Vitamin A supplementation during pregnancy for maternal and newborn outcomes (Review)

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[Intervention Review]

Vitamin A supplementation during pregnancy for maternal and newborn outcomes

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ABSTRACT

Background

The World Health Organization recommends routine vitamin A supplementation during pregnancy or lactation in areas with endemic vitamin A deficiency (where night blindness occurs), based on the expectation that supplementation will improve maternal and newborn outcomes including mortality, morbidity and prevention of anaemia or infection.

Objectives

To review the effects of supplementation of vitamin A, or one of its derivatives, during pregnancy, alone or in combination with other vitamins and micronutrients, on maternal and newborn clinical outcomes.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (15 July 2010).

Selection criteria

All randomised or quasi-randomised trials, including cluster-randomised trials, evaluating the effect of vitamin A supplementation in pregnant women.

Data collection and analysis

Two review authors independently assessed all studies for inclusion and resolved any disagreement through discussion with a third person. We used pre-prepared data extraction sheets.

Main results

We examined 88 reports of 31 trials, published between 1931 and 2010, for inclusion in this review. We included 16 trials, excluded 14, and one is awaiting assessment.

Overall when trial results are pooled, Vitamin A supplementation does not affect the risk of maternal mortality (risk ratio (RR) 0.78, 95% confidence interval (CI) 0.55 to 1.10, 3 studies, Nepal, Ghana,UK), perinatal mortality, neonatal mortality, stillbirth, neonatal anaemia, preterm birth or the risk of having a low birthweight baby. Vitamin A supplementation reduces the risk of maternal night blindness (risk ratio (RR) 0.70, 95% CI 0.60 to 0.82, 1 trial Nepal). In vitamin A deficient populations and HIV-positive women, vitamin A supplementation reduces maternal anaemia (risk ratio (RR) 0.64, 95% confidence interval (CI) 0.43 to 0.94, 3 trials, Indonesia, Nepal,Tanzania). There is evidence that vitamin A supplements may reduce maternal clinical infection (RR 0.37, 95% CI 0.18 to 0.77, 3 trials, South Africa, Nepal and UK).

In HIV-positive women vitamin A supplementation given with other micronutrients was associated with fewer low birthweight babies (< 2.5 kg) in the supplemented group in one study (RR 0.67, CI 0.47 to 0.96).

Authors' conclusions

The pooled results of two large trials in Nepal and Ghana (with almost 95,000 women) do not currently suggest a role for antenatal vitamin A supplementation to reduce maternal or perinatal mortality. However the populations studied were probably different with regard to baseline vitamin A status and there were problems with follow-up of women. There is good evidence that antenatal vitamin A supplementation reduces maternal anaemia for women who live in areas where vitamin A deficiency is common or who are HIV-positive. In addition the available evidence suggests a reduction in maternal infection, but these data are not of a high quality.

PLAIN LANGUAGE SUMMARY

Vitamin A supplementation during pregnancy for maternal and newborn health outcomes

Vitamin A is a fat-soluble vitamin derived from the retinoids retinal and retinoic acid, found in liver, kidney, eggs, and dairy produce. Carotenoids are converted to vitamin A in the liver, where vitamin A is stored; beta-carotene is found in dark or yellow vegetables and carrots. Low dietary fat intake or intestinal infections may interfere with the absorption of vitamin A. Natural retinoids are required for a wide range of biological processes including vision, immune function, bone metabolism and haematopoiesis. In pregnancy, extra vitamin A may be required. Currently, the WHO and other international agencies recommend routine vitamin A supplementation during pregnancy or at any time during lactation in areas with endemic vitamin A deficiency (where night blindness occurs).

The principal forms used as nutritional supplements are vitamin A palmitate (retinyl palmitate) and vitamin A acetate (retinyl acetate) but carotenoids (most commonly beta-carotene) and retinoids (retinol, retinal, retinoic acid) can also be used as nutritional supplements. Signs of vitamin A deficiency include night blindness, dryness of the conjunctiva and cornea and a diminished ability to fight infections, especially respiratory and gastroenteric infections.

Findings of this review do not suggest a role for antenatal vitamin A supplementation to reduce maternal or perinatal mortality. There is, however, good evidence that antenatal vitamin A supplementation reduces maternal anaemia in women who live in areas where Vitamin A deficiency is common or who are HIV-positive. The available evidence suggests a reduction in maternal infection but these data are not of a high quality and further trials would be needed to confirm or refute this.

We included 16 randomised trials where vitamin A was commenced pre-pregnancy or during pregnancy and in some cases continued into the postnatal period. Seven trials were conducted in Africa, five in Indonesia and one each in India, Nepal, UK and USA. The trials were conducted in populations considered to be vitamin A deficient except for the trials in the USA and UK.

Vitamin A supplementation did not reduce the risk of maternal mortality, perinatal and newborn mortality, stillbirth, preterm birth, low birthweight or newborn anaemia. The risk of maternal anaemia, infection and night blindness was reduced. In one study, for women who were HIV-positive, the addition of vitamin A to supplements of iron and folate did result in fewer low birthweight babies (less than 2.5 kg at birth). The trials published so far did not report any side effects, adverse events or congenital malformations. The dose of vitamin A given, in combination with additional micronutrients and the duration of supplementation differed in the trials and varied between 5000 IU and 10,000 IU for daily doses, around 200,000 IU vitamin A for weekly supplementation and 200,000 IU vitamin A at time of delivery.

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

Vitamin A for maternal and newborn mortality and morbidity

Patient or population: Pregnant women
Settings: Areas with endemic vitamin A deficiency (inadequate intake)/areas with adequate intake as defined by the WHO global database on vitamin A deficiency
Intervention: Vitamin A

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				
Maternal mortality	Low risk population[1]		RR 0.78 (0.55 to 1.1)	94373 (3 studies)	⊕⊕⊕⊕ high[2,3]	
	4 per 1000	3 per 1000 (2 to 4)				
	Medium risk population[1]					
	4 per 1000	3 per 1000 (2 to 4)				
	High risk population[1]					
	6 per 1000	5 per 1000 (3 to 6)				
Perinatal mortality	55 per 1000	56 per 1000 (52 to 59)	RR 1.01 (0.95 to 1.07)	76176 (1 study)	⊕⊕⊕⊕ high[2]	
Preterm birth	Low risk population[4]		RR 0.77 (0.57 to 1.04)	1937 (4 studies)	⊕⊕◯◯ low[5,6]	
	0 per 1000	0 per 1000 (0 to 0)				

	Medium risk population[4]				
	64 per 1000	**49 per 1000** (36 to 67)			
	High risk population[4]				
	190 per 1000	**146 per 1000** (108 to 197)			
Maternal anaemia	**Low risk population**[1]		**RR 0.64** (0.43 to 0.94)	2401 (3 studies)	⊕⊕⊕⊕ **high**
	178 per 1000	**114 per 1000** (77 to 167)			
	Medium risk population[1]				
	456 per 1000	**292 per 1000** (196 to 428)			
	High risk population[1]				
	839 per 1000	**537 per 1000** (361 to 788)			
Maternal infection	**Low risk population**[1]		**RR 0.37** (0.18 to 0.77)	1458 (3 studies)	⊕⊕◯◯ **low**[7,8]
	29 per 1000	**11 per 1000** (5 to 22)			
	Medium risk population[1]				
	58 per 1000	**21 per 1000** (10 to 44)			
	High risk population[1]				

	356 per 1000	**132 per 1000** (64 to 274)	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

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

[1] Control event rates sourced from study control groups
[2] The authors considered that the pooled effect estimate was not biased by the design of the studies or their analysis of data. Following correspondence received from the trialists for Kirkwood 2010, the loss to follow-up for this study was 8%: the data from this study are not at risk of attrition bias.
[3] Although the confidence intervals included both a substantial reduction in the risk of death, and a possible small increase in the risk of death, the low rates of maternal deaths in the control group mean that variation in the absolute effect is small.
[4] Of the four studies, medium risk taken from the second lowest as the highest and second highest control event rate were similar (17.48 and 18.97%),
[5] The authors have concerns about the accuracy of assessment of gestational age.
[6] The confidence interval around the pooled estimate included possible values that indicate a substantial reduction in the risk of maternal death as well as a small increase in the risk of maternal death with vitamin A.
[7] Green 1931 was judged to be at risk of selection and detection bias and strongly influenced the pooled effect estimate.
[8] The authors have concerns about the accuracy of the measurement of infection in the studies.

BACKGROUND

Description of the condition

Vitamin A general

Vitamin A is a fat-soluble vitamin that is derived from two sources: preformed retinoids and provitamin carotenoids. Retinoids, such as retinal and retinoic acid, are found in animal sources like liver, kidney, eggs, and dairy produce. Carotenoids like beta-carotene are found in plants such as dark or yellow vegetables and carrots. Carotenoids can be converted to vitamin A in the liver where vitamin A is stored. Absorption from plant sources is thought to be low and animal sources (i.e. including dairy products) may be needed to achieve adequate levels (Borel 2005; Tang 2005).

The digestion and absorption of vitamin A is closely associated with lipid absorption. Factors such as low dietary fat intake or intestinal infections may interfere with the absorption of vitamin A (Mahalanabis 1979; Sivakumar 1972).

Natural retinoids are present in all living organisms, either as preformed vitamin A or as carotenoids, and are required for a vast number of biological processes including vision, gene transcription, immune function, bone metabolism, haematopoiesis, skin health and antioxidant activity (Combs 2008; McGuire 2007). Sufficient stores (in the liver) may be able to maintain a person's requirement for months (FAO and WHO 2002).

In humans, vitamin A has three active forms (retinal, retinol and retinoic acid) and a storage form (retinyl ester). The absorption of vitamin A depends on the amount of lipids ingested in the diet, with lipids increasing uptake of beta - carotene and vitamin A (Lidén 2006). Beta-carotene can be cleaved into retinoids in the liver and the intestines by enzymes known as carotenoid oxygenases, via two pathways - central or eccentric cleavage. Central cleavage uses beta-carotene-15,15'-monooxygenase (EC 1.14.99.36), whereby beta-carotene is cleaved at its central 15,15'-double bond to yield two retinal molecules, which are then converted to two molecules of retinol (vitamin A). Eccentric (or asymmetric) cleavage splits beta-carotene at double bonds other than the central one, yielding beta-apocarotenals of different chain lengths and carotenoic acids, which can then be converted to one molecule of retinol. Under normal physiological conditions, central cleavage is the predominant pathway (Lidén 2006; Moffa 1970; Von Lintig 2000).

Circulating vitamin A is transported in plasma in a 1:1 complex with retinol-binding protein (RBP). RBP is bound to thyroxine binding pre-albumin (TBPA) and this complex functions as a vitamin A transport system. Binding is specific for vitamin A and RBP is the only carrier of retinol in plasma.

The retina and other vitamin A dependent tissues have specific binding sites for RBP and vitamin A. RBP is reduced in proteinuria which may pose a serious threat for transport of retinol to tissues. In conditions like kwashiorkor (protein malnutrition), levels of RBP correct with improved protein nutrition even without vitamin A supplements. RBP is also reduced in zinc deficiency states.

Diseases and conditions that impair the conversion of carotene to vitamin A or reduce the levels of RBP can contribute to the development of vitamin A deficiency as RBP is the main transport protein for Vitamin A.

Vitamin A in pregnancy and the newborn

In pregnancy, some extra vitamin A is required for growth and tissue maintenance in the fetus, for providing fetal reserves, and for maternal metabolism. Pregnant women have a basal requirement of 370 mcg/d (microgram/day), maximum dose of 3000 mcg/d and recommended daily allowance (RDA) of 770 mcg/d (FNB 2001; Stipanuk 2006; WHO 1995). In the non-pregnant woman (or pre-pregnancy) the daily basal requirement is estimated to be 300 mcg/d with a RDA of 700 mcg/d (Stipanuk 2006; WHO 1995). Generally it is considered that liver stores are sufficient to cover these extra needs in non-vitamin A deficient populations.

There are potentially adverse effects associated with Vitamin A supplementation during pregnancy. In the first 60 days post-conception, retinol is thought to be teratogenic (Rothman 1995; WHO 1998). A relationship has been suggested between the incidence of birth defects and high vitamin A intakes during pregnancy, with an apparent threshold of near 10,000 international units (IU) per day (Mills 1997; Rothman 1995). Increased maternal levels of preformed vitamin A (retinoic acid) have been shown to be associated with miscarriage and with malformations involving the central nervous and cardiac systems (Miller 1998; WHO 1998). A World Health Organization (WHO) expert group consultation concluded that daily doses of up to 10,000 IU (equivalent to 3000 mcg retinol) or 25,000 IU weekly after day 60 are probably safe, especially in areas where vitamin A deficiency is thought to be common (WHO 1998).

The UK National Institute for Health and Clinical Excellence (NICE) guidelines advise that, owing to potential teratogenic effects, women in developed (non vitamin A deficiency) countries should avoid taking vitamin A supplements and liver; in other words, avoiding the intake of vitamin A above 700 mcg per day (NCCWCH 2008).

During pregnancy, vitamin A is transferred to the fetus via the placenta by active mechanisms that maintain the transfer over a wide range of maternal dietary intake. In contrast, during lactation, vitamin A concentration in breast milk is more sensitive to variations in maternal intake (Ross 1994). The estimated requirement for vitamin A in newborn infants up to six months of age is 180 mcg/d, with a safe intake level of 350 mcg/d.

Newborn infants normally have a low level of vitamin A in the liver and they increase these stores in the first few months if the breast milk has adequate levels. Preterm infants have reduced hepatic (liver) stores and lower levels of retinol binding protein (the vitamin A carrier protein) in the plasma compared to babies born at term. Insufficient intake and reduced absorption by the imma-

ture gut may exacerbate deficiencies in preterm infants (Darlow 2007).

Measurement of vitamin A status

In the literature on vitamin A, authors have used a variety of different indicators and units of measurement. This can be confusing. In general, the following conversions can be used:

- serum retinol 1 µmol/l = 28.6 µg/dl or 10 µg/dl = 100 µg/l = 0.35 µmol/l;
- for supplement doses 1 µg retinol equivalent = 0.00349 µmol retinol = 3.33 IU vitamin A or, expressed differently, 1 IU vitamin A = 0.3 µg retinol and 0.00105 µmol retinol.

For this review we will endeavour to report whenever known the supplemented dose of Vitamin A given in or converted to IU.
There are problems associated with the biochemical assessment of vitamin A deficiency. Serum retinol, because of homeostatic control exerted by the liver, is not a good general indicator of vitamin A status.
Serum retinol levels reflect liver vitamin A stores only when they are severely depleted (less than 0.07 µmol/g liver) or extremely high (more than 1.05 µmol/g liver). Between these extremes, serum retinol is homeostatically controlled and thus not always correlated with vitamin A intake or clinical signs of deficiency. Consequently, serum retinol is not useful in assessing the vitamin A status of individuals. Rather, the distribution of serum retinol values in populations, and the prevalence of individuals with serum retinol values below a given cut off, can provide important information on the vitamin A status of a population and can indicate the severity of vitamin A deficiency as a public health problem (Sommer 1995; WHO 1996). Serum retinol concentrations of 1.05, 0.70 and 0.35 µmol/l have been used in the published literature to indicate inadequate, moderately inadequate and very inadequate liver stores respectively (Underwood 1990).

Clinical manifestations of vitamin A deficiency

Symptoms of vitamin A deficiency include a variety of eye symptoms, such as night blindness, xerophthalmia (dry eyes, failure to produce tears), keratomalacia (drying and clouding of the cornea with ulceration), Bitot spots (keratin debris in the conjunctiva) and photophobia. Follicular hyperkeratosis (excessive development of keratin in hair follicles), which is also seen with general malnutrition, can be a manifestation of vitamin A deficiency. Ocular changes can be documented quantitatively using a dark adaptation test (e.g. the papillary threshold test - PTT) or using electroretinography. Often change in night blindness is assessed via a simple before (the intervention) and after (the intervention or treatment) questionnaire. In babies born prematurely, symptoms of vitamin A deficiency include bronchopulmonary dysplasia (a form of chronic lung disease).
Night blindness is thought to be one of the first signs of vitamin A deficiency, followed by a diminished ability to fight infections especially respiratory and gastroenteric infections (Sommer 1982; Stephens 1996).

Description of the intervention

Vitamin A supplementation

In non-pregnant populations, vitamin A supplementation together with iron has led to improved haemoglobin levels in a number of studies (Bloem 1990; Mejia 1988). Fortification of food stuffs with vitamin A in Guatemala (sugar) and Indonesia (monosodium glutamate) was reported to improve ferritin levels (Mejia 1982) and haemoglobin concentration (Muhilal 1988). Intervention studies in Indonesian girls showed that a multivitamin regimen including vitamin A together with iron supplementation was more effective than iron alone or a multivitamin without vitamin A for improving ferritin levels (Angeles-Agdeppa 1997).
Trials of vitamin A supplementation to reduce the risk of mother-to-child transmission of HIV infection in HIV-positive pregnant women and the effect of vitamin A supplementation in the postnatal period are reviewed in separate Cochrane reviews (Oliveira 2008; Wiysonge 2008).
An early study suggested that vitamin A supplementation at time of delivery (oral not intramuscular) may result in an increase of vitamin A in colostrum (Ajans 1965).
A number of studies have assessed the role of vitamin A supplementation on infectious mortality and morbidity in children in developing countries. These have been systematically reviewed (Glasziou 1993). Vitamin A supplementation was associated with a 30% reduction of death with a larger reduction (66%) in children hospitalised with measles. Similar results were found in another review (Fawzi 1993).

