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

McCauley ME, van den Broek N, Dou L, Othman M

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[Intervention Review]

Vitamin A supplementation during pregnancy for maternal and newborn outcomes

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Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 10, 2015.
Review content assessed as up-to-date: 30 March 2015.

Citation: McCauley ME, van den Broek N, Dou L, Othman M. Vitamin A supplementation during pregnancy for maternal and newborn outcomes. *Cochrane Database of Systematic Reviews* 2015, Issue 10. Art. No.: CD008666. DOI: 10.1002/14651858.CD008666.pub3.

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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 methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 March 2015) and reference lists of retrieved studies.

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 trials for inclusion and risk of bias, extracted data and checked them for accuracy.

Main results

We reviewed 106 reports of 35 trials, published between 1931 and 2015. We included 19 trials including over 310,000 women, excluded 15 trials and one is ongoing. Overall, seven trials were judged to be of low risk of bias, three were high risk of bias and for nine it was unclear.

1) Vitamin A alone versus placebo or no treatment

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Overall, when trial results are pooled, vitamin A supplementation does not affect the risk of maternal mortality (risk ratio (RR) 0.88, 95% confidence interval (CI) 0.65 to 1.20; four trials Ghana, Nepal, Bangladesh, UK, *high quality evidence*), perinatal mortality (RR 1.01, 95% CI 0.95 to 1.07; one study, *high quality evidence*), neonatal mortality, stillbirth, neonatal anaemia, preterm birth (RR 0.98, 95% CI 0.94 to 1.01, five studies, *high quality evidence*), or the risk of having a low birthweight baby.

Vitamin A supplementation reduces the risk of maternal night blindness (RR 0.79, 95% CI 0.64 to 0.98; two trials). There is evidence that vitamin A supplements may reduce maternal clinical infection (RR 0.45, 95% CI 0.20 to 0.99, five trials; South Africa, Nepal, Indonesia, Tanzania, UK, *low quality evidence*) and maternal anaemia (RR 0.64, 95% CI 0.43 to 0.94; three studies, *moderate quality evidence*).

2) Vitamin A alone versus micronutrient supplements without vitamin A

Vitamin A alone compared to micronutrient supplements without vitamin A does not decrease maternal clinical infection (RR 0.99, 95% CI 0.83 to 1.18, two trials, 591 women). No other primary or secondary outcomes were reported

3) Vitamin A with other micronutrients versus micronutrient supplements without vitamin A

Vitamin A supplementation (with other micronutrients) does not decrease perinatal mortality (RR 0.51, 95% CI 0.10 to 2.69; one study, *low quality evidence*), maternal anaemia (RR 0.86, 95% CI 0.68 to 1.09; three studies, *low quality evidence*), maternal clinical infection (RR 0.95, 95% CI 0.80 to 1.13; I^2 = 45%, two studies, *low quality evidence*) or preterm birth (RR 0.39, 95% CI 0.08 to 1.93; one study, *low quality evidence*).

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, 95% CI 0.47 to 0.96; one study, 594 women).

Authors' conclusions

The pooled results of three large trials in Nepal, Ghana and Bangladesh (with over 153,500 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 night blindness, 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

What is the issue?

Vitamin A is a fat-soluble vitamin found in liver, kidney, eggs, and dairy produce. 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 blood production. In pregnancy, extra vitamin A may be required. Currently, the World Health Organization (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).

Why is this important?

It has been suggested that a low intake of vitamin A may be associated with complications in pregnancy such as death of the mother or baby, increased infections for the mother or baby, low iron level for the mother or baby or having a baby with any of the following complications: early delivery, low birthweight or a congential abnormality.

What evidence did we find?

This review included 19 studies involving over 310,000 women. Seven trials were conducted in Africa, six in Indonesia, two in Bangladesh, and one each in Nepal, China, India, UK and USA. Most of the trials were conducted in populations considered to be vitamin A deficient (except USA and UK). The overall risk of bias was low to unclear in most of the trials, and the body of evidence was moderate to high quality. The findings indicate that routine supplementation with vitamin A (either alone or in combination with other supplements) during pregnancy did not reduce mother or newborn baby deaths. There is good evidence that antenatal vitamin

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A supplementation does reduce maternal anaemia in women who live in areas where vitamin A deficiency is common or who are HIV-positive. The trials published so far did not report any side effects or adverse events. 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.

What does this mean?

Taking vitamin A supplements during pregnancy does not help to prevent maternal deaths (related to pregnancy) or perinatal or newborn baby deaths. Taking vitamin A supplements during pregnancy does not help to prevent other problems that can occur such as stillbirth, preterm birth, low birthweight of babies or newborn babies with anaemia. However, the risk of maternal anaemia, maternal infection and maternal night blindness is reduced.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Vitamin A alone versus placebo or no treatment

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 alone versus placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with vitamin A alone				
Maternal mortality	Study population		RR 0.88 (0.65 to 1.20)	154,039 (4 RCTs)	⊕⊕⊕⊕ HIGH [1]	Inverse variance.
	5 per 1000	5 per 1000 (4 to 7)				
Perinatal mortality	Study population		RR 1.01 (0.95 to 1.07)	76,176 (1 RCT)	⊕⊕⊕⊕ HIGH	Inverse variance.
	54 per 1000	54 per 1000 (51 to 57)				
Maternal anaemia	Study population		RR 0.64 (0.43 to 0.94)	15,649 (3 RCTs)	⊕⊕⊕◯ MODERATE [2]	Inverse variance.
	191 per 1000	122 per 1000 (82 to 180)				
Maternal clinical infection	Study population		RR 0.45 (0.20 to 0.99)	17,313 (5 RCTs)	⊕⊕◯◯ LOW [2,3]	Inverse variance.
	18 per 1000	8 per 1000 (4 to 18)				
Preterm birth	Study population		RR 0.98 (0.94 to 1.01)	48,007 (5 RCTs)	⊕⊕⊕⊕ HIGH	

	249 per 1000	244 per 1000 (234 to 251)		
	Moderate			
	190 per 1000	186 per 1000 (178 to 192)		

*__The risk in the intervention group__ (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: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] 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.
[2] Statistical Heterogeneity ($I^2 > 60\%$).
[3] Most studies contributing data had design limitations.

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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

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at term. Insufficient intake and reduced absorption by the immature 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:

1. serum retinol 1 µmol/L = 28.6 µg/dL or 10 µg/dL = 100 µg/L = 0.35 µmol/L;
2. 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 (Hb) 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 Hb 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 2010; Wiysonge 2011).

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).

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It is also known that a diet devoid of vitamin A results in decreased Hb 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 Hb 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 Cochrane review (Wiysonge 2011), but we included data from randomised controlled trials 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.

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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 (haemoglobin (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 'Characteristics of included studies' tables and included outcomes in the analyses wherever possible.

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 March 2015).

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

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

Details of the search strategies for CENTRAL, MEDLINE, Embase and CINAHL, 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.

Searching other resources

We searched the reference lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, *see* van den Broek 2010.

For this update, the following methods were used for assessing the 23 reports that were identified as a result of the updated search.

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted the third review author.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved

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discrepancies through discussion or, if required, we consulted the third review author. Data were entered into Review Manager software (RevMan 2014) and checked for accuracy.
When information regarding any of the above was unclear, we planned 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 2011). Any disagreement was resolved by discussion or by involving a third assessor.

(1) Random 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:

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

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

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We assessed the methods as:

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

(3.1) Blinding of participants and personnel (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 were at low risk of bias if they were blinded, or if we judged that the lack of blinding unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

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 and 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 could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.
We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

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

- low risk of bias (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);
- high risk of bias (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 risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

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

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(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we planned to assess 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.

Assessment of the quality of the evidence using GRADE

For this update we assessed the quality of the evidence using the GRADE approach as outlined in the GRADE handbook in order to determine the quality of the body of evidence relating to the following outcomes

1. Maternal mortality
2. Perinatal mortality
3. Preterm birth
4. Maternal anaemia
5. Maternal infection

for the following main comparisons: vitamin A (or derivative):

1. alone versus placebo or no treatment;
2. in combination with other micronutrients versus micronutrient supplements without vitamin A.

We used GRADEpro Guideline Development Tool to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

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

Continuous data

No continuous data was analysed in this update. If appropriate, in future updates, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We included cluster-randomised trials in the updated review.

One study (West 2011) had reported the results using generalised estimating equation linear regression model and generalised estimating equations binomial regression. These methods had accounted for the clustering in the data. Hence, effect estimates and standard errors were meta-analysed using the generic inverse-variance method in RevMan.

For other studies and outcomes we adjusted their standard error using the methods described in the *Handbook [Section 16.3.6]* using an estimate of the intra cluster correlation co-efficient (ICC) derived from the trial. We synthesised the relevant information and considered wether it was 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 sensitivity analysis to investigate the effects of the randomisation unit.

Other unit of analysis issues

Multiple-arms trials

Where a trial had multiple intervention arms we avoided 'doubling' of participants by combining groups to create a single pair-wise comparison if possible. Where this was not possible we split the 'shared' groups into two or more groups with smaller sample size and included two or more (reasonably independent) comparisons.

Dealing with missing data

For included studies, we noted levels of attrition. In future updates, if more eligible studies are included, we will explore 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, analyses were carried out, 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. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either the Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity. If we identified substantial heterogeneity (above 30%), we planned to explore it by pre-specified subgroup analysis.

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Assessment of reporting biases

In future updates, if there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. 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. The random-effects summary was treated as the average of the 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, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

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

Where possible, we carried 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.

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2014). We reported the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We planned to carry out out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates, or both, with poor quality studies being excluded from the analyses in order to assess whether this makes any difference to the overall result. These sensitivity analyses were not conducted in this update.

RESULTS

Description of studies

Results of the search

We reviewed 106 reports of 35 trials, published between 1931 and 2015. We included 19 trials including over 310,000 women, excluded 15 trials and one is ongoing.

Included studies

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

Study designs

Of the 19 included trials, three were cluster-randomised (Kirkwood 2010; West 1999; West 2011), while the rest were based on randomisation of individual women. Only two trials were quasi-randomised (Green 1931; Suprapto 2002).

Settings

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). Six of the included trials were conducted in Indonesia (Dijkhuizen 2004; Hakimi 1999; Muslimatun 2001; Suharno 1993; Suprapto 2002; Tanumihardjo 2002). Two trials were conducted in Bangladesh (Ahmad 2009; West 2011). One trial was conducted in Nepal (West 1999), one in China (Sun 2010) and one in India (Radhika 2003).

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Population

All trials were conducted in populations considered to be moderately vitamin A deficient before the relevant trial was commenced except one trial (West 1999) that 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 the USA and UK were conducted in populations that were not a considered vitamin A deficient (Ajans 1965; Green 1931).

Interventions/Controls

Ten trials used Vitamin A (or one of its derivatives) supplementation alone compared with a control group (Ajans 1965; Coutsoudis 1999; Cox 2005; Green 1931; Kirkwood 2010; Kumwenda 2002; Radhika 2003; van den Broek 2006; West 1999; West 2011).

Five trials used Vitamin A in combination with other supplements compared to a control group (Dijkhuizen 2004; Muslimatun 2001; Semba 2001; Sun 2010; Suprapto 2002).

Four trials investigated both the use of Vitamin A (or one of its derivatives) supplementation alone and Vitamin A in combination with other supplements compared with a control group (Fawzi 1998; Hakimi 1999; Suharno 1993;Tanumihardjo 2002).

The control group included either a placebo, no treatment or another intervention (for example, iron).

Researchers reported vitamin A measurements in different units.

Included studies addressing primary outcomes

Maternal Mortality

Four trials reported maternal mortality as a primary outcome. Women of reproductive age were given weekly vitamin A supplements.

Green 1931 is a quasi-randomised trial conducted in the UK. Two hundred and seventy-five women received the vitamin A preparation and 275 women did not, serving as controls . Vitamin A 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, and should have been taken commencing one month prior 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. Maternal mortality was one of the outcomes assessed.

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, which are small subdistricts, 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. 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.

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. 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. The primary outcomes of the trial were pregnancy-related mortality and to compare this with the effect on overall all-cause female mortality. Secondary outcomes were severe maternal morbidity and perinatal and infant mortality. A secondary analysis (Hurt 2013) was conducted of the Kirkwood 2010 trial to determine the effect of weekly vitamin A supplementation on cause-specific mortality in women.

West 2011 conducted a double-blind cluster-randomised placebo-controlled trial in 596 sectors in the rural northwestern district of Gaibandha and Rangpur in Bangladesh between 2001 and 2007. Married women (n = 125,257) underwent five-week surveillance for pregnancy, ascertained by a history of amenorrhoea and confirmed by urine test. Blood samples were obtained from participants in 32 sectors (5%) for biochemical studies. A total of 59,666 women were eligible for inclusion in this study and were divided into three intervention groups: 7000 ug of retinol equivalent as retinyl palmitate, 42 mg of all-trans beta- carotene, or placebo. One of the primary outcomes was all-cause mortality of women related to pregnancy. Other outcomes included stillbirth and infant mortality to 12 weeks (84 days) following the pregnancy outcome and are described under neonatal outcomes.

Perinatal mortality

None of the included trials investigated perinatal mortality as a primary outcome.

Included studies addressing secondary outcomes

Maternal anaemia

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

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There are five studies from Indonesia which assess effect of vitamin A on Hb.

Suharno 1993 included 305 women from 20 rural villages in West Java, 16 to 24 weeks pregnant, with Hb 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.

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 four 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 sulphate 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 sulphate 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 sulphate and folic acid.

In Dijkhuizen 2004, all women were recruited before 20 weeks' gestational age from 13 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 sulphate/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 Hb.

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 Hb concentration and erythropoietin. Iron status was measured using serum ferritin and markers of inflammation included C-reactive protein (CRP) 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 A 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). Thirty-two per cent of women recruited were HIV-positive. Mean duration of supplementation was 14 weeks. The three main outcome measures were Hb 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 and one study from China assessed the effect of antenatal supplementation on Hb 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.

Sun 2010 is a double-blind randomised trial with a two-month duration, conducted in the Shen County in a central rural area of China. In this trial, 186 anaemic pregnant women with a Hb concentration > 80 and < 110 g/L were allocated to four groups. Group one (n = 47) was supplemented daily with 60 mg iron as ferrous sulphate; Group two (n = 46) with 60 mg and 0.4 mg folic acid; Group three (n = 46) with 60 mg iron, 2.0 mg retinol and 0.4 mg folic acid; and Group four (n = 47) was the placebo control group.

Three studies trials were conducted in HIV-positive pregnant women with the main intent of looking at the effect of vitamin A

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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 the effect of vitamin A on Hb 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.

