-0.07257069 (0.17488653)		29.3 %	0.93 [0.66, 1.31]
West 1991	-0.43078292 (0.15751191)		36.1 %	0.65 [0.48, 0.89]
Subtotal (95% CI)			**100.0 %**	**0.79 [0.65, 0.95]**

Heterogeneity: Chi² = 2.87, df = 3 (P = 0.41); I² =0.0%

Test for overall effect: Z = 2.52 (P = 0.012)

Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² =0.0%

0.2 0.5 1 2 5

Favours Vitamin A   Favours control

Analysis 1.4. Comparison 1 Vitamin A versus Control, Outcome 4 Mortality (all-cause) at Longest Follow-up (Sensitivity Analysis including DEVTA trial).

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

Comparison: 1 Vitamin A versus Control

Outcome: 4 Mortality (all-cause) at Longest Follow-up (Sensitivity Analysis including DEVTA trial)

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Lin 2008	0 (0)			Not estimable
Dibley 1994	-1.12232882 (1.63299316)		0.0 %	0.33 [0.01, 7.99]
Barreto 1994	0 (0.99838579)		0.1 %	1.00 [0.14, 7.08]
Chowdhury 2002	-1.94194975 (0.75418055)		0.1 %	0.14 [0.03, 0.63]
Venkatarao 1996	-1.00252208 (0.67056359)		0.2 %	0.37 [0.10, 1.37]
Benn 1997	-0.77629472 (0.59367542)		0.2 %	0.46 [0.14, 1.47]
Donnen 1998	-0.51082562 (0.48464603)		0.4 %	0.60 [0.23, 1.55]
Ross 1993 HEALTH	-1.21578729 (0.46547467)		0.4 %	0.30 [0.12, 0.74]

0.02 0.1 1 10 50

Favours experimental   Favours control

(*Continued* . . .)

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Agarwal 1995	0.19717994 (0.31208317)		0.9 %	1.22 [0.66, 2.25]
Vijayaraghavan 1990	0.01685569 (0.2971801)		1.0 %	1.02 [0.57, 1.82]
Pant 1996	-0.56211892 (0.222204)		1.7 %	0.57 [0.37, 0.88]
Rahmathullah 1990	-0.77652879 (0.21976998)		1.7 %	0.46 [0.30, 0.71]
Sommer 1986	-0.30788478 (0.15462932)		3.5 %	0.73 [0.54, 1.00]
Daulaire 1992	-0.30110509 (0.14994833)		3.7 %	0.74 [0.55, 0.99]
Herrera 1992	0.05826891 (0.13093651)		4.9 %	1.06 [0.82, 1.37]
West 1991	-0.35667494 (0.11530445)		6.3 %	0.70 [0.56, 0.88]
Ross 1993 SURVIVAL	-0.21072103 (0.09323125)		9.7 %	0.81 [0.67, 0.97]
DEVTA 2007	-0.040821 (0.03587)		65.2 %	0.96 [0.89, 1.03]
Total (95% CI)			**100.0 %**	**0.88 [0.84, 0.94]**

Heterogeneity: Chi² = 44.31, df = 16 (P = 0.00018); I² =64%

Test for overall effect: Z = 4.26 (P = 0.000021)

Test for subgroup differences: Not applicable

0.02   0.1   1   10   50

Favours experimental   Favours control

Analysis 1.5. Comparison 1 Vitamin A versus Control, Outcome 5 Mortality due to Diarrhoea at Longest Follow-up.

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

Comparison: 1 Vitamin A versus Control

Outcome: 5 Mortality due to Diarrhoea at Longest Follow-up

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Venkatarao 1996	-1.63103702 (1.54640217)		0.6 %	0.20 [0.01, 4.05]
Agarwal 1995	-0.20721746 (0.97927464)		1.4 %	0.81 [0.12, 5.54]
Chowdhury 2002	-1.09465189 (0.81487815)		2.0 %	0.33 [0.07, 1.65]
Rahmathullah 1990	-0.73396918 (0.35365302)		10.8 %	0.48 [0.24, 0.96]
Ross 1993 SURVIVAL	-0.40047757 (0.28906104)		16.2 %	0.67 [0.38, 1.18]
Herrera 1992	0.00995033 (0.20011557)		33.8 %	1.01 [0.68, 1.50]
Daulaire 1992	-0.43078292 (0.1963524)		35.1 %	0.65 [0.44, 0.96]
Total (95% CI)			**100.0 %**	**0.72 [0.57, 0.91]**

Heterogeneity: Chi² = 6.12, df = 6 (P = 0.41); I² =2%

Test for overall effect: Z = 2.81 (P = 0.0050)

Test for subgroup differences: Not applicable

0.2   0.5   1   2   5

Favours experimental   Favours control

Analysis 1.6. Comparison 1 Vitamin A versus Control, Outcome 6 Mortality due to Measles at Longest Follow-up.

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

Comparison: 1 Vitamin A versus Control

Outcome: 6 Mortality due to Measles at Longest Follow-up

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Daulaire 1992	-0.40047757 (1.15075061)		3.8 %	0.67 [0.07, 6.39]
Agarwal 1995	-0.08776798 (0.82108156)		7.5 %	0.92 [0.18, 4.58]
Herrera 1992	-0.01005034 (0.81548188)		7.6 %	0.99 [0.20, 4.90]
Rahmathullah 1990	-0.54472718 (0.61845066)		13.2 %	0.58 [0.17, 1.95]
Ross 1993 SURVIVAL	-0.19845094 (0.27307681)		67.8 %	0.82 [0.48, 1.40]
Total (95% CI)			**100.0 %**	**0.80 [0.51, 1.24]**

Heterogeneity: Chi² = 0.40, df = 4 (P = 0.98); I² =0.0%

Test for overall effect: Z = 1.02 (P = 0.31)

Test for subgroup differences: Not applicable

0.2   0.5   1   2   5

Favours experimental   Favours control

Review: Vitamin A supplementation for preventing morbidity and mortality in children from 6 months to 5 years of age
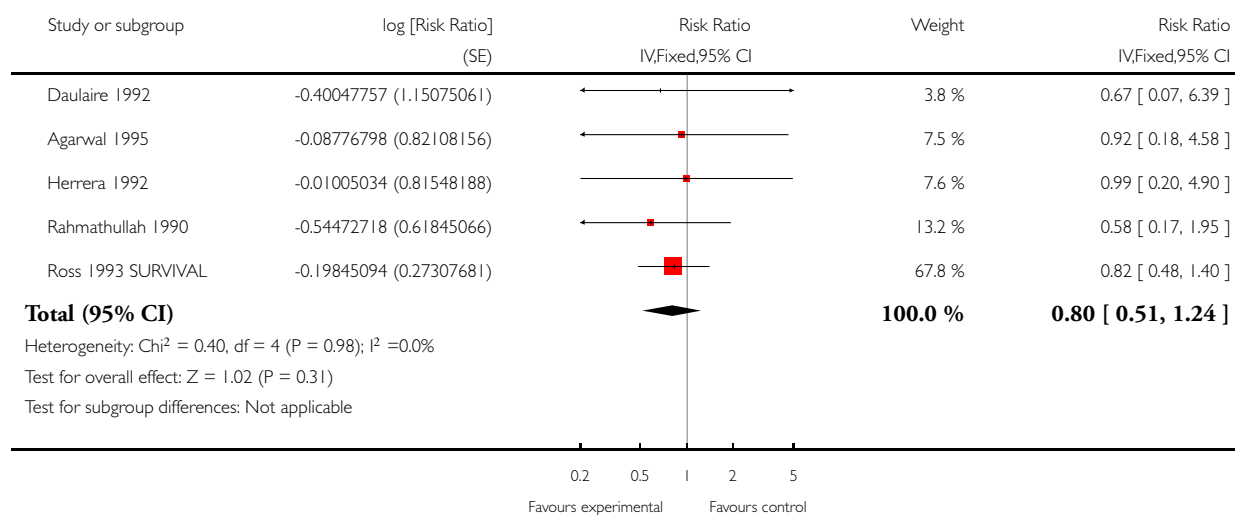
Comparison: 1 Vitamin A versus Control

Outcome: 7 Mortality due to Meningitis at Longest Follow-up

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Agarwal 1995	1.75683202 (4.64421868)		1.7 %	5.79 [0.00, 52017.39]
Chowdhury 2002	-1.60548273 (1.54834208)		15.5 %	0.20 [0.01, 4.18]
Ross 1993 SURVIVAL	-0.41551544 (0.67018608)		82.8 %	0.66 [0.18, 2.45]
Total (95% CI)			**100.0 %**	**0.57 [0.17, 1.88]**

Heterogeneity: Chi² = 0.75, df = 2 (P = 0.69); I² =0.0%

Test for overall effect: Z = 0.92 (P = 0.36)

Test for subgroup differences: Not applicable

0.2   0.5   1   2   5

Favours experimental   Favours control

Analysis 1.8. Comparison 1 Vitamin A versus Control, Outcome 8 Mortality due to LRTI at Longest Follow-up.

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

Comparison: 1 Vitamin A versus Control

Outcome: 8 Mortality due to LRTI at Longest Follow-up

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Agarwal 1995	0.65812976 (2.04734345)		0.9 %	1.93 [0.03, 106.79]
Chowdhury 2002	-2.1932694 (1.48982732)		1.6 %	0.11 [0.01, 2.07]
Venkatarao 1996	-2.41949439 (1.47417023)		1.7 %	0.09 [0.00, 1.60]
Rahmathullah 1990	-0.41960374 (0.97794112)		3.8 %	0.66 [0.10, 4.47]
Daulaire 1992	-0.0512933 (0.46262388)		17.0 %	0.95 [0.38, 2.35]
Herrera 1992	-0.84397007 (0.44990332)		18.0 %	0.43 [0.18, 1.04]
Ross 1993 SURVIVAL	0 (0.25229866)		57.1 %	1.00 [0.61, 1.64]
Total (95% CI)			**100.0 %**	**0.78 [0.54, 1.14]**

Heterogeneity: Chi² = 7.00, df = 6 (P = 0.32); I² =14%

Test for overall effect: Z = 1.29 (P = 0.20)

Test for subgroup differences: Not applicable

0.2   0.5   1   2   5

Favours experimental   Favours control

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

Comparison: 1 Vitamin A versus Control

Outcome: 9 Diarrhoea Incidence at Longest Follow-up

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Ramakrishnan 1995	0 (0)			Not estimable
Arya 2000	-0.05239118 (0.37658957)		0.2 %	0.95 [0.45, 1.99]
Florentino 1990	0.06586282 (0.17621784)		0.8 %	1.07 [0.76, 1.51]
Cheng 1993	-0.908 (0.148)		1.1 %	0.40 [0.30, 0.54]
Herrera 1992	-0.56211892 (0.14529176)		1.2 %	0.57 [0.43, 0.76]
Biswas 1994	-0.24965025 (0.12277836)		1.6 %	0.78 [0.61, 0.99]
Venkatarao 1996	0.00509449 (0.09449959)		2.7 %	1.01 [0.84, 1.21]
Long 2007	-0.08320386 (0.09312839)		2.8 %	0.92 [0.77, 1.10]
Sempertegui 1999	0.07696104 (0.08224603)		3.6 %	1.08 [0.92, 1.27]
Shankar 1999	0.15829506 (0.08218736)		3.6 %	1.17 [1.00, 1.38]
Dibley 1994	0.06023817 (0.05528549)		8.0 %	1.06 [0.95, 1.18]
Chowdhury 2002	-0.483344 (0.0297044)		27.6 %	0.62 [0.58, 0.65]
Barreto 1994	-0.05304077 (0.02280902)		46.8 %	0.95 [0.91, 0.99]
Total (95% CI)			**100.0 %**	**0.85 [0.82, 0.87]**

Heterogeneity: Chi^2 = 218.62, df = 11 (P<0.00001); I^2 =95%

Test for overall effect: Z = 10.73 (P < 0.00001)

Test for subgroup differences: Not applicable

0.2   0.5   1   2   5

Favours experimental   Favours control

Analysis 1.10. Comparison 1 Vitamin A versus Control, Outcome 10 Diarrhoea Prevalence at Longest Follow-up.