How the intervention might work

Vitamin A deficiency

For many countries there are still no accurate data on vitamin A status of pregnant women. However, in areas where night blindness is common, vitamin A deficiency is often assumed to be widespread. Vitamin A deficiency is thought to be a significant problem in many developing countries in Africa, South and South-East Asia and areas of Latin America and the Western Pacific (WHO 1995). Reports of population deficiency are often based on the assessment of night blindness and other eye symptoms among pre-school children in various countries. The most obvious deficiency signs are dryness of the conjunctiva and the cornea (xerophthalmia), which can lead to permanent eye damage (McGuire 2007).
It is also known that a diet devoid of vitamin A results in decreased haemoglobin levels (Hodges 1978). Vitamin A deficiency has been

found to co-exist with iron deficiency in a number of developing countries (Karyadi 1996). Several international studies have documented a positive association between serum retinol and haemoglobin concentration in children (Mejia 1977; Wolde-Gabriel 1993) and pregnant women (Suharno 1992). Anaemia in pregnancy has been associated with vitamin A deficiency (Van den Broek 1998; Van den Broek 2000).

Vitamin A is involved in the growth and differentiation of epithelial tissues and also has a role in immunoprotection (Thurnham 1989; Tomkins 1989). Infections most closely associated with vitamin A deficiency are those in which structure or function of the epithelium may be impaired such as measles, diarrhoea and respiratory disease. Febrile infections are associated with reduced serum levels of retinol binding protein and retinol. This is thought to be an acute phase reaction (Cox 2006; Long 2007). On the other hand, infection and inflammation can depress serum retinol values, as can other micronutrient deficiencies (Thurnham 1989; Tomkins 1989).

Other changes associated with vitamin A deficiency include impaired immunity, and squamous metaplasia of the epithelium lining the upper respiratory passages and urinary bladder leading to a keratinised epithelium. In relation to dentistry, a deficiency in vitamin A leads to enamel hypoplasia (Underwood 1994; WHO 1995).

Finally, there is some evidence that dietary carotenoids have protective function against some human cancers (Rousseau 1992).

Why it is important to do this review

Vitamin A supplementation in pregnancy

Currently, the WHO recommends routine vitamin A supplementation during pregnancy or at any time during lactation in areas with endemic vitamin A deficiency (where night blindness occurs) (WHO 1998). The principal forms used as nutritional supplements are vitamin A palmitate (retinyl palmitate) and vitamin A acetate (retinyl acetate) but carotenoids (most commonly beta-carotene) and retinoids (retinol, retinal, retinoic acid) can also be used as nutritional supplements (DRI 2001).

Vitamin A supplementation during pregnancy and (extended into) the postnatal period may be expected to affect outcomes such as maternal and newborn mortality, maternal and newborn anaemia or infection or other morbidity and there is also a need to document if supplementation with vitamin A has been associated with any harmful effects. A number of new trials have been published since the first review on vitamin A supplementation for pregnancy outcomes in 2002 (Van den Broek 2002) and it is therefore important to review all current evidence regarding vitamin A supplementation to inform and review the existing recommendations for practice.

OBJECTIVES

To review the effectiveness of the supplementation of vitamin A or one of its derivatives during pregnancy, alone or in combination with other vitamins and minerals, on maternal and newborn clinical and laboratory outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised or quasi-randomised trials, including cluster-randomised trials, evaluating the effect of vitamin A supplementation in pregnant women.

We excluded trials where vitamin A is given only in the postnatal period but included trials where vitamin A was commenced pre-pregnancy or during pregnancy and continued into the postnatal period.

The outcome 'HIV transmission' was not considered in this review as it is covered in another review (Wiysonge 2008) but we included data from randomised controlled trials (RCTs) aimed at preventing vertical transmission if they meet our criteria for inclusion and report obstetric and infant outcomes relevant to our review. In addition, this current review is different from Haider 2008 which reviews the effects of multi-micronutrient supplements which could include vitamin A but does not assess the effect of vitamin A alone.

Types of participants

Pregnant women receiving vitamin A supplementation either in areas with endemic vitamin A deficiency (inadequate intake) or in areas with adequate intake as defined by the WHO global database on vitamin A deficiency.

Types of interventions

Vitamin A (or one of its derivatives) supplementation, alone or in combination with other supplements compared with a control group. The control group could be placebo, no treatment or another intervention (for example, iron).

Researchers report vitamin A measurements in different units. Accordingly, we used the following tables for conversions: Table 1; Table 2.

Table 1. Retinol supplementation to vitamin A conversion table

Retinol supplementation in mcg	Vitamin A in IU
1	3.33
2	6.66
3	9.99

Table 2. Serum retinol conversion table

Serum retinol mcg/dl	Serum retinol mc mol/L
10	0.35
20	0.7
30	1.05

Comparisons included: vitamin A (or derivative)

1. alone versus placebo or no treatment;
2. alone versus micronutrient supplements (may include iron or/and folic acid) without vitamin A;
3. in combination with other micronutrients versus micronutrient supplements without vitamin A.

Types of outcome measures

The outcomes of this review are maternal and perinatal clinical outcomes.

This review focuses on effects on maternal and newborn mortality and morbidity such as anaemia and infection (but not on HIV which is reviewed elsewhere).

We sought information on the following outcomes for this review.

Primary outcomes

1. Maternal mortality (defined as the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes (ICD-10 2007)).
2. Perinatal mortality (defined as number of stillbirths and deaths in the first week of life per 1000 live births (HAP 2008; PNM 2005)).

Secondary outcomes

1. Neonatal mortality (defined as the number of deaths during the first 28 completed days of life per 1000 live births in a given year or period (PNM 2005)).
2. Stillbirths (as defined by the trial author).
3. Maternal anaemia ((Hb) less than 11.0 g/dl).
4. Maternal clinical infection (as defined by the investigator).
5. Maternal night blindness (reported or with demonstrable ocular lesion or abnormal adaptation test).
6. Preterm birth (less than 37^{+0} weeks gestational age).
7. Neonatal anaemia (as defined by investigator).
8. Neonatal clinical infection (as defined by investigator).
9. Congenital malformations (any reported).
10. Low birthweight (less than 2.5 kg).

Where outcomes were not given according to the definitions specified above, we have noted this in the summary tables and included outcomes in the analyses wherever possible.

Search methods for identification of studies

Electronic searches

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (15 July 2010).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy and a third author reviewed these. We resolved any disagreement through discussion.

Data extraction and management

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

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). We resolved any disagreement by discussion or by involving a third assessor.

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

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

We assessed the method as:

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

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

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

We assessed the methods as:

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

(3) Blinding (checking for possible performance bias)

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

We assessed the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

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

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake. We assessed methods as:

- adequate (where there was no or less than 20% missing data and where reasons for missing data are balanced across groups);
- inadequate (where more than 20% participants' data are missing or where data are not balanced across groups);
- unclear.

(5) Selective reporting bias

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

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

(6) Other sources of bias

We described for each included study any important concerns we have about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- yes;
- no;
- unclear.

(7) Overall risk of bias

We made explicit judgments about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials. We used the standardised mean difference to combine trials that measure the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We included cluster-randomised trials in the analyses along with individually randomised trials, using the generic inverse method to combine studies using different designs. The standard errors of the two cluster randomised trials were inflated using an estimate of the intracluster correlation co-efficient (ICC) derived from data in the trial reports, as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, section 16.3.6 (Higgins 2009) using an estimate of the ICC derived from the trial (if possible), from a similar trial or from a study of a similar population. If we used ICCs from other sources, we reported this and conducted sensitivity analyses to investigate the effect of variation in the ICC. If we identified both cluster-randomised trials and individually-randomised trials, we synthesised the relevant information. We considered it reasonable to combine the results from both if there was little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit was considered to be unlikely.

We also acknowledged heterogeneity in the randomisation unit and performed a subgroup analysis to investigate the effects of the randomisation unit.

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if T^2 was greater than zero and either I^2 was greater than 30% or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there were 10 or more studies in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes we used the test proposed by Egger 1997, and for dichotomous outcomes we used the test proposed by Harbord 2006. If we detected asymmetry in any of these tests or by a visual assessment, we performed exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2008). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: that is, where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. We treated the random-effects summary as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful we did not combine trials.

If we used random-effects analyses, we presented the results as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identified substantial heterogeneity, we investigated it using subgroup analyses and Sensitivity analysis. We considered whether an overall summary was meaningful, and if it was, used random-effects analysis to produce it.

We plan to carry out the following subgroup analyses.

1. Countries with high versus low infant mortality rates (high infant mortality rate greater than or equal to 30/1000 live births (IMCI- TAG 2008)).
2. Countries with high versus low maternal mortality rates (high maternal mortality rate greater than 100 per 100,000 live births (WHR 2005)).
3. High versus low prevalence of vitamin A deficiency (as defined by WHO for the country or by the investigator).
4. Countries with a low versus high prevalence of HIV in the general population (high-prevalence countries defined as countries with national prevalence that exceeded 3% of the general population (AIDS Report 2008)).
5. Dose daily 10,000 IU versus other doses.
6. Regimen: daily versus weekly.
7. Duration of intervention: by number of weeks
8. Trimester of pregnancy in which supplementation was started (prepregnancy supplementation versus first trimester versus second trimester versus third trimester).

We used only primary outcomes in subgroup analysis.

For fixed-effect inverse variance meta-analyses, we assessed differences between subgroups by interaction tests. For random-effects and fixed-effect meta-analyses using methods other than inverse variance, we assessed differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

We carried out sensitivity analyses to explore the effect of trial quality for important outcomes in the review. Where there was risk of bias associated with a particular aspect of study quality (e.g. inadequate allocation concealment), we explored this by sensitivity analyses. We explored only primary outcomes by sensitivity analyses.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

Initially we examined 88 reports of 31 trials, published between 1931 and 2010, for inclusion in this review. We included 16 trials and excluded 14. One trial awaits classification (Hakimi 1999).

Included studies

For detailed characteristics of the included studies, *see* Characteristics of included studies.

Of the 16 included trials, two were cluster-randomised (Kirkwood 2010; West 1999) while the rest were based on randomisation of individual women. Only two trials were quasi-randomised (Green 1931; Suprapto 2002). One trial was conducted in the UK (Green 1931) and one in the USA (Ajans 1965).

Seven trials were conducted in Africa: three in Malawi (Kumwenda 2002; Semba 2001; van den Broek 2006), one in South Africa (Coutsoudis 1999), two in Ghana (Cox 2005; Kirkwood 2010) and one in Tanzania (Fawzi 1998). Five of the included trials were conducted in Indonesia (Dijkhuizen 2004; Muslimatun 2001; Suharno 1993; Suprapto 2002; Tanumihardjo 2002). One trial

was conducted in India (Radhika 2003) and one in Nepal (West 1999).

All trials were conducted in populations considered to be moderately vitamin A deficient before the relevant trial was commenced except three trials: West 1999 was conducted in Nepal in which the population was considered to be severely deficient in vitamin A (FAO and WHO 2002; FNB 2001; WHO 1996) two trials in USA and UK were conducted in populations which were not a considered Vitamin A deficient (Ajans 1965 and Green 1931).

Two trials were specifically designed with maternal mortality as the primary outcome. Women of reproductive age were given weekly Vitamin A supplements:

In the Nepal trial by West 1999, more than 36,800 deliveries were analysed as part of a cluster-randomised field trial conducted in South-East Nepal among a total of 30 village development communities (VDC), which are small sub-districts, each of which comprises nine wards. A total of 270 wards were randomised to three groups of 90 each, including 44,646 women of reproductive age receiving a weekly single oral supplement of vitamin A (23 310 IU vitamin A or 7000 mcg retinol equivalents) or beta carotene (42 mcg, or 7000 mcg retinol equivalent) or placebo. Local field workers visited the women weekly at home and administered the supplements. Pregnant women were eligible to be included in the analysis if they had received supplements for at least five months before conception. The primary outcome of the trial was pregnancy related and direct mortality occurring up to 12 weeks postpartum and included injury related deaths. Baseline characteristics such as age, arm circumference, diet or socioeconomic status were similar between the three groups. Compliance was assessed biochemically and through interviews. Serum retinol and beta-carotene concentrations were measured at mid-pregnancy in a sub-sample of women to assess compliance. Levels for vitamin A and beta-carotene were found to be raised in the supplemented (not placebo) groups and taken to imply good compliance with intake of supplements. It was noted that pregnant women were more likely to have received their supplements than women who did not become pregnant during the period of the trial. More than 75% of pregnant women received at least half their eligible doses of supplement but only half received 80% or more of the intended supplement.

The trial from Ghana, Kirkwood 2010, is the largest trial with the inclusion of more than 207,000 pregnant women. This was a cluster-randomised trial. All women aged 15 to 45 years living in seven predominantly rural districts in Brong Ahafo Region in Ghana who were capable of giving informed consent and who planned to live in the trial area for at least three months were eligible for enrolment. Implementation was phased by district; field workers visited all compounds over a four- to eight-week period. Women were randomly assigned, according to their cluster of residence, to receive a vitamin capsule or placebo capsule orally once every week. The vitamin A capsule consisted of 25 000 IU (7500 μg) retinol equivalents in soybean oil in a dark red opaque soft gel. The placebo capsule consisted of soybean oil only. Women were visited at home every four weeks, and given four capsules to be taken over the next four weeks; capsules were kept in vials, with cotton wool to absorb humidity in the rainy season. There was no direct observation of capsule taking during home visits. Instead, adherence was supported by an extensive information, education, and communication (IEC) programme, based on formative research undertaken before the trial began, with women encouraged to take their capsules on the same day, Sunday, to foster social support and reduce forgetfulness. Randomisation was by cluster to keep the possibility of women receiving the wrong capsules to a minimum. The primary outcomes of the trial were pregnancy-related mortality and all-cause female mortality. Secondary outcomes were severe maternal morbidity and perinatal and infant mortality.

A total of eight trials specifically assessed the effect of Vitamin A on haemoglobin levels. Vitamin A was given during the antenatal period in combination with other micronutrients, generally iron and folic acid.

There are five studies from Indonesia which assess effect of Vitamin A on haemoglobin.

Suharno 1993 included 305 women from 20 rural villages in West Java, 16 to 24 weeks pregnant, with haemoglobin concentrations between 8.0 and 10.9 g/dl. Women were assigned to one of four groups to receive daily supplements: one group received vitamin A (2.4 mg retinol as retinyl palmitate which equates to about 8000 IU vitamin A) and placebo iron tablets; the second group received iron (60 mg elemental iron as ferrous sulphate) and placebo vitamin A; the third group received both the vitamin A and iron supplements (as described in groups one and two); and the fourth group received placebos only. Blood samples for haematologic parameters were taken before supplementation (which lasted two weeks) and two to seven days after the last supplements were given. The supplements were administered under the direct daily supervision of field workers.

In Tanumihardjo 2002, pregnant women in the second or early third trimester were recruited from the suburban areas of Bogor in West Java, Indonesia. Ages ranged from 18 to 37 years and parity from 0 to 4 children. Women were randomly assigned to the following four supplementation groups: placebo, 8.4 mol (8000 IU) vitamin A as retinyl palmitate with an iron placebo, 1.07 mmol (60 mg) ferrous sulfate with a vitamin A placebo and vitamin A plus iron. The daily supplementation was monitored using a control card and check list by the volunteers who were responsible for administration of the doses.

Suprapto 2002 was a quasi-randomised trial. It took place in the rural area of Banyudono subdistrict, Boyolali regency, Central Java province, Indonesia. All pregnant women who visited the Banyudono health centres' antenatal clinics from July to November 2000 were asked to participate in the study. All pregnant women were numbered and listed. They were then allocated alternately into groups according to their numbers. Group IF (n = 29)

received iron-folate tablets + 5 mg glucose (placebo); group IFR (n = 22) received iron-folate tablets + 5 mg riboflavin; group IFA (n = 29) received iron-folate tablets + 2.75 mg retinyl palmitate (equal to 5000 IU vitamin A); and group IFRA (n = 23) received iron-folate tablets + 5 mg riboflavin + 2.75 mg retinyl palmitate. These were administered seven days a week for 60 days.

Muslimatun 2001 was carried out in the rural subdistrict of Leuwiliang, West Java, Indonesia. Pregnant women were supplemented once weekly from enrolment until delivery with two tablets each containing 60 mg iron as ferrous sulfate and 250 mg folic acid or with two tablets each containing 2400 retinol equivalents (RE) vitamin A in addition to the same amount of ferrous sulfate and folic acid.

In Dijkhuizen 2004 all women were recruited before 20 weeks' gestational age from13 adjacent villages in a rural area in Bogor District, West Java, Indonesia. Each woman was supplemented daily during pregnancy until delivery. All women received iron and folic acid (30 mg iron as ferrous fumarate/d and 0.4 mg pteroylglutamic acid/d). In addition, one group of women received -carotene (4.5 mg as water-soluble granulate/d; -carotene group), one group received zinc (30 mg zinc as sulfate/d; zinc group), one group received -carotene plus zinc (4.5 mg -carotene and 30 mg zinc/d; -carotene zinc group), and one group received only iron and folic acid (control group).

There are two trials from Malawi where the primary outcome was effect of Vitamin A on haemoglobin.

The Semba 2001 trial was conducted in women attending a teaching hospital antenatal clinic. Pregnant women were given daily supplements of either vitamin A (3000 mcg retinol equivalent which equals 10,000 IU vitamin A) or placebo. All women received daily iron (30 mg) and folate (400 mcg). In addition, all women received two doses of Fansidar during pregnancy as presumptive treatment for malaria. Outcomes were measured at 38 weeks and included haemoglobin concentration and erythropoietin. Iron status was measured using serum ferritin and markers of inflammation included C-reactive protein and alpha-acid glycoprotein. Vitamin A status was measured using serum retinol. Compliance with supplements was assessed via monthly tablet counts.