Maternal Infection

For three trials the main outcome measure was maternal infection. Ajans 1965 conducted a randomised controlled trail in the USA in 44 parturient women who were allotted at random to one of three groups after admission to the delivery suite of the American University Hospital. Group one was the control group that included 18 women who were not given any form of vitamin A therapy prepartum. 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. 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. The main outcome was levels of maternal infection in breast milk.

Green 1931 described previously, also assessed maternal infection as one of the main outcomes defined as puerperal fever > 38^{o} C.

Hakimi 1999 describe the Zibuvita trial, a double-blind randomised controlled trial conducted in Central Java, Indonesia. One group received vitamin A 2400 retinol equivalent, the second group received zinc 20 mg/day, the third group received both vitamin A and zinc, while the fourth group received placebo. The main objective was to assess puerperal pyrexia (body temperature > 37.5 C) and puerperal sepsis (body temperature > 38.0 C) on at least one day in the postpartum period. Of note, this study information is from a draft of a publication which was not published in any peer review journal. However, two follow-up studies using this original trial data have been published (Prawirohartono 2011; Prawirohartono 2013).

Six follow-up studies of five included trials (Cox 2005; Dijkhuizen 2004; Fawzi 1998; Sun 2010; West 2011) reported on maternal infection as a secondary outcome.

Dijkhuizen 2001 measured maternal puerperal fever as an secondary outcome in a trial described previously, Dijkhuizen 2004.

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.

A short two-month duration trial in China (Sun 2010) described previously, assessed the effect of iron combined with retinol supplements in an anaemic pregnant population. The proxy measurements of interleukin 2 (IL-2) level and lymphocyte proliferation were assessed in an attempt to measure the impact on the maternal immune system and as an indirect measure of the maternal ability to combat infection.

Arsenault 2010 assessed a subgroup of the 1078 trial participants in the study of HIV-positive women in Tanzania (Fawzi 1998) for subclinical mastitis, defined as a ratio of the sodium to potassium (Na:K) breast milk concentration > 0.6. A total of 1642 breast milk samples were obtained by manual expression from 674 women from delivery and every three months up to two years postpartum.

Olofin 2014 also assessed the incidence of malaria in this same trial population (Fawzi 1998). Malaria was defined in two ways: presumptive diagnosis based on a physicians's or nurses's clinical judgement or periodic examination of blood smears for malaria parasites.

Christian 2011 conducted a trial as a substudy of the West 2011 trial and assessed the risk of maternal bacterial vaginosis in the study population. Thirty-three of the total 596 clusters were randomly assigned to the three intervention groups (West 2011) and women were examined for bacterial vaginosis by using self admin-

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istered swabs and the Nugent scoring method in early pregnancy, at 32 weeks' gestation and three months postpartum.

Neonatal outcomes

Four follow-up studies of four included trials reported neonatal outcomes.

Dijkhuizen 2001 assessed neonatal outcomes in a trial described previously, Dijkhuizen 2004. Outcomes described included preterm delivery, stillbirth, neonatal mortality and low birthweight.

Edmond 2012 conducted a follow-up study of the trial in Ghana (Kirkwood 2010) and assessed the effects of vitamin A supplementation on neonatal mortality (< one month) expressed per 1000 live births amongst other neonatal outcomes.

Christian 2013 conducted a follow-up study of the West 2011 trial to assess the effects of maternal weekly vitamin A and beta-carotene supplementation on birthweight, and length of gestation, including preterm birth.

Prawirohartono 2013 is a follow-up study of the Hakimi 1999 trial. Out of 2173 supplement pregnant women, 1956 neonates were assessed to determine whether vitamin A and/or zinc supplement given during pregnancy improved birthweight or neonatal morbidity. Neonatal morbidity included neonatal clinical infection by using measurements of fever, hypothermia, diarrhoea, and vomiting in neonates up to 20 days of life.

Excluded studies

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

Of the 15 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 beta-carotene), so lycopene cannot form vitamin A and its biological effects are due to mechanisms other than forming vitamin A. One study was excluded as the intervention was unfortified soybean oil and did not include vitamin A or any of its derivatives (Alam 2010). 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). 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.

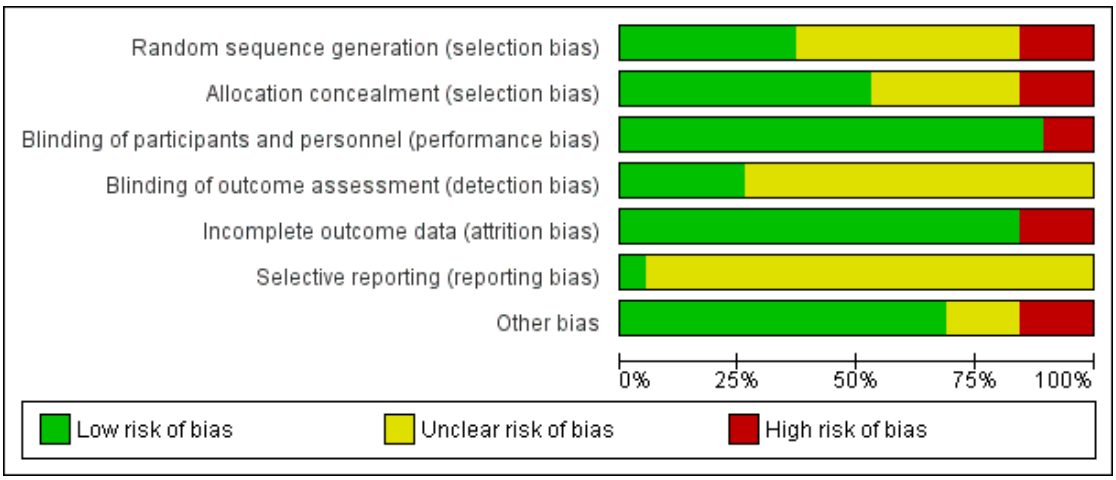

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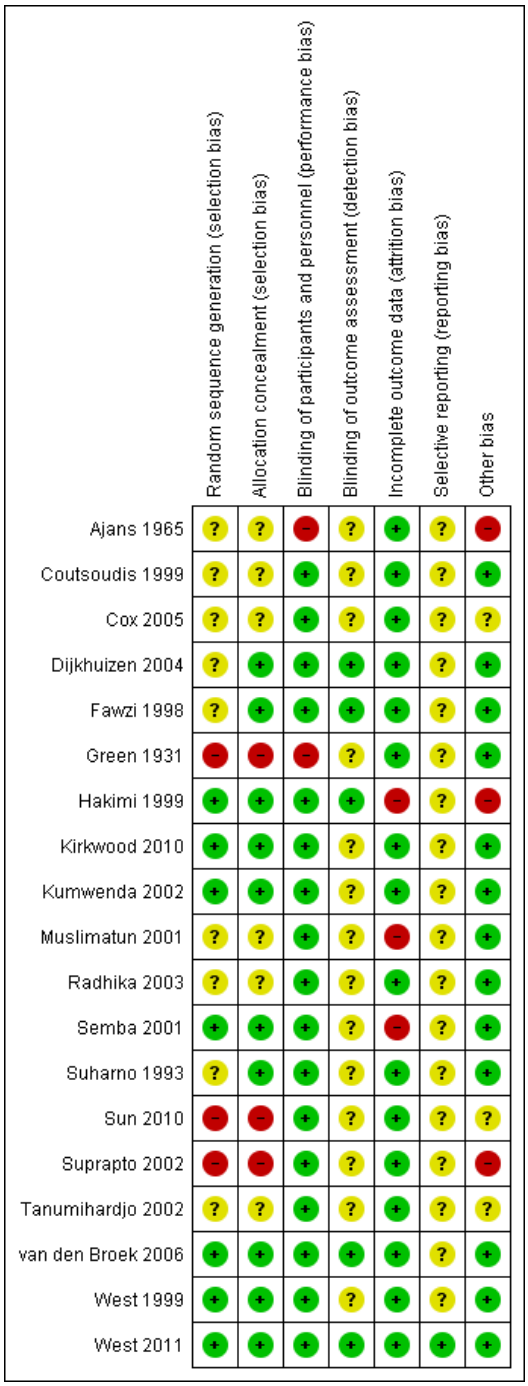
Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



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Allocation

Three of the included studies did not report adequate methods for either random sequence generation or allocation concealment (Green 1931; Sun 2010; Suprapto 2002) Six of the included studies were not clear regarding both the allocation concealment and the random sequence generation (Ajans 1965; Coutsoudis 1999; Cox 2005; Muslimatun 2001; Radhika 2003; Tanumihardjo 2002). Three studies were not clear simply with regards to the random sequence generation, but did report adequate allocation concealment (Dijkhuizen 2004; Fawzi 1998; Suharno 1993).The remaining seven trials reported adequate allocation concealment and generation (Hakimi 1999; Kirkwood 2010; Kumwenda 2002; Semba 2001; van den Broek 2006; West 1999; West 2011).

Blinding

Only two studies reported no blinding of participants and personnel and were unclear regarding the blinding of the outcome (Ajans 1965; Green 1931).

Eleven studies described blinding of participants and personnel, but blinding for outcome assessment was unclear (Coutsoudis 1999; Cox 2005; Kirkwood 2010; Kumwenda 2002; Muslimatun 2001; Radhika 2003; Semba 2001; Suharno 1993; Suprapto 2002; Tanumihardjo 2002; West 1999).

One study Sun 2010 was not clear regarding the blinding of the outcome only but did report adequate blinding of participants and personnel.

The remaining five studies reported adequate double blinding and outcome assessment (Dijkhuizen 2004; Fawzi 1998; Hakimi 1999; van den Broek 2006; West 2011).

Incomplete outcome data

Three studies were high risk of attrition bias (Hakimi 1999; Muslimatun 2001; Semba 2001), with the remaining 16 included trials adequately addressed the issue of incomplete outcome data and were low risk. the 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 other included studies were not generally available and accordingly we cannot comment on selective reporting bias except for West 2011 which was free from any selective reporting bias.

Other potential sources of bias

Three studies were unclear regarding potential sources of bias (Cox 2005; Sun 2010; Tanumihardjo 2002), either because, presence of differences in educational level and gestational age at enrolment (Cox 2005) or the study report is not detailed enough (Tanumihardjo 2002). Three trials had a potential source of bias which were reported (Ajans 1965; Hakimi 1999; Suprapto 2002) 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 alone versus placebo or no treatment; **Summary of findings 2** Combination vitamin A and micronutrients for maternal and newborn mortality and morbidity

1. Vitamin A alone versus placebo or no treatment

Primary outcomes

Vitamin A supplementation does not significantly affect the risk of maternal mortality (risk ratio (RR) 0.88, 95% confidence interval (CI) 0.65 to 1.20, four studies; $Tau^2 = 0.04$, $I^2 = 50\%$, 101,574 women; Analysis 1.1) or perinatal mortality (RR 1.01, 95% CI 0.95 to 1.07; one study, 76,176 women; Analysis 1.2).

Secondary outcomes

Vitamin A supplementation does not significantly affect the risk of neonatal mortality (RR 0.97, 95% CI 0.90 to 1.05; three studies , $I^2 = 23\%$, 89,556 women; Analysis 1.3), or stillbirth (RR 1.04, 95% CI 0.98 to 1.10, two studies,122,850 women; Analysis 1.4).

Vitamin A supplementation reduces the risk of maternal anaemia (RR 0.64, 95% CI 0.43 to 0.94; three studies, $Tau^2 = 0.08$, $I^2 = 68\%$, 3,818 women; Analysis 1.5), maternal clinical infection (RR 0.45, 95% CI 0.20 to 0.99; five studies, $Tau^2 = 0.59$, $I^2 = 88\%$, 1,918 women; Analysis 1.6), and maternal night blindness (RR 0.79, 95% CI 0.64 to 0.98; two studies, 10,608 women; Analysis 1.7).

Vitamin A supplementation does not significantly affect the risk of neonatal anaemia (RR 0.99, 95% CI 0.92 to 1.08, one study, 409 women; Analysis 1.9), preterm birth (RR 0.98, 95% CI 0.94 to 1.01, five studies, $I^2 = 29\%$, 40,137 women; Analysis 1.8), or the risk of having a low birthweight baby (RR 1.02, 95% CI 0.89 to 1.16, four studies, $Tau^2 = 0.00$, $I^2 = 10\%$, 14,599 women; Analysis 1.12).

Neonatal clinical infection or congential malformations were not reported in the studies.

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2. Vitamin A alone versus micronutrient supplements without vitamin A

Primary outcomes

No trial investigated maternal or perinatal mortality as primary outcomes for vitamin A alone versus micronutrient supplements without vitamin A.

Secondary outcomes

Vitamin A alone compared to micronutrient supplements without vitamin A does not decrease maternal clinical infection (RR 0.99, 95% CI 0.83 to 1.18, two studies, I^2 = 0%, 591 women) Analysis 2.6. No other secondary outcomes were reported.

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

Primary outcomes

Vitamin A supplementation (with other micronutrients) does not decrease perinatal mortality (RR 0.51, 95% CI 0.10 to 2.69; one study, 179 women) Analysis 3.2. Maternal mortality was not reported.

Secondary outcomes

Vitamin A supplementation (with other micronutrients) does not decrease maternal anaemia (RR 0.86, 95% CI 0.68 to 1.09; three studies, 706 women) Analysis 3.5, or maternal clinical infection (RR 0.95, 95% CI 0.80 to 1.13; I^2 = 45%, two studies, 597 women) Analysis 3.6.

Vitamin A supplementation (with other micronutrients) does not decrease neonatal mortality (RR 0.65, 95% CI 0.32 to 1.31; one study, 594 women) Analysis 3.3, stillbirth (RR 1.41, 95% CI 0.57 to 3.47; two studies, 866 women) Analysis 3.4, preterm birth (RR 0.39, 95% CI 0.08 to 1.93; one study, 136 women) Analysis 3.8, neonatal anaemia (RR 0.75, 95% CI 0.38 to 1.51; Tau^2 = 0.24, I^2 = 97%; two studies, 1052 women) Analysis 3.9, congential malformations (RR 0.34, 95% CI 0.04 to 3.18; one study, 179 women) Analysis 3.11, or low birthweight (RR 0.67, 95% CI 0.47 to 0.96; one study, 594 women) 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.

Subgroup analysis for vitamin A alone versus placebo or no treatment

Countries with high versus low infant mortality rates (high infant mortality rate greater than or equal to 30/1000 live births (IMCI- TAG 2008)).