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

Comparison: 1 Vitamin A versus Control

Outcome: 10 Diarrhoea Prevalence at Longest Follow-up

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Long 2006 (2)	-0.14912003 (0.07061765)		6.1 %	0.86 [0.75, 0.99]
Long 2006	0.23629885 (0.06888881)		6.5 %	1.27 [1.11, 1.45]
Stansfield 1993	0.0861777 (0.01873184)		87.4 %	1.09 [1.05, 1.13]
Total (95% CI)			**100.0 %**	**1.08 [1.05, 1.12]**

Heterogeneity: Chi² = 15.78, df = 2 (P = 0.00038); I² =87%

Test for overall effect: Z = 4.65 (P < 0.00001)

Test for subgroup differences: Not applicable

0.2   0.5   1   2   5

Favours experimental   Favours control

Analysis 1.11.   Comparison 1 Vitamin A versus Control, Outcome 11 Measles Incidence at Longest Follow-up.

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

Comparison: 1 Vitamin A versus Control

Outcome: 11 Measles Incidence at Longest Follow-up

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Bahl 1999	-0.84729786 (0.68535975)		4.9 %	0.43 [0.11, 1.64]
Barreto 1994	-0.58778667 (0.55487413)		7.5 %	0.56 [0.19, 1.65]
Benn 1997	-0.75382186 (0.53127063)		8.2 %	0.47 [0.17, 1.33]
Herrera 1992	-0.51082562 (0.46579746)		10.7 %	0.60 [0.24, 1.49]
Semba 1995	-0.59969157 (0.30298271)		25.2 %	0.55 [0.30, 0.99]
Chowdhury 2002	-0.79838607 (0.2303533)		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 =0.0%

Test for overall effect: Z = 4.61 (P < 0.00001)

Test for subgroup differences: Not applicable

0.05   0.2   1   5   20

Favours experimental   Favours control

Analysis 1.12. Comparison 1 Vitamin A versus Control, Outcome 12 Malaria Incidence at Longest Follow-up.

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

Comparison: 1 Vitamin A versus Control

Outcome: 12 Malaria Incidence at Longest Follow-up

Study or subgroup	Vitamin A n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Shankar 1999	178/86184	249/87948		100.0 %	0.73 [0.60, 0.88]
Total (95% CI)	**86184**	**87948**		**100.0 %**	**0.73 [0.60, 0.88]**
Total events: 178 (Vitamin A), 249 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.22 (P = 0.0013)					
Test for subgroup differences: Not applicable					

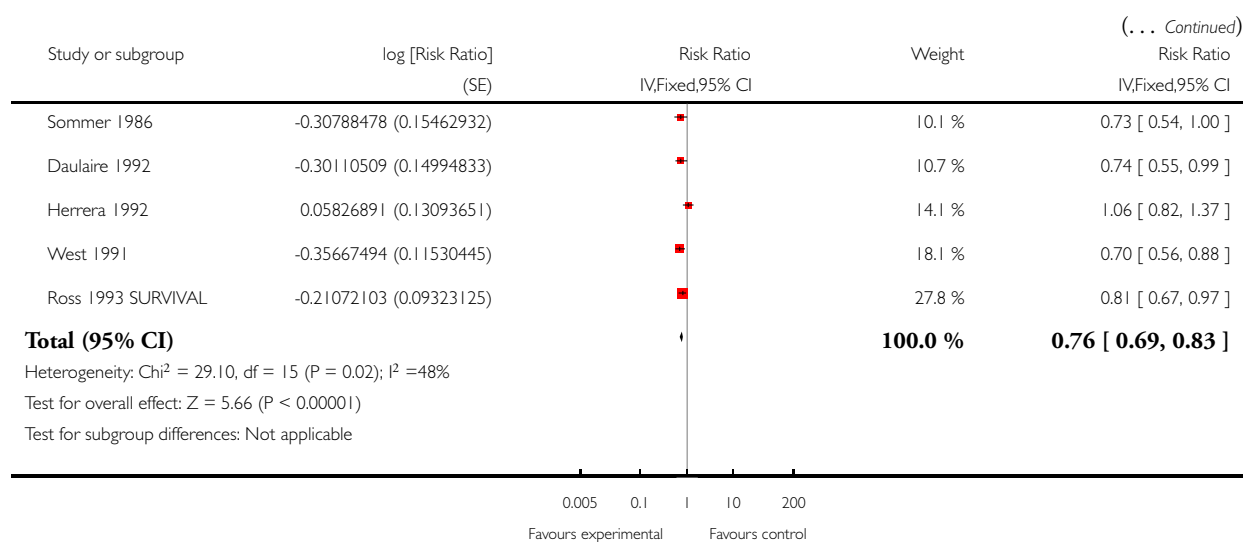0.5 0.7 1 1.5 2

Favours experimental   Favours control

Analysis 1.13. Comparison 1 Vitamin A versus Control, Outcome 13 Malaria Prevalence at Longest Follow-up.

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

Comparison: 1 Vitamin A versus Control
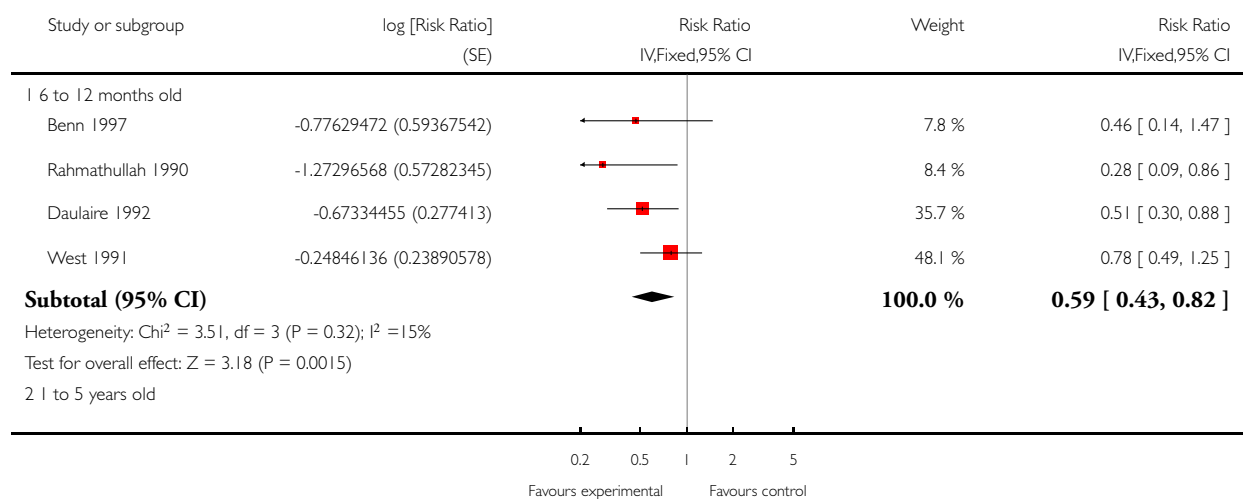
Outcome: 13 Malaria Prevalence at Longest Follow-up

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Ross 1993 HEALTH	-0.26678172 (0.44848533)		41.9 %	0.77 [0.32, 1.84]
Ross 1993 SURVIVAL	-0.35762368 (0.38106886)		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 =0.0%				
Test for overall effect: Z = 1.10 (P = 0.27)				
Test for subgroup differences: Not applicable				

0.2 0.5 1 2 5
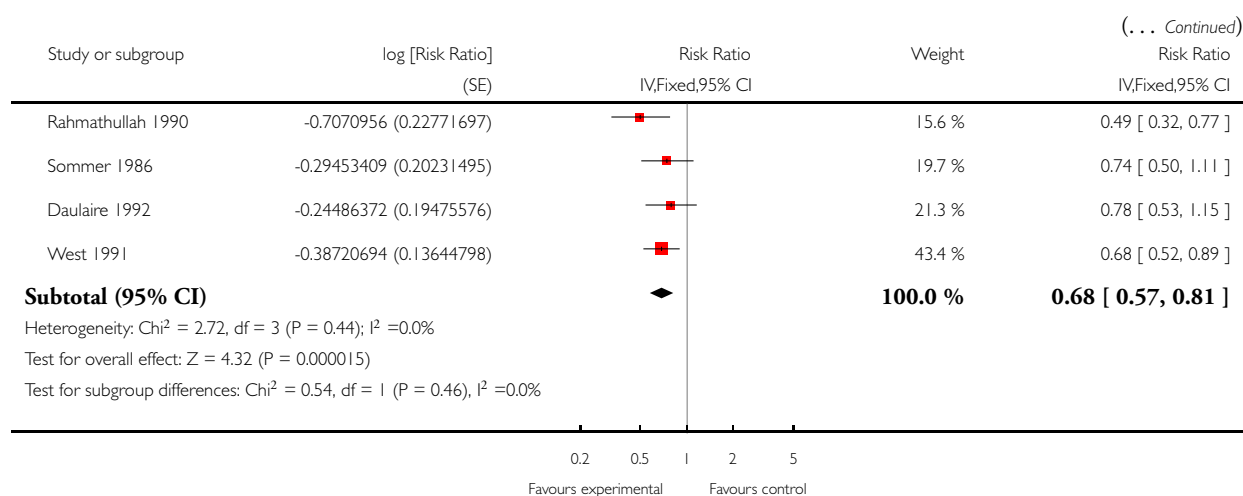
Favours experimental   Favours control

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

Comparison: 1 Vitamin A versus Control

Outcome: 14 Lower Respiratory Tract Infection Incidence at Longest Follow-up

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Barreto 1994	0 (0)			Not estimable
Venkatarao 1996	0 (0)			Not estimable
Cheng 1993	-1.37951467 (1.14438444)		0.7 %	0.25 [0.03, 2.37]
Kartasasmita 1995	0.12656272 (0.35766972)		6.7 %	1.13 [0.56, 2.29]
Biswas 1994	-0.37970097 (0.35042279)		7.0 %	0.68 [0.34, 1.36]
Long 2007	0.4069042 (0.31700189)		8.6 %	1.50 [0.81, 2.80]
Rahmathullah 1990	0.00995033 (0.27014451)		11.8 %	1.01 [0.59, 1.72]
Sempertegui 1999	-0.05286182 (0.19176712)		23.5 %	0.95 [0.65, 1.38]
Chowdhury 2002	0.33021493 (0.14380055)		41.7 %	1.39 [1.05, 1.84]
Total (95% CI)			**100.0 %**	**1.14 [0.95, 1.37]**