The van den Broek 2006 trial included a representative group of rural women attending antenatal clinic in southern Malawi. Women received daily supplements of either vitamin 10,000 IU or vitamin A 5000 IU or a placebo. In addition, all women received daily iron supplements (60 mg elemental iron as ferrous sulphate with 0.25 mg folic acid). All women also received presumptive malaria treatment at around 20 and 34 weeks' gestation consisting of three tablets of Fansidar (500 mg sulphadoxine with 25 mg pyrimethamine). Inclusion criteria included haemoglobin level less than or equal to 11.0 g/dl and more than 5.0 g/dl after determination of haemoglobin using the HemoCue screening method. Subsequent haemoglobin measurements were made using an automated (Coulter) counter. Thirty-two per cent of women recruited were HIV-positive. Mean duration of supplementation was 14 weeks. Gestational age at recruitment was not less than 12 weeks and not more than 24 weeks as assessed by ultrasonography. Blood samples were taken before supplementation was commenced and for up to two times during the antenatal period and two times postnatally. Vitamin A status was determined using serum retinol as well as the modified relative dose response test (MRDR). Iron status was measured using serum ferritin and serum transferrin receptor levels. Measures of infection status included C-reactive protein (CRP), malaria and HIV status. Compliance was measured by two-weekly tablet counts and serum retinol measurements. The three main outcome measures were haemoglobin level, prevalence of anaemia ((Hb) < 11.0 g/dl) and severe anaemia ((Hb) < 8.0 g/dl) after supplementation. Secondary outcomes included vitamin A status, iron status and infection status.

One study from India assessed effect of antenatal supplementation on haemoglobin levels.

Radhika 2003 is a randomised clinical trial of red palm oil supplementation and was conducted in pregnant women attending the outpatient department of Niloufer Hospital, Hyderabad, India, between January 2001 and March 2002. The women in the experimental group received red palm oil providing 2173 to 2307 μg of β-carotene per day with a dosage schedule of one sachet per day (8 ml). The women in the control group received one sachet of groundnut oil (8 ml). A detailed clinical anthropometric and obstetric examination was conducted in all the women at baseline and every two weeks up to 36 weeks and thereafter every week until delivery. All the women received iron folate tablets (60 mg of iron and 500 μg of folic acid) for 100 days and routine prenatal care.

Three trials were conducted in HIV-positive pregnant women with the main intent of looking at the effect of Vitamin A supplementation on mother to child transmission of HIV. These trials also report on other outcomes relevant to this review and are included.

In the trial by van den Broek 2006 in rural Malawi, 32% of all recruited women were HIV-positive but this trial was designed to assess effect of Vitamin A on haemoglobin levels and HIV transmission was not measured.

In Kumwenda 2002 the study population consisted of HIV-positive pregnant women of 18 to 28 weeks' gestation who were seen at the antenatal clinic of the Queen Elizabeth Central Hospital (Blantyre, Malawi) from November 1995 through December 1996. All women received orally administered daily doses of iron (30 mg of elemental iron) and folate (400 mg) from the time of study enrolment until delivery. One-half of the women were randomised to receive daily doses of orally administered vitamin A (3 mg retinol equivalent (10,000 IU); the vitamin A group) from the time of study enrolment until delivery.

One trial was conducted in the republic of South Africa: Coutsoudis 1999 is a double-blind randomised trial conducted in King Edward VIII Hospital and McCords Hospital, in Durban, South Africa. HIV-positive women of 28 to 32 weeks' gestation were randomised to receive either placebo or a daily dose of 5000

IU retinyl palmitate and 30 mg beta-carotene during the third trimester of pregnancy and 200,000 IU retinyl palmitate at delivery.

One study from Tanzania: Fawzi 1998 recruited pregnant women between 12 and 27 weeks' gestation who were HIV infected and resident in Dar es Salaam. Women were assigned in a two-by-two factorial design. One thousand and seventy-five women received a daily oral dose of: vitamin A (30 mg beta-carotene plus 5000 IU preformed vitamin A, n = 269); multivitamins excluding vitamin A (20 mg B1, 20 mg B2, 25 mg B6, 100 mg niacin, 50 μg B12, 500 mg C, 30 mg E, and 0·8 mg folic acid, n = 269); multivitamins including vitamin A (n = 270), all formulated in two tablets; or two tablets of placebo (n = 267). Eighty-five per cent of women took the single large dose of the supplement or placebo at delivery; the other 15% were not given this dose because they delivered at home or at another clinic. Compliance was assessed as the percentage of prescribed tablets absent from the returned bottles. To further assess compliance, plasma vitamin A concentrations were measured at baseline and at delivery in 100 women.

For three trials the main outcome measure was maternal infection. Ajans 1965 conducted a study in the USA in which 44 parturient women in good health from the lower and middle socioeconomic groups were allotted at random to one of three groups after admission to the delivery suite of the American University Hospital. Group one included 18 women who were not given any form of vitamin A therapy prepartum; they formed the control group of the study. Group two comprised 15 women who were all given a single intramuscular injection of 600,000 lU of vitamin A palmitate in oil at parturition. Group three was made up of 11 women who were given 600,000 lU of water-dispersible vitamin A palmitate orally shortly before delivery. Blood samples were collected from all women before delivery and, in the case of groups two and three, before dosing with vitamin A. Four samples of 2 ml to 3 ml of colostrum were also collected from each woman: one antepartum sample and three postpartum samples, one on each consecutive day of hospitalisation. Following discharge, women in group three were followed up further by public health nurses at their homes where bi-weekly samples of milk were collected during the first week after discharge and then weekly samples for a total period ranging between 38 and 59 days postpartum. Women in groups one and two were studied in the summer (June to August 1963) and those of group three in the following winter (October 1963 to March 1964). Group three was excluded from analysis in this review because they were conducted in a different time and conditions than the other two groups.

Green 1931 is a quasi-randomised trial conducted in the Jessop Hospital and the Nether Edge municipal hospital in the UK. Six hundred women were recruited. All women not delivered in hospital were rejected from the series, so that a total of 275 women treated with the vitamin preparation and 275 untreated to serve as controls remained for analysis. Vitamin preparation was given as 1 oz of the vitamin preparation radiostoleum, an amount equivalent in vitamins A and D roughly to 30 oz of a good cod-liver oil, should have been taken commencing one month previous to the calculated day of labour. The first 76 cases prior to June 1929 were given the preparation for only 14 days before delivery (daily). It was, however, continued for the first seven days of the puerperium. It was then decided that a more logical procedure would probably be to begin the administration earlier and thus build up a larger reserve at the time of labour.

Cox 2005 recruited primigravid pregnant women from antenatal clinics at Nkoranza District Hospital and three rural health clinics in Brong Ahafo region, Central Ghana. Women were randomised to either capsules which were given weekly and contained 10,000 IU of vitamin A as retinyl palmitate in groundnut oil, plus tocopherol as a preservative from enrolment until six weeks' postpartum, or groundnut oil and tocopherol only in the placebo capsules from enrolment until six weeks' postpartum.

Excluded studies

For detailed characteristics of the excluded trials, *see* Characteristics of excluded studies.

Of the 14 excluded studies, we excluded two because they used lycopene as the intervention (Banerjee 2009; Sharma 2003). Lycopene lacks beta-ion ring (that is present in the β-carotene), so lycopene cannot form vitamin A and its biological effects are due to mechanisms other than forming vitamin A. We excluded three studies because they were not randomised trials (Chawla 1995; Howells 1986; Laitinen 2009). We excluded four studies because both arms of the trial contained the same product and so lacked any comparison (Christian 2003; Haskell 2005; Lietz 2001; Roberfroid 2010). We excluded three studies because the intervention only started after delivery (Darboe 2007; Humphrey 2006; Roy 1997). We excluded one study because the only outcome was HIV transmission and although secondary outcomes are relevant to this review no data are available (Chikobvu 2001). Finally, we excluded one study because participants were not pregnant women (Van Vliet 2001).

Risk of bias in included studies

See Figure 1 and Figure 2.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

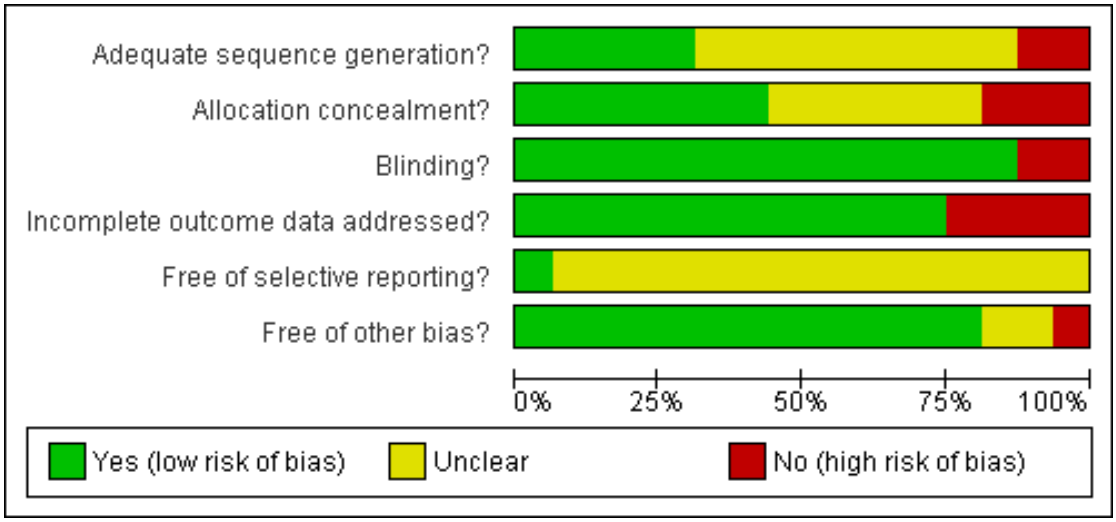
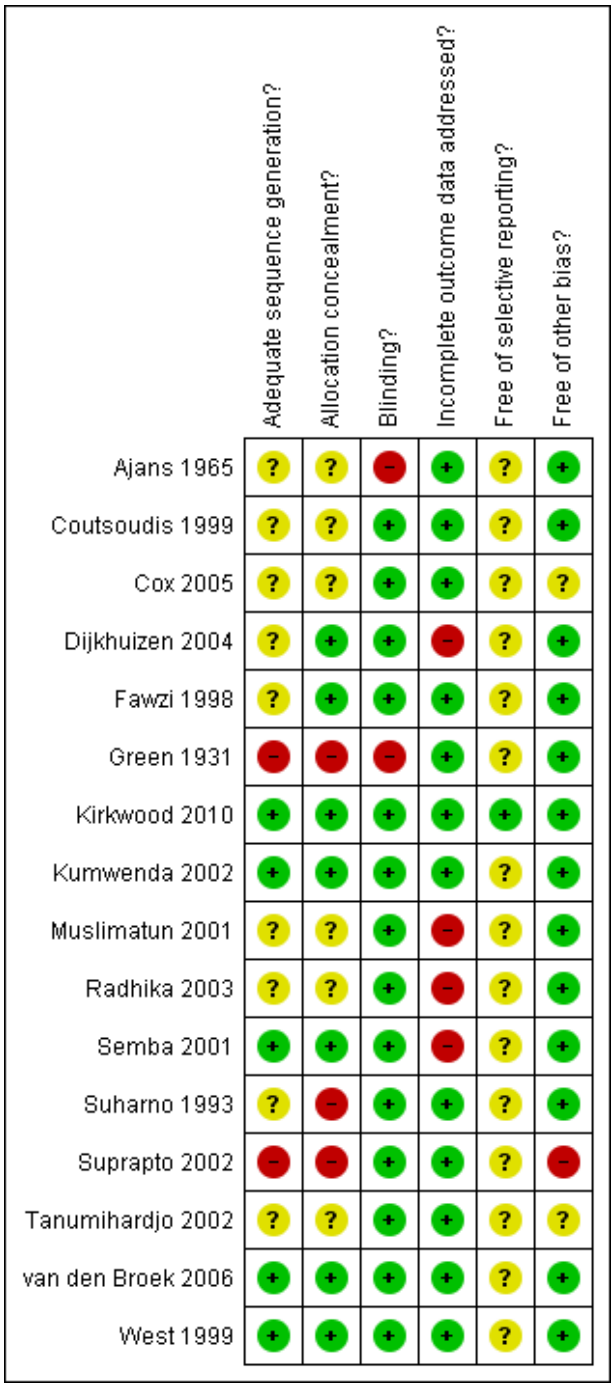


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Only four studies did not report at all on the allocation concealment and generation (Ajans 1965; Coutsoudis 1999; Radhika 2003; Tanumihardjo 2002). Two of the included studies were not clear on the allocation concealment and generation (Cox 2005; Muslimatun 2001). Three studies reported inadequate allocation concealment and generation (Green 1931; Suharno 1993; Suprapto 2002). The remaining seven trials reported adequate allocation concealment and generation (Dijkhuizen 2004; Fawzi 1998; Kirkwood 2010; Kumwenda 2002; Semba 2001; van den Broek 2006; West 1999).

Blinding

All included studies reported on blinding. Only two studies reported no blinding while all other included trials reported double blinding (Ajans 1965; Green 1931).

Incomplete outcome data

Four studies did not address the incomplete outcome data issue (Dijkhuizen 2004; Muslimatun 2001; Radhika 2003; Semba 2001). The rest of the included trials adequately addressed the issue of incomplete outcome data. Authors of the Kirkwood 2010 trial provided supplementary data to confirm that although 43% of women migrated out of the trial area and 1% withdrew consent, the loss to follow up for pregnancy-related mortality was calculated to be 8%.

Selective reporting

The protocols of the included studies were not generally available and accordingly we can not comment on selective reporting bias except for Kirkwood 2010 which was free from any selective reporting bias.

Other potential sources of bias

Three studies were unclear, either because only an abstract was available (Chikobvu 2001), presence of differences in educational level and gestational age at enrolment (Cox 2005) or the study report is not detailed enough (Tanumihardjo 2002). Two trials had a potential source of bias. Suprapto 2002 had reported that women in group IFRA were shorter and lighter than those in other groups. The rest of the included trials were free from any potential source of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Vitamin A for maternal and newborn mortality and morbidity; **Summary of findings 2** Combination vitamin A and micronutrients for maternal and newborn mortality and morbidity

Vitamin A alone versus placebo or no treatment

Vitamin A supplementation does not significantly affect the risk of maternal mortality (risk ratio (RR) 0.78, 95% confidence interval (CI) 0.55 to 1.10, three studies; Tau^2 0.04, I^2 37%; Analysis 1.1), perinatal mortality (RR 1.01, 95% CI 0.95 to 1.07; 1 study, Analysis 1.2), neonatal mortality (RR 0.97, 95% CI 0.90 to 1.05; three studies , I^2 23% Analysis 1.3) or stillbirth (RR 1.06, 95% CI 0.98 to 1.14, 1 study; Analysis 1.4).

Vitamin A supplementation does not significantly affect the risk of neonatal anaemia (RR 0.99, 95% CI 0.92 to 1.08; 1 study, Analysis 1.9), preterm birth (RR 0.77, 95% CI 0.57 to 1.04, four studies, I^2 0% Analysis 1.8) or the risk of having a low birthweight baby (RR 0.98, 95% CI 0.62 to 1.54; three studies, Tau^2 0.06, I^2 23%, Analysis 1.12).

Vitamin A supplementation significantly reduces the risk of maternal anaemia (RR 0.64, 95% CI 0.43 to 0.94; three studies, Tau^2 0.08, I^2 68%, Analysis 1.5), maternal clinical infection (RR 0.37, 95% CI 0.18 to 0.77; three studies, Tau^2 0.19, I^2 39%, Analysis 1.6), and maternal night blindness (RR 0.70, 95% CI 0.60 to 0.82; 1 study, Analysis 1.7).

No trials investigated vitamin A alone versus micronutrient supplement without vitamin A.

Vitamin A with other micronutrients versus micronutrient supplements without vitamin A

Vitamin A supplementation (with other micronutrients) does not have a significant effect on the risk of stillbirth (RR 1.41, 95% CI 0.57 to 3.47; two studies, Analysis 3.4), maternal anaemia (RR 0.86, 95% CI 0.68 to 1.09; three studies, Analysis 3.5) preterm birth (RR 0.39, 95% CI 0.08 to 1.93; one study, Analysis 3.8), neonatal mortality (RR 0.65, 95% CI 0.32 to 1.31; one study, Analysis 3.3), or neonatal anaemia (RR 0.75, 95% CI 0.38 to 1.51; two studies, Tau^2 0.24, I^2 97%, Analysis 3.9). There were fewer low birthweight babies in the supplemented groups (RR 0.67, CI 0.47 to 0.96; one study, Analysis 3.12).

Subgroup analysis

Only the specified primary outcomes maternal and perinatal mortality were included in the subgroup analysis. Subgroup analysis was by country statistics for vitamin A deficiency (high or low),

maternal mortality (high or low), infant morality (high or low) and HIV status (high or low).

All trials investigating the effects on maternal and perinatal mortality were cluster-randomised trials.

For maternal mortality

In countries with high maternal mortality or high prevalence of vitamin A deficiency, the RR for maternal mortality was 0.83, (95% CI 0.68 to 1.02) in the overall analysis. There was no significant reduction in the odds of maternal mortality in countries with low maternal mortality or low prevalence of vitamin A deficiency (RR 0.33, 95% CI 0.01 to 8.19).

For countries described as having low infant mortality rates, maternal mortality decreased by two thirds (RR 0.33, 95% CI 0.01 to 9.44) but maternal mortality was not significantly reduced for countries with high infant mortality rates (RR 0.77, 95% CI 0.51 to 1.17).

In countries with low HIV prevalence the RR for maternal mortality was 0.83 (95% CI 0.68 to 1.01). The trials in countries with high HIV prevalence did not set out to assess the effect of vitamin A on maternal mortality.

For perinatal mortality

Perinatal mortality in countries with high infant mortality rates remained unchanged (RR 1.01, 95% CI 0.95 to 1.07). Perinatal mortality was not assessed in countries with low infant mortality rates.

Perinatal mortality in countries with high maternal mortality rates or high prevalence of vitamin A deficiency remained unchanged (RR 0.95, 95% CI 0.87 to 1.03). No trials reported on perinatal mortality from countries with low maternal mortality rates or countries with low prevalence of vitamin A deficiency.