Perinatal mortality in countries with high infant mortality rates remained unchanged (RR 1.01, 95% CI 0.95 to 1.07, one study, 76,176 women) Analysis 4.1. 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, one study, 73,743 women) Analysis 4.4. No trials reported on perinatal mortality from countries with low maternal mortality rates or countries with low prevalence of vitamin A deficiency.

Countries with high versus low maternal mortality rates (high maternal mortality rate greater than 100 per 100,000 live births (WHR 2005)).

In countries with high maternal mortality, the RR for maternal mortality was 0.91, (95% CI 0.76 to 1.08, four studies, I^2=55%, 161,240 women) Analysis 4.3 in the overall analysis. There was no interaction between countries with low maternal mortality and countries with high maternal mortality (Test for subgroup differences P = 0.54, I^2 = 0%). Maternal mortality rate did not change in countries with low infant mortality (RR 0.33, 95% CI 0.01 to 9.44, one study, 550 women) Analysis 4.2.

High versus low prevalence of vitamin A deficiency (as defined by WHO for the country or by the investigator).

Maternal mortality demonstrated no changes in countries with low (RR 0.33, 95% CI 0.01 to 8.15; one study, 550 women), or high (RR 0.88, 95% CI 0.63 to 1.23; three studies, 160,690 women; I^2 = 68%) prevalence of vitamin A deficiency Analysis 4.5.

Perinatal mortality showed no changes in countries with high prevalence of vitamin A deficiency (RR 1.01, 95% CI 0.95 to 1.07; one study, 76,176 women) Analysis 4.6 .

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.

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In countries with low HIV prevalence the RR for maternal mortality was (RR 0.87, 95% CI 0.64 to 1.20, four studies, I^2 = 55%, 161,240 women) Analysis 4.7. The trials in countries with high HIV prevalence did not set out to assess the effect of vitamin A on maternal mortality.

In countries with low HIV prevalence, RR for perinatal mortality was 1.01 (95% CI 0.95 to 1.07, one study, 76,176 women) Analysis 4.8. For countries with high HIV prevalence, no trials investigated the effect of vitamin A supplementation to the mother on perinatal mortality.

Dose and regimen 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 (RR 0.88, 95% CI 0.63 to 1.23, three studies, I^2 = 68%, 160,690 women), and for perinatal mortality 1.01 (95% CI 0.95 to 1.07, one study, 76,176 women), Analysis 4.9; Analysis 4.10.

For daily vitamin A supplementation, the RR for maternal mortality was 0.33 (95% CI 0.01 to 8.15) and weekly supplementation was 0.88 (95% CI 0.63 to 1.23, four studies, I^2 = 55%, 161,240 women), Analysis 4.11. For weekly vitamin A supplement, the RR for perinatal mortality was 1.01 (95% CI 0.95 to 1.07, one study, 76,176 women), Analysis 4.12.

Duration of intervention

There was no difference in the duration of the intervention of vitamin A supplementation on maternal mortality; for one month or less, the RR was 0.33, 95% CI 0.01 to 8.15, one study, 550 women) and more than one month RR was (RR 1.18, 95% CI 0.83 to 1.68, one study, 59,666 women), Analysis 4.13. No trial assessed the effect of the duration of intervention with vitamin A supplementation on perinatal mortality.

Trimester of pregnancy

There was no trial to assess vitamin A supplementation started in the second trimester on the maternal mortality. However, the RR of vitamin A on maternal mortality started in pre-pregnancy was RR 0.77, (95% CI 0.50 to 1.17, two studies, I^2 = 71%, 101,024 women), first trimester was RR 1.18, (95% CI 0.83 to 1.68, one study, I^2 = 0%, 59,666 women), and third trimester was RR 0.33, (95% CI 0.01 to 8.15, one study, 550 women), Analysis 4.15. Although, there was no subgroup interaction in Analysis 4.15 (P= 0.25, I^2=28.3%).

One trial assessed the vitamin A supplementation started in pre-pregnancy on perinatal mortality (RR 1.01, 95% CI 0.95 to 1.07, one study, 76,176 women), Analysis 4.16.

Sensitivity analysis

Randomisation

No individual-randomised trial assessed the effect of vitamin A supplementation on maternal and perinatal mortality. For cluster-randomisation trials the RR of vitamin A on was 0.88, (95% CI 0.63 to 1.23, three studies, I^2 = 68%, 160,690 women) and 1.01, (95% CI 0.95 to 1.07, one study, 76,176 women) respectively, Analysis 4.17; Analysis 4.18.

Subgroup analysis for vitamin A (with other micronutrients) versus micronutrient supplements without vitamin A

For all subgroup analysis, the RR of vitamin A supplementation (with other micronutrients) on perinatal mortality was 0.51, (95% CI 0.10 to 2.69, one study, 179 women) Analysis 6.2. There were no data on maternal mortality for these subgroups.

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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	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with micronutrient supplements without vitamin A	Risk with vitamin A with other micronutrients				
Maternal mortality	Study population		not estimable	(0 studies)	See comment	No study reported results for this outcome.
	not pooled	not pooled				
Perinatal mortality	Study population		RR 0.51 (0.10 to 2.69)	179 (1 RCT)	⊕⊕◯◯ LOW [1]	
	44 per 1000	23 per 1000 (4 to 120)				
	Moderate					
	44 per 1000	23 per 1000 (4 to 119)				
Maternal anaemia	Study population		RR 0.86 (0.68 to 1.09)	706 (3 RCTs)	⊕⊕◯◯ LOW [2]	
	269 per 1000	231 per 1000 (183 to 293)				
	Moderate					

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	346 per 1000	298 per 1000 (235 to 377)			
Maternal clinical infection	Study population		RR 0.95 (0.80 to 1.13)	597 (2 RCTs)	⊕⊕◯◯ LOW [2]
	382 per 1000	363 per 1000 (306 to 432)			
	Moderate				
	339 per 1000	322 per 1000 (271 to 383)			
Preterm birth	Study population		RR 0.39 (0.08 to 1.93)	136 (1 RCT)	⊕⊕◯◯ LOW [2]
	75 per 1000	29 per 1000 (6 to 144)			
	Moderate				
	75 per 1000	29 per 1000 (6 to 144)			

*__The risk in the intervention group__ (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: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Wide confidence interval crossing the line of no effect, few events & small sample size.
[2] Wide confidence interval crossing the line of no effect & small sample size.

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.

Nineteen trials are included in this review out of a total of 35 trials. In countries where night blindness is reported, maternal night blindness is significantly improved with vitamin A supplementation.

Overall, the analysis shows that there is no evidence that vitamin A supplementation to women of reproductive age or during pregnancy decreases maternal mortality. The three largest studies from Nepal, Ghana and Bangladesh specifically assessed the effect on maternal mortality with over 153,500 women included. 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. Two subsequent large studies, both conducted in countries with moderate vitamin A deficiency (Ghana and Bangladesh), did not show an effect of vitamin A supplementation on maternal mortality.

In vitamin A deficient populations and HIV-positive women, vitamin A supplementation reduces maternal anaemia and there is evidence that vitamin A supplements alone may reduce maternal clinical infection.

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 (Hb) 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.

Five studies measured maternal infection after supplementation with vitamin A in just under 1800 women. It was noted that the criteria for the outcome 'infection' varied between the studies. We note that one study included in the analysis is from a draft of a publication which was not published in any peer review journal. In one trial, the proxy measurements of interleukin 2 (IL-2) level and lymphocyte proliferation were used to as an indirect measure of the maternal ability to combat infection. 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.

Of the included trials, 15 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 the effect of vitamin A on mother to child transmission of HIV. We have included these because the secondary outcomes are relevant to this review.

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 alone does not affect the risk of perinatal mortality or stillbirth or neonatal mortality separately. Similarly, analysis of available data shows no effect on preterm birth or low birthweight. There were no reported side effects or adverse events in any of the trials. One study did report on congential abnormalities but the effect was not significant. For one study supplementing vitamin A together with other micronutrients (versus other micronutrients in control group) in HIV-positive women, the risk of low birthweight was found to reduced.

The trials are from a variety of countries, including high-, middle- and low-income 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 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). In one trial, the proxy measurements of interleukin 2 (IL-2) level and lymphocyte proliferation were used as an indirect measure of the maternal ability to combat infection. The data from this trial were continuous, and could not be combined with other studies with dichotomous outcome data and hence this study did not contribute any data to the review results.

Maternal anaemia was more consistently defined (Hb < 11.0 g/dL, Hb < 10.0 g/dL). However, one study from Malawi and one from

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China reported change in Hb rather than percentage of women not anaemic and thus we have not included it in the meta-analysis.
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.
There were no differences in outcomes for any of the subgroup analyses performed.

Overall completeness and applicability of evidence

The three 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

In the majority of studies, adequate methods of allocation concealment were described; only three trials described inadequate methods (Green 1931; Sun 2010; Suprapto 2002). Green 1931 and Suprapto 2002 used an alternation 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 Sun 2010 women were randomised in order of enrolment. 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. Three clinical trials included lost more than 20% of the participants (Hakimi 1999; Muslimatun 2001; 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 overall risk of bias is low to unclear for most of the studies.
For comparison vitamin A alone versus placebo or no treatment, the quality of the evidence as assessed using GRADE was high for maternal mortality, perinatal mortality, and preterm birth, moderate for maternal anaemia and low for maternal clinical infection (Summary of findings for the main comparison). Reasons for downgrading the evidence include statistical heterogeneity and design limitations. For combination vitamin A and micronutrients, due to wide confidence interval crossing the line of no effect, few events and small sample size, all the outcomes were rated as low quality of the evidence (Summary of findings 2).

Potential biases in the review process

We acknowledge that there was the potential for bias at all stages in the reviewing process. We attempted to minimise bias in a number of ways; for example, two review authors independently carried out data extraction and assessed risk of bias. However, we acknowledge that such assessments involve subjective judgments, and another review team may not have agreed with all of our decisions.

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 or adverse events 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

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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 19 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 and Bangladesh this is less likely as women are moderately vitamin A deficient and supplementation did not reduce mortality. In the study from Ghana there was a substantial number of women lost to follow-up. In all three trials, (Ghana and Nepal and Bangladesh) results are in the same direction (a reduction in maternal mortality). The trials from Ghana and Bangladesh showed non-significant results. In Ghana, 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 and Bangladesh 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 high-quality evidence on whether vitamin A can reduce infection including maternal sepsis is needed.

To improve haemoglobin (Hb), 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 Hb 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.

ACKNOWLEDGEMENTS

Lisa Hurt, on behalf of the ObaapaVitA trial team, for providing additional data about the Kirkwood 2010 trial.

We thank Erika Ota for her help with the 2015 update. Erika Ota's work was financially supported by the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization. The named authors alone are responsible for the views expressed in this publication.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Pregnancy and Childbirth. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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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 group 1: 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. 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
Outcomes	Primary outcome: levels of vitamin A and carotenoids in the maternal blood. Other outcomes: levels of vitamin A and carotenoids in the colostrum prenatal and postnatal
Notes	Vitamin 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description except allotted at random.
Allocation concealment (selection bias)	Unclear risk	No description except allotted at random.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding methods were reported. The routes of medication administration methods varied across groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information was provided.

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Ajans 1965 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusion or loss of follow-up reported.
Selective reporting (reporting bias)	Unclear risk	The protocol of the study is not available at the moment.
Other bias	High risk	The 3 groups were not studied during the same period. The authors reported "subjects in groups 1 and 2 were studied in the summer and those of group 3 in the following winter"

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 vitamin 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 vitamin 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 birthweight and morbidity
Notes	Vitamin 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel "double-blind".

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Coutsoudis 1999 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	57 (7.8%) women did not deliver in the hospitals and cannot be traced
Selective reporting (reporting bias)	Unclear risk	The protocol of the study is not available at the moment.
Other bias	Low risk	No other bias awarded.

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: Hb and birthweight.
Notes	Vitamin A levels were measured before starting supplementation Country: Ghana. Study setting: Nkoranza District Hospital and 3 rural health clinics in Brong Ahafo region, Central Ghana

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"balanced block randomisation."
Allocation concealment (selection bias)	Unclear risk	No information provided.

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Cox 2005 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel "double-blind".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 (12%) women were excluded from the analysis: 1 false pregnancy, 1 early miscarriage, 10 missed late pregnancy visit
Selective reporting (reporting bias)	Unclear risk	The protocol of the study is not available at the moment.
Other bias	Unclear risk	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 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 vitamin 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 sulphate/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 Hb and zinc levels. Other outcomes: maternal and fetal ferritin, retinol and carotene levels Other outcomes from this same trial were recorded by Dijkhuizen 2001- see notes below.

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Dijkhuizen 2004 (*Continued*)

Notes	Vitamin 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 Dijkhuizen 2001 assessed maternal and neonatal complications in this same trial described above. Outcomes described included maternal puerperal fever, preterm delivery, stillbirth, neonatal mortality and birthweight

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided except factorial randomisation.
Allocation concealment (selection bias)	Low risk	"Capsules were indistinguishable and given a letter code."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel double-blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No information given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	35 (20%) women were not followed up or included in the analyses
Selective reporting (reporting bias)	Unclear risk	The protocol of the study is not available at the moment.
Other bias	Low risk	No other bias awarded.

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 vitamin 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

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Fawzi 1998 (*Continued*)

	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: birthweight, preterm birth (delivery less than 37 completed weeks estimated using LMP) and Hb in both mother and fetus (Hb < 10.0 g/dL)
Notes	Vitamin A levels were measured before starting supplementation Country: Tanzania. Duration: 1995-1997. Study setting: 4 ANCs with several smaller peripheral clinics Other secondary outcomes of interest in this review (maternal infection) from this trial are described by Arsenault 2010 and Olofin 2014.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomisation was done in blocks of 20."
Allocation concealment (selection bias)	Low risk	"At enrolment, we assigned each eligible women the next numbered bottle of regimen."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel "double blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No information.
Incomplete outcome data (attrition bias) All outcomes	Low risk	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.
Selective reporting (reporting bias)	Unclear risk	The protocol of the study is not available at the moment.
Other bias	Low risk	No other bias awarded.

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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 vitamin A), should have been taken daily commencing 1 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 7 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	Vitamin A levels were not measured before starting supplementation Country: UK. Study setting: the Jessop Hospital and the Nether Edge municipal hospital

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"the first patient was given the preparation and the next due for delivery about the same time was indexed as a control."
Allocation concealment (selection bias)	High risk	"the first patient was given the preparation and the next due for delivery about the same time was indexed as a control."
Blinding of participants and personnel (performance bias) All outcomes	High risk	The control group received no intervention.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	50 (8.3%) women delivered somewhere else and were excluded.
Selective reporting (reporting bias)	Unclear risk	The protocol of the study is not available at the moment.
Other bias	Low risk	No other bias awarded.