Heterogeneity: Chi² = 7.66, df = 6 (P = 0.26); I² =22%

Test for overall effect: Z = 1.45 (P = 0.15)

Test for subgroup differences: Not applicable

```
       0.05    0.2     1      5     20
       Favours experimental   Favours control
```
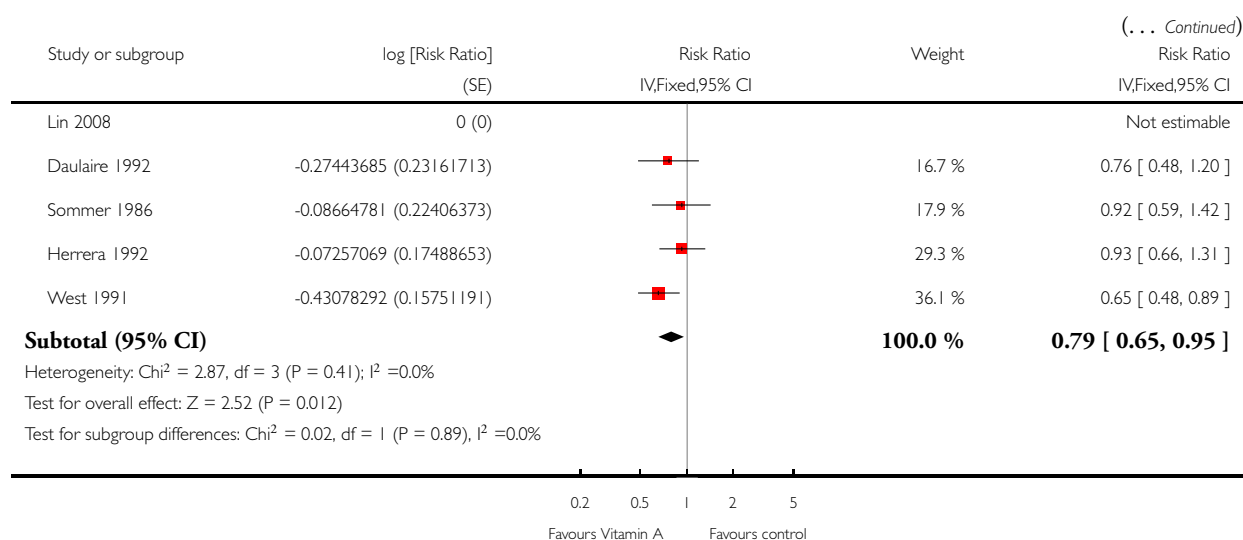
Analysis 1.15.   Comparison 1 Vitamin A versus Control, Outcome 15 Bitot's Spots Prevalence at Longest Follow-up.

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

Comparison: 1 Vitamin A versus Control

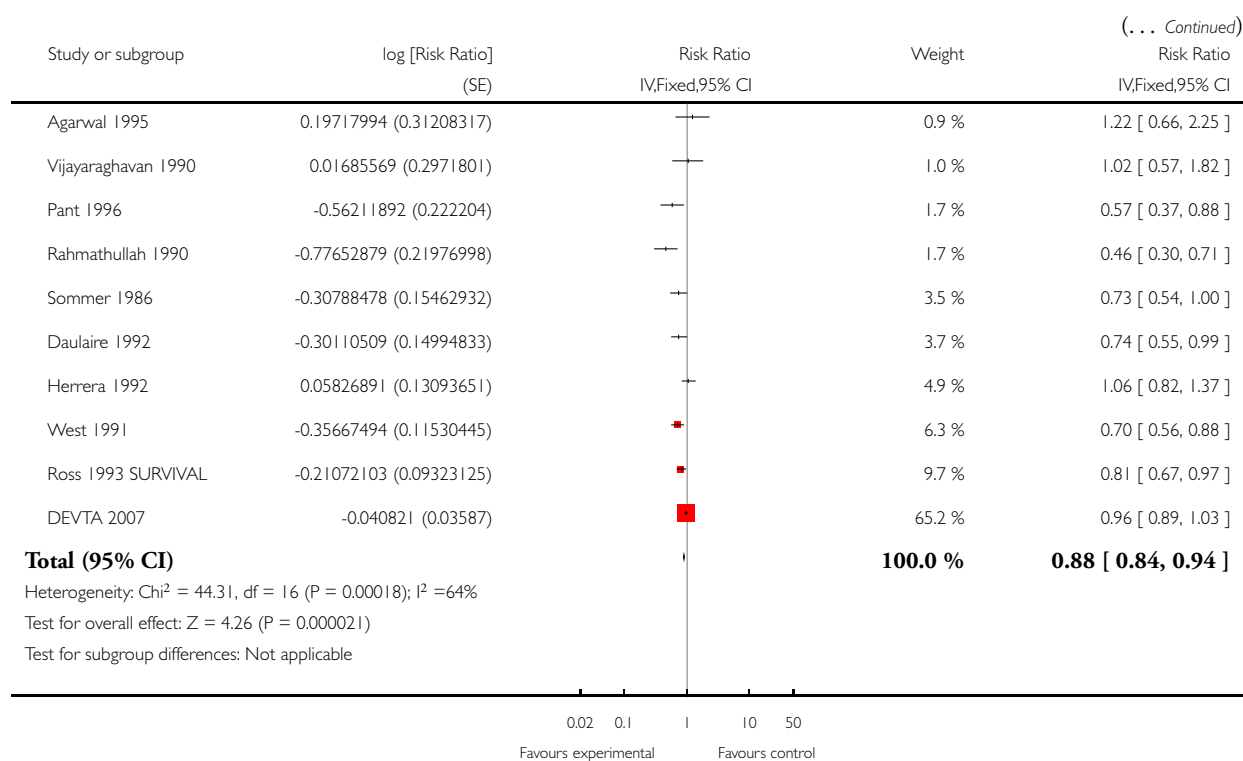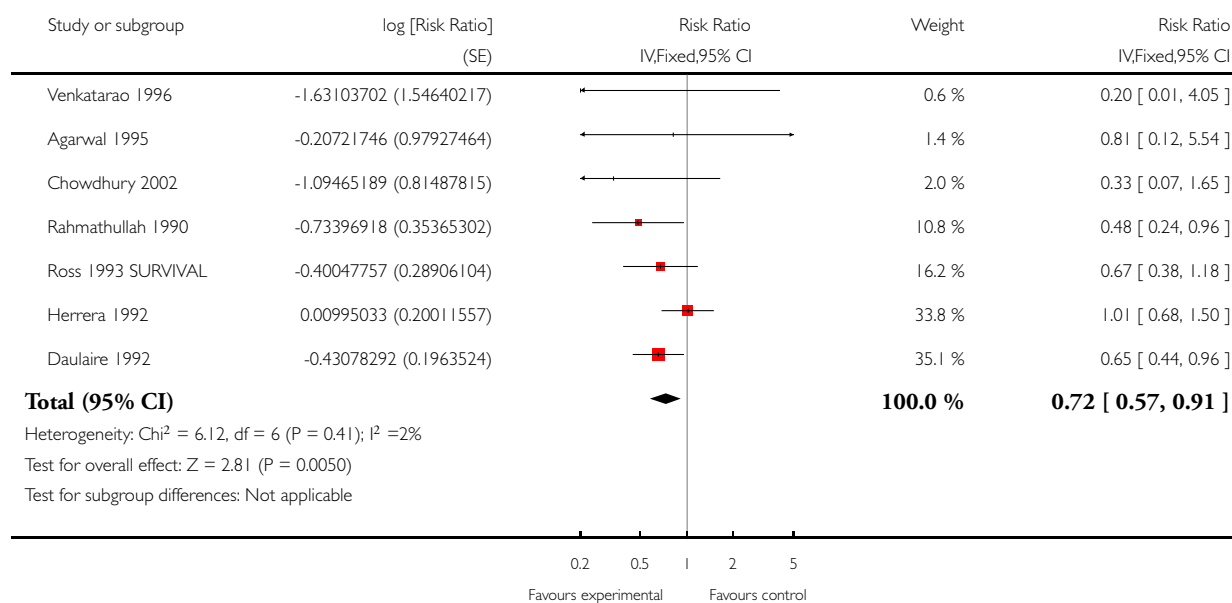Outcome: 15 Bitot's Spots Prevalence at Longest Follow-up

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
West 1991	-1.07022431 (0.42961474)		13.3 %	0.34 [0.15, 0.80]
Sommer 1986	-1.64309041 (0.36822214)		18.1 %	0.19 [0.09, 0.40]
Sinha 1976	-0.54361545 (0.27338933)		32.9 %	0.58 [0.34, 0.99]
Pant 1996	-0.52763274 (0.26293555)		35.6 %	0.59 [0.35, 0.99]
Total (95% CI)			**100.0 %**	**0.45 [0.33, 0.61]**

Heterogeneity: Chi² = 7.59, df = 3 (P = 0.06); I² =60%

Test for overall effect: Z = 5.15 (P < 0.00001)

Test for subgroup differences: Not applicable

0.1   0.2   0.5   1   2   5   10

Favours experimental   Favours control

Analysis 1.16.   Comparison 1 Vitamin A versus Control, Outcome 16 Night Blindness Incidence at Longest Follow-up.

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

Comparison: 1 Vitamin A versus Control

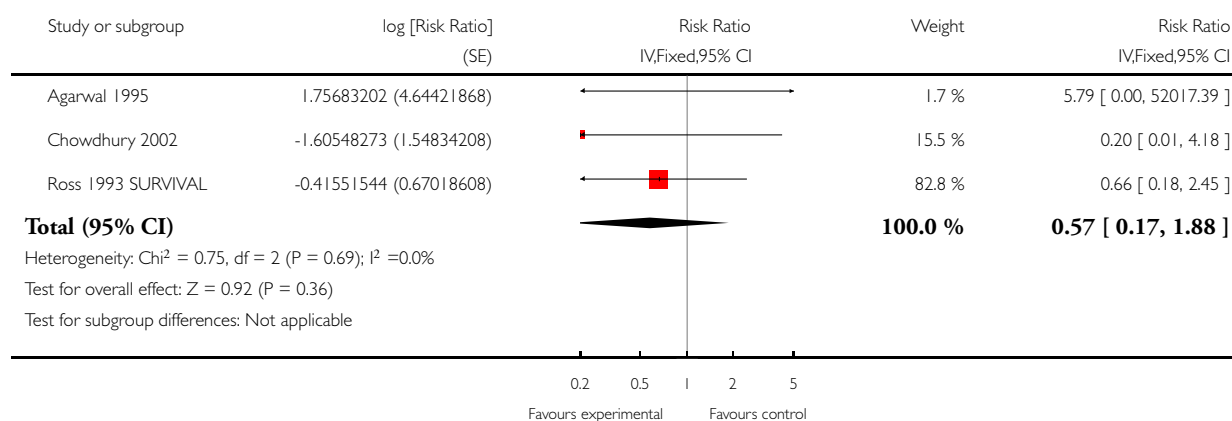Outcome: 16 Night Blindness Incidence at Longest Follow-up

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Herrera 1992	-0.63638856 (0.31997024)		100.0 %	0.53 [0.28, 0.99]
Total (95% CI)			**100.0 %**	**0.53 [0.28, 0.99]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.99 (P = 0.047)

Test for subgroup differences: Not applicable

0.2   0.5   1   2   5

Favours experimental   Favours control

Analysis 1.17. Comparison I Vitamin A versus Control, Outcome 17 Night Blindness Prevalence at Longest Follow-up.