In countries with low HIV prevalence, RR for perinatal mortality was 1.01 (95% CI 0.95 to 1.07). For countries with high HIV prevalence, no trials investigated the effect of vitamin A supplementation to the mother on perinatal mortality.

Dose of vitamin A

In relation to the dose, no trials investigated the effect of daily 10,000 IU vitamin A supplementation on maternal mortality, but for other doses the RR for vitamin A supplementation for maternal mortality was 0.83 (CI 0.68 to 1.02) and for perinatal mortality 1.01 (95% CI 0.95 to 1.07).

For weekly vitamin A supplementation the RR for maternal mortality was 0.83 (95% CI 0.68 to 1.02) and for perinatal mortality 1.01 (95% CI 0.95 to 1.07).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Combination vitamin A and micronutrients for maternal and newborn mortality and morbidity

Patient or population: Pregnant women
Settings: Areas with endemic vitamin A deficiency (inadequate intake)/areas with adequate intake as defined by the WHO global database on vitamin A deficiency
Intervention: Combination vitamin A and micronutrients
Comparison: Other micronutrients

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Other micronutrients	Combination vitamin A and micronutrients				
Maternal mortality	See comment	See comment	Not estimable	0 (0)	See comment	
Perinatal mortality	See comment	See comment	Not estimable	0 (0)	See comment	
Preterm birth	**75 per 1000**	**29 per 1000** (6 to 145)	**RR 0.39** (0.08 to 1.93)	136 (1 study)	⊕○○○ **very low**[1,2,3]	
Maternal anaemia	**Low risk population**		**RR 0.86** (0.68 to 1.09)	706 (3 studies)	⊕⊕○○ **low**[4,5]	
	136 per 1000	**117 per 1000** (92 to 148)				
	Medium risk population					
	346 per 1000	**298 per 1000** (235 to 377)				
	High risk population					

	667 per 1000	**574 per 1000** (454 to 727)			
Maternal infection	See comment	See comment	Not estimable	0 (0)	See comment

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

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

[1] 22.2% women were not included in the analyses. The study was at a high risk of attrition bias.
[2] The confidence intervals covered a range of values that included a substantial reduction and increase in the risk of preterm birth with vitamin A.
[3] The study protocols were not available, precluding full assessments of the outcomes that were measured but not reported. Publication bias could not be excluded on this basis.
[4] Most of the weight was assigned to studies where there was a high risk of attrition bias.
[5] The confidence intervals covered a range of values that included a substantial reduction in the risk of maternal anaemia and a potential increase in the risk of maternal anaemia with vitamin A.

DISCUSSION

Summary of main results

This review investigates the effectiveness of vitamin A supplementation during pregnancy, alone or in combination with other micronutrients, on maternal and newborn clinical outcomes. Sixteen trials are included in this review out of a total of 31.

In countries where night blindness is reported, maternal night blindness is significantly improved with vitamin A supplementation (RR 0.70, 95% CI 0.60 to 0.82).

We conducted a meta-analysis for the first time in this review; this had not been possible in the previous review. Although there are limitations to this, overall the analysis shows that there is no evidence that Vitamin A supplementation to women of reproductive age or during pregnancy decreases maternal mortality (RR 0.78, 95% CI 0.55,1.10). In vitamin A deficient populations and HIV-positive women, vitamin A supplementation reduces maternal anaemia (RR 0.64, 95% CI 0.43 , 0.94) and there is evidence that vitamin A supplements may reduce maternal clinical infection (RR 0.37, 95% CI 0.18 to 0.77).

Of the included trials, 13 were designed to measure the effect of vitamin A supplementation during pregnancy on maternal mortality or maternal anaemia or maternal infection. Other maternal and neonatal clinical outcomes were also determined in the studies but not as primary outcomes. Three trials were designed to assess effect of Vitamin A on mother to child transmission of HIV - we have included these because the secondary outcomes are relevant to this review.

The trials are from a variety of countries, including both developing and high-resource countries, with large differences between the countries with regard to baseline maternal and perinatal mortality as well as baseline vitamin A status and prevalence of anaemia of the populations studied. In some studies vitamin A status of the trial population was assessed specifically at baseline (by serum retinol levels or using the more accurate Modified Relative Dose Response (MRDR) test), whereas in other studies this was not done.

It was difficult to compare the results of supplementation with Vitamin A (or derivatives) on maternal and newborn health outcomes, especially where these outcomes were differently defined in the different studies. For example, maternal clinical infection was variously defined as temperature above 37 or 38 degrees Celsius at different times during pregnancy and the postnatal period (e.g. 12 weeks antenatal or one week or three months postnatal); or infectious morbidity was defined by recorded diagnosis (gastroenteritis, sepsis, respiratory infection etc). Maternal anaemia was more consistently defined (Hb < 11.0 g/dl, Hb < 10.0 g/dl) but one study from Malawi reported change in Hb rather than percentage of women not anaemic and thus we have not included it in the meta-analysis.

The two largest studies from Nepal and Ghana specifically assessed the effect on maternal mortality with almost 95,000 women included. The risk ratio (RR) of maternal mortality was found to be 0.78 (95% CI 0.55 to 1.1). Vitamin A deficiency is considered to be endemic in Nepal and night blindness is commonly reported. The main trial from Nepal by West 1999 reported a substantial reduction in pregnancy-related mortality (including injuries) with most of the mortality contributing to the difference between supplementation and placebo groups occurring in death from injury, chronic illness and uncertain cause of death which was difficult to explain. The large study subsequently conducted in Ghana, a country with moderate vitamin A deficiency, did not show an effect of vitamin A supplementation on maternal mortality.

Several trials specifically assessed the effect of vitamin A supplementation during the antenatal period on maternal anaemia. Vitamin A was given together with other micronutrients, principally iron and folic acid. The Malawi study reported no effect of Vitamin A in addition to iron supplementation on haemoglobin levels. Assessment of Vitamin A status revealed the women were generally vitamin A replete. The other three studies were from countries where vitamin A deficiency is considered to be endemic (Indonesia and Nepal) and from Tanzania, where the population studied were all HIV-positive women. For the three studies included in the meta-analysis, for a total of almost 2500 pregnant women, maternal anaemia (Hb < 11.0g/dl) was found to be reduced with a RR of 0.64 (95% CI 0.43 to 0.94).

Three studies measured maternal infection with a combined RR of 0.37 (95% CI 0.18 to 0.77) after supplementation with vitamin A in just under 1500 women studied. It was noted (as above) that the criteria for the outcome 'infection' varied between the studies. The most significant study included in the meta-analysis was conducted in the 1930s (Green 1931) and there are questions related to the accuracy of the design of this study. Also it has not been possible to calculate the exact dosage of Vitamin A given (in the form of radiostoleum). In addition it must be noted that one of the three studies was in HIV-positive women, who may have a different overall risk of infection compared to non-HIV-positive women.

No studies of supplementation in the antenatal period were specifically designed to assess neonatal outcomes, but where these were reported we have included them in the analyses. For studies reporting these outcomes, vitamin A supplementation does not affect the risk of perinatal mortality (RR 1.01, 95% CI 0.95 to 1.07) or stillbirth or neonatal mortality separately. Similarly, analysis of available data shows no effect on preterm birth (RR 0.77, 95% CI 0.57 to 1.04) or low birthweight (RR 0.98, 95% CI 0.62 to1.54). There were no reported side effects, adverse events or congenital malformations in any of the trials.

The dose of vitamin A given, in combination with additional micronutrients and the duration of supplementation differed in the trials and varied between 5000 IU and 10,000 IU for daily doses, around 200,000 IU vitamin A for weekly supplementation and 200,000 IU vitamin A at time of delivery.

For one study supplementing vitamin A together with other mi-

cronutrients (versus other micronutrients in control group) in HIV-positive women, the risk of low birthweight was found to reduced (RR 0.67, 95% CI 0.47 to 0.96).
There were no statistically significant differences in outcome for any of the subgroup analyses performed.

Overall completeness and applicability of evidence

The two cluster-randomised trials with a large number of participants were included in the meta-analysis and increased the accuracy and reliability of the evidence produced. Added to that, the different populations studied by different included randomised clinical trials amplified the applicability of the evidence produced. Most of the specified outcomes were reported by some of the included trials but the different trials were not designed to measure the same primary outcomes and many of the specified secondary outcomes were either not reported and/or defined differently in the different country settings. The underlying baseline statistics for maternal mortality, perinatal mortality and vitamin A status of pregnant women were not available for the specific population studies, and country estimates were therefore used in most cases.

Quality of the evidence

There was no lack of allocation concealment between the included clinical trials; only three trials showed low concealment level. Green 1931 and Suprapto 2002 used an alteration method for the allocation generation and concealment; marking each first woman as a participant and the next woman due to deliver as the control. Suharno 1993 did not report how the allocation was generated or concealed. In the case of blinding, all trials included were double blinded except Ajans 1965 and Green 1931, both of which did not use any intervention in the control group. Four clinical trials included lost more than 20% of the participants (Dijkhuizen 2004; Kirkwood 2010; Radhika 2003; Semba 2001); these clinical trials were conducted in rural areas with participants moving in and out of the study area. None of the included trials were stopped early. Accordingly, none of the included trials suffered any limitation at the design or implementation level. Furthermore, all the included trials directly compared the effects of vitamin A supplementation on the mother and baby.
Heterogenity between trials in the meta-analysis was minimal (0% to 40%). Added to that, the precision of the results can be considered good, with narrow confidence intervals in most cases except for the subgroup analyses.
The underlying quality of methodology incorporated in the included clinical trials as mentioned above and of the meta-analysis mandate a general moderate to high quality rating of the body of evidence based on the the GRADE approach used in this review.
For each outcome, the evidence could be rated. Analysis of RR for preterm birth had a wide CI added to that; there were concerns about the accuracy of assessment of gestational age, causing the rating of the evidence to be low quality. For maternal anaemia the evidence is strong and of high quality. In case of maternal clinical infection, Green 1931 strongly influenced the pooled effect estimate. Green 1931 was judged to be at risk of selection and detection bias and there was concerns about the accuracy of the measurement of infection in the studies; therefore, the evidence for maternal clinical infection is of low quality.
For the use of vitamin A with other micronutrients versus micronutrient supplements without vitamin A regarding maternal anaemia outcome, results have a wide CI. Added to that, there was a high risk of attrition bias in the three trials used for the comparison; Semba 2001 excluded 32.5% of the participants from the analysis, and Fawzi 1998 excluded 10.8%; in the case of Muslimatun 2001, 25.1% of the participants were lost for a variety of reasons. Therefore, the rating of evidence for maternal anaemia for trials using vitamin A with other micronutrients is considered to be of low quality.

Potential biases in the review process

None known.

Agreements and disagreements with other studies or reviews

The trials included in this review were carefully planned and executed.
The absence of an effect on stillbirth rate, neonatal mortality, or perinatal mortality accords with the findings of the two large cluster trials (Cox 2005; Kirkwood 2010).
It has been suggested that vitamin A supplementation, especially in the postpartum period, will reduce the incidence of sepsis. In the trials reviewed, maternal clinical infection was assessed in a number of ways and there is evidence to suggest that vitamin A could have a significant effect on maternal infection. Maternal anaemia evidence is of high quality with data to support that supplementation with vitamin A reduces anaemia in vitamin A deficient and HIV positive women.
There are no reports of side effects, adverse events or congenital malformations in the trials published so far.

AUTHORS' CONCLUSIONS

Implications for practice

Overall the findings of this review do not currently support a role for antenatal vitamin A supplementation to reduce maternal or

perinatal mortality. There is, however, evidence that antenatal vitamin A supplementation (in addition to iron and folic acid) reduces maternal anaemia in populations that are vitamin A deficient and in HIV-positive pregnant women. Although the available evidence suggests a reduction in maternal infection when vitamin A is given antenatally or around the time of delivery, the data are not of a high quality and further evidence is needed to explore the effect of antenatal vitamin A supplementation on maternal infection in the antenatal and postnatal periods. The effect of vitamin A is likely to depend on whether the population who receive supplements are vitamin A deficient or not.

Implications for research

Results of 16 trials to assess effect of vitamin A supplementation during pregnancy are presented in this review. The three main outcomes examined are maternal mortality, maternal anaemia and maternal infection.

It must be said that for any of these individual outcomes there were between two and four trials that could be included in a meta-analysis and even within this group of trials there was significant difference in population with regard to Vitamin A status, baseline anaemia and infection prevalence and maternal mortality ratio.

It seems unlikely that vitamin A supplementation per se contributes directly to reducing maternal mortality. The evidence that this might be possible originally came from the trial in Nepal where vitamin A deficiency is common but reduction in deaths was not in the category of direct maternal deaths. In Ghana it is less likely women are vitamin A deficient and supplementation did not reduce mortality. However, in this study there was a substantial number of women lost to follow-up. Both the Ghana and Nepal trial results are in the same direction (a reduction in maternal mortality). The trial from Ghana showed non-significant results. For this trial 43% of women migrated outside the study area and 1% withdrew consent. These women contributed to the final analysis either by completing a pregnancy before they migrated or contributed data to the analysis of all-cause female mortality by contributing person time to the denominator of this analysis. Loss to follow up for pregnancy related mortality was subsequently calculated to be 8% (supplementary information provided by authors). For Nepal the reduction in deaths is difficult to explain with biological plausibility, but it was a significant reduction. The baseline vitamin A status in each of these trials was not assessed. Vitamin A deficiency in Nepal is considered to be severe whereas for Ghana this is considered to be moderate. For populations with no or less deficiency in vitamin A , supplementation is likely to be less effective.

It would seem that if any new trials are designed, it will be crucially important to assess baseline vitamin A status as well as accurate cause of maternal (and neonatal) death and to ensure follow-up of women is possible. In resource-poor settings where maternal mortality is highest and research most needed, this will also be most difficult to ensure.

Further evidence on whether vitamin A can reduce infection including maternal sepsis is needed.

To improve haemoglobin vitamin A supplementation in addition to iron and folic acid is beneficial in women who are vitamin A deficient or HIV-positive. The optimal dose of vitamin A, length of supplementation and the maximum expected increase in haemoglobin have not been established. Also effect change will depend on baseline degree of anaemia and vitamin A deficiency, and this requires further study.

It was noted that there are differences between the trials with regard to the dose of vitamin A given, the combination with additional micronutrients and the duration of supplementation. In addition, baseline assessments of vitamin A status are often not available even outside the study population, methods of assessment vary and comparisons are therefore very difficult to make. For future studies it is recommended that these are designed to take account of these limitations. It would also be helpful if neonatal outcomes are measured according to international criteria so that studies can be compared.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Ajans 1965

Methods	RCT.
Participants	Inclusion criteria: 44 parturient women in good health from the lower and middle socioeconomic groups (in a population in which vitamin A deficiency occurs).
Interventions	Intervention group1: 15 women. Single intramuscular injection of 600,000 lU of vitamin A palmitate in oil at parturition. 4 samples of 2 to 3 ml of colostrum were collected. 1 antepartum sample and 3 postpartum samples, 1 on each consecutive day of hospitalisation. Intervention group 2: 11 women. Given 600,000 lU of water-dispersible vitamin A palmitate orally shortly before delivery. 4 samples of 2 to 3 ml of colostrum were collected. 1 antepartum sample and 3 postpartum samples, 1 on each consecutive day of hospitalisation. Followed by public health nurses at their homes where bi-weekly samples of milk were collected during the first week after discharge and then weekly samples for a total period ranging between 38 and 59 days postpartum. Control group:18 women not given any form of vitamin A therapy prepartum. Four samples of 2 to 3 ml of colostrum were collected. 1 antepartum sample and 3 postpartum samples, 1 on each consecutive day of hospitalisation.
Outcomes	Primary outcome: levels of vit A and carotenoids in the maternal blood. Other outcomes: levels of vit A and carotenoids in the colostrum prenatal and postnatal.
Notes	Vit A levels measured before starting supplementation in group 1 and 2. Study was done in a population in which vitamin A deficiency occurs. Study setting: American university hospital.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No description except allotted at random.
Allocation concealment?	Unclear	No description except allotted at random.
Blinding? All outcomes	No	No placebo was used in this study.
Incomplete outcome data addressed? All outcomes	Yes	No exclusion or loss of follow up reported.
Free of selective reporting?	Unclear	The protocol of the study is not available at the moment.

Ajans 1965 (*Continued*)

Free of other bias?	Yes	

Coutsoudis 1999

Methods	Double-blind RCT.
Participants	Inclusion criteria: • pregnant women 28-32 weeks' gestation; • HIV-positive. (HIV-seropositive women identified through antenatal screening programmes. All the women enrolled were black Africans.)
Interventions	Intervention group: 368 women received daily dose of 5000 IU retinyl palmitate and 30 mg beta-carotene during the third trimester of pregnancy (together corresponding to 43,400 IU vit A daily for 12 weeks) and 200,000 IU retinyl palmitate at delivery. Control group: 360 women received placebo on the same schedule.
Outcomes	Primary outcome: effects of vit A on HIV viral load and HIV transmission. Other outcomes: neonatal mortality (the number of deaths during the first 28 completed days of life per 1000 live births in a given year or period) and anaemia, maternal anaemia, clinical infection (fever > 1 week at 1 week postnatally), preterm birth (delivery less than 37 completed weeks' gestational age estimated using LMP) , low birth weight and morbidity.
Notes	Vit A levels were measured before starting supplementation. Country: South Africa. Study setting: King Edward VIII Hospital and McCords Hospital, in Durban, South Africa

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	"double-blind."
Incomplete outcome data addressed? All outcomes	Yes	57 (7.8%) women did not deliver in the hospitals and cannot be traced.
Free of selective reporting?	Unclear	The protocol of the study is not available at the moment.
Free of other bias?	Yes	

Cox 2005

Methods	A randomised double-blind controlled trial.
Participants	Inclusion criteria: • primigravid pregnant women; • resident within the study area; • in good health; • less than 24 weeks pregnant. Exclusion criteria: HIV infection or tuberculosis.
Interventions	Intervention group: 48 women received weekly capsules of 10,000 IU of vitamin A as retinyl palmitate in groundnut oil, plus tocopherol as a preservative from enrolment until 6 weeks postpartum. Suplimintation was for a minimum of 18 weeks. Control group: 50 women received groundnut oil and tocopherol only in the placebo capsules from enrolment until 6 weeks postpartum.
Outcomes	Primary outcome: maternal infections (presence of placental malaria and peripheral parasitaemia). Other outcomes: haemoglobin and birth weight.
Notes	Vit A levels were measured before starting supplementation. Country: Ghana. Study setting: Nkoranza District Hospital and three rural health clinics in Brong Ahafo region, Central Ghana.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"balanced block randomisation."
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	"double-blind."
Incomplete outcome data addressed? All outcomes	Yes	12 (12%) women were excluded from the analysis: 1 false pregnancy, 1 early miscarriage, 10 missed late pregnancy visit.
Free of selective reporting?	Unclear	The protocol of the study is not available at the moment.
Free of other bias?	Unclear	The most marked difference was in educational level and gestational age at enrolment. Levels of anti-VSACSA IgG to the FCR3CSA parasite line differed between the treatment groups at baseline. There were considerably fewer data available for the placebo than the vitamin A group at the

Cox 2005 (*Continued*)

		late pregnancy follow-up.