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Hakimi 1999

Methods	Randomised, placebo-controlled double masked community-based trial
Participants	Inclusion: women with positive pregnancy test in the first 120 days of pregnancy Exclusion: • women who were not married or did not have a life partner; • women whose gestational age > first trimester; • women using hormonal contraception or intrauterine device; • peri-menopausal women.
Interventions	Group 1: 248 received vitamin A 2400 retinol equivalent, second group 254 received zinc 20 mg/day, third group 243 received both vitamin A and zinc, while the fourth group 263 received placebo
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 termed the ZIBUVITA trial Setting: Central Java, Indonesia. Of note this study information is from a draft of a publication which was not published in any peer review journal However, 2 follow-up studies using this original trial have been published, Prawirohartono 2011 and Prawirohartono 2013.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"1:1:1:1 ratio in blocks of 12 based on a list of treatment numbers derived from a pseudo-random number generator in SAS. "
Allocation concealment (selection bias)	Low risk	"treatment allocation sequence was prepared and held at ..a site remote from the trial."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"supplements were packaged in ..identical opaque pink capsules." "all investigators, field and laboratory staff and participants were blinded to the treatment code."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"a survey of sample of field workers and their supervisors revealed they were unable to identify which treatments the study participants were receiving."
Incomplete outcome data (attrition bias) All outcomes	High risk	> 20% loss to follow-up.

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Hakimi 1999 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	The protocol of this study is not available.
Other bias	High risk	Of note this information is from a draft of a publication which was not published in any peer review journal. However, 2 follow-up studies using this original trial have been published, Prawirohartono 2011 and Prawirohartono 2013.

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 vitamin 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	Setting: 7 districts in Brong Ahafo region in Ghana. Sample size: more that 207,000 pregnant women.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A computer-generated randomisation list."
Allocation concealment (selection bias)	Low risk	"The capsules were packaged in labelled jars."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel "Double blind".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given.

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Incomplete outcome data (attrition bias) All outcomes	Low risk	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
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available.
Other bias	Low risk	No other bias awarded.

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 vitamin 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 vitamin A levels in blood and breast milk and HIV transmission in mother and baby Other outcomes: Hb and birthweight.
Notes	Vitamin A levels were measured before starting supplementation Country: Malawi. Study setting: Queen Elizabeth Central Hospital (Blantyre, Malawi)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"a computer random-number generator."

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Kumwenda 2002 (*Continued*)

Allocation concealment (selection bias)	Low risk	"pre packing study supplements in sequentially numbered series assigned to study identification numbers."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel "Double blind".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	63 (9%) women were excluded from the analysis: 57 moved out, 6 could not be located
Selective reporting (reporting bias)	Unclear risk	The protocol of the study is not available at the moment.
Other bias	Low risk	Not aware of any other bias.

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 2 tablets each of which contained 3000 RE vitamin A in addition to the ferrous sulphate and 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 2 tablets each containing 60 mg elemental iron as ferrous sulphate and 250 mg folic acid
Outcomes	Primary outcome: infant growth in 1 year of life. Other outcomes: maternal Hb and fetal morbidity.
Notes	Vitamin 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Assigned randomly."
Allocation concealment (selection bias)	Unclear risk	No information provided.

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Muslimatun 2001 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel "Double blind".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given.
Incomplete outcome data (attrition bias) All outcomes	High risk	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. Overall, the loss to follow-up of the intervention group was 32.8 % and the control group was 27.3%
Selective reporting (reporting bias)	Unclear risk	The protocol of the study is not available at the moment.
Other bias	Low risk	Not aware of any other bias.

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
Interventions	Intervention group: 85 women received red palm oil providing 2173 to 2307 µg of β-carotene per day with a dosage schedule of 1 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 vitamin A) daily for a period of 8 weeks Control group: 85 women received 1 sachet of groundnut oil (8 mL) for a period of 8 weeks
Outcomes	Primary outcome: maternal and neonatal vitamin A status. Other outcomes: Hb levels in mother and baby, preterm birth (delivery less than 37 completed weeks as confirmed by ultrasound examination), birthweight and gestational age

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Radhika 2003 (*Continued*)

Notes	Vitamin A levels were measured before starting supplementation Country: India. Study setting: the outpatient department of Niloufer Hospital, Hyderabad, India

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel "Double blind".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	41 (24.1%) women were excluded from the analysis: 23 were not available for supplementation, while 18 dropped out after initiating supplementation Overall, the loss to follow-up of the intervention group was 9.5 % and the control group was 15.1%
Selective reporting (reporting bias)	Unclear risk	The protocol of the study is not available at the moment.
Other bias	Low risk	No other bias awarded.

Semba 2001

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

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Semba 2001 (*Continued*)

Outcomes	Primary outcome: Hb concentrations and plasma erythropoietin concentrations Other outcomes: levels of ferritin, ? 1-acid glycoprotein, CRP and plasma vitamin A
Notes	Vitamin A levels were measured before starting supplementation Country: Malawi. Study setting: the Queen Elizabeth Central Hospital in Blantyre, Malawi Semba 2001 is linked to the Semba 2000 trial; the difference being that Semba 2000 investigated slightly different outcomes in HIV-positive women and Semba 2001 assessed HIV negative women.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"a computer random-number generator."
Allocation concealment (selection bias)	Low risk	"sequentially numbered opaque bottle."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel "Double blind".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given.
Incomplete outcome data (attrition bias) All outcomes	High risk	66 (32.5%) women were excluded from the analysis: 42 missed the study visit, 9 did not have their Hb analysed, 15 moved out
Selective reporting (reporting bias)	Unclear risk	The protocol of the study is not available at the moment.
Other bias	Low risk	No other bias awarded.

Suharno 1993

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

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Suharno 1993 (*Continued*)

Interventions	Intervention group 1: 63 women received vitamin A (2.4 mg retinol as retinyl palmitate) (equivalent to 8000 IU of vitamin 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	Vitamin A levels were measured before starting supplementation Country: Indonesia. Study setting: rural villages in 3 subdistricts of Bogo, West Java

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly."
Allocation concealment (selection bias)	Low risk	'An independent researcher randomly labelled' the preparations
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel "Double blind".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	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.
Selective reporting (reporting bias)	Unclear risk	The protocol of the study is not available at the moment.
Other bias	Low risk	No other bias awarded.

Sun 2010

Methods	Double-blind RCT.
Participants	Inclusion criteria: • anaemic (Hb > 80 but < 110g/L); • pregnant women, 12-24 weeks' gestation, age between 20-30 years; • no dietary supplements during previous 2 months; • no abnormal pregnancy response.

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Interventions	4 groups: • group 1 (n = 47) was supplemented daily with 60 mg iron as ferrous sulphate; • group 2 (n = 46) with 60 mg and 0.4 mg folic acid; • group 3 (n = 46) with 60 mg iron, 2.0 mg retinol and 0.4 mg folic acid; • group 4 (n = 47) was the placebo control group.
Outcomes	Primary outcomes: • iron status; • Cytokine Interleukin -2 (IL -2) levels; • Lymphocyte proliferation.
Notes	Short intervention time of 2 months duration. Patient were recruited between March 2004 - September 2005. Setting: Shen county in a central rural area of China. Total number of patients - 186.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"Patients were randomised in order of enrolment."
Allocation concealment (selection bias)	High risk	"Patients were randomised in order of enrolment."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Adequate blinding of participants and personnel reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss of participants < 5% - 6 women did not complete the trial due to moving to other villages (3), and stopped taking supplements during the trial (3)
Selective reporting (reporting bias)	Unclear risk	No details given.
Other bias	Unclear risk	No details given.

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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 (Hb < 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.
Interventions	Intervention group 1: 22 women; group IFR received iron-folate tablets + 5 mg riboflavin 7 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) 7 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 7 days a week for 60 days Control group: 29 women; group IF received iron-folate tablets + 5 mg glucose 7 days a week for 60 days
Outcomes	Maternal levels of vitamin A and riboflavin.
Notes	Vitamin A levels were measured before starting supplementation Country: Indonesia. Study setting: health centre ANC.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"allocated alternately."
Allocation concealment (selection bias)	High risk	"allocated alternately."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"participants and personnel double-blind. "
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	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

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Suprapto 2002 (*Continued*)

		for last menstruation but with normal deliveries
Selective reporting (reporting bias)	Unclear risk	The protocol of the study is not available at the moment.
Other bias	High risk	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.
Interventions	Intervention group 1: 5 women received 1.07 mmol (60 mg) ferrous sulphate 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 Hb and retinol levels.
Notes	Vitamin 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Subjects and village volunteers were unaware of group assignment."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.

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Tanumihardjo 2002 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss of follow-up reported.
Selective reporting (reporting bias)	Unclear risk	The protocol of the study is not available at the moment.
Other bias	Unclear risk	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 2 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 2 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 2 doses of Fansidar (500 mg sulphadoxine with 25 mg pyrimethamine
Outcomes	Primary outcome: Hb concentrations and anaemia. Other outcomes: iron status, preterm birth (delivery less than 37 completed weeks as confirmed by ultrasound examination), markers of infections included CRP, malaria parasitaemia and HIV status
Notes	Vitamin A levels were measured before starting supplementation Country: Malawi. Study setting: rural southern Malawi attending ANC at Health Centres

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"a random-generation procedure."

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Allocation concealment (selection bias)	Low risk	"consecutive numbers" "in sealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The supplements in vitamin A and placebo treatments allocated were prepared in identical capsules."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The supplements in vitamin A and placebo treatments allocated were prepared in identical capsules."
Incomplete outcome data (attrition bias) All outcomes	Low risk	96 (13.7%) women were excluded from the analyses: 18 women moved out from the area, 68 declined to continue, 10 missed appointment
Selective reporting (reporting bias)	Unclear risk	The protocol of the study is not available at the moment.
Other bias	Low risk	Not aware of other bias.

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 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 vitamin A and retinol levels, and maternal morbidity
Notes	Vitamin A levels were not measured before starting supplementation Country: Nepal. Study setting: 270 wards in 30 subdistricts.

Risk of bias

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

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West 1999 (*Continued*)

Random sequence generation (selection bias)	Low risk	"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 (selection bias)	Low risk	"'three identical coded supplements."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel "double-blind".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not included.
Incomplete outcome data (attrition bias) All outcomes	Low risk	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)
Selective reporting (reporting bias)	Unclear risk	The protocol of the study is not available at the moment.
Other bias	Low risk	No other bias awarded.

West 2011

Methods	Double-blind cluster-randomised placebo-controlled trial.
Participants	Inclusion criteria: all married women of reproductive age (13-45 years of age) were under surveillance living in the study settings and all who became pregnant were included in this study Exclusion criteria: > first trimester of pregnancy; women who during surveillance: • permanently moved outside study settings; • became menopausal; • were sterilised; • who died; • whose husbands died. Sample size: 60,294.
Interventions	7000 ug of retinol equivalent as retinyl palmitate, 42 mg of all-trans beta-carotene or placebo
Outcomes	Primary outcome: all-cause mortality of women related to pregnancy, stillbirth, and infant mortality up to 12 weeks (84 days) following pregnancy outcome

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Notes	Vitamin A levels were not measured before starting supplementation Country: Bangladesh. Duration: 2001-2007 termed the JiVitA-1 trial. Study setting: 596 sectors in the rural northwestern district of Gaibandha and Rangpur between 2001 and 2007 Christian 2013 is a follow-up study of this trials that describes secondary outcomes of interest (low birthweight and preterm birth) in this review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"cluster randomization" "sectors were randomized in blocks of nine, to one of three codes - 1,2,3." "field supervisor [were engaged] to in the process of randomization to increase the transparency of sector allocation."
Allocation concealment (selection bias)	Low risk	"three sets of 3 identical coins on which the numbers 1, 2 or 3 were written were placed into a container, mixed and removed randomly, without replacement and the 3 digit code of each sector was read aloud sequentially."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"study participants, interviewers, field supervisors, and investigators remained masked to treatment assignments until the end of the trial."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"study participants, interviewers, field supervisors, and investigators remained masked to treatment assignments until the end of the trial."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss of participants < 5%, except for outcome of low birthweight, which was only measured for less than 36%
Selective reporting (reporting bias)	Low risk	Nil reported in the protocol.
Other bias	Low risk	No other bias awarded.

ANC: antenatal clinic
CRP: C-reactive protein
Hb: haemoglobin
IU: international unit

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LMP: last menstrual period
RCT: randomised controlled trial
RE: retinol equivalents

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

Study	Reason for exclusion
Alam 2010	The intervention did not include vitamin A.
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.

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

Ahmad 2009

Trial name or title	Vitamin A and maternal-infant flu vaccine response
Methods	Placebo-controlled double-masked and randomised trial.
Participants	Inclusion criteria: • female 22-35 years; • mothers at the beginning of second trimester ~ 12 weeks' gestation; • willing to stay in Dhaka during pregnancy and willing to admit in the clinic at delivery. Exclusion criteria: • history of systemic disease; • previous complicated pregnancies or of a preterm delivery; • abortion; • congenital anomaly; • hypersensitivity to influenza vaccine or receipt of the vaccine.
Interventions	Weekly 10,000 IU vitamin A or placebo.
Outcomes	Main outcomes: IgG cord blood plasma; vitamin A cord blood; plasma influenza IgG; colostrum vitamin A; colostrum influenza sIgA Other outcomes: • mothers (6 months postpartum) serum vitamin A; • serum influ IgG; • breast milk vitamin A; • Influ sIgA; • infants (6 months) anthropometry; • serum vitamin A; • serum influ IgG; • nasal Influ sIgA.
Starting date	February 2009.
Contact information	International Centre for Diarrhoeal Disease Research, Bangladesh
Notes	66 women randomised. Setting: Dhaka, Bangladesh. 3 urban maternity clinics. 2010 - no results reported.