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

Comparison: I Vitamin A versus Control

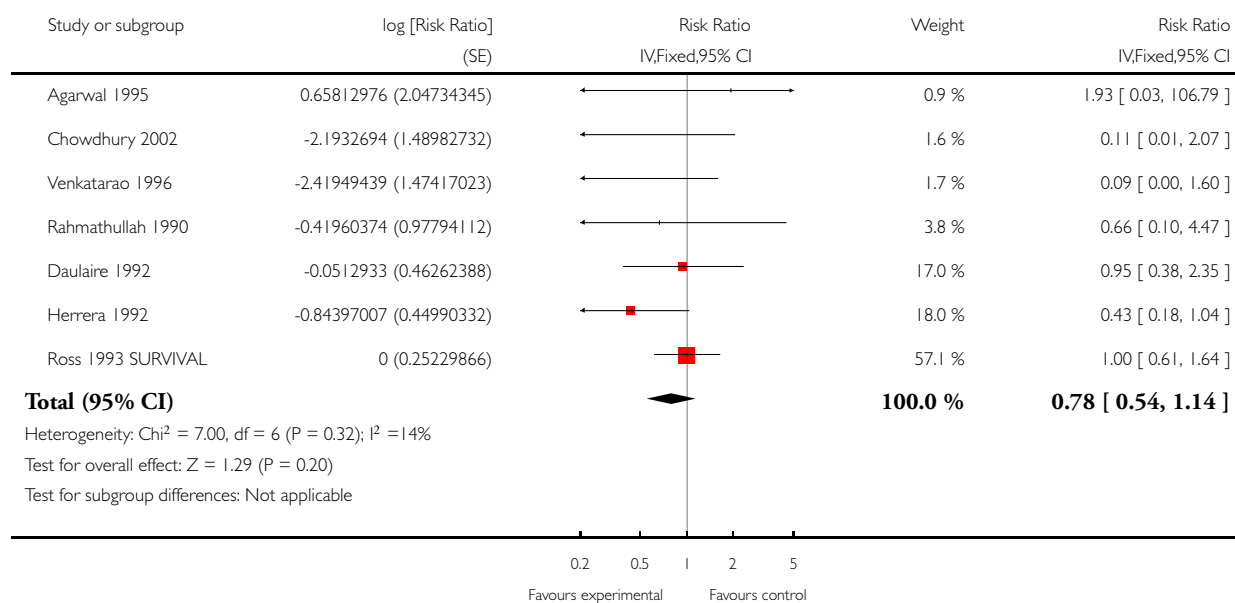Outcome: 17 Night Blindness Prevalence at Longest Follow-up

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
West 1991	-0.99425227 (0.39190376)		33.9 %	0.37 [0.17, 0.80]
Sommer 1986	-1.2039728 (0.28074884)		66.1 %	0.30 [0.17, 0.52]
Total (95% CI)			**100.0 %**	**0.32 [0.21, 0.50]**

Heterogeneity: Chi² = 0.19, df = I (P = 0.66); I² =0.0%

Test for overall effect: Z = 4.96 (P < 0.00001)

Test for subgroup differences: Not applicable

```
          0.05   0.2    I    5    20
        Favours experimental   Favours control
```
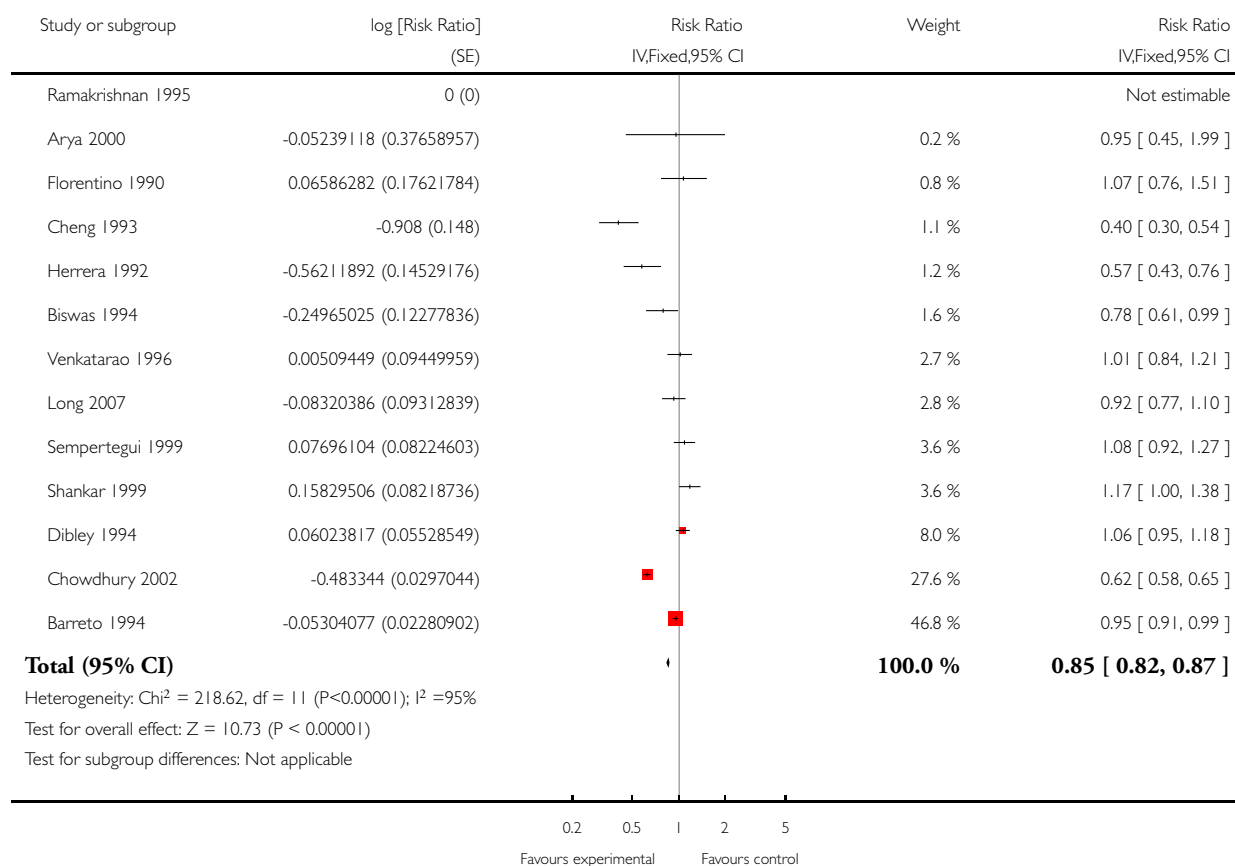
Analysis 1.18. Comparison 1 Vitamin A versus Control, Outcome 18 Xerophthalmia Incidence at Longest Follow-up.

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

Comparison: 1 Vitamin A versus Control

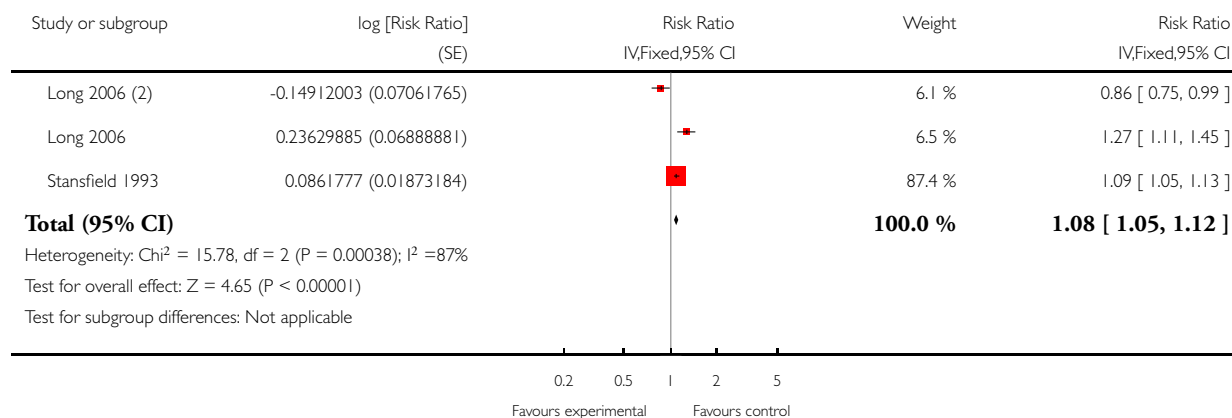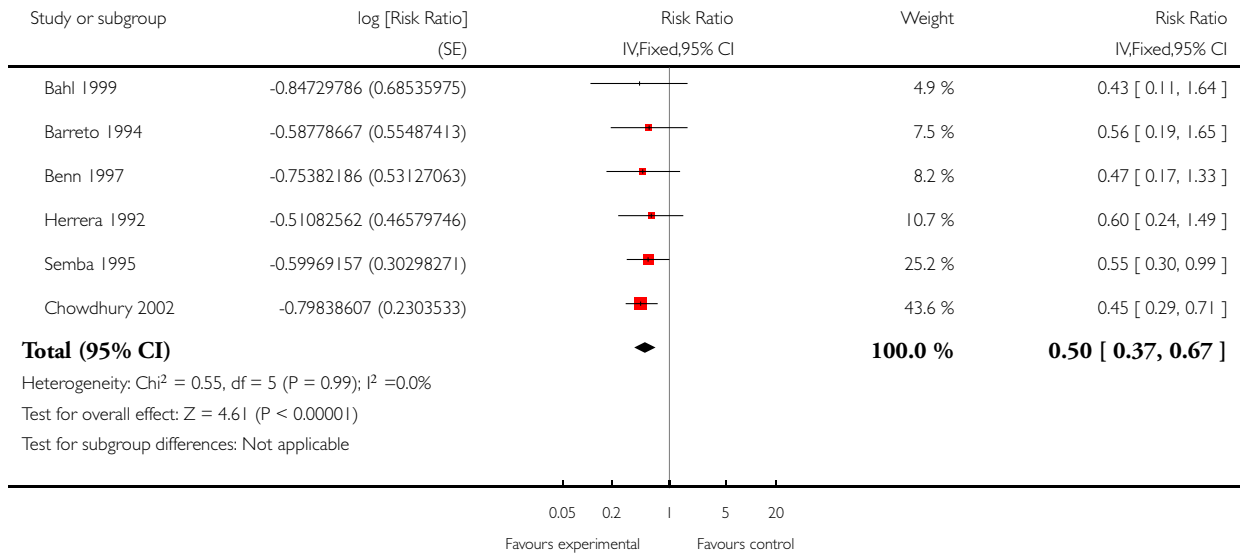Outcome: 18 Xerophthalmia Incidence at Longest Follow-up