Dijkhuizen 2004

Methods	Double-blind RCT, factorial design.
Participants	Inclusion criteria: all women were recruited before 20 weeks' gestational age. Exclusion criteria: twin pregnancy and congenital abnormalities that interfered with growth, development, or metabolism.
Interventions	Intervention group 1: 37 women received iron and folic acid supplements together with ß -carotene (4.5 mg as water-soluble granulate/d (representing 5750 IU of vit A)). Each woman was supplemented daily during pregnancy until delivery for a minimum of 16 weeks. Intervention group 2: 37 women received iron and folic acid supplements together with zinc (30 mg zinc as sulfate/d). Each woman was supplemented daily during pregnancy until delivery. Intervention group 3: 37 women received iron and folic acid supplements together with zinc and carotene. Each woman was supplemented daily during pregnancy until delivery. Control group: 37 women received iron and folic acid.
Outcomes	Primary outcome: maternal and fetal haemoglobin and zinc levels. Other outcomes: maternal and fetal ferritin, retinol and carotene levels.
Notes	Vit A levels were not measured before starting supplementation. Country: Indonesia. Study setting:13 adjacent villages in a rural area in Bogor District, West Java, Indonesia.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No information provided except factorial randomisation.
Allocation concealment?	Yes	"Capsules were indistinguishable and given a letter code."
Blinding? All outcomes	Yes	"double-blind."
Incomplete outcome data addressed? All outcomes	No	51 (22.2%) women were not included in the analyses.
Free of selective reporting?	Unclear	The protocol of the study is not available at the moment.
Free of other bias?	Yes	

Fawzi 1998

Methods	2-by-2 factorial design.
Participants	Inclusion criteria: • pregnant women 12-27 weeks' gestation;. • HIV-positive women; • resident in Dar es Salaam at the time of baseline interview; • intend to stay in the city until delivery and 1 year breastfeeding thereafter.
Interventions	Intervention group 1: 270 women received a daily (for at least 10 weeks) oral dose of multivitamins including vitamin A (30 mg b-carotene (representing 38,000 IU vit A) and 5000 IU of preformed vitamin A, 20 mg of B1, 20 mg of B2, 25 mg of B6, 100 mg of niacin, 50 mg of B12, 500 mg of C, 30 mg of vitamin E, and 0.8 mg of folic acid); an additional oral dose of vitamin A (200,000 IU) at delivery. Intervention group 2: 269 women received a daily oral dose of vitamin A alone (30 mg b-carotene and 5000 IU of preformed vitamin A), plus an additional oral dose of vitamin A (200,000 IU) at delivery. Intervention group 3: 269 women received a daily oral dose of multivitamins excluding vitamin A, plus an additional oral placebo at delivery. Intervention group 4: 267 women received a daily oral dose of placebo. An additional oral placebo at delivery.
Outcomes	Primary outcome: CD levels in both mother and fetus and HIV transmission. Other outcomes: birth weight, preterm birth (delivery less than 37 completed weeks estimated using LMP) and haemoglobin in both mother and fetus (Hb < 10.0 g/dl).
Notes	Vit A levels were measured before starting supplementation. Country: Tanzania. Study setting: four antenatal clinics with several smaller peripheral clinics.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"Randomisation was done in blocks of 20."
Allocation concealment?	Yes	"At enrolment, we assigned each eligible women the next numbered bottle of regimen."
Blinding? All outcomes	Yes	Double blind.
Incomplete outcome data addressed? All outcomes	Yes	117 (10.8%) women were excluded from the analysis: • 3 not pregnant; • 7 died before delivery and excluded; • 54 lost to follow-up; • 53 no date of delivery or gestational age.
Free of selective reporting?	Unclear	The protocol of the study is not available at the moment.

Free of other bias?	Yes	

Green 1931

Methods	Quasi-RCT, multi-centred.
Participants	Inclusion criteria: pregnant women. Exclusion criteria: cases not delivered in hospital.
Interventions	Intervention group: 275 women received 1 oz of the vitamin preparation radiostoleum, an amount equivalent in vitamins A and D roughly to 30 oz of a good cod-liver oil (equivalent to 444,000 IU vit A) , should have been taken daily commencing one month previous to the calculated day of labour. The first 76 cases prior to June 1929 were given the preparation for only 14 days before delivery (daily). It was, however, continued for the first seven days of the puerperium. It was then decided that a more logical procedure would probably be to begin the administration earlier and thus build up a larger reserve at the time of labour. Control group:275 women received an untreated version.
Outcomes	Maternal infection (puerperal fever > 38^{o} C) and maternal and baby mortality and morbidity.
Notes	Vit A levels were not measured before starting supplementation. Country: UK. Study setting: the Jessop Hospital and the Nether Edge municipal hospital.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	No	"the first patient was given the preparation and the next due for delivery about the same time was indexed as a control."
Allocation concealment?	No	"the first patient was given the preparation and the next due for delivery about the same time was indexed as a control."
Blinding? All outcomes	No	The control group received no intervention.
Incomplete outcome data addressed? All outcomes	Yes	50 (8.3%) women delivered somewhere else and were excluded.
Free of selective reporting?	Unclear	The protocol of the study is not available at the moment.
Free of other bias?	Yes	

Kirkwood 2010

Methods	Cluster-randomised trial.
Participants	Inclusion criteria: women aged 15 to 45 years giving informed consent and who planned to live in the trial area for at least 3 months were eligible for enrolment.
Interventions	Intervention group: 104,484 women in 544 clusters received weekly vitamin A capsule consisted of 25,000 IU (7500 ug) retinol equivalents (equivalent to 25,000 IU vit A) in soybean oil in a dark red opaque soft gel for 12 weeks. Control group: 103,297 women in 542 clusters received placebo capsule consisted of soybean oil only.
Outcomes	Primary outcome: maternal mortality and all-cause female mortality. Other outcomes: maternal morbidity, perinatal and neonatal mortality (the number of deaths during the first 28 completed days of life per 1000 live births in a given year or period).
Notes	Vit A levels were not measured before starting supplementation. Country: Ghana. Study setting: rural districts in Brong Ahafo Region in Ghana.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"A computer-generated randomisation list."
Allocation concealment?	Yes	"The capsules were packaged in labelled jars."
Blinding? All outcomes	Yes	Double blind.
Incomplete outcome data addressed? All outcomes	Yes	44% of enrolled women initially reported as loss to follow up: 1% withdrew consent, 43% moved. However, supplementary information provided by authors in February 2011 at the time of more detailed analysis reported overall loss to follow up for analysis for pregnancy-related mortality analysis as 8%: 4657 pregnancies excluded because outcome not known (with 2340 in vitamin A arm and 2317 in placebo arm). 4192 pregnancies excluded because status of woman at 42 days not known (2174 Vitamin A; 2018 placebo). Before these exclusions, the total number of pregnancies captured was 111,801; after exclusions, the total number of pregnancies with a known outcome was 102,952.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Kumwenda 2002

Methods	RCT.
Participants	Inclusion criteria: • pregnant women of 18-28 weeks' gestation; • HIV-positive women.
Interventions	Intervention group: 340 women received daily doses of orally administered vitamin A (3 mg retinol equivalent (10,000 IU of vit A) + iron and folate for minimum of 12 weeks. Oral vitamin A (30 mg retinol equivalent) at 6 weeks' postpartum Control group: 357 women received daily doses of iron (30 mg of elemental iron) and folate (400 mg) from the time of study enrolment until delivery. Oral vitamin A (30 mg retinol equivalent) at 6 weeks postpartum.
Outcomes	Primary outcome: maternal vit A levels in blood and breast milk and HIV transmission in mother and baby. Other outcomes: haemoglobin and birth weight.
Notes	Vit A levels were measured before starting supplementation. Country: Malawi. Study setting: Queen Elizabeth Central Hospital (Blantyre, Malawi).

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"a computer random-number generator."
Allocation concealment?	Yes	"prepacking study supplements in sequentially numbered series assigned to study identification numbers."
Blinding? All outcomes	Yes	Double blind.
Incomplete outcome data addressed? All outcomes	Yes	63 (9%) women were excluded from the analysis: 57 moved out, 6 could not be located.
Free of selective reporting?	Unclear	The protocol of the study is not available at the moment.
Free of other bias?	Yes	

Muslimatun 2001

Methods	A randomised double-blind community-based trial.
Participants	Inclusion criteria: 16 to 20 weeks pregnant, aged 17-35 years and parity < 6.
Interventions	Intervention group: 122 women received each week from enrolment until delivery two tablets each of which contained 3000 RE vitamin A in addition to the ferrous sulfate and

Muslimatun 2001 (*Continued*)

	folic acid. So intervention was 6000 RE vitamin A (20,000 IU) weekly for a minimum of 16 weeks. Control group: 121 women received each week from enrolment until delivery two tablets each containing 60 mg elemental iron as ferrous sulfate and 250 mg folic acid.
Outcomes	Primary outcome: infant growth in y 1 of life. Other outcomes: maternal haemoglobin and fetal morbidity.
Notes	Vit A levels were measured before starting supplementation. Country: Indonesia. Study setting: 9 villages in the rural subdistrict of Leuwiliang, West Java, Indonesia.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	"Assigned randomly."
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	"double-blind."
Incomplete outcome data addressed? All outcomes	No	Out of 243 pregnant women initially enrolled, 18 dropped out during pregnancy, 5 gave birth to a stillborn child, 1 had twins (only 1 survived), 7 had infants who died before reaching 3 months of age and 11 moved from the research area. Among the remaining 201 eligible participants, 182 participants attended the postpartum examination.
Free of selective reporting?	Unclear	The protocol of the study is not available at the moment.
Free of other bias?	Yes	

Radhika 2003

Methods	"double-blinded, randomized, controlled study."
Participants	Inclusion criteria: • 16 and 24 weeks' gestation; • willing to have a follow up every 2 weeks and who resided in the city area were chosen for the study. Exclusion criteria: women with recurrent pregnancy loss or earlier preterm delivery and those with diabetes, hypertension, or any other metabolic disorder.

Radhika 2003 (*Continued*)

Interventions	Intervention group: 85 women received red palm oil providing 2173 to 2307 μg of β-carotene per day with a dosage schedule of one sachet per day (8 ml), which provided 91% to 96% of the daily requirement of vitamin A in pregnancy, (i.e., 2400 μg of β-carotene which is equivalent to 3000 IU of vit A) daily for a period of 8 weeks. Control group: 85 women received one sachet of groundnut oil (8 ml) for a period of 8 weeks.
Outcomes	Primary outcome: maternal and neonatal vitamin A status. Other outcomes: haemoglobin levels in mother and baby, preterm birth (delivery less than 37 completed weeks as confirmed by ultrasound examination), birthweight and gestational age.
Notes	Vit A levels were measured before starting supplementation. Country: India. Study setting: the outpatient department of Niloufer Hospital, Hyderabad, India.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	"double-blind."
Incomplete outcome data addressed? All outcomes	No	41 (24.1%) women were excluded from the analysis: 23 were not available for supplementation, while 18 dropped out after initiating supplementation.
Free of selective reporting?	Unclear	The protocol of the study is not available at the moment.
Free of other bias?	Yes	

Semba 2001

Methods	A randomised, double-blind, controlled clinical trial.
Participants	Inclusion criteria: • pregnant women; • 18-28 weeks' gestation; • HIV-negative women.

Semba 2001 (*Continued*)

Interventions	Intervention group: 109 women received daily supplement containing iron (30 mg elemental iron), folate (400 mg), and vitamin A (3000 µg retinol equivalent, which is 10,000 IU of vit A) until delivery for a minimum of 8 weeks. Control group: 94 women received daily supplement containing iron (30 mg) and folate (400 mg) until delivery.
Outcomes	Primary outcome: haemoglobin concentrations and plasma erythropoietin concentrations. Other outcomes: levels of ferritin, ?1-acid glycoprotein, C-reactive protein and plasma vitamin A.
Notes	Vit A levels were measured before starting supplementation. Country: Malawi. Study setting: the Queen Elizabeth Central Hospital in Blantyre, Malawi.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"a computer random-number generator."
Allocation concealment?	Yes	"sequentially numbered opaque bottle."
Blinding? All outcomes	Yes	"double-blind."
Incomplete outcome data addressed? All outcomes	No	66 (32.5%) women were excluded from the analysis: 42 missed the study visit, 9 did not have their haemoglobin analysed, 15 moved out.
Free of selective reporting?	Unclear	The protocol of the study is not available at the moment.
Free of other bias?	Yes	

Suharno 1993

Methods	Double-blinded RCT.
Participants	Inclusion criteria: • middle and low socioeconomic; • 16-24 weeks pregnant; • 17-35 years old; • parity 0-4; • haemoglobin 80-109 g/l.

Suharno 1993 (*Continued*)

Interventions	Intervention group 1: 63 women received vitamin A (2.4 mg retinol as retinyl palmitate) (equivalent to 8000 IU of vit A) and placebo iron tablets daily for 8 weeks. Intervention group 2: 63 women received iron tablets (60 mg ferrous sulphate) and placebo vitamin A daily for 8 weeks. Intervention group 3: 63 women received vitamin A and iron daily for 8 weeks. Control group: 62 women received both placebo daily for 8 weeks.
Outcomes	Maternal anaemia indices.
Notes	Vit A levels were measured before starting supplementation. Country: Indonesia. Study setting: rural villages in 3 subdistricts of Bogo, West Java.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"randomly."
Allocation concealment?	No	
Blinding? All outcomes	Yes	"double-blind."
Incomplete outcome data addressed? All outcomes	Yes	54 (17%) women were excluded from the analysis: 11 moved, 23 taken supplement less than 8 weeks, 10 refused blood sample, 10 not available for 2^{nd} blood sample.
Free of selective reporting?	Unclear	The protocol of the study is not available at the moment.
Free of other bias?	Yes	

Suprapto 2002

Methods	Quasi-RCT. A double-blind, placebo, controlled trial.
Participants	Inclusion criteria: • aged less than 35 years; • between 13 and 28 weeks' gestation; • single pregnancy; • in good health; • anaemia (haemoglobin < 11.0 g/dL). Exclusion criteria: • pregnant women with pre-eclampsia, congestive heart disease, tuberculosis and acute infections; • women in the first trimester of pregnancy.

Suprapto 2002 (*Continued*)

Interventions	Intervention group 1: 22 women; group IFR received iron-folate tablets + 5 mg riboflavin seven days a week for 60 days. Intervention group 2: 29 women; group IFA received iron-folate tablets + 2.75 mg retinyl palmitate (equal to 5000 IU vitamin A) seven days a week for 60 days. Intervention group 3: 23 women; group IFRA received iron-folate tablets + 5 mg riboflavin + 2.75 mg retinyl palmitate seven days a week for 60 days. Control group: 29 women; group IF received iron-folate tablets + 5 mg glucose seven days a week for 60 days.
Outcomes	Maternal levels of vitamin A and riboflavin.
Notes	Vit A levels were measured before starting supplementation. Country: Indonesia. Study setting: health centre antenatal clinic.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	"allocated alternately."
Allocation concealment?	No	"allocated alternately."
Blinding? All outcomes	Yes	"double-blind."
Incomplete outcome data addressed? All outcomes	Yes	19 (18.4%) were excluded from the analyses: 9 premature labour, 1 stillbirth, 1 migration, 1 refusal to give blood, 2 nausea and vomiting and 5 incorrect dates given for last menstruation but with normal deliveries.
Free of selective reporting?	Unclear	The protocol of the study is not available at the moment.
Free of other bias?	No	Women in group IFRA were shorter and lighter than those in other groups.

Tanumihardjo 2002

Methods	RCT.
Participants	Inclusion criteria: • pregnant women in the second or early third trimester; • 18 to 37 years old; • parity from 0 to 4 children.