IgG: immunoglobulin G

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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	4		Risk Ratio (Random, 95% CI)	0.88 [0.65, 1.20]
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	2	122850	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.98, 1.10]
5 Maternal anaemia	3		Risk Ratio (Random, 95% CI)	0.64 [0.43, 0.94]
6 Maternal clinical infection	5		Risk Ratio (Random, 95% CI)	0.45 [0.20, 0.99]
7 Maternal night blindness	2		Risk Ratio (Random, 95% CI)	0.79 [0.64, 0.98]
8 Preterm birth	5	40137	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.94, 1.01]
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)	0.0 [0.0, 0.0]
11 Congenital malformations	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Low birthweight	4	14599	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.89, 1.16]

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)	0.0 [0.0, 0.0]
2 Perinatal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Neonatal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Stillbirth	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Maternal anaemia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Maternal clinical infection	2	591	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.83, 1.18]
7 Maternal night blindness	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Preterm birth	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Neonatal anaemia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Neonatal clinical infection	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Congenital malformations	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Low birthweight	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

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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)	0.0 [0.0, 0.0]
2 Perinatal mortality	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.69]
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	2	597	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.80, 1.13]
7 Maternal night blindness	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
11 Congenital malformations	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.04, 3.18]
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 Perinatal mortality (infant mortality level)	1	76176	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
1.1 Countries with low infant mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Countries with high infant mortality	1	76176	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
2 Maternal mortality (infant mortality level)	4		Risk Ratio (Random, 95% CI)	0.88 [0.65, 1.20]
2.1 Countries with low infant mortality	1		Risk Ratio (Random, 95% CI)	0.33 [0.01, 9.44]
2.2 Countries with high infant mortality	3		Risk Ratio (Random, 95% CI)	0.89 [0.64, 1.23]
3 Maternal mortality (maternal mortality level)	4	161240	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.76, 1.08]
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	3	160690	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.76, 1.08]
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)	0.0 [0.0, 0.0]
4.2 Countries with high maternal mortality	1	73743	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.88, 1.03]

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5 Maternal mortality (prevalence of vitamin A deficiency)	4	161240	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.64, 1.20]
5.1 Low prevalence of vitamin A deficiency	1	550	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.15]
5.2 High prevalence of vitamin A deficiency	3	160690	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.63, 1.23]
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)	0.0 [0.0, 0.0]
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)	4	161240	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.64, 1.20]
7.1 Countries with low HIV prevalence	4	161240	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.64, 1.20]
7.2 Countries with high HIV prevalence	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
9 Maternal mortality (dose)	3	160690	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.63, 1.23]
9.1 Daily 10,000 IU	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Others	3	160690	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.63, 1.23]
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)	0.0 [0.0, 0.0]
10.2 Others	1	76176	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
11 Maternal mortality (regimen)	4	161240	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.64, 1.20]
11.1 Daily	1	550	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.15]
11.2 Weekly	3	160690	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.63, 1.23]
11.3 Other regimen	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
13 Maternal mortality (duration of intervention)	2	60216	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.82, 1.64]
13.1 One month or less	1	550	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.15]
13.2 More than one month	1	59666	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.83, 1.68]
14 Perinatal mortality (duration of intervention)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Maternal mortality (trimester of pregnancy)	4	161240	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.64, 1.20]
15.1 Pre-pregnancy	2	101024	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.50, 1.17]
15.2 First trimester	1	59666	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.83, 1.68]
15.3 Second trimester	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.4 Third trimester	1	550	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.15]

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15.5 Mixed	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]
16.3 Second trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.4 Third trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.5 Mixed	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Maternal mortality (randomisation)	3	160690	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.63, 1.23]
17.1 Cluster-randomised	3	160690	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.63, 1.23]
17.2 Individual-randomised	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
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)	0.0 [0.0, 0.0]

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)	0.0 [0.0, 0.0]
1.1 Countries with low infant mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Countries with high infant mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Perinatal mortality (infant mortality level)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 Countries with low infant mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Countries with high infant mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Maternal mortality (maternal mortality level)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.1 Countries with low maternal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Countries with high maternal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Perinatal mortality (maternal mortality level)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.1 Countries with low maternal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Countries with high maternal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Maternal mortality (prevalence of vitamin A deficiency)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

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5.1 Low prevalence of vitamin A deficiency	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 High prevalence of vitamin A deficiency	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Perinatal mortality (prevalence of vitamin A deficiency)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.1 Low prevalence of vitamin A deficiency	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 High prevalence of vitamin A deficiency	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Maternal mortality (prevalence of HIV in the general population)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.1 Countries with low HIV prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Countries with high HIV prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Perinatal mortality (prevalence of HIV in the general population)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.1 Countries with low HIV prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Countries with high HIV prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Maternal mortality (dose)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.1 Daily 10,000 IU	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Others	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Perinatal mortality (dose)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.1 Daily 10,000 IU	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Others	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Maternal mortality (regimen)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.1 Daily	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Weekly	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 Other regimen	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Perinatal mortality (regimen)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.1 Daily	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Weekly	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 Other regimen	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Maternal mortality (duration of intervention)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Perinatal mortality (duration of intervention)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Maternal mortality (trimester of pregnancy)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.1 Pre-pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 First trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.3 Second trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.4 Third trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.5 Mixed	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Perinatal mortality (trimester of pregnancy)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.1 Pre-pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

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16.2 First trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.3 Second trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.4 Third trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.5 Mixed	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Maternal mortality (randomisation)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.1 Cluster-randomised	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Individual-randomised	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Perinatal mortality (randomisation)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.1 Cluster-randomised	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Individual-randomised	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

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)	0.0 [0.0, 0.0]
1.1 Countries with low infant mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Countries with high infant mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Perinatal mortality (infant mortality level)	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.69]
2.1 Countries with low infant mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Countries with high infant mortality	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.69]
3 Maternal mortality (maternal mortality level)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.1 Countries with low maternal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Countries with high maternal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Perinatal mortality (maternal mortality level)	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.69]
4.1 Countries with low maternal mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Countries with high maternal mortality	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.69]
5 Maternal mortality (prevalence of vitamin A deficiency)	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.69]
5.1 Low prevalence of vitamin A deficiency	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

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5.2 High prevalence of vitamin A deficiency	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.69]
6 Perinatal mortality (prevalence of vitamin A deficiency)	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.69]
6.1 Low prevalence of vitamin A deficiency	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.69]
6.2 High prevalence of vitamin A deficiency	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Maternal mortality (prevalence of HIV in the general population)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.1 Countries with low HIV prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Countries with high HIV prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Perinatal mortality (prevalence of HIV in the general population)	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.69]
8.1 Countries with low HIV prevalence	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.69]
8.2 Countries with high HIV prevalence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Maternal mortality (dose)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.1 Daily 10,000 IU	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Others	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Perinatal mortality (dose)	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.69]
10.1 Daily 10,000 IU	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Others	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.69]
11 Maternal mortality (regimen)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.1 Daily	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Weekly	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 Other regimen	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Perinatal mortality (regimen)	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.69]
12.1 Daily	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.69]
12.2 Weekly	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 Other regimen	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Maternal mortality (duration of intervention)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Perinatal mortality (duration of intervention)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Maternal mortality (trimester of pregnancy)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.1 Pre-pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 First trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.3 Second trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.4 Third trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.5 Mixed	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Perinatal mortality (trimester of pregnancy)	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.69]
16.1 Pre-pregnancy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 First trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.3 Second trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.4 Third trimester	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

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16.5 Mixed	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.69]
17 Maternal mortality (randomisation)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.1 Cluster-randomised	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Individual-randomised	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Perinatal mortality (randomisation)	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.69]
18.1 Cluster-randomised	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Individual-randomised	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.69]

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

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Green 1931	-1.10866 (1.711246)		0.8 %	0.33 [0.01, 9.44]
Kirkwood 2010	-0.08338 (0.120335)		41.5 %	0.92 [0.73, 1.16]
West 1999	-0.51083 (0.221012)		26.0 %	0.60 [0.39, 0.93]
West 2011	0.1655 (0.1795)		31.7 %	1.18 [0.83, 1.68]
Total (95% CI)			**100.0 %**	**0.88 [0.65, 1.20]**

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 6.01$, df = 3 (P = 0.11); $I^2 = 50\%$

Test for overall effect: Z = 0.80 (P = 0.42)

Test for subgroup differences: Not applicable

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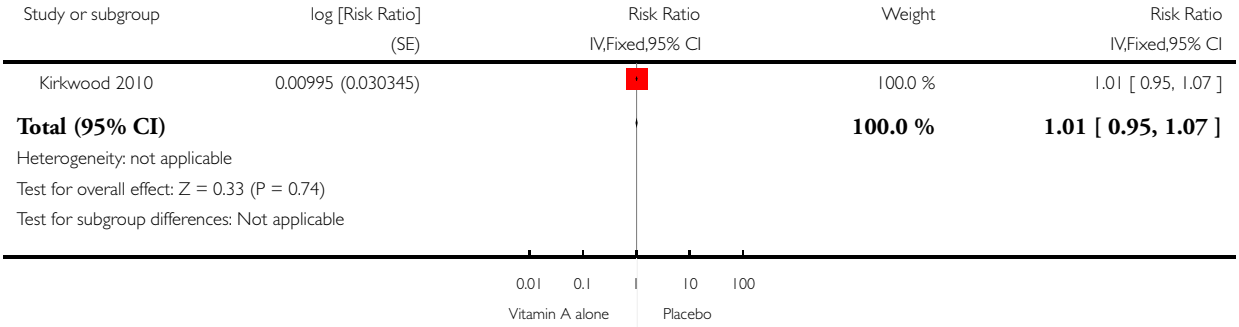
Analysis 1.2. Comparison 1 Vitamin A alone versus placebo or no treatment, Outcome 2 Perinatal mortality.

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

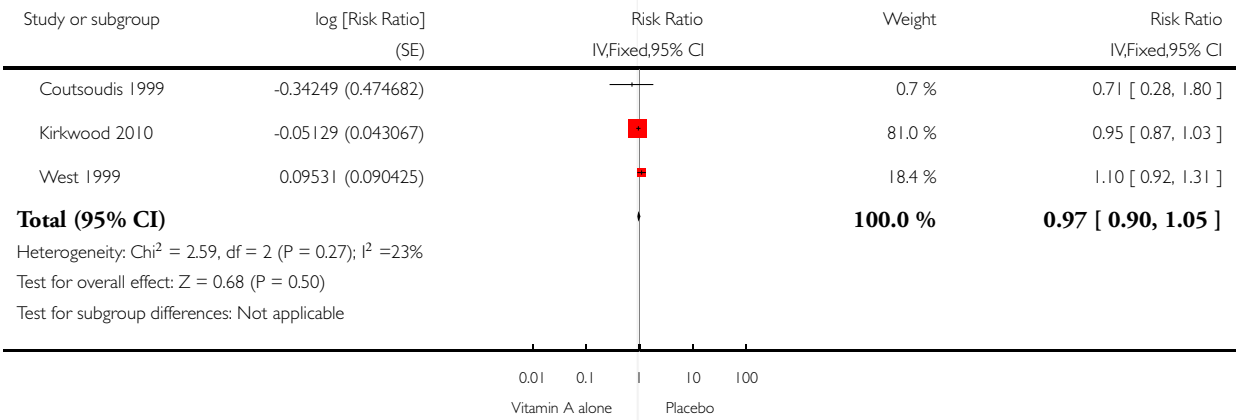


Analysis 1.3. Comparison 1 Vitamin A alone versus placebo or no treatment, Outcome 3 Neonatal mortality.

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



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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

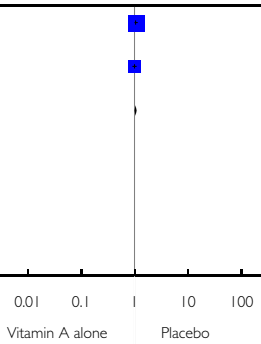
Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kirkwood 2010	1249/39512	1175/39323		55.7 %	1.06 [0.98, 1.14]
West 2011	1431/29347	703/14668		44.3 %	1.02 [0.93, 1.11]
Total (95% CI)	**68859**	**53991**		**100.0 %**	**1.04 [0.98, 1.10]**

Total events: 2680 (Vit A), 1878 (Placebo or no treatment)

Heterogeneity: Chi^2 = 0.42, df = 1 (P = 0.52); I^2 =0.0%

Test for overall effect: Z = 1.31 (P = 0.19)

Test for subgroup differences: Not applicable



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)

Test for subgroup differences: Not applicable

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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)		14.4 %	0.57 [0.13, 2.47]
Fawzi 1998	0.1986 (0.1011)		27.6 %	1.22 [1.00, 1.49]
Green 1931	-0.77653 (0.200388)		26.3 %	0.46 [0.31, 0.68]
Hakimi 1999	-1.5702 (0.6172)		17.1 %	0.21 [0.06, 0.70]
West 1999	-2.12026 (0.735802)		14.7 %	0.12 [0.03, 0.51]
Total (95% CI)			**100.0 %**	**0.45 [0.20, 0.99]**

Heterogeneity: $Tau^2 = 0.59$; $Chi^2 = 33.59$, df = 4 ($P<0.00001$); $I^2 = 88\%$

Test for overall effect: Z = 1.98 (P = 0.047)

Test for subgroup differences: Not applicable

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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,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
West 1999	-0.35677 (0.078366)		44.3 %	0.70 [0.60, 0.82]
West 2011	-0.1391 (0.028)		55.7 %	0.87 [0.82, 0.92]
Total (95% CI)			**100.0 %**	**0.79 [0.64, 0.98]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 6.84$, df = 1 (P = 0.01); $I^2 = 85\%$

Test for overall effect: Z = 2.18 (P = 0.029)

Test for subgroup differences: Not applicable

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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

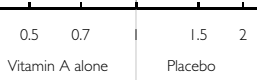
Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Coutsoudis 1999	38/335	57/326		1.3 %	0.65 [0.44, 0.95]
Green 1931	1/275	0/275		0.0 %	3.00 [0.12, 73.32]
Radhika 2003	9/64	11/58		0.3 %	0.74 [0.33, 1.66]
van den Broek 2006	29/401	13/203		0.4 %	1.13 [0.60, 2.12]
West 2011	6474/25487	3293/12713		98.1 %	0.98 [0.95, 1.02]
Total (95% CI)	**26562**	**13575**		**100.0 %**	**0.98 [0.94, 1.01]**

Total events: 6551 (Vit A), 3374 (Placebo or no treatment)

Heterogeneity: Chi^2 = 5.60, df = 4 (P = 0.23); I^2 =29%

Test for overall effect: Z = 1.30 (P = 0.19)

Test for subgroup differences: Not applicable



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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)					
Test for subgroup differences: Not applicable					

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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

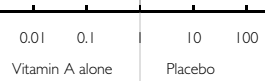
Study or subgroup	Vit A n/N	Placebo or no treatment n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Coutsoudis 1999	42/346	48/343		10.0 %	0.87 [0.59, 1.28]
Cox 2005	11/41	5/38		1.8 %	2.04 [0.78, 5.33]
Radhika 2003	10/64	12/58		2.8 %	0.76 [0.35, 1.62]
West 2011	4147/9129	2020/4580		85.5 %	1.03 [0.99, 1.07]
Total (95% CI)	**9580**	**5019**		**100.0 %**	**1.02 [0.89, 1.16]**

Total events: 4210 (Vit A), 2085 (Placebo or no treatment)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.34$, df = 3 (P = 0.34); $I^2 = 10\%$

Test for overall effect: Z = 0.24 (P = 0.81)

Test for subgroup differences: Not applicable



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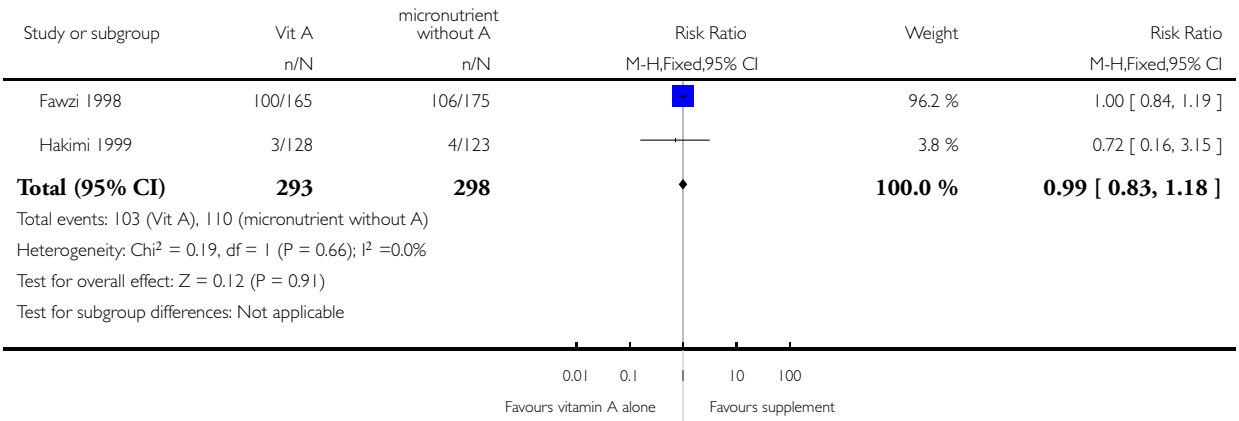
Analysis 2.6. Comparison 2 Vitamin A alone versus micronutrient supplement without vitamin A, Outcome 6 Maternal clinical infection.