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Barreto 1994	0 (0)			Not estimable
West 1991	-0.96758403 (0.50156862)		3.9 %	0.38 [0.14, 1.02]
Herrera 1992	-0.12783337 (0.10106377)		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

$$0.2 \quad 0.5 \quad 1 \quad 2 \quad 5$$
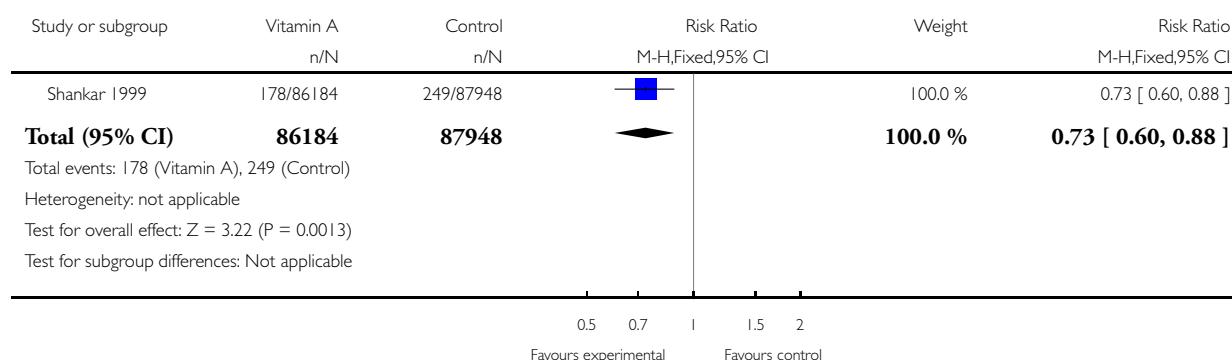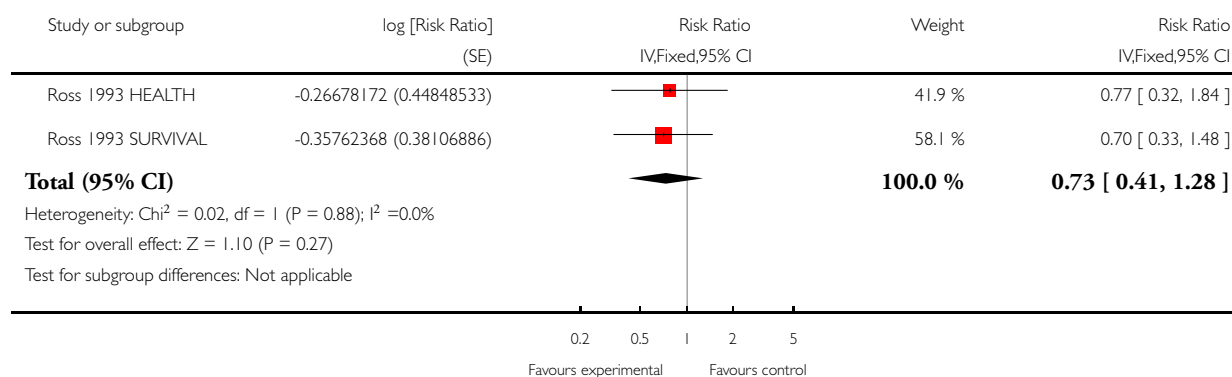
Favours experimental   Favours control

Analysis 1.19. Comparison 1 Vitamin A versus Control, Outcome 19 Xerophthalmia Prevalence at Longest Follow-up.

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

Comparison: 1 Vitamin A versus Control

Outcome: 19 Xerophthalmia Prevalence at Longest Follow-up

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
West 1991	-0.99425227 (0.39190376)		21.8 %	0.37 [0.17, 0.80]
Sommer 1986	-1.2039728 (0.20687375)		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 =0.0%
Test for overall effect: Z = 6.33 (P < 0.00001)
Test for subgroup differences: Not applicable

$$0.2 \quad 0.5 \quad 1 \quad 2 \quad 5$$

Favours experimental   Favours control

Analysis 1.20.   Comparison 1 Vitamin A versus Control, Outcome 20 Vitamin A Deficient at Longest Follow-up.

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

Comparison: 1 Vitamin A versus Control

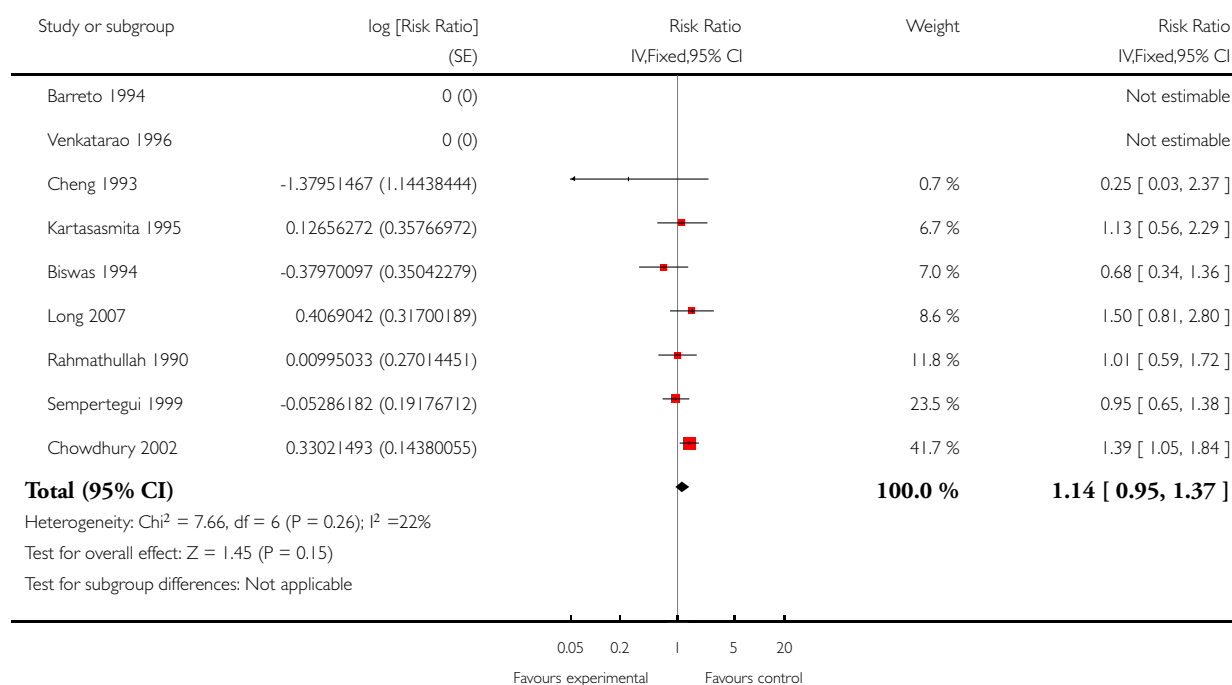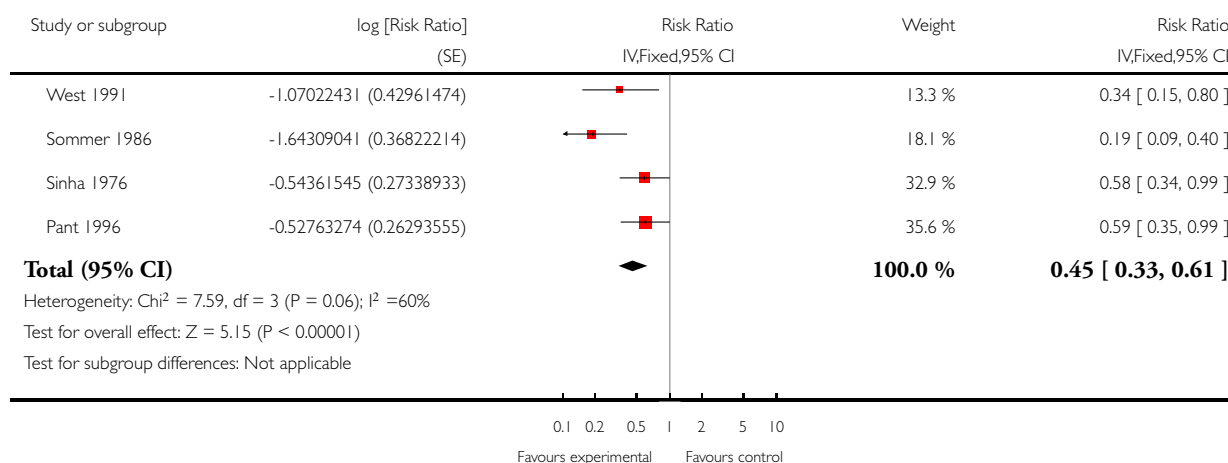Outcome: 20 Vitamin A Deficient at Longest Follow-up

Study or subgroup	Vitamin A n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ranjini 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 1994	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 (Vitamin A), 576 (Control)

Heterogeneity: Chi^2 = 13.58, df = 3 (P = 0.004); I^2 =78%

Test for overall effect: Z = 7.23 (P < 0.00001)

0.5   0.7   1   1.5   2

Favours experimental   Favours control

Vitamin A supplementation for preventing morbidity and mortality in children from 6 months to 5 years of age (Review)   **116**