Tanumihardjo 2002 (*Continued*)

Interventions	Intervention group 1: 5 women received 1.07 mmol (60 mg) ferrous sulfate with a vitamin A placebo daily for 8 weeks. Intervention group 2: 8 women received vitamin A plus iron. Intervention group 3: 7 women received 8.4 µmol (8000 IU) vitamin A as retinyl palmitate with an iron placebo. Control group: 7 women received placebo.
Outcomes	Maternal haemoglobin and retinol levels.
Notes	Vit A levels were measured before starting supplementation. Country: Indonesia. Study setting: local health posts the suburban areas of Bogor in West Java.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	"Subjects and village volunteers (caders) were unaware of group assignment."
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	The protocol of the study is not available at the moment.
Free of other bias?	Unclear	Not enough information provided.

van den Broek 2006

Methods	RCT.
Participants	Inclusion criteria: • (Hb) < 11.0 g/dl by HemoCue screening method at first antenatal visit; • singleton pregnancy with gestational age > 12 weeks and < 24 weeks measured by ultrasound scan; • no fetal abnormality detectable by ultrasound at time of booking; • residing in the catchment area of the health centre; • signed informed consent. Exclusion criteria: twin pregnancy.
Interventions	Intervention group 1: 234 women; 5000 IU vitamin A and iron tablets daily (60 mg elemental iron as ferrous sulphate with 0.25 mg folic acid) and antimalarial prophylaxis as two doses of Fansidar (500 mg sulphadoxine with 25 mg pyrimethamine. Tablets

	given daily from enrolment till delivery minimum of 8 weeks. Intervention group 2: 234 women; 10,000 IU vitamin A and iron tablets daily (60 mg elemental iron as ferrous sulphate with 0.25 mg folic acid) and antimalarial prophylaxis as two doses of Fansidar (500 mg sulphadoxine with 25 mg pyrimethamine). Control group: 232 women; placebo and iron tablets daily (60 mg elemental iron as ferrous sulphate with 0.25 mg folic acid) and antimalarial prophylaxis as two doses of Fansidar (500 mg sulphadoxine with 25 mg pyrimethamine.
Outcomes	Primary outcome: haemoglobin concentrations and anaemia. Other outcomes: iron status, preterm birth (delivery less than 37 completed weeks as confirmed by ultrasound examination), markers of infections included C-reactive protein (CRP), malaria parasitaemia and HIV status.
Notes	Vit A levels were measured before starting supplementation. Country: Malawi. Study setting: rural southern Malawi attending ANC at Health Centres.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"a random-generation procedure."
Allocation concealment?	Yes	"consecutive numbers" "in sealed envelopes."
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	96 (13.7%) women were excluded from the analyses: 18 women moved out from the area, 68 declined to continue, 10 missed appointment.
Free of selective reporting?	Unclear	The protocol of the study is not available at the moment.
Free of other bias?	Yes	

West 1999

Methods	Double-blind cluster RCT.
Participants	Inclusion criteria: • women of childbearing age who were married and living with their husbands; • newly married women. Exclusion criteria: women who were already married who had moved into study wards.
Interventions	Intervention group 1: 15,305 women in 90 wards received opaque, gelatinous capsules containing peanut oil and 23,300 IU of preformed vitamin A (7000 µg retinol equivalents) as retinyl palmitate weekly for a minimum of 12 weeks.

West 1999 (*Continued*)

	Intervention group 2: 14,536 women in 90 wards received 42 mg of all trans-b carotene (7000 µg retinol equivalents, assuming a conversion ratio to retinol of 6 to 1 after uptake) weekly. Control group: 14,805 women in 90 wards received no vitamin A or b carotene (placebo) weekly.
Outcomes	Primary outcome: mortality of mother and baby (the number of deaths during the first 28 completed days of life per 1000 live births in a given year or period). Other outcomes: maternal vit A and retinol levels, and maternal morbidity.
Notes	Vit A levels were not measured before starting supplementation. Country: Nepal. Study setting: 270 wards in 30 subdistricts.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"All wards were assigned in Kathmandu by a random draw of numbered chits, blocked on subdistrict, for eligible women to receive one of three identical coded supplements."
Allocation concealment?	Yes	"'three identical coded supplements."
Blinding? All outcomes	Yes	"double-blind."
Incomplete outcome data addressed? All outcomes	Yes	1136 (2.5%) women were excluded because they emigrated before becoming pregnant or dying or because they declined to be recruited. 157 women were lost to follow-up during the postpartum period (their median follow-up time postpartum was around 2 weeks in each group.
Free of selective reporting?	Unclear	The protocol of the study is not available at the moment.
Free of other bias?	Yes	

ANC: antenatal clinic
CRP: C-reactive protein
IU: international unit
RCT: randomised controlled trial

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

Study	Reason for exclusion
Banerjee 2009	Intervention uses lycopene which is a compound that lacks beta-ion ring (in the β-carotene), so lycopene cannot form vitamin A and its biological effects are due to mechanism other than forming vitamin A.
Chawla 1995	Not a randomised trial.
Chikobvu 2001	Double blind randomised trial with outcomes on HIV transmission and HIV complications, only abstract available.
Christian 2003	Cluster-randomised trial with all arms of intervention containing vitamin A and no comparison for vitamin A.
Darboe 2007	Intervention started after delivery.
Haskell 2005	Both arms of intervention containing vitamin A and no comparison for vitamin A.
Howells 1986	Not a randomised trial.
Humphrey 2006	Intervention started after delivery.
Laitinen 2009	Not a randomised trial and vitamin A present in both arms of intervention.
Lietz 2001	Both arms of intervention containing vitamin A and no comparison for vitamin A.
Roberfroid 2010	Both arms of intervention containing iron and folic acid and no comparison for vitamin A.
Roy 1997	Intervention started after delivery.
Sharma 2003	Intervention uses lycopene which is a compound that lacks beta-ion ring (in the β-carotene), so lycopene cannot form vitamin A and its biological effects are due to mechanism other than forming vitamin A.
Van Vliet 2001	Participants are non-pregnant women.

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

Hakimi 1999

Methods	No information provided.
Participants	Women with positive pregnancy test in the first 120 days of pregnancy.
Interventions	Group received vitamin A 2400 retinol equivalent, second group received zinc 20 mg/day, third group received both vitamin A and zinc, while the fourth group received placebo.

Hakimi 1999 (*Continued*)

Outcomes	Maternal sepsis (temp > 38^{o}C between day 2-14 postpartum), haemorrhage (bleeding during labour or within 2 days of delivery).
Notes	Trial run between 1995 and 1997 in Indonesia.

DATA AND ANALYSES

Comparison 1. Vitamin A alone versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal mortality	3		Risk Ratio (Random, 95% CI)	0.78 [0.55, 1.10]
2 Perinatal mortality	1		Risk Ratio (Fixed, 95% CI)	1.01 [0.95, 1.07]
3 Neonatal mortality	3		Risk Ratio (Fixed, 95% CI)	0.97 [0.90, 1.05]
4 Stillbirth	1	78835	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.98, 1.14]
5 Maternal anaemia	3		Risk Ratio (Random, 95% CI)	0.64 [0.43, 0.94]
6 Maternal clinical infection	3		Risk Ratio (Random, 95% CI)	0.37 [0.18, 0.77]
7 Maternal night blindness	1		Risk Ratio (Fixed, 95% CI)	0.70 [0.60, 0.82]
8 Preterm birth	4	1937	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.57, 1.04]
9 Neonatal anaemia	1	406	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.92, 1.08]
10 Neonatal clinical infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11 Congenital malformations	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12 Low birthweight	3	890	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.62, 1.54]

Comparison 2. Vitamin A alone versus micronutrient supplement without vitamin A

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Perinatal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Neonatal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Stillbirth	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Maternal anaemia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Maternal clinical infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Maternal night blindness	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Preterm birth	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Neonatal anaemia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Neonatal clinical infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11 Congenital malformations	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12 Low birthweight	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 3. Vitamin A with other micronutrients versus micronutrient supplements without vitamin A

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Perinatal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Neonatal mortality	1	594	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.32, 1.31]
4 Stillbirth	2	866	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.57, 3.47]
5 Maternal anaemia	3	706	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.68, 1.09]
6 Maternal clinical infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Maternal night blindness	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Preterm birth	1	136	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.08, 1.93]
9 Neonatal anaemia	2	1052	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.38, 1.51]
10 Neonatal clinical infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11 Congenital malformations	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12 Low birthweight	1	594	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.47, 0.96]

Comparison 4. Vitamin A alone versus placebo or no treatment (subgroups)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal mortality (infant mortality level)	3		Risk Ratio (Random, 95% CI)	0.78 [0.55, 1.10]
1.1 Countries with low infant mortality	1		Risk Ratio (Random, 95% CI)	0.33 [0.01, 9.44]
1.2 Countries with high infant mortality	2		Risk Ratio (Random, 95% CI)	0.77 [0.51, 1.17]
2 Perinatal mortality (infant mortality level)	1	76176	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
2.1 Countries with low infant mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 Countries with high infant mortality	1	76176	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
3 Maternal mortality (maternal mortality level)	3	101574	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.01]
3.1 Countries with low maternal mortality	1	550	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.15]
3.2 Countries with high maternal mortality	2	101024	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.02]
4 Perinatal mortality (maternal mortality level)	1	73743	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.88, 1.03]
4.1 Countries with low maternal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 Countries with high maternal mortality	1	73743	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.88, 1.03]

5 Maternal mortality (prevalence of vitamin A deficiency)	3	101574	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.01]
5.1 Low prevalence of vitamin A deficiency	1	550	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.15]
5.2 High prevalence of vitamin A deficiency	2	101024	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.02]
6 Perinatal mortality (prevalence of vitamin A deficiency)	1	76176	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
6.1 Low prevalence of vitamin A deficiency	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2 High prevalence of vitamin A deficiency	1	76176	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
7 Maternal mortality (prevalence of HIV in the general population)	3	101574	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.01]
7.1 Countries with low HIV prevalence	3	101574	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.01]
7.2 Countries with high HIV prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Perinatal mortality (prevalence of HIV in the general population)	1	76176	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
8.1 Countries with low HIV prevalence	1	76176	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
8.2 Countries with high HIV prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Maternal mortality (dose)	2	101024	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.02]
9.1 Daily 10,000 IU	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.2 Others	2	101024	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.02]
10 Perinatal mortality (dose)	1	76176	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
10.1 Daily 10,000 IU	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.2 Others	1	76176	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
11 Maternal mortality (regimen)	3	101574	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.01]
11.1 Daily	1	550	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.15]
11.2 Weekly	2	101024	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.02]
11.3 Other regimen	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12 Perinatal mortality (regimen)	1	76176	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
12.1 Daily	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.2 Weekly	1	76176	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
12.3 Other regimen	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13 Maternal mortality (duration of intervention)	1	550	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.15]
13.1 One month or less	1	550	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.15]
14 Perinatal mortality (duration of intervention)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15 Maternal mortality (trimester of pregnancy)	3	101574	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.01]
15.1 Pre-pregnancy	2	101024	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.02]
15.2 First trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.3 Second trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.4 Third trimester	1	550	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.15]
15.5 Mixed	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

16 Perinatal mortality (trimester of pregnancy)	1	76176	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
16.1 Pre-pregnancy	1	76176	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
16.2 First trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.3 Second trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.4 Third trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.5 Mixed	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
17 Maternal mortality (randomisation)	2	101024	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.02]
17.1 Cluster-randomised	2	101024	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.02]
17.2 Individual-randomised	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18 Perinatal mortality (randomisation)	1	76176	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
18.1 Cluster-randomised	1	76176	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
18.2 Individual-randomised	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 5. Vitamin A alone versus micronutrient supplement without vitamin A (subgroups)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal mortality (infant mortality level)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.1 Countries with low infant mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 Countries with high infant mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Perinatal mortality (infant mortality level)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.1 Countries with low infant mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 Countries with high infant mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Maternal mortality (maternal mortality level)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.1 Countries with low maternal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2 Countries with high maternal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Perinatal mortality (maternal mortality level)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.1 Countries with low maternal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 Countries with high maternal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Maternal mortality (prevalence of vitamin A deficiency)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.1 Low prevalence of vitamin A deficiency	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

5.2 High prevalence of vitamin A deficiency	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Perinatal mortality (prevalence of vitamin A deficiency)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.1 Low prevalence of vitamin A deficiency	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2 High prevalence of vitamin A deficiency	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Maternal mortality (prevalence of HIV in the general population)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.1 Countries with low HIV prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.2 Countries with high HIV prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Perinatal mortality (prevalence of HIV in the general population)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8.1 Countries with low HIV prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8.2 Countries with high HIV prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Maternal mortality (dose)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.1 Daily 10,000 IU	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.2 Others	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Perinatal mortality (dose)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.1 Daily 10,000 IU	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.2 Others	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11 Maternal mortality (regimen)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.1 Daily	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.2 Weekly	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.3 Other regimen	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12 Perinatal mortality (regimen)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.1 Daily	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.2 Weekly	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.3 Other regimen	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13 Maternal mortality (duration of intervention)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14 Perinatal mortality (duration of intervention)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15 Maternal mortality (trimester of pregnancy)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.1 Pre-pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.2 First trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.3 Second trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.4 Third trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.5 Mixed	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16 Perinatal mortality (trimester of pregnancy)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.1 Pre-pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.2 First trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.3 Second trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.4 Third trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

16.5 Mixed	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
17 Maternal mortality (randomisation)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
17.1 Cluster-randomised	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
17.2 Individual-randomised	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18 Perinatal mortality (randomisation)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18.1 Cluster-randomised	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18.2 Individual-randomised	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 6. Vitamin A with other micronutrients versus micronutrient supplements without vitamin A (subgroups)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal mortality (infant mortality level)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.1 Countries with low infant mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 Countries with high infant mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Perinatal mortality (infant mortality level)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.1 Countries with low infant mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 Countries with high infant mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Maternal mortality (maternal mortality level)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.1 Countries with low maternal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2 Countries with high maternal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Perinatal mortality (maternal mortality level)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.1 Countries with low maternal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 Countries with high maternal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Maternal mortality (prevalence of vitamin A deficiency)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.1 Low prevalence of vitamin A deficiency	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.2 High prevalence of vitamin A deficiency	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Perinatal mortality (prevalence of vitamin A deficiency)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

6.1 Low prevalence of vitamin A deficiency	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2 High prevalence of vitamin A deficiency	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Maternal mortality (prevalence of HIV in the general population)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.1 Countries with low HIV prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.2 Countries with high HIV prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Perinatal mortality (prevalence of HIV in the general population)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8.1 Countries with low HIV prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8.2 Countries with high HIV prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Maternal mortality (dose)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.1 Daily 10,000 IU	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.2 Others	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Perinatal mortality (dose)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.1 Daily 10,000 IU	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.2 Others	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11 Maternal mortality (regimen)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.1 Daily	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.2 Weekly	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.3 Other regimen	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12 Perinatal mortality (regimen)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.1 Daily	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.2 Weekly	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.3 Other regimen	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13 Maternal mortality (duration of intervention)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14 Perinatal mortality (duration of intervention)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15 Maternal mortality (trimester of pregnancy)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.1 Pre-pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.2 First trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.3 Second trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.4 Third trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.5 Mixed	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16 Perinatal mortality (trimester of pregnancy)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.1 Pre-pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.2 First trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.3 Second trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.4 Third trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.5 Mixed	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
17 Maternal mortality (randomisation)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
17.1 Cluster-randomised	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

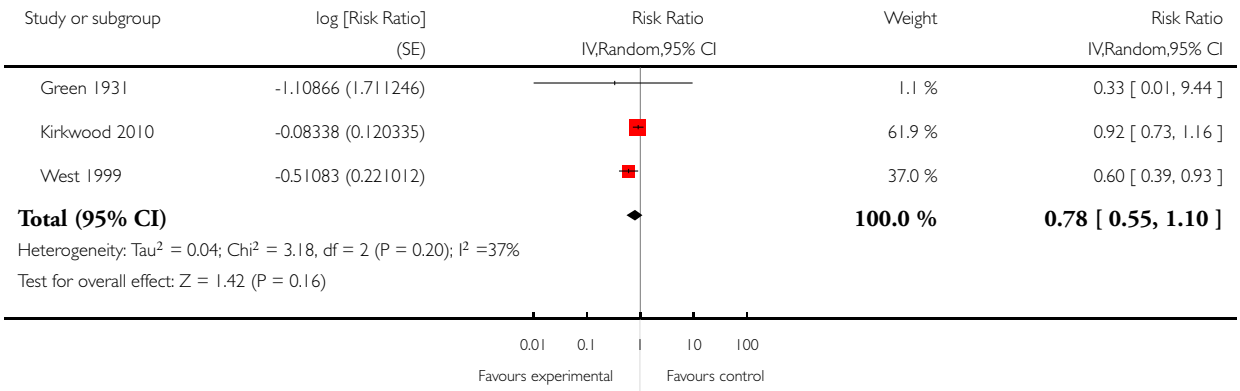
17.2 Individual-randomised	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18 Perinatal mortality (randomisation)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18.1 Cluster-randomised	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18.2 Individual-randomised	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 1.1. Comparison 1 Vitamin A alone versus placebo or no treatment, Outcome 1 Maternal mortality.

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 1 Vitamin A alone versus placebo or no treatment

Outcome: 1 Maternal mortality



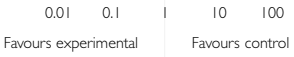
Analysis 1.2. Comparison 1 Vitamin A alone versus placebo or no treatment, Outcome 2 Perinatal mortality.

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 1 Vitamin A alone versus placebo or no treatment

Outcome: 2 Perinatal mortality

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Kirkwood 2010	0.00995 (0.030345)		100.0 %	1.01 [0.95, 1.07]
Total (95% CI)			**100.0 %**	**1.01 [0.95, 1.07]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.33 (P = 0.74)				



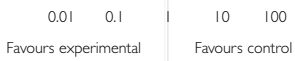
Analysis 1.3. Comparison 1 Vitamin A alone versus placebo or no treatment, Outcome 3 Neonatal mortality.

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 1 Vitamin A alone versus placebo or no treatment

Outcome: 3 Neonatal mortality

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Coutsoudis 1999	-0.34249 (0.474682)		0.7 %	0.71 [0.28, 1.80]
Kirkwood 2010	-0.05129 (0.043067)		81.0 %	0.95 [0.87, 1.03]
West 1999	0.09531 (0.090425)		18.4 %	1.10 [0.92, 1.31]
Total (95% CI)			**100.0 %**	**0.97 [0.90, 1.05]**
Heterogeneity: Chi^2 = 2.59, df = 2 (P = 0.27); I^2 =23%				
Test for overall effect: Z = 0.68 (P = 0.50)				



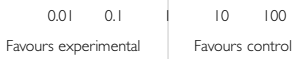
Analysis 1.4. Comparison 1 Vitamin A alone versus placebo or no treatment, Outcome 4 Stillbirth.