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

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

Outcome: 6 Maternal clinical infection

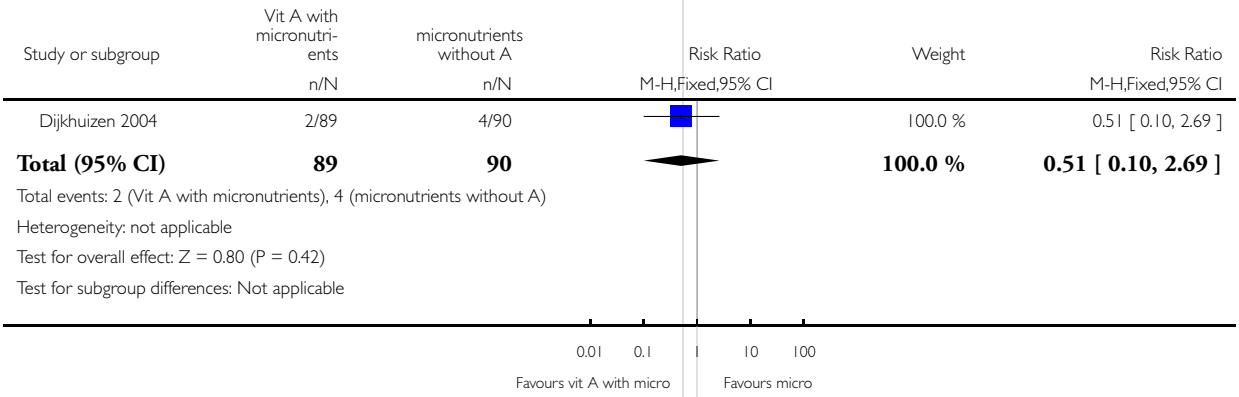


Analysis 3.2. Comparison 3 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A, Outcome 2 Perinatal mortality.

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: 2 Perinatal mortality



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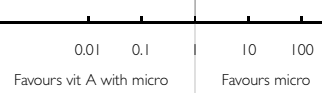
Analysis 3.3. Comparison 3 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A, Outcome 3 Neonatal mortality.

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 micronutri-ents 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)					
Test for subgroup differences: Not applicable					



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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

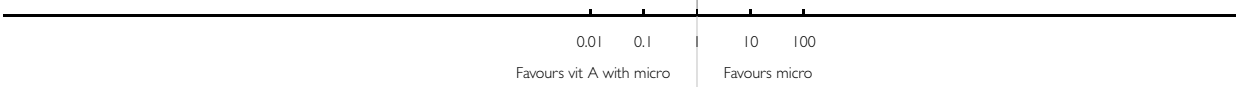
Study or subgroup	Vit A with micronutri-ents n/N	micronutrients without A n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kumwenda 2002	8/306	6/317		74.6 %	1.38 [0.48, 3.93]
Muslimatun 2001	3/122	2/121		25.4 %	1.49 [0.25, 8.75]
Total (95% CI)	**428**	**438**		**100.0 %**	**1.41 [0.57,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

Test for subgroup differences: Not applicable



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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

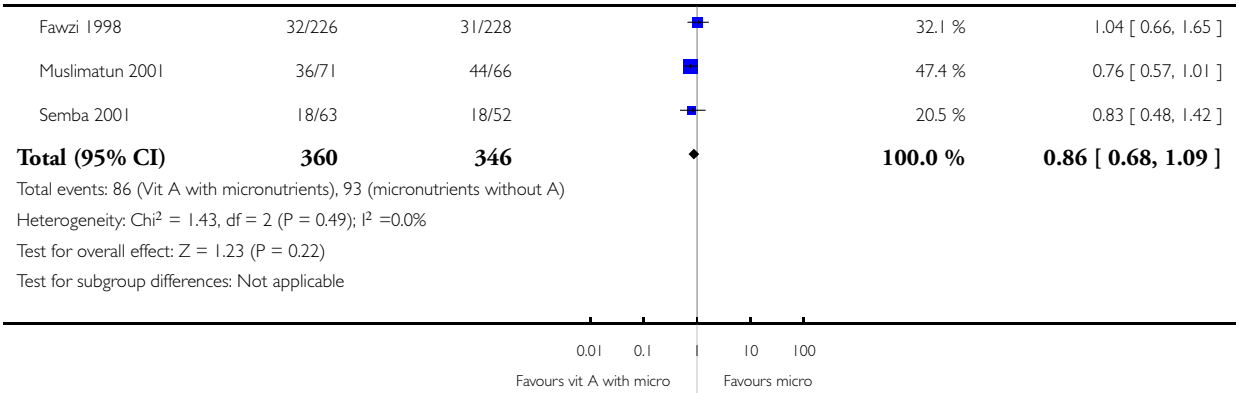
Study or subgroup	Vit A with micronutri-ents n/N	micronutrients without A n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fawzi 1998	32/226	31/228		32.1 %	1.04 [0.66, 1.65]
Muslimatun 2001	36/71	44/66		47.4 %	0.76 [0.57, 1.01]
Semba 2001	18/63	18/52		20.5 %	0.83 [0.48, 1.42]
Total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

Test for subgroup differences: Not applicable



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Analysis 3.6. Comparison 3 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A, Outcome 6 Maternal clinical infection.

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: 6 Maternal clinical infection

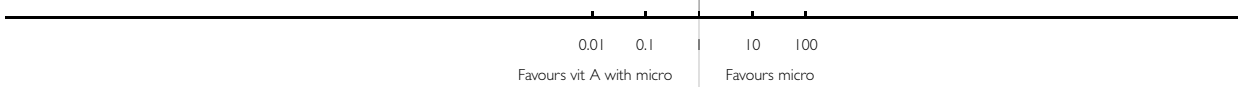
Study or subgroup	Vit A with micronutri-ents n/N	micronutrients without A n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fawzi 1998	104/173	106/175		92.2 %	0.99 [0.84, 1.18]
Hakimi 1999	4/123	9/126		7.8 %	0.46 [0.14, 1.44]
Total (95% CI)	**296**	**301**		**100.0 %**	**0.95 [0.80, 1.13]**

Total events: 108 (Vit A with micronutrients), 115 (micronutrients without A)

Heterogeneity: Chi^2 = 1.82, df = 1 (P = 0.18); I^2 =45%

Test for overall effect: Z = 0.58 (P = 0.56)

Test for subgroup differences: Not applicable



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

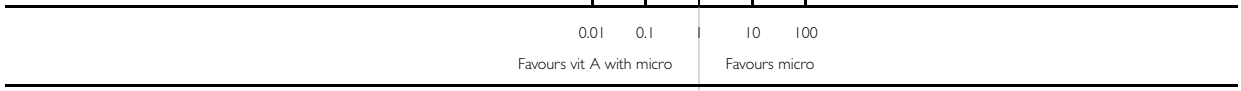
Study or subgroup	Vit A with micronutri-ents n/N	micronutrients without A n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dijkhuizen 2004	2/69	5/67		100.0 %	0.39 [0.08, 1.93]
Total (95% CI)	**69**	**67**		**100.0 %**	**0.39 [0.08, 1.93]**

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

Heterogeneity: not applicable

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

Test for subgroup differences: Not applicable



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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

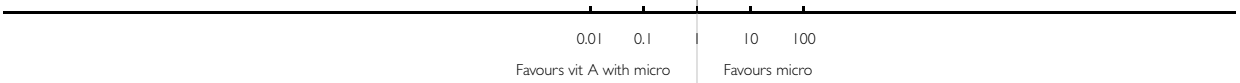
Study or subgroup	Vit A with micronutri-ents n/N	micronutrients without A n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Fawzi 1998	185/219	182/211		51.4 %	0.98 [0.91, 1.06]
Kumwenda 2002	69/297	132/325		48.6 %	0.57 [0.45, 0.73]
Total (95% CI)	**516**	**536**		**100.0 %**	**0.75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

Test for subgroup differences: Not applicable



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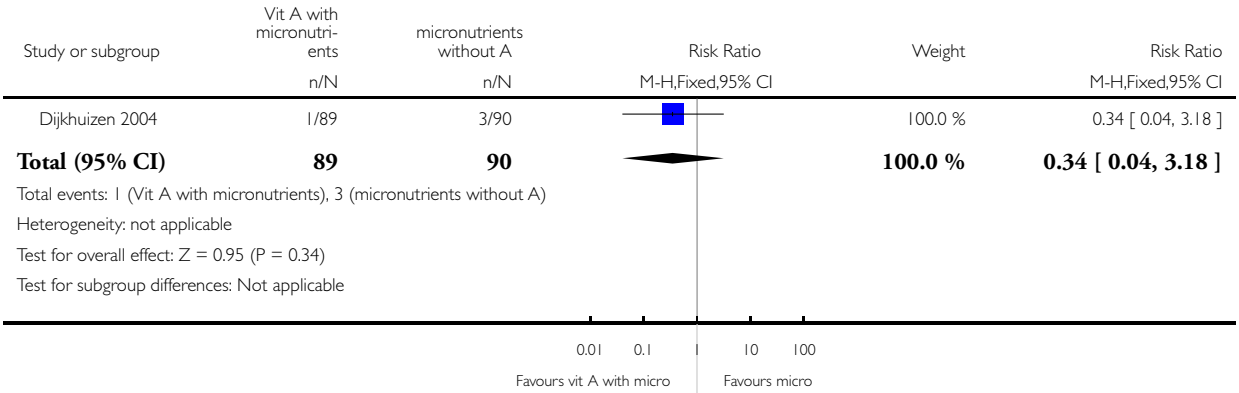
Analysis 3.11. Comparison 3 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A, Outcome 11 Congenital malformations.

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: 11 Congenital malformations

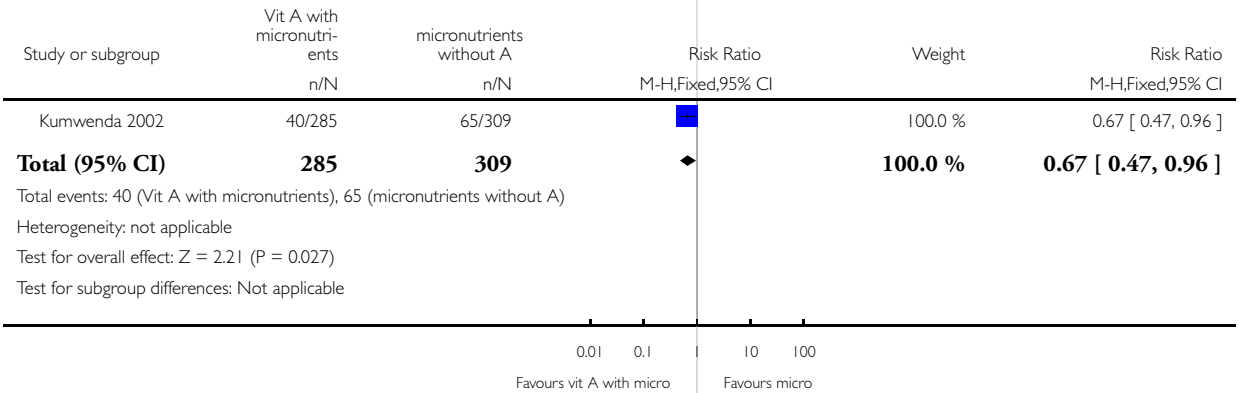


Analysis 3.12. Comparison 3 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A, Outcome 12 Low birthweight.