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

Comparison: 1 Vitamin A versus Control
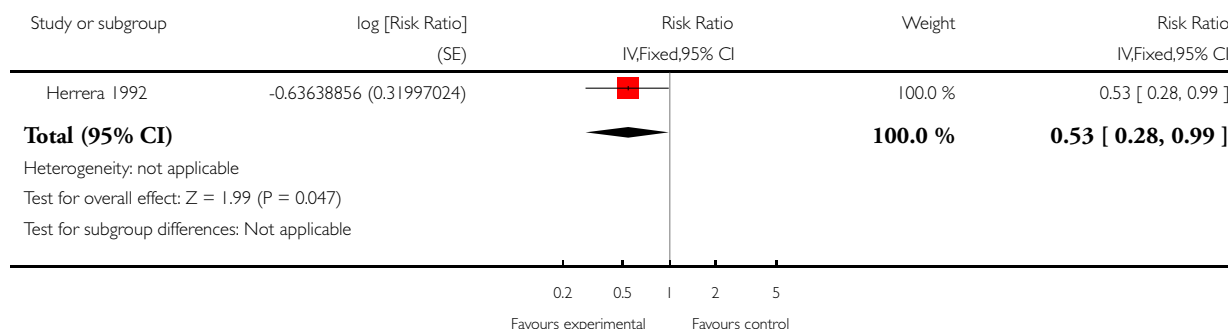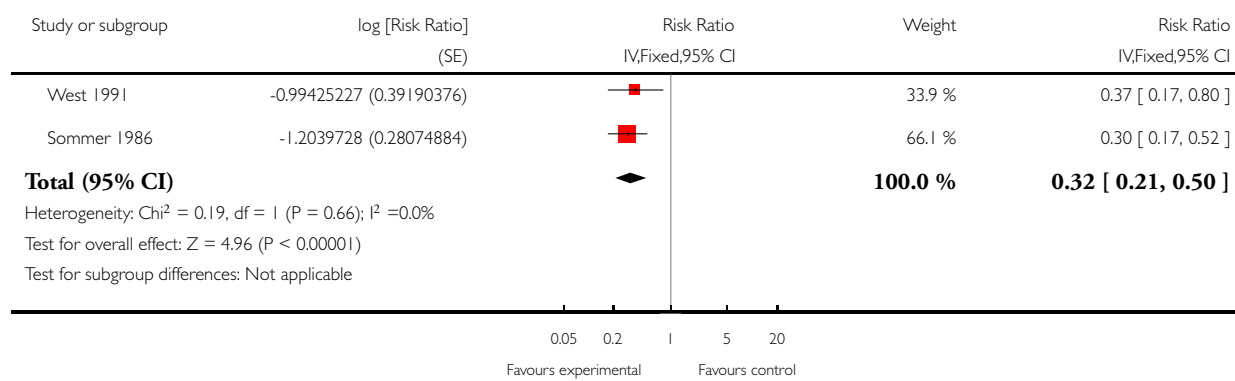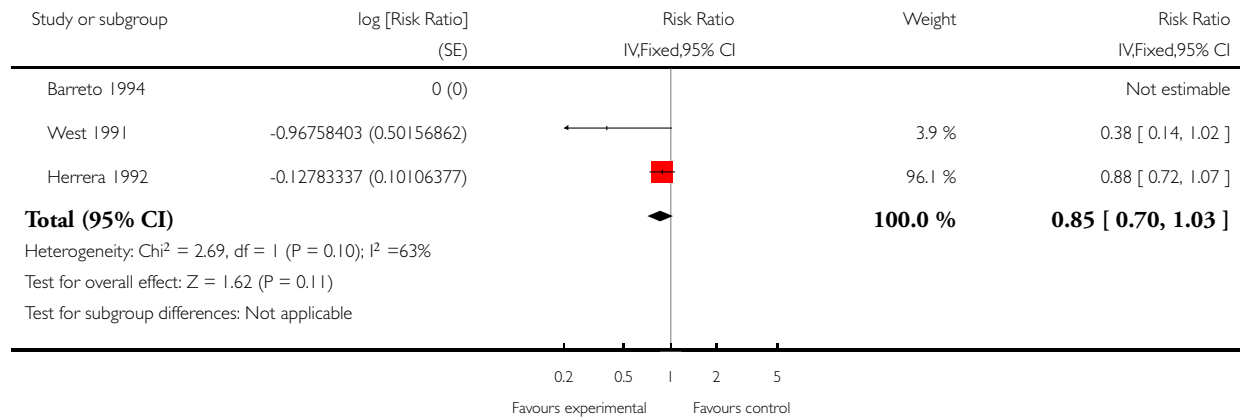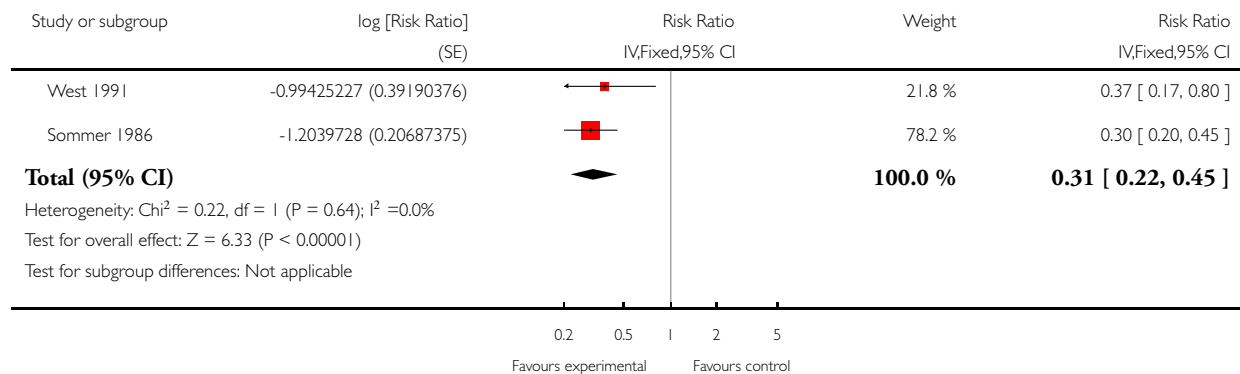
Outcome: 21 Vitamin A Serum Level at Longest Follow-up

Study or subgroup	Experimental		Control		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Ranjini 2001	26	33.9 (10.5)	28	32.3 (7)		0.9 %	0.18 [-0.36, 0.71]
Lin 2009	35.3977273 (29.152)	44	42	23 (35.726)		1.4 %	0.38 [-0.05, 0.80]
Sempertegui 1999	46	48.5 (12.6)	43	42.9 (10.5)		1.4 %	0.48 [0.06, 0.90]
Cheng 1993	56	30.89 (12.24)	40	23.32 (13.39)		1.5 %	0.59 [0.18, 1.00]
Pinnock 1986	47	50.2 (11.65)	43	49.9 (10.49)		1.5 %	0.03 [-0.39, 0.44]
Reddy 1986 (2)	98	31.6 (9.44)	53	23.6 (5.53)		2.0 %	0.96 [0.61, 1.31]
Semba 1992	117	1.7 (0.5)	115	0.7 (0.2)		2.0 %	2.61 [2.26, 2.96]
Pinnock 1988	68	36.5 (8.2462113)	62	35.5 (7.0866)		2.1 %	0.13 [-0.22, 0.47]
Reddy 1986	110	30.1 (10.83)	66	24.5 (6.31)		2.6 %	0.59 [0.28, 0.90]
Kartasasmita 1995	103	26.6 (9.4)	101	25.9 (9.1)		3.3 %	0.08 [-0.20, 0.35]
Shankar 1999	201	21.9 (7.2)	209	19.2 (7.8)		6.6 %	0.36 [0.16, 0.55]
Dibley 1994	423	0.89 (0.255)	426	0.71 (0.228)		12.9 %	0.74 [0.60, 0.88]
Ross 1993 HEALTH	556	0.68 (0.294746)	541	0.6 (0.290743)		17.7 %	0.27 [0.15, 0.39]
Ross 1993 SURVIVAL	1894	0.7 (1.741068)	1065	0.61 (1.142576)		44.3 %	0.06 [-0.02, 0.13]
Total (95% CI)	**3789**		**2834**			**100.0 %**	**0.31 [0.26, 0.36]**

Heterogeneity: Chi² = 270.23, df = 13 (P<0.00001); I² =95%

Test for overall effect: Z = 12.09 (P < 0.00001)

Test for subgroup differences: Not applicable

-4   -2   0   2   4

Favours control   Favours experimental

Analysis 1.22.   Comparison 1 Vitamin A versus Control, Outcome 22 Hospitalisation, Number of Children Hospitalised Once or More at Longest Follow-up.

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

Comparison: 1 Vitamin A versus Control

Outcome: 22 Hospitalisation, Number of Children Hospitalised Once or More at Longest Follow-up

Study or subgroup	Vitamin A	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Ross 1993 HEALTH	27/596	42/589		100.0 %	0.64 [0.40, 1.02]
Total (95% CI)	**596**	**589**		**100.0 %**	**0.64 [0.40, 1.02]**

Total events: 27 (Vitamin A), 42 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.89 (P = 0.058)

Test for subgroup differences: Not applicable

```
        0.5   0.7   1    1.5   2
    Favours experimental     Favours control
```

Analysis 1.23.   Comparison 1 Vitamin A versus Control, Outcome 23 Hospitalisation due to Diarrhoea at Longest Follow-up.

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

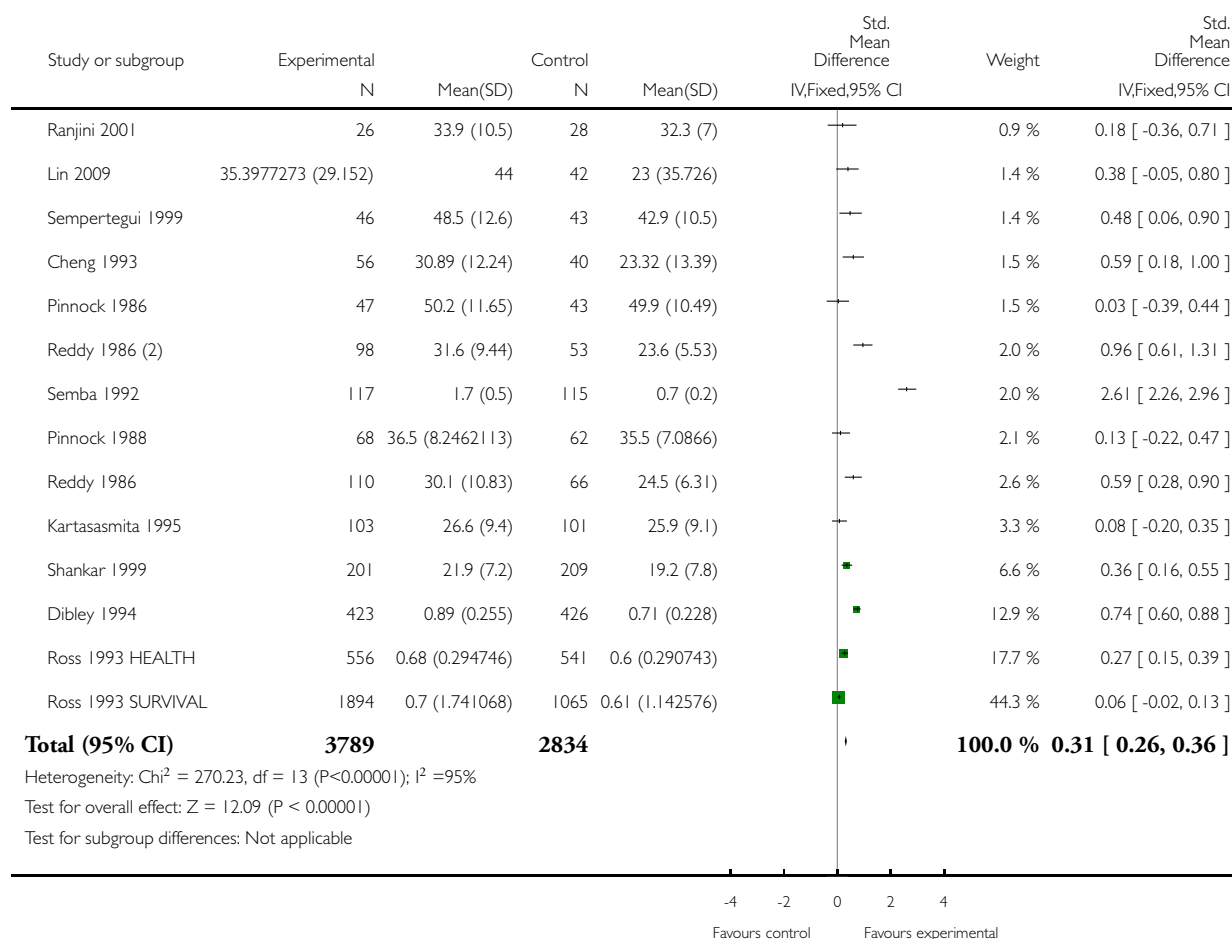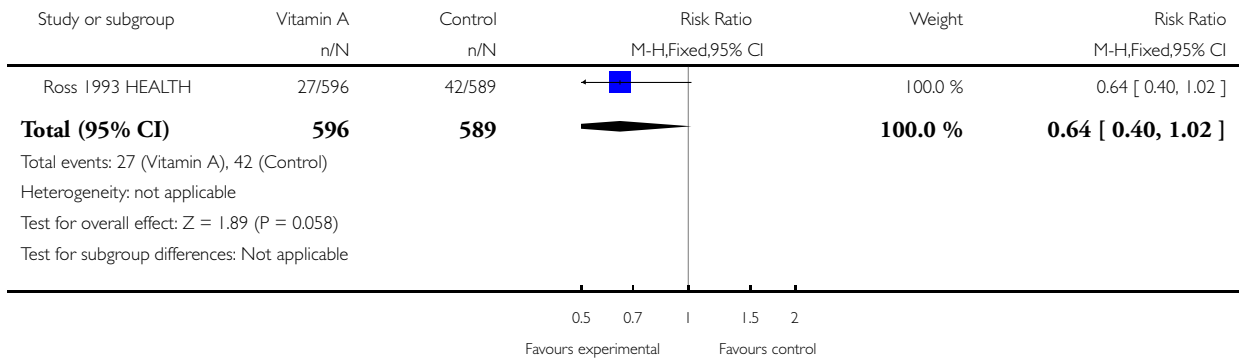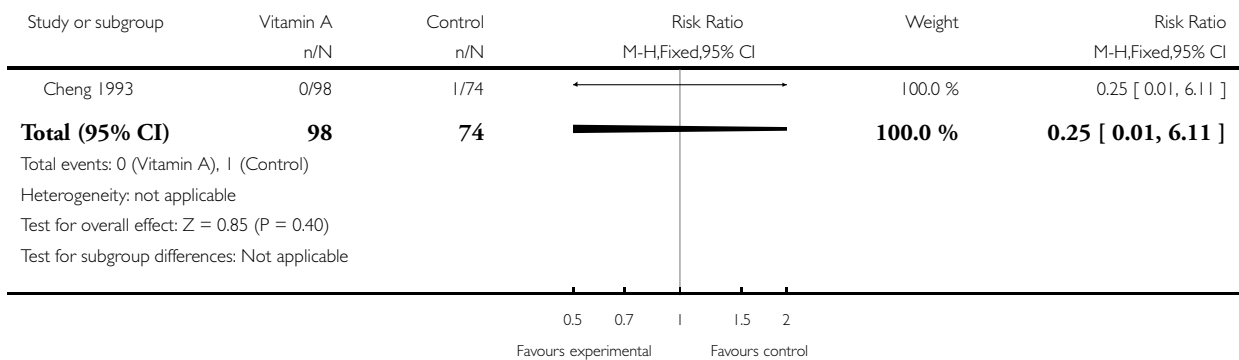Comparison: 1 Vitamin A versus Control