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 1 Vitamin A alone versus placebo or no treatment

Outcome: 4 Stillbirth

Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kirkwood 2010	1249/39512	1175/39323		100.0 %	1.06 [0.98, 1.14]
Total (95% CI)	**39512**	**39323**		**100.0 %**	**1.06 [0.98, 1.14]**
Total events: 1249 (Vit A), 1175 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.41 (P = 0.16)					



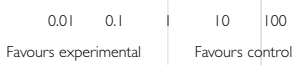
Analysis 1.5. Comparison 1 Vitamin A alone versus placebo or no treatment, Outcome 5 Maternal anaemia.

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 1 Vitamin A alone versus placebo or no treatment

Outcome: 5 Maternal anaemia

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Fawzi 1998	-0.17435 (0.255778)		27.7 %	0.84 [0.51, 1.39]
Suharno 1993	-0.96758 (0.261069)		27.2 %	0.38 [0.23, 0.63]
West 1999	-0.31471 (0.090425)		45.2 %	0.73 [0.61, 0.87]
Total (95% CI)			**100.0 %**	**0.64 [0.43, 0.94]**
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 6.19$, df = 2 (P = 0.05); $I^2 = 68\%$				
Test for overall effect: Z = 2.24 (P = 0.025)				



Analysis 1.6. Comparison 1 Vitamin A alone versus placebo or no treatment, Outcome 6 Maternal clinical infection.

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

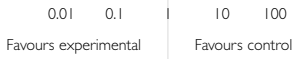
Comparison: 1 Vitamin A alone versus placebo or no treatment

Outcome: 6 Maternal clinical infection

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Coutsoudis 1999	-0.56212 (0.748015)		19.0 %	0.57 [0.13, 2.47]
Green 1931	-0.77653 (0.200388)		61.5 %	0.46 [0.31, 0.68]
West 1999	-2.12026 (0.735802)		19.5 %	0.12 [0.03, 0.51]
Total (95% CI)			**100.0 %**	**0.37 [0.18, 0.77]**

Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 3.26$, df = 2 (P = 0.20); $I^2 = 39\%$

Test for overall effect: Z = 2.64 (P = 0.0083)



Analysis 1.7. Comparison 1 Vitamin A alone versus placebo or no treatment, Outcome 7 Maternal night blindness.

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

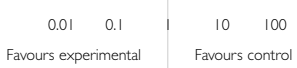
Comparison: 1 Vitamin A alone versus placebo or no treatment

Outcome: 7 Maternal night blindness

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
West 1999	-0.35677 (0.078366)		100.0 %	0.70 [0.60, 0.82]
Total (95% CI)			**100.0 %**	**0.70 [0.60, 0.82]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.55 (P < 0.00001)



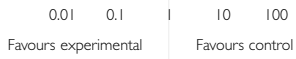
Analysis 1.8. Comparison 1 Vitamin A alone versus placebo or no treatment, Outcome 8 Preterm birth.

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 1 Vitamin A alone versus placebo or no treatment

Outcome: 8 Preterm birth

Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Coutsoudis 1999	38/335	57/326		66.3 %	0.65 [0.44, 0.95]
Green 1931	1/275	0/275		0.6 %	3.00 [0.12, 73.32]
Radhika 2003	9/64	11/58		13.3 %	0.74 [0.33, 1.66]
van den Broek 2006	29/401	13/203		19.8 %	1.13 [0.60, 2.12]
Total (95% CI)	**1075**	**862**		**100.0 %**	**0.77 [0.57, 1.04]**
Total events: 77 (Vit A), 81 (Placebo or no treatment)					
Heterogeneity: Chi^2 = 2.89, df = 3 (P = 0.41); I^2 =0.0%					
Test for overall effect: Z = 1.72 (P = 0.086)					



Analysis 1.9. Comparison 1 Vitamin A alone versus placebo or no treatment, Outcome 9 Neonatal anaemia.

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 1 Vitamin A alone versus placebo or no treatment

Outcome: 9 Neonatal anaemia

Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fawzi 1998	177/209	168/197		100.0 %	0.99 [0.92, 1.08]
Total (95% CI)	**209**	**197**		**100.0 %**	**0.99 [0.92, 1.08]**
Total events: 177 (Vit A), 168 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.17 (P = 0.87)					

Analysis 1.12. Comparison 1 Vitamin A alone versus placebo or no treatment, Outcome 12 Low birthweight.

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 1 Vitamin A alone versus placebo or no treatment

Outcome: 12 Low birthweight

Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Coutsoudis 1999	42/346	48/343		55.8 %	0.87 [0.59, 1.28]
Cox 2005	11/41	5/38		18.2 %	2.04 [0.78, 5.33]
Radhika 2003	10/64	12/58		26.0 %	0.76 [0.35, 1.62]
Total (95% CI)	**451**	**439**		**100.0 %**	**0.98 [0.62, 1.54]**

Total events: 63 (Vit A), 65 (Placebo or no treatment)

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 2.98$, df = 2 (P = 0.23); $I^2 = 33\%$

Test for overall effect: Z = 0.10 (P = 0.92)

Analysis 3.3. Comparison 3 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A, Outcome 3 Neonatal mortality.

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 3 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A

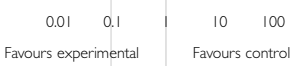
Outcome: 3 Neonatal mortality

Study or subgroup	Vit A with micronutrients n/N	micronutrients without A n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kumwenda 2002	12/285	20/309		100.0 %	0.65 [0.32, 1.31]
Total (95% CI)	**285**	**309**		**100.0 %**	**0.65 [0.32, 1.31]**

Total events: 12 (Vit A with micronutrients), 20 (micronutrients without A)

Heterogeneity: not applicable

Test for overall effect: Z = 1.21 (P = 0.23)



Analysis 3.4. Comparison 3 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A, Outcome 4 Stillbirth.

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 3 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A

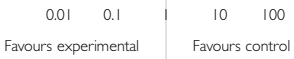
Outcome: 4 Stillbirth

Study or subgroup	Vit A with micronutrients n/N	micronutrients without A n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kumwenda 2002	8/306	6/317		74.6 %	1.38 [0.48, 3.93]
Muslimatun 2001	3/122	2/121		25.4 %	1.49 [0.25, 8.75]
Total (95% CI)	**428**	**438**		**100.0 %**	**1.41 [0.57, 3.47]**

Total events: 11 (Vit A with micronutrients), 8 (micronutrients without A)

Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.94); I^2 =0.0%

Test for overall effect: Z = 0.74 (P = 0.46)



Analysis 3.5. Comparison 3 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A, Outcome 5 Maternal anaemia.

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 3 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A

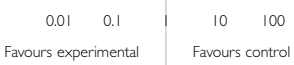
Outcome: 5 Maternal anaemia

Study or subgroup	Vit A with micronutrients n/N	micronutrients without A n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fawzi 1998	32/226	31/228		32.1 %	1.04 [0.66, 1.65]
Muslimatun 2001	36/71	44/66		47.4 %	0.76 [0.57, 1.01]
Semba 2001	18/63	18/52		20.5 %	0.83 [0.48, 1.42]
Total (95% CI)	**360**	**346**		**100.0 %**	**0.86 [0.68, 1.09]**

Total events: 86 (Vit A with micronutrients), 93 (micronutrients without A)

Heterogeneity: Chi^2 = 1.43, df = 2 (P = 0.49); I^2 =0.0%

Test for overall effect: Z = 1.23 (P = 0.22)



Analysis 3.8. Comparison 3 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A, Outcome 8 Preterm birth.

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 3 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A

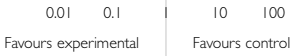
Outcome: 8 Preterm birth

Study or subgroup	Vit A with micronutrients n/N	micronutrients without A n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dijkhuizen 2004	2/69	5/67		100.0 %	0.39 [0.08, 1.93]
Total (95% CI)	**69**	**67**		**100.0 %**	**0.39 [0.08, 1.93]**

Total events: 2 (Vit A with micronutrients), 5 (micronutrients without A)

Heterogeneity: not applicable

Test for overall effect: Z = 1.15 (P = 0.25)



Analysis 3.9. Comparison 3 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A, Outcome 9 Neonatal anaemia.

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 3 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A

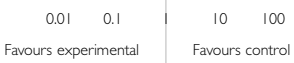
Outcome: 9 Neonatal anaemia

Study or subgroup	Vit A with micronutrients n/N	micronutrients without A n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Fawzi 1998	185/219	182/211		51.4 %	0.98 [0.91, 1.06]
Kumwenda 2002	69/297	132/325		48.6 %	0.57 [0.45, 0.73]
Total (95% CI)	**516**	**536**		**100.0 %**	**0.75 [0.38, 1.51]**

Total events: 254 (Vit A with micronutrients), 314 (micronutrients without A)

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 29.31$, df = 1 ($P<0.00001$); $I^2 = 97\%$

Test for overall effect: Z = 0.79 (P = 0.43)

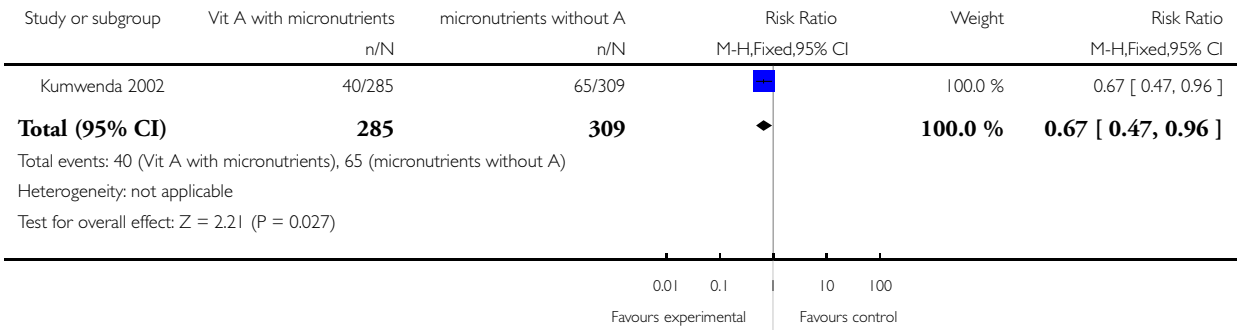


Analysis 3.12. Comparison 3 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A, Outcome 12 Low birthweight.

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 3 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A

Outcome: 12 Low birthweight

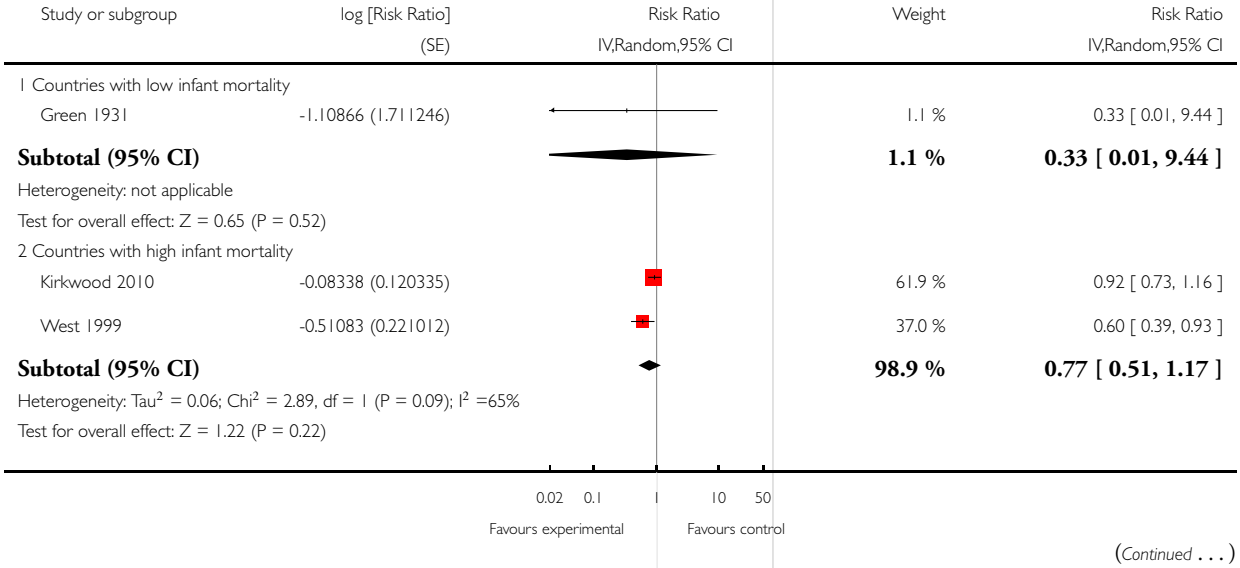


Analysis 4.1. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 1 Maternal mortality (infant mortality level).

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 4 Vitamin A alone versus placebo or no treatment (subgroups)

Outcome: 1 Maternal mortality (infant mortality level)



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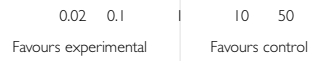
Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Total (95% CI)			**100.0 %**	**0.78 [0.55, 1.10]**
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 3.18$, df = 2 (P = 0.20); $I^2 = 37\%$				
Test for overall effect: Z = 1.42 (P = 0.16)				



Analysis 4.2. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 2 Perinatal mortality (infant mortality level).

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 4 Vitamin A alone versus placebo or no treatment (subgroups)

Outcome: 2 Perinatal mortality (infant mortality level)

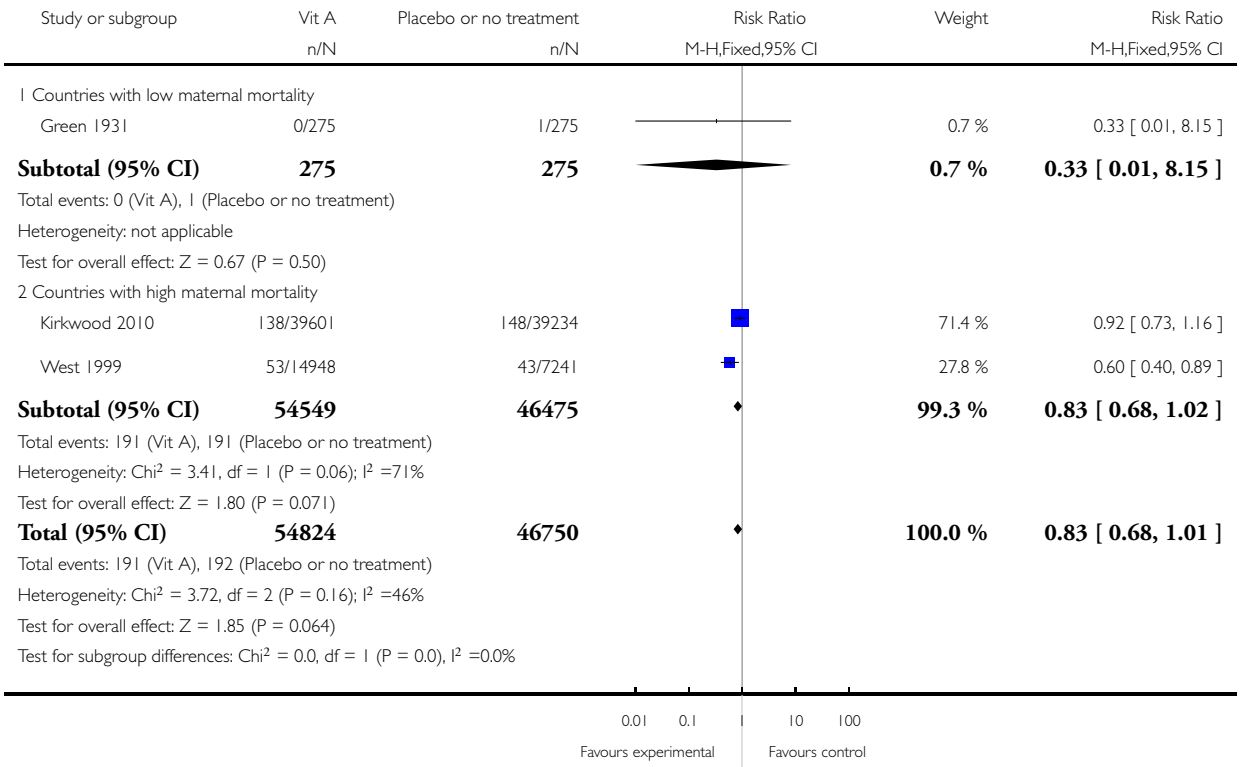
Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Countries with low infant mortality					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Countries with high infant mortality					
Kirkwood 2010	2117/38283	2083/37893		100.0 %	1.01 [0.95, 1.07]
Subtotal (95% CI)	**38283**	**37893**		**100.0 %**	**1.01 [0.95, 1.07]**
Total events: 2117 (Vit A), 2083 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					
Total (95% CI)	**38283**	**37893**		**100.0 %**	**1.01 [0.95, 1.07]**
Total events: 2117 (Vit A), 2083 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					

Analysis 4.3. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 3 Maternal mortality (maternal mortality level).

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 4 Vitamin A alone versus placebo or no treatment (subgroups)

Outcome: 3 Maternal mortality (maternal mortality level)



Analysis 4.4. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 4 Perinatal mortality (maternal mortality level).