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



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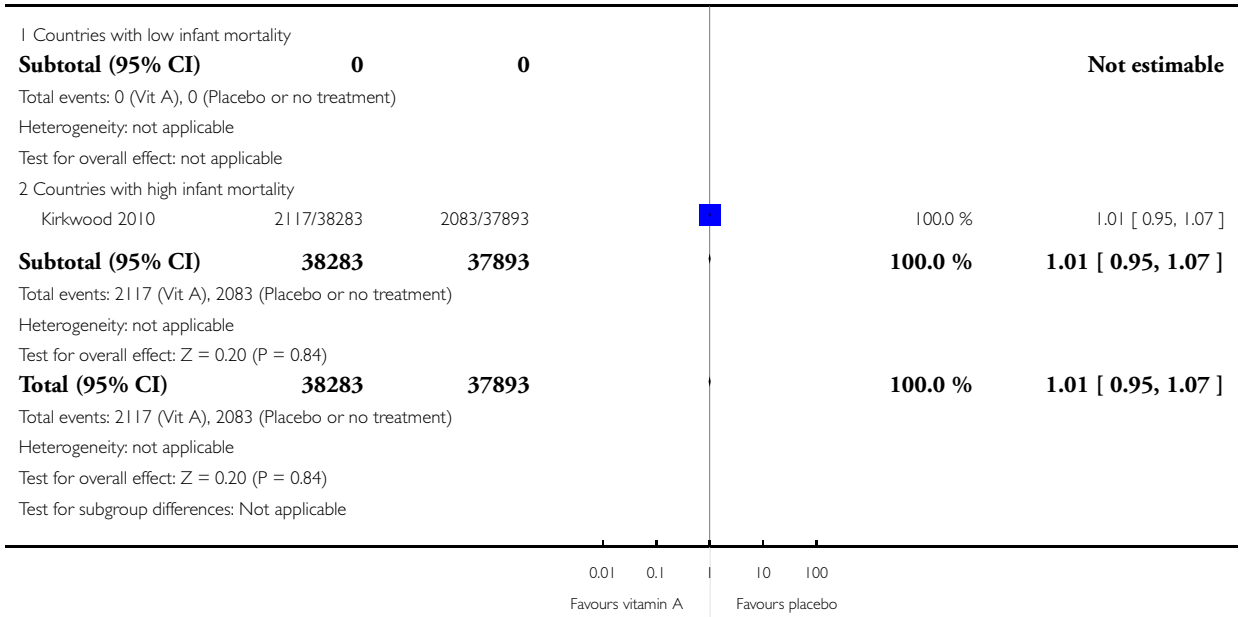
Analysis 4.1. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 1 Perinatal mortality (infant mortality level).

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

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

Outcome: 1 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**			**Not estimable**
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)					
Test for subgroup differences: Not applicable					



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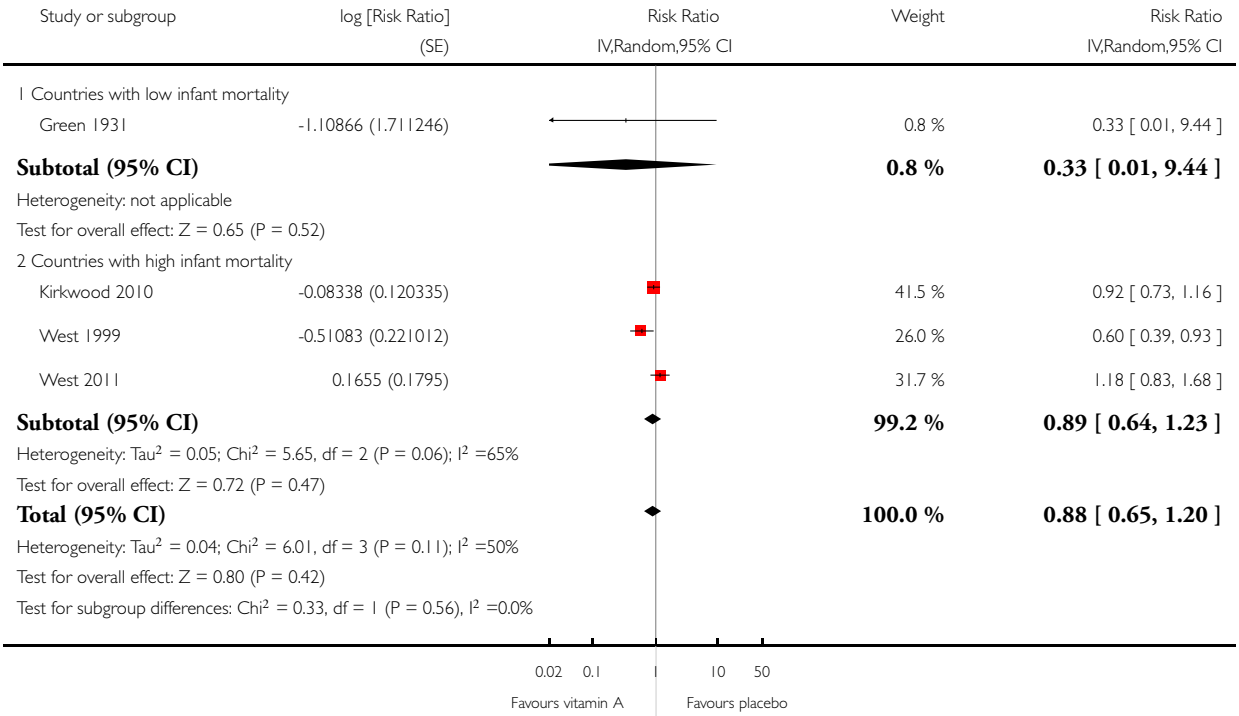
Analysis 4.2. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 2 Maternal mortality (infant mortality level).

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

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

Outcome: 2 Maternal mortality (infant mortality level)



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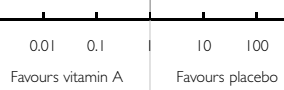
Analysis 4.3. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 3 Maternal mortality (maternal mortality level).

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)

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					
Green 1931	0/275	1/275		0.6 %	0.33 [0.01, 8.15]
Subtotal (95% CI)	**275**	**275**		**0.6 %**	**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 Countries with high maternal mortality					
Kirkwood 2010	138/39601	148/39234		55.7 %	0.92 [0.73, 1.16]
West 1999	53/14948	43/7241		21.7 %	0.60 [0.40, 0.89]
West 2011	104/39804	44/19862		22.0 %	1.18 [0.83, 1.68]
Subtotal (95% CI)	**94353**	**66337**		**99.4 %**	**0.91 [0.76, 1.08]**
Total events: 295 (Vit A), 235 (Placebo or no treatment)					
Heterogeneity: Chi^2 = 6.34, df = 2 (P = 0.04); I^2 =68%					
Test for overall effect: Z = 1.08 (P = 0.28)					
Total (95% CI)	**94628**	**66612**		**100.0 %**	**0.91 [0.76, 1.08]**
Total events: 295 (Vit A), 236 (Placebo or no treatment)					
Heterogeneity: Chi^2 = 6.71, df = 3 (P = 0.08); I^2 =55%					
Test for overall effect: Z = 1.12 (P = 0.26)					
Test for subgroup differences: Chi^2 = 0.38, df = 1 (P = 0.54), I^2 =0.0%					



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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**			**Not estimable**
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)					
Test for subgroup differences: Not applicable					

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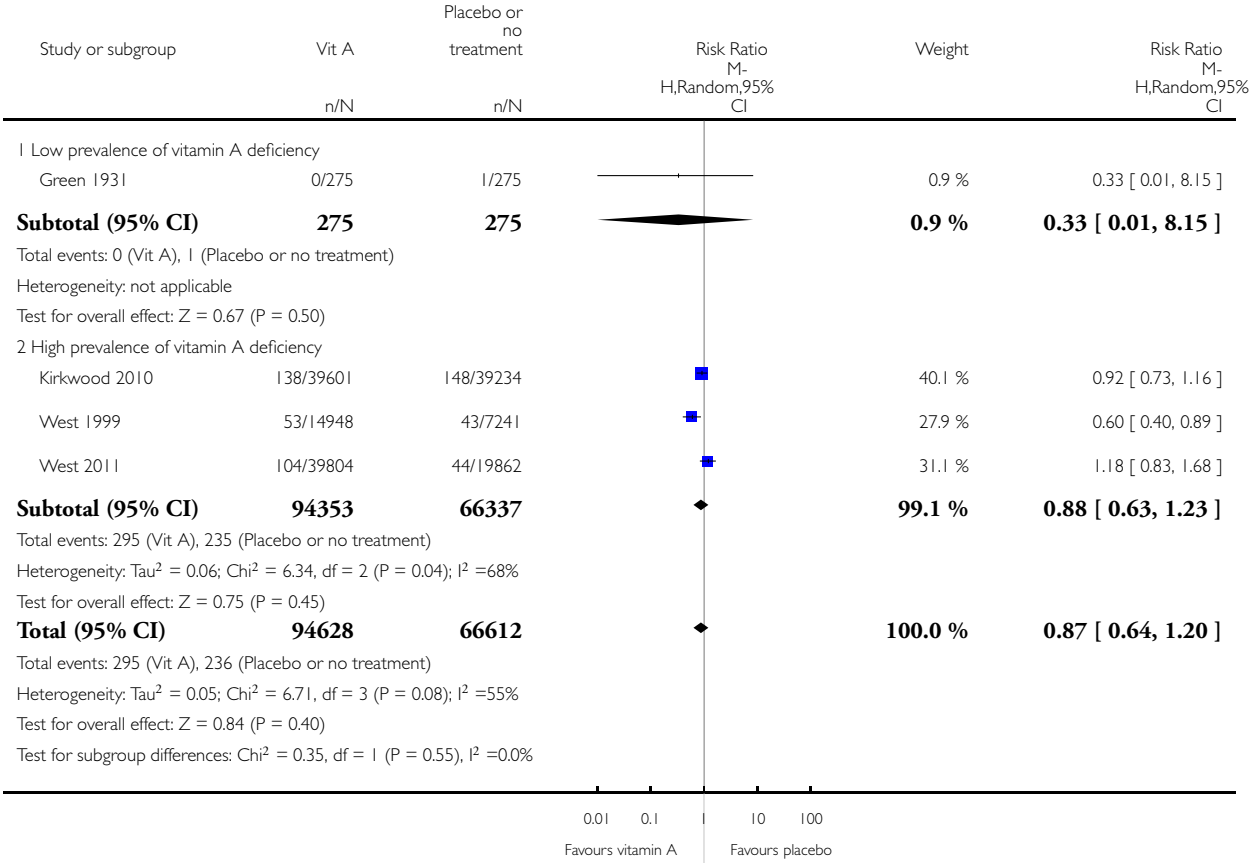
Analysis 4.5. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 5 Maternal mortality (prevalence of vitamin A deficiency).

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)



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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**			**Not estimable**
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)					
Test for subgroup differences: Not applicable					

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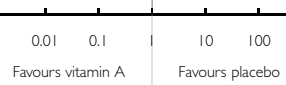
Analysis 4.7. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 7 Maternal mortality (prevalence of HIV in the general population).

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,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Countries with low HIV prevalence					
Green 1931	0/275	1/275		0.9 %	0.33 [0.01, 8.15]
Kirkwood 2010	138/39601	148/39234		40.1 %	0.92 [0.73, 1.16]
West 1999	53/14948	43/7241		27.9 %	0.60 [0.40, 0.89]
West 2011	104/39804	44/19862		31.1 %	1.18 [0.83, 1.68]
Subtotal (95% CI)	**94628**	**66612**		**100.0 %**	**0.87 [0.64, 1.20]**
Total events: 295 (Vit A), 236 (Placebo or no treatment)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 6.71$, df = 3 (P = 0.08); $I^2 = 55\%$					
Test for overall effect: Z = 0.84 (P = 0.40)					
2 Countries with high HIV prevalence					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**94628**	**66612**		**100.0 %**	**0.87 [0.64, 1.20]**
Total events: 295 (Vit A), 236 (Placebo or no treatment)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 6.71$, df = 3 (P = 0.08); $I^2 = 55\%$					
Test for overall effect: Z = 0.84 (P = 0.40)					
Test for subgroup differences: Not applicable					



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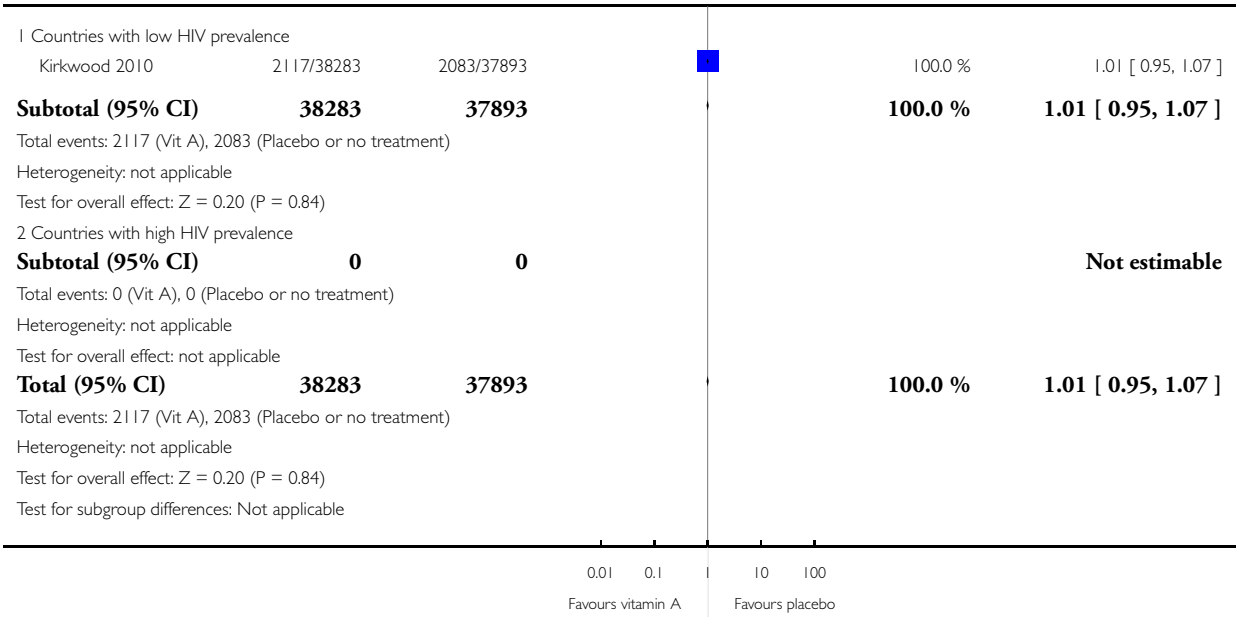
Analysis 4.8. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 8 Perinatal mortality (prevalence of HIV in the general population).

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**			**Not estimable**
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)					
Test for subgroup differences: Not applicable					



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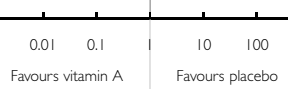
Analysis 4.9. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 9 Maternal mortality (dose).