Outcome: 23 Hospitalisation due to Diarrhoea at Longest Follow-up

Study or subgroup	Vitamin A	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Cheng 1993	0/98	1/74		100.0 %	0.25 [0.01, 6.11]
Total (95% CI)	**98**	**74**		**100.0 %**	**0.25 [0.01, 6.11]**

Total events: 0 (Vitamin A), 1 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.85 (P = 0.40)

Test for subgroup differences: Not applicable

```
        0.5   0.7   1    1.5   2
    Favours experimental     Favours control
```
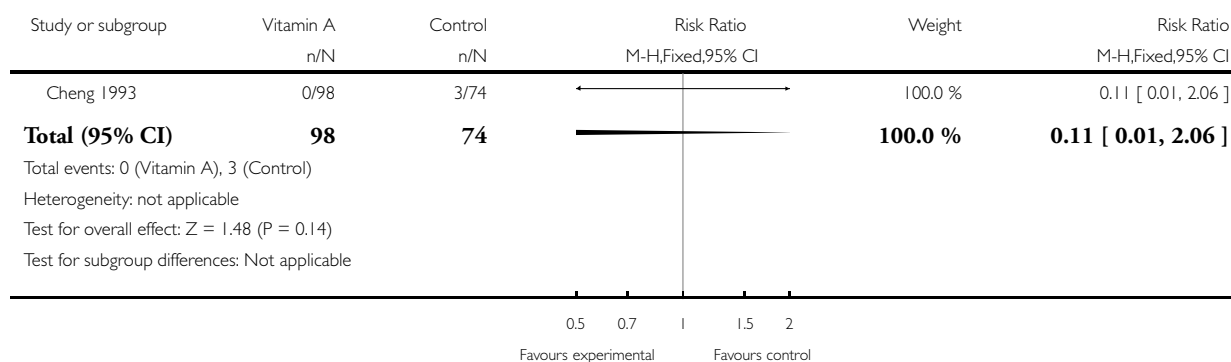
Analysis 1.24. Comparison 1 Vitamin A versus Control, Outcome 24 Hospitalisation due to Lower Respiratory Tract Infection at Longest Follow-up.

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

Comparison: 1 Vitamin A versus Control

Outcome: 24 Hospitalisation due to Lower Respiratory Tract Infection at Longest Follow-up

Study or subgroup	Vitamin A n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cheng 1993	0/98	3/74		100.0 %	0.11 [0.01, 2.06]
Total (95% CI)	**98**	**74**		**100.0 %**	**0.11 [0.01, 2.06]**

Total events: 0 (Vitamin A), 3 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 1.48 (P = 0.14)
Test for subgroup differences: Not applicable

```
        0.5   0.7    1    1.5    2
     Favours experimental   Favours control
```
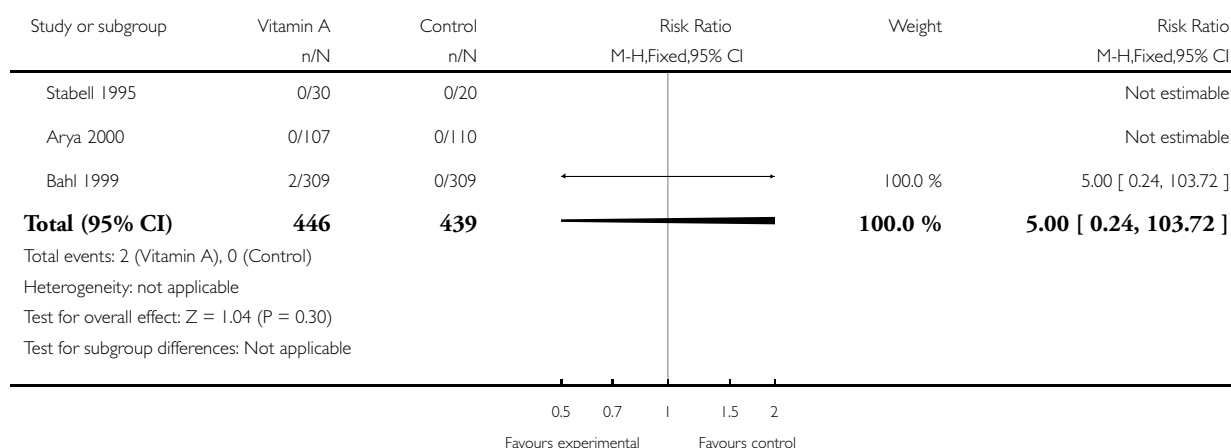
Analysis 1.25. Comparison 1 Vitamin A versus Control, Outcome 25 Side effect - Bulging Fontanelle.

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

Comparison: 1 Vitamin A versus Control
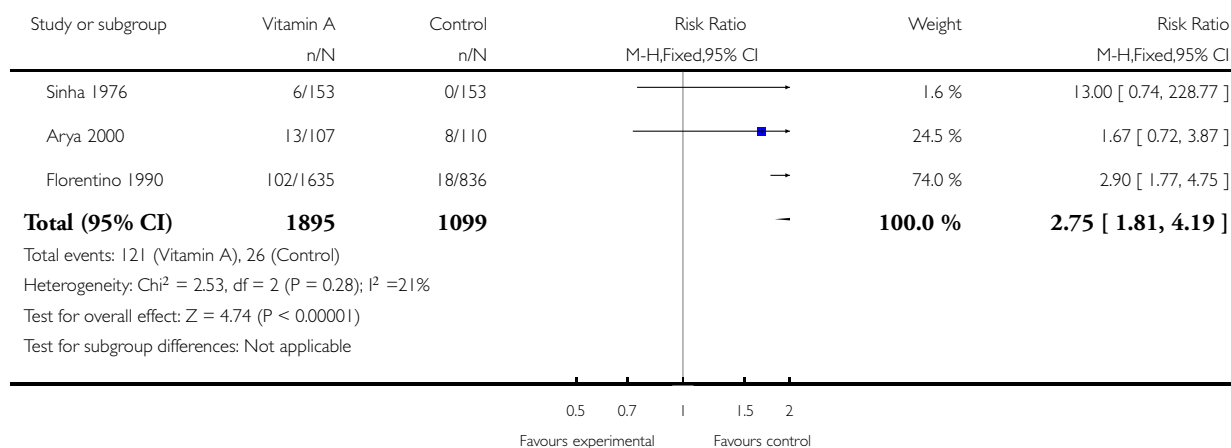
Outcome: 25 Side effect - Bulging Fontanelle

Study or subgroup	Vitamin A n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Stabell 1995	0/30	0/20			Not estimable
Arya 2000	0/107	0/110			Not estimable
Bahl 1999	2/309	0/309		100.0 %	5.00 [0.24, 103.72]
Total (95% CI)	**446**	**439**		**100.0 %**	**5.00 [0.24, 103.72]**

Total events: 2 (Vitamin A), 0 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable

```
        0.5   0.7    1    1.5    2
     Favours experimental   Favours control
```

Analysis 1.26. Comparison I Vitamin A versus Control, Outcome 26 Side effect - Vomiting.