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 4 Vitamin A alone versus placebo or no treatment (subgroups)

Outcome: 4 Perinatal mortality (maternal mortality level)

Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Countries with low maternal mortality					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Countries with high maternal mortality					
Kirkwood 2010	1140/37042	1187/36701		100.0 %	0.95 [0.88, 1.03]
Subtotal (95% CI)	**37042**	**36701**		**100.0 %**	**0.95 [0.88, 1.03]**
Total events: 1140 (Vit A), 1187 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.22 (P = 0.22)					
Total (95% CI)	**37042**	**36701**		**100.0 %**	**0.95 [0.88, 1.03]**
Total events: 1140 (Vit A), 1187 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.22 (P = 0.22)					

Analysis 4.5. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 5 Maternal mortality (prevalence of vitamin A deficiency).

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 4 Vitamin A alone versus placebo or no treatment (subgroups)

Outcome: 5 Maternal mortality (prevalence of vitamin A deficiency)

Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low prevalence of vitamin A deficiency					
Green 1931	0/275	1/275		0.7 %	0.33 [0.01, 8.15]
Subtotal (95% CI)	**275**	**275**		**0.7 %**	**0.33 [0.01, 8.15]**
Total events: 0 (Vit A), 1 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.67 (P = 0.50)					
2 High prevalence of vitamin A deficiency					
Kirkwood 2010	138/39601	148/39234		71.4 %	0.92 [0.73, 1.16]
West 1999	53/14948	43/7241		27.8 %	0.60 [0.40, 0.89]
Subtotal (95% CI)	**54549**	**46475**		**99.3 %**	**0.83 [0.68, 1.02]**
Total events: 191 (Vit A), 191 (Placebo or no treatment)					
Heterogeneity: Chi^2 = 3.41, df = 1 (P = 0.06); I^2 =71%					
Test for overall effect: Z = 1.80 (P = 0.071)					
Total (95% CI)	**54824**	**46750**		**100.0 %**	**0.83 [0.68, 1.01]**
Total events: 191 (Vit A), 192 (Placebo or no treatment)					
Heterogeneity: Chi^2 = 3.72, df = 2 (P = 0.16); I^2 =46%					
Test for overall effect: Z = 1.85 (P = 0.064)					
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 0.0), I^2 =0.0%					

Analysis 4.6. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 6 Perinatal mortality (prevalence of vitamin A deficiency).

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 4 Vitamin A alone versus placebo or no treatment (subgroups)

Outcome: 6 Perinatal mortality (prevalence of vitamin A deficiency)

Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low prevalence of vitamin A deficiency					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 High prevalence of vitamin A deficiency					
Kirkwood 2010	2117/38283	2083/37893		100.0 %	1.01 [0.95, 1.07]
Subtotal (95% CI)	**38283**	**37893**		**100.0 %**	**1.01 [0.95, 1.07]**
Total events: 2117 (Vit A), 2083 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					
Total (95% CI)	**38283**	**37893**		**100.0 %**	**1.01 [0.95, 1.07]**
Total events: 2117 (Vit A), 2083 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					

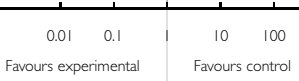
Analysis 4.7. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 7 Maternal mortality (prevalence of HIV in the general population).

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 4 Vitamin A alone versus placebo or no treatment (subgroups)

Outcome: 7 Maternal mortality (prevalence of HIV in the general population)

Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Countries with low HIV prevalence					
Green 1931	0/275	1/275		0.7 %	0.33 [0.01, 8.15]
Kirkwood 2010	138/39601	148/39234		71.4 %	0.92 [0.73, 1.16]
West 1999	53/14948	43/7241		27.8 %	0.60 [0.40, 0.89]
Subtotal (95% CI)	**54824**	**46750**		**100.0 %**	**0.83 [0.68, 1.01]**
Total events: 191 (Vit A), 192 (Placebo or no treatment)					
Heterogeneity: Chi^2 = 3.72, df = 2 (P = 0.16); I^2 =46%					
Test for overall effect: Z = 1.85 (P = 0.064)					
2 Countries with high HIV prevalence					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**54824**	**46750**		**100.0 %**	**0.83 [0.68, 1.01]**
Total events: 191 (Vit A), 192 (Placebo or no treatment)					
Heterogeneity: Chi^2 = 3.72, df = 2 (P = 0.16); I^2 =46%					
Test for overall effect: Z = 1.85 (P = 0.064)					



Analysis 4.8. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 8 Perinatal mortality (prevalence of HIV in the general population).

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 4 Vitamin A alone versus placebo or no treatment (subgroups)

Outcome: 8 Perinatal mortality (prevalence of HIV in the general population)

Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Countries with low HIV prevalence					
Kirkwood 2010	2117/38283	2083/37893		100.0 %	1.01 [0.95, 1.07]
Subtotal (95% CI)	**38283**	**37893**		**100.0 %**	**1.01 [0.95, 1.07]**
Total events: 2117 (Vit A), 2083 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					
2 Countries with high HIV prevalence					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**38283**	**37893**		**100.0 %**	**1.01 [0.95, 1.07]**
Total events: 2117 (Vit A), 2083 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					

Analysis 4.9. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 9 Maternal mortality (dose).

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 4 Vitamin A alone versus placebo or no treatment (subgroups)

Outcome: 9 Maternal mortality (dose)

Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Daily 10,000 IU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Others					
Kirkwood 2010	138/39601	148/39234		72.0 %	0.92 [0.73, 1.16]
West 1999	53/14948	43/7241		28.0 %	0.60 [0.40, 0.89]
Subtotal (95% CI)	**54549**	**46475**		**100.0 %**	**0.83 [0.68, 1.02]**
Total events: 191 (Vit A), 191 (Placebo or no treatment)					
Heterogeneity: Chi^2 = 3.41, df = 1 (P = 0.06); I^2 =71%					
Test for overall effect: Z = 1.80 (P = 0.071)					
Total (95% CI)	**54549**	**46475**		**100.0 %**	**0.83 [0.68, 1.02]**
Total events: 191 (Vit A), 191 (Placebo or no treatment)					
Heterogeneity: Chi^2 = 3.41, df = 1 (P = 0.06); I^2 =71%					
Test for overall effect: Z = 1.80 (P = 0.071)					

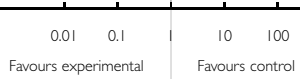
Analysis 4.10. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 10 Perinatal mortality (dose).

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 4 Vitamin A alone versus placebo or no treatment (subgroups)

Outcome: 10 Perinatal mortality (dose)

Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Daily 10,000 IU					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Others					
Kirkwood 2010	2117/38283	2083/37893		100.0 %	1.01 [0.95, 1.07]
Subtotal (95% CI)	**38283**	**37893**		**100.0 %**	**1.01 [0.95, 1.07]**
Total events: 2117 (Vit A), 2083 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					
Total (95% CI)	**38283**	**37893**		**100.0 %**	**1.01 [0.95, 1.07]**
Total events: 2117 (Vit A), 2083 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					

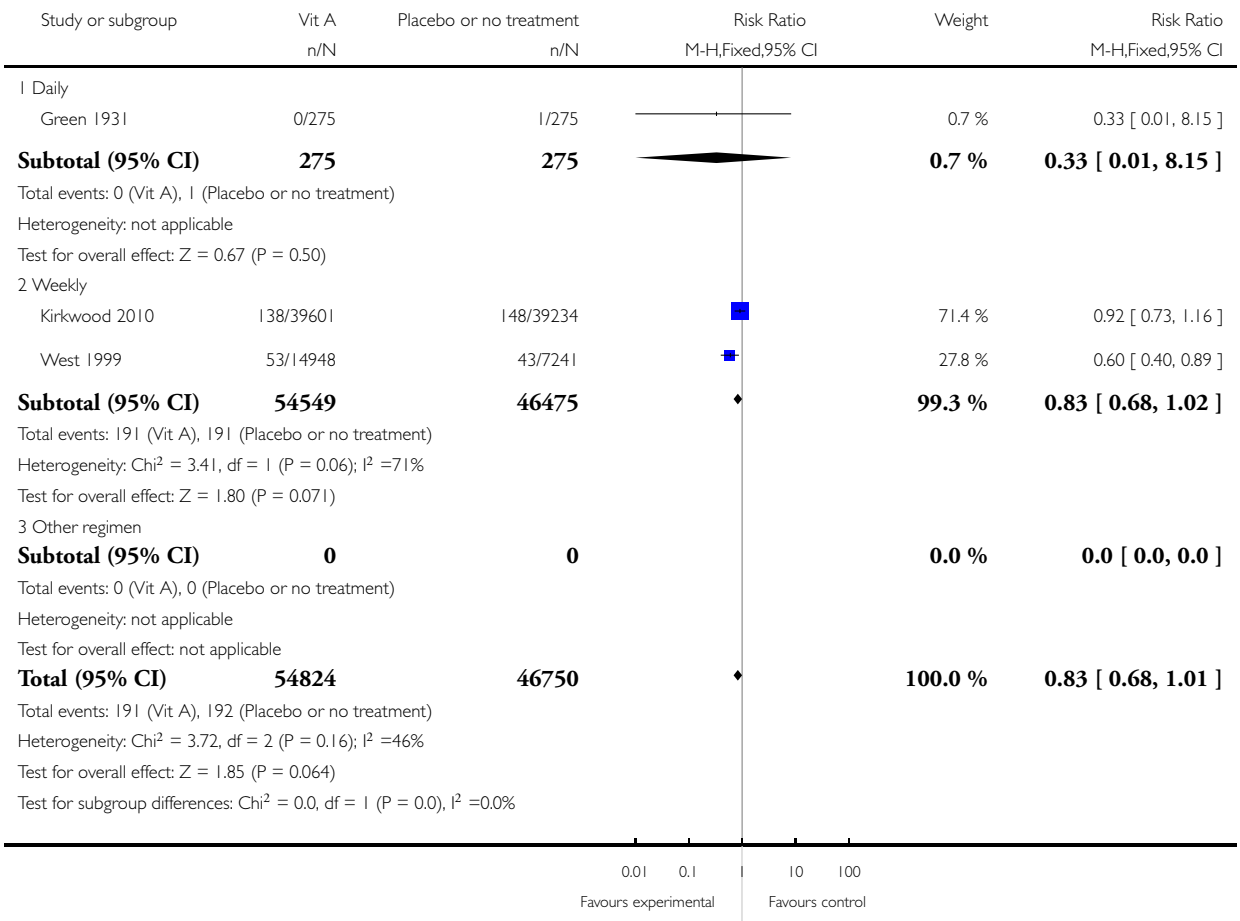


Analysis 4.11. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 11 Maternal mortality (regimen).

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 4 Vitamin A alone versus placebo or no treatment (subgroups)

Outcome: 11 Maternal mortality (regimen)



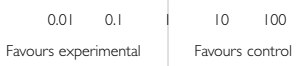
Analysis 4.12. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 12 Perinatal mortality (regimen).

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 4 Vitamin A alone versus placebo or no treatment (subgroups)

Outcome: 12 Perinatal mortality (regimen)

Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Daily					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Weekly					
Kirkwood 2010	2117/38283	2083/37893		100.0 %	1.01 [0.95, 1.07]
Subtotal (95% CI)	**38283**	**37893**		**100.0 %**	**1.01 [0.95, 1.07]**
Total events: 2117 (Vit A), 2083 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					
3 Other regimen					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**38283**	**37893**		**100.0 %**	**1.01 [0.95, 1.07]**
Total events: 2117 (Vit A), 2083 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					



Analysis 4.13. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 13 Maternal mortality (duration of intervention).

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 4 Vitamin A alone versus placebo or no treatment (subgroups)

Outcome: 13 Maternal mortality (duration of intervention)

Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 One month or less					
Green 1931	0/275	1/275		100.0 %	0.33 [0.01, 8.15]
Total (95% CI)	**275**	**275**		**100.0 %**	**0.33 [0.01, 8.15]**
Total events: 0 (Vit A), 1 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.67 (P = 0.50)					

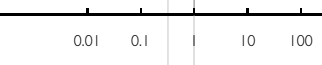
Analysis 4.15. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 15 Maternal mortality (trimester of pregnancy).

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 4 Vitamin A alone versus placebo or no treatment (subgroups)

Outcome: 15 Maternal mortality (trimester of pregnancy)

Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Pre-pregnancy					
Kirkwood 2010	138/39601	148/39234		71.4 %	0.92 [0.73, 1.16]
West 1999	53/14948	43/7241		27.8 %	0.60 [0.40, 0.89]
Subtotal (95% CI)	**54549**	**46475**		**99.3 %**	**0.83 [0.68, 1.02]**
Total events: 191 (Vit A), 191 (Placebo or no treatment)					
Heterogeneity: Chi^2 = 3.41, df = 1 (P = 0.06); I^2 =71%					
Test for overall effect: Z = 1.80 (P = 0.071)					
2 First trimester					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					



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Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Second trimester					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Third trimester					
Green 1931	0/275	1/275		0.7 %	0.33 [0.01, 8.15]
Subtotal (95% CI)	**275**	**275**		**0.7 %**	**0.33 [0.01, 8.15]**
Total events: 0 (Vit A), 1 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.67 (P = 0.50)					
5 Mixed					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**54824**	**46750**		**100.0 %**	**0.83 [0.68, 1.01]**
Total events: 191 (Vit A), 192 (Placebo or no treatment)					
Heterogeneity: Chi^2 = 3.72, df = 2 (P = 0.16); I^2 =46%					
Test for overall effect: Z = 1.85 (P = 0.064)					
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 0.0), I^2 =0.0%					

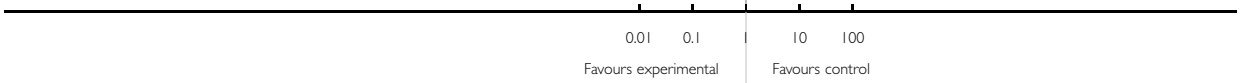
Analysis 4.16. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 16 Perinatal mortality (trimester of pregnancy).

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 4 Vitamin A alone versus placebo or no treatment (subgroups)

Outcome: 16 Perinatal mortality (trimester of pregnancy)

Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Pre-pregnancy					
Kirkwood 2010	2117/38283	2083/37893		100.0 %	1.01 [0.95, 1.07]
Subtotal (95% CI)	**38283**	**37893**		**100.0 %**	**1.01 [0.95, 1.07]**
Total events: 2117 (Vit A), 2083 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					
2 First trimester					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Second trimester					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Third trimester					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
5 Mixed					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**38283**	**37893**		**100.0 %**	**1.01 [0.95, 1.07]**
Total events: 2117 (Vit A), 2083 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					



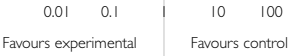
Analysis 4.17. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 17 Maternal mortality (randomisation).

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 4 Vitamin A alone versus placebo or no treatment (subgroups)

Outcome: 17 Maternal mortality (randomisation)

Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Cluster-randomised					
Kirkwood 2010	138/39601	148/39234		72.0 %	0.92 [0.73, 1.16]
West 1999	53/14948	43/7241		28.0 %	0.60 [0.40, 0.89]
Subtotal (95% CI)	**54549**	**46475**		**100.0 %**	**0.83 [0.68, 1.02]**
Total events: 191 (Vit A), 191 (Placebo or no treatment)					
Heterogeneity: Chi^2 = 3.41, df = 1 (P = 0.06); I^2 =71%					
Test for overall effect: Z = 1.80 (P = 0.071)					
2 Individual-randomised					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**54549**	**46475**		**100.0 %**	**0.83 [0.68, 1.02]**
Total events: 191 (Vit A), 191 (Placebo or no treatment)					
Heterogeneity: Chi^2 = 3.41, df = 1 (P = 0.06); I^2 =71%					
Test for overall effect: Z = 1.80 (P = 0.071)					



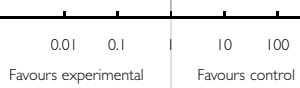
Analysis 4.18. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 18 Perinatal mortality (randomisation).

Review: Vitamin A supplementation during pregnancy for maternal and newborn outcomes

Comparison: 4 Vitamin A alone versus placebo or no treatment (subgroups)

Outcome: 18 Perinatal mortality (randomisation)

Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Cluster-randomised					
Kirkwood 2010	2117/38283	2083/37893		100.0 %	1.01 [0.95, 1.07]
Subtotal (95% CI)	**38283**	**37893**		**100.0 %**	**1.01 [0.95, 1.07]**
Total events: 2117 (Vit A), 2083 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					
2 Individual-randomised					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**38283**	**37893**		**100.0 %**	**1.01 [0.95, 1.07]**
Total events: 2117 (Vit A), 2083 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					



WHAT'S NEW

Last assessed as up-to-date: 4 October 2010.

Date	Event	Description
15 February 2011	Amended	Authors of the Kirkwood 2010 trial provided additional information about the loss to follow up figure for the pregnancy-related mortality analysis, which was 8% and not 44%.

HISTORY

Protocol first published: Issue 9, 2010

Review first published: Issue 11, 2010

CONTRIBUTIONS OF AUTHORS

M Othman and L Dou wrote the first draft of the protocol, which was adapted from the original protocol for Van den Broek 2002, with input from N van den Broek and J Neilson. A Metin Gülmezoglu commented on the revised draft protocol.

This new review was written by N van den Broek, M Othman, L Dou and J Neilson with comments from M Gülmezoglu. L Dou, M Othman and N van den Broek carried out the data extraction. S Gates provided statistical support and conducted the meta-analyses.

DECLARATIONS OF INTEREST

N van den Broek and J Neilson were investigators in the trial van den Broek 2006.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.
- HRP-UNDP/UNFPA/WHO/World Bank Special Programme in Human Reproduction, Geneva, Switzerland.
- Department of Obstetrics and Gynaecology, University of Geneva, Switzerland.

External sources

- Department of Nutrition for Health and Development, World Health Organization, Switzerland.

Provided funding for the preparation of this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Anemia [prevention & control]; Infant Mortality; Infant, Newborn; Maternal Mortality; Night Blindness [drug therapy]; Pregnancy Complications [*drug therapy]; Pregnancy Complications, Infectious [drug therapy]; Vitamin A [*administration & dosage]; Vitamin A Deficiency [*drug therapy]; Vitamins [*administration & dosage]

MeSH check words

Female; Humans; Pregnancy