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

Comparison: I Vitamin A versus Control

Outcome: 26 Side effect - Vomiting

Study or subgroup	Vitamin A n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sinha 1976	6/153	0/153		1.6 %	13.00 [0.74, 228.77]
Arya 2000	13/107	8/110		24.5 %	1.67 [0.72, 3.87]
Florentino 1990	102/1635	18/836		74.0 %	2.90 [1.77, 4.75]
Total (95% CI)	**1895**	**1099**		**100.0 %**	**2.75 [1.81, 4.19]**

Total events: 121 (Vitamin A), 26 (Control)

Heterogeneity: Chi² = 2.53, df = 2 (P = 0.28); I² =21%

Test for overall effect: Z = 4.74 (P < 0.00001)

Test for subgroup differences: Not applicable

0.5 0.7 I I.5 2

Favours experimental   Favours control

ADDITIONAL TABLES

Table 1. Sensitivity and subgroup analyses

Outcome or Sub-group	Studies	Heterogeneity	Statistical Method	Effect Estimate	Test for Subgroup difference (p-value)
Mortality (all-cause) at Longest Follow-up (Sensitivity analysis using random effects model)	17	Heterogeneity: Tau² = 0.04; Chi² = 29.10, df = 15 (P = 0.02); I² = 48%	Risk Ratio (IV, Random, 95% CI)	0.71 [0.61, 0.84]	NA

Table 1. **Sensitivity and subgroup analyses** (*Continued*)

Mortality (all-cause) at Longest Follow-up (Sensitivity Analysis assumes NO impact of clustering for studies with unknown ICC)	17	Heterogeneity: Chi² = 48.83, df = 15 (P < 0.0001); I² = 69%	Risk Ratio (IV, Fixed, 95% CI)	0.81 [0.75, 0.89]	NA
Mortality (all-cause) at Longest Follow-up (Sensitivity Analysis assumes HIGH impact of clustering for studies with unknown ICC)	17	Heterogeneity: Chi² = 25.67, df = 15 (P = 0.04); I² = 42%	Risk Ratio (IV, Fixed, 95% CI)	0.75 [0.68, 0.83])	NA
Mortality (all-cause) at Longest Follow-up (by National Child Mortality Rate): High (> 40/1000)	15	Heterogeneity: Chi² = 29.02, df = 14 (P = 0.01); I² = 52%	Risk Ratio (IV, Fixed, 95% CI)	0.76 [0.69, 0.83]	0.78
Mortality (all-cause) at Longest Follow-up (by National Child Mortality Rate): Low (<40/1000)	2	Heterogeneity: Not applicable	Risk Ratio (IV, Fixed, 95% CI)	1.00 [0.14, 7.08]	
Mortality (all-cause) at Longest Follow-up (by Region): Asia	11	Heterogeneity: Chi² = 15.00, df = 9 (P = 0.09); I² = 40%	Risk Ratio (IV, Fixed, 95% CI)	0.69 [0.61, 0.79]	0.12
Mortality (all-cause) at Longest Follow-up (by Region): Africa	5	Heterogeneity: Chi² = 9.81, df = 4 (P = 0.04); I² = 59%	Risk Ratio (IV, Fixed, 95% CI)	0.85 [0.73, 0.98]	
Mortality (all-cause) at Longest Follow-up (by Region): Latin America	1	Heterogeneity: Not applicable	Risk Ratio (IV, Fixed, 95% CI)	1.00 [0.14, 7.08]	

Table 1. Sensitivity and subgroup analyses (*Continued*)

Mortality (all-cause), outcomes < 1 year since randomisation	13	Heterogeneity: Chi² = 33.85, df = 11 (P = 0. 0004); I² = 67%	Risk Ratio (IV, Fixed, 95% CI)	0.82 [0.74, 0.91]	NA
Mortality due to Diarrhoea, outcomes < 1 year since randomisation	5	Heterogeneity: Chi² = 5.14, df = 4 (P = 0.27) ; I² = 22%	Risk Ratio (IV, Fixed, 95% CI)	0.75 [0.59, 0.96]	NA
Mortality due to LRTI, outcomes < 1 year since randomisation	5	Heterogeneity: Chi² = 5.70, df = 6 (P = 0.46) ; I² = 0%	Risk Ratio (IV, Fixed, 95% CI)	0.71 [0.41, 1.21]	NA
Mortality due to Measles, outcomes < 1 year since randomisation	4	Heterogeneity: Chi² = 0.52, df = 3 (P = 0.91) ; I² = 0%	Risk Ratio (IV, Fixed, 95% CI)	0.85 [0.52, 1.37]	NA
Mortality due to Meningitis, outcomes < 1 year since randomisation	1	Heterogeneity: Not applicable	Risk Ratio (IV, Fixed, 95% CI)	5.79 [0.22, 153.24]	NA
Diarrhoea Incidence at Longest Follow-up (Sensitivity analysis using random effects model)	13	Heterogeneity: Chi² = 218.62, df = 11 (P<0. 00001); I² = 95%	Risk Ratio (IV, Random, 95% CI)	0.85 [0.72, 1.00]	NA
Diarrhoea Incidence, outcomes < 1 year since randomisation	10	Heterogeneity: Chi² = 49.93, df = 8 (P<0. 00001); I² = 84%	Risk Ratio (IV, Fixed, 95% CI)	0.93 [0.89, 0.97]	NA
Lower Respiratory Tract Infection Incidence, outcomes <1 year since randomisation	8	Heterogeneity: Chi² = 4.47, df = 5 (P = 0.48) ; I² = 0%	Risk Ratio (IV, Fixed, 95% CI)	0.99 [0.78, 1.26]	NA
Malaria Incidence, outcomes 1+ year since randomisation (by Age)	1	Heterogeneity: Not applicable	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.60, 0.88]	NA

Table 1. Sensitivity and subgroup analyses (*Continued*)

Measles Incidence, outcomes < 1 year since randomisation	5	Heterogeneity: Chi² = 0.24, df = 4 (P = 0.99) ; I² = 0%	Risk Ratio (IV, Fixed, 95% CI)	0.54 [0.36, 0.80]	NA
Bitot's Spots Incidence, outcomes < 1 year since randomisation	1	Heterogeneity: Not applicable	Risk Ratio (IV, Fixed, 95% CI)	0.93 [0.76, 1.14]	NA
Bitot's Spots Prevalence, outcomes < 1 year since randomisation	3	Heterogeneity: Chi² = 6.06, df = 2 (P = 0.05) ; I² = 67%	Risk Ratio (IV, Fixed, 95% CI)	0.43 [0.33, 0.56]	NA
Night Blindness Prevalence, outcomes < 1 year since randomisation	1	Heterogeneity: Not applicable	Risk Ratio (IV, Fixed, 95% CI)	0.30 [0.17, 0.52]	NA
Xerophthalmia Incidence, outcomes < 1 year since randomisation	2	Heterogeneity: Not applicable	Risk Ratio (IV, Fixed, 95% CI)	0.88 [0.72, 1.07]	NA
Vitamin A Serum Level at Longest Follow-up (Sensitivity analysis using random effects model)	14	Heterogeneity: Tau² = 0.22; Chi² = 270.23, df = 13 (P < 0.000001); I² = 95%	Std. Mean Difference (IV, Random, 95% CI)	0.53 [0.27, 0.79]	NA
Vitamin A Serum Level, outcomes < 1 year since randomisation	11	Heterogeneity: Chi² = 178.42, df 10, (P<0.000001), I² = 94%	Std. Mean Difference (IV, Fixed, 95% CI)	0.45 [0.37, 0.53]	NA

APPENDICES

Appendix 1. Search strategies

MEDLINE (1950 to April Week 2 2010)

1   exp infant/ or exp child/ or exp child, preschool/
2   (baby or babies or infant$ or toddler$ or child$ or girl$ or boy$ or pre school$ or pre-school$ or preschool$).tw.
3   1 or 2
4   exp Vitamin A/
5   (retinol$ or retinal$ or aquasol a or vitamin a).ab,ti.
6   4 or 5
7   randomised controlled trial.pt.
8   controlled clinical trial.pt.
9   randomized.ab.
10   placebo.ab.
11   drug therapy.fs.
12   randomly.ab.
13   trial.ab.
14   groups.ab.
15   7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16   exp animals/ not humans.sh.
17   15 not 16
18   3 and 6 and 17

Global Health (1973 to March 2010)

For the search of Global Health database, replacement subject headings mapped to the Global Health database were used when possible, otherwise the text was used similar to the MEDLINE searches conducted previously.

1   exp school children/ or exp children/ or exp preschool children/
2   (baby or babies or infant$ or toddler$ or child$ or girl$ or boy$ or pre school$ or pre-school$ or preschool$).tw.
3   1 or 2
4   retinol.sh.
5   (retinol$ or retinal$ or aquasol a or vitamin a).ab,ti.
6   4 or 5
7   exp randomized controlled trials/ or exp clinical trials/
8   random*.mp.
9   placebo.mp.
10   trial.mp.
11   7 or 8 or 9 or 10
12   3 and 6 and 11

EMBASE (1980 to 2010 Week 16)

EMTREE index terms were used when possible. The UK Cochrane Centre's suggested combination of EMTREE and free text words were used to search for randomized-controlled trials.

1   exp infant/ or exp child/ or exp child, preschool/
2   (baby or babies or infant$ or toddler$ or child$ or girl$ or boy$ or pre school$ or pre-school$ or preschool$).tw.
3   1 or 2
4   exp Vitamin A/
5   (retinol$ or retinal$ or aquasol a or vitamin a).ab,ti.
6   4 or 5
7   exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or exp single-blind procedure/
8   (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).mp.
9   7 or 8
10   3 and 6 and 9

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#1   MeSH descriptor Child explode all trees

#2   MeSH descriptor Infant explode all trees

#3   MeSH descriptor Child, Preschool explode all trees

#4   (baby or babies or infant* or toddler* or child* or (pre next school*) or preschool* or girl* or boy*):ti,ab,kw

#5   (#1 OR #2 OR #3 OR #4)

#6   MeSH descriptor Vitamin A explode all trees

#7   retinol* or retinal$ or "aquasol a" or "vitamin a"

#8   (#6 OR #7)

#9   (#5 AND #8)

Latino Americana e do Caribe em Ciências da Saúde (LILACS) 27 April 2010

Mh vitamin a or tw retinol$ or tw aquasol$ or tw retinal$ [Words] AND [Tw baby or Tw babies or Tw child$ or Tw infant$ or Tw toddler$ or Tw girl$ or Tw boy$ or Tw prescshool$ or Tw pre-school$ or Tw niño or Tw niños or Tw niña or Tw niñas or Tw bebé or Tw bebés or Tw preescolar or Tw prescolares [Words]

AND ((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal))) [Words]

African Index Medicus 27 April 2010

1. retinol$ or retinal$ or aquasol a or vitamin a [Descriptor]

metaRegister of Controlled Trials 27 April 2010

(baby or babies or infant or child) and (vitamin a or aquasol or retinol or retinal)

WHAT'S NEW

Last assessed as up-to-date: 26 October 2010.

Date	Event	Description
7 December 2010	Amended	Edited to correct typographical errors and improve readability

CONTRIBUTIONS OF AUTHORS

AI and EMW contributed to the background. EMW, KH and AI were primarily responsible for the methods. Margaret Anderson (from CDPLPG) developed the search strategy and KH conducted the literature search. AI, YY and KH reviewed citations for inclusion, disagreements were resolved through consultation with EMW. AI, KH, YY and EMW extracted data with three members from the Cochrane Editorial Unit (Toby Lasserson, Rachel Murphey, and Karla Soares-Weiser). KH and EMW entered outcome data into RevMan, analysed the data and wrote results. AI made the included studies and risk of bias tables. KH, EMW and AI contributed to writing the discussion. Toby Lasserson drafted the summary of findings table, which was agreed by all authors. ZB provided supervision and contributed to the writing and analyses.

DECLARATIONS OF INTEREST

None known.

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Internal sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1) Sensitivity analyses are performed only for all-cause mortality, diarrhoea incidence and vitamin A serum levels.

2) Post-hoc analyses were performed for Imputed ICC and studies awaiting assessment.

3) Subgroup analysis based on baseline HIV status was not performed as none of the included studies gave a baseline status of study population on HIV and we excluded studies conducted on children with HIV.

4) Post-hoc, we included two studies in which participants were assigned using a quasi-random method.

INDEX TERMS

Medical Subject Headings (MeSH)

Cause of Death; Diarrhea [mortality]; Measles [mortality]; Meningitis [mortality]; Randomized Controlled Trials as Topic; Respiration Disorders [mortality]; Vitamin A [*administration & dosage; adverse effects]; Vitamin A Deficiency [complications; *drug therapy; mortality]; Vitamins [*administration & dosage; adverse effects]

MeSH check words

Child, Preschool; Humans; Infant