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,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Daily 10,000 IU					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
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		39.7 %	0.92 [0.73, 1.16]
West 1999	53/14948	43/7241		28.6 %	0.60 [0.40, 0.89]
West 2011	104/39804	44/19862		31.7 %	1.18 [0.83, 1.68]
Subtotal (95% CI)	**94353**	**66337**		**100.0 %**	**0.88 [0.63, 1.23]**
Total events: 295 (Vit A), 235 (Placebo or no treatment)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 6.34$, df = 2 (P = 0.04); $I^2 = 68\%$					
Test for overall effect: Z = 0.75 (P = 0.45)					
Total (95% CI)	**94353**	**66337**		**100.0 %**	**0.88 [0.63, 1.23]**
Total events: 295 (Vit A), 235 (Placebo or no treatment)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 6.34$, df = 2 (P = 0.04); $I^2 = 68\%$					
Test for overall effect: Z = 0.75 (P = 0.45)					
Test for subgroup differences: Not applicable					



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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**			**Not estimable**
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)					
Test for subgroup differences: Not applicable					

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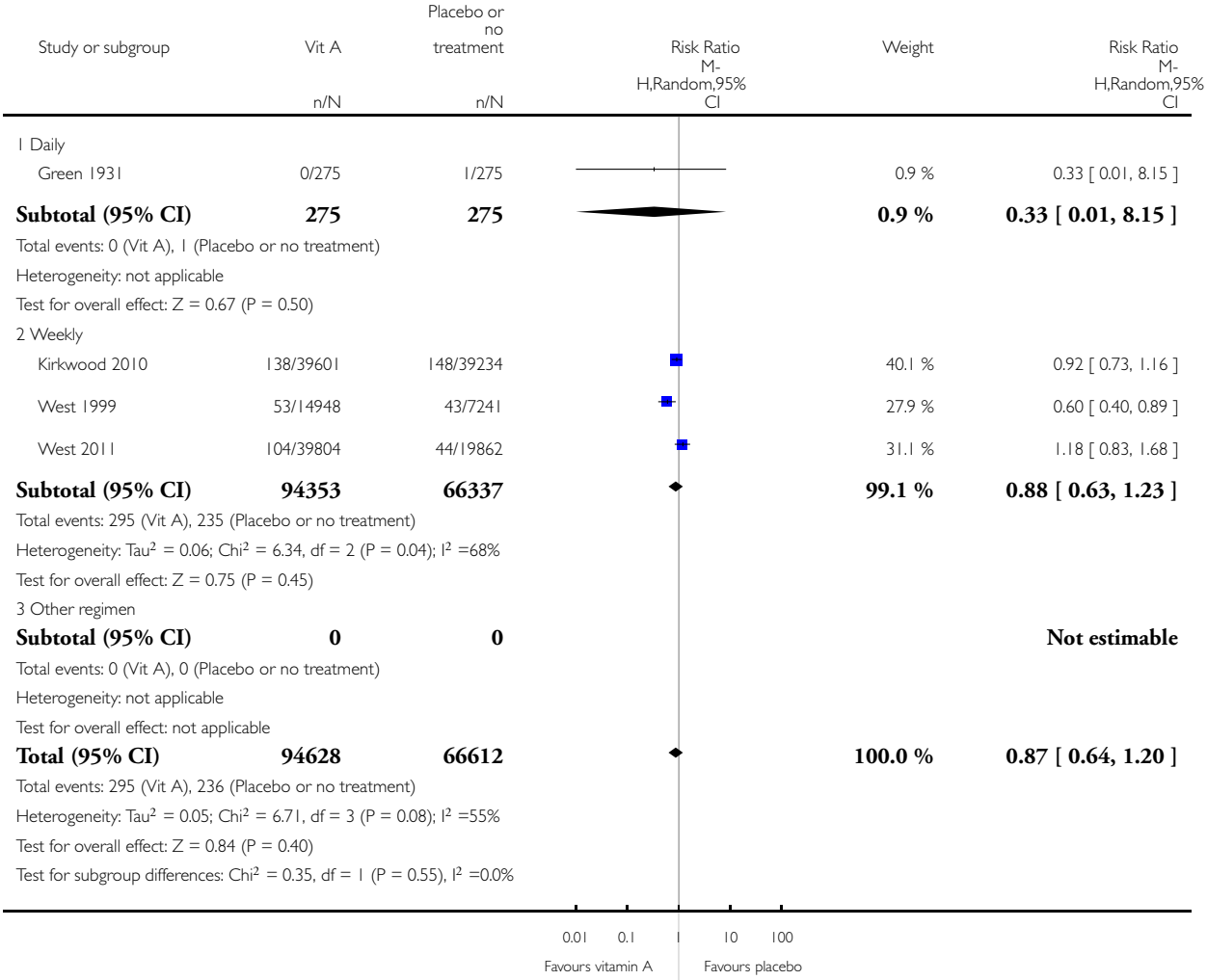
Analysis 4.11. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 11 Maternal mortality (regimen).

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)



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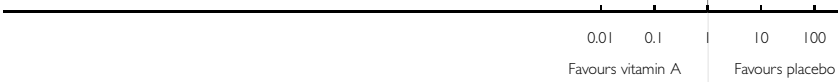
Analysis 4.12. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 12 Perinatal mortality (regimen).

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**			**Not estimable**
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**			**Not estimable**
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)					
Test for subgroup differences: Not applicable					



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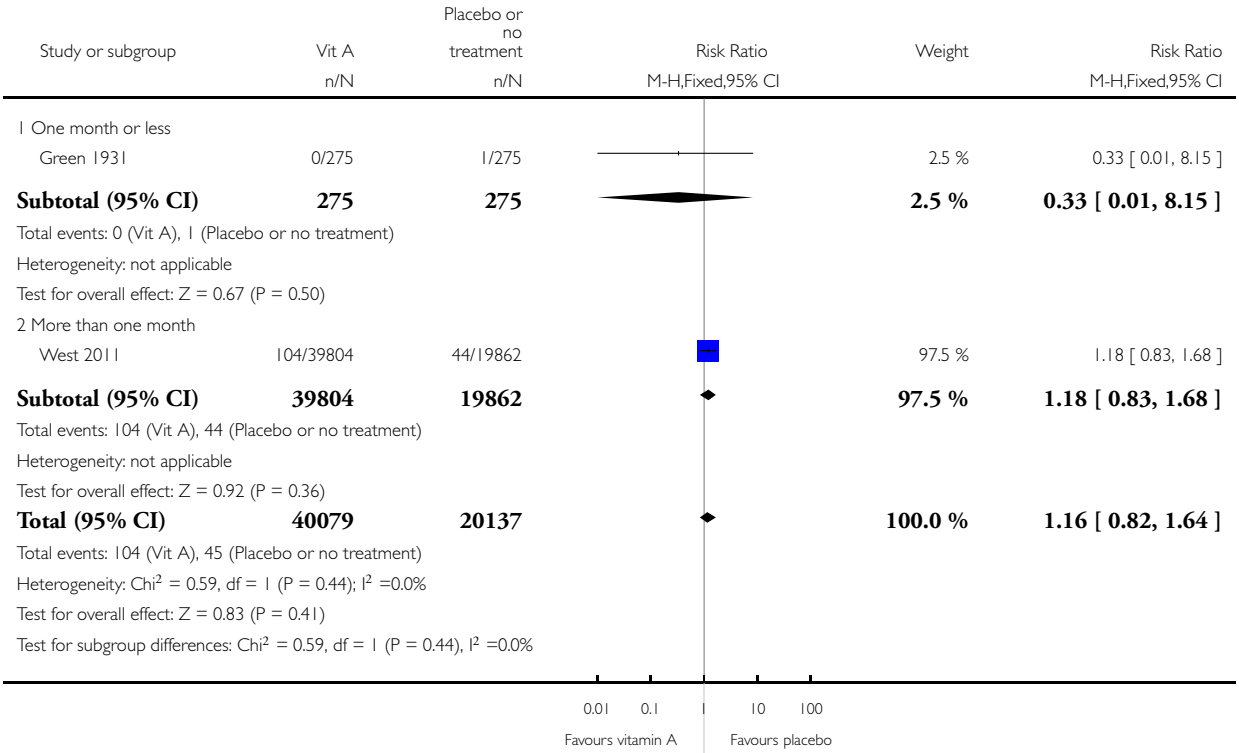
Analysis 4.13. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 13 Maternal mortality (duration of intervention).

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)



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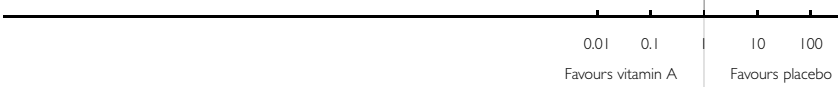
Analysis 4.15. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 15 Maternal mortality (trimester of pregnancy).

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,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Pre-pregnancy					
Kirkwood 2010	138/39601	148/39234		40.1 %	0.92 [0.73, 1.16]
West 1999	53/14948	43/7241		27.9 %	0.60 [0.40, 0.89]
Subtotal (95% CI)	**54549**	**46475**		**67.9 %**	**0.77 [0.50, 1.17]**
Total events: 191 (Vit A), 191 (Placebo or no treatment)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 3.41, df = 1 (P = 0.06); I^2 =71%					
Test for overall effect: Z = 1.23 (P = 0.22)					
2 First trimester					
West 2011	104/39804	44/19862		31.1 %	1.18 [0.83, 1.68]
Subtotal (95% CI)	**39804**	**19862**		**31.1 %**	**1.18 [0.83, 1.68]**
Total events: 104 (Vit A), 44 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.92 (P = 0.36)					
3 Second trimester					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
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		0.9 %	0.33 [0.01, 8.15]
Subtotal (95% CI)	**275**	**275**		**0.9 %**	**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**			**Not estimable**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**94628**	**66612**		**100.0 %**	**0.87 [0.64, 1.20]**
Total events: 295 (Vit A), 236 (Placebo or no treatment)					
Heterogeneity: Tau^2 = 0.05; Chi^2 = 6.71, df = 3 (P = 0.08); I^2 =55%					
Test for overall effect: Z = 0.84 (P = 0.40)					
Test for subgroup differences: Chi^2 = 2.79, df = 2 (P = 0.25), I^2 =28%					



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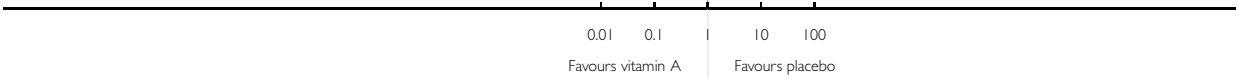
Analysis 4.16. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 16 Perinatal mortality (trimester of pregnancy).

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**			**Not estimable**
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**			**Not estimable**
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**			**Not estimable**
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**			**Not estimable**
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)					
Test for subgroup differences: Not applicable					



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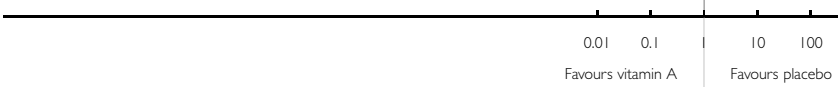
Analysis 4.17. Comparison 4 Vitamin A alone versus placebo or no treatment (subgroups), Outcome 17 Maternal mortality (randomisation).

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,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Cluster-randomised					
Kirkwood 2010	138/39601	148/39234		39.7 %	0.92 [0.73, 1.16]
West 1999	53/14948	43/7241		28.6 %	0.60 [0.40, 0.89]
West 2011	104/39804	44/19862		31.7 %	1.18 [0.83, 1.68]
Subtotal (95% CI)	**94353**	**66337**		**100.0 %**	**0.88 [0.63, 1.23]**
Total events: 295 (Vit A), 235 (Placebo or no treatment)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 6.34$, df = 2 (P = 0.04); $I^2 = 68\%$					
Test for overall effect: Z = 0.75 (P = 0.45)					
2 Individual-randomised					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vit A), 0 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**94353**	**66337**		**100.0 %**	**0.88 [0.63, 1.23]**
Total events: 295 (Vit A), 235 (Placebo or no treatment)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 6.34$, df = 2 (P = 0.04); $I^2 = 68\%$					
Test for overall effect: Z = 0.75 (P = 0.45)					
Test for subgroup differences: Not applicable					



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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**			**Not estimable**
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)					
Test for subgroup differences: Not applicable					

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Analysis 6.2. Comparison 6 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A (subgroups), Outcome 2 Perinatal mortality (infant mortality level).

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

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

Outcome: 2 Perinatal mortality (infant mortality level)

Study or subgroup	Vit A with micronutri-ents n/N	micronutrients without A 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**			**Not estimable**
Total events: 0 (Vit A with micronutrients), 0 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Countries with high infant mortality					
Dijkhuizen 2004	2/89	4/90		100.0 %	0.51 [0.10, 2.69]
Subtotal (95% CI)	**89**	**90**		**100.0 %**	**0.51 [0.10, 2.69]**
Total events: 2 (Vit A with micronutrients), 4 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
Total (95% CI)	**89**	**90**		**100.0 %**	**0.51 [0.10, 2.69]**
Total events: 2 (Vit A with micronutrients), 4 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
Test for subgroup differences: Not applicable					

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Analysis 6.4. Comparison 6 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A (subgroups), Outcome 4 Perinatal mortality (maternal mortality level).

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

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

Outcome: 4 Perinatal mortality (maternal mortality level)

Study or subgroup	Vit A with micronutri-ents n/N	micronutrients without A 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**			**Not estimable**
Total events: 0 (Vit A with micronutrients), 0 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Countries with high maternal mortality					
Dijkhuizen 2004	2/89	4/90		100.0 %	0.51 [0.10, 2.69]
Subtotal (95% CI)	**89**	**90**		**100.0 %**	**0.51 [0.10, 2.69]**
Total events: 2 (Vit A with micronutrients), 4 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
Total (95% CI)	**89**	**90**		**100.0 %**	**0.51 [0.10, 2.69]**
Total events: 2 (Vit A with micronutrients), 4 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
Test for subgroup differences: Not applicable					

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Analysis 6.5. Comparison 6 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A (subgroups), Outcome 5 Maternal mortality (prevalence of vitamin A deficiency).

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

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

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

Study or subgroup	Vit A with micronutri-ents n/N	micronutrients without A 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**			**Not estimable**
Total events: 0 (Vit A with micronutrients), 0 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 High prevalence of vitamin A deficiency					
Dijkhuizen 2004	2/89	4/90		100.0 %	0.51 [0.10, 2.69]
Subtotal (95% CI)	**89**	**90**		**100.0 %**	**0.51 [0.10, 2.69]**
Total events: 2 (Vit A with micronutrients), 4 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
Total (95% CI)	**89**	**90**		**100.0 %**	**0.51 [0.10, 2.69]**
Total events: 2 (Vit A with micronutrients), 4 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
Test for subgroup differences: Not applicable					

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Analysis 6.6. Comparison 6 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A (subgroups), Outcome 6 Perinatal mortality (prevalence of vitamin A deficiency).

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

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

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

Study or subgroup	Vit A with micronutri-ents n/N	micronutrients without A n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low prevalence of vitamin A deficiency					
Dijkhuizen 2004	2/89	4/90		100.0 %	0.51 [0.10, 2.69]
Subtotal (95% CI)	**89**	**90**		**100.0 %**	**0.51 [0.10, 2.69]**
Total events: 2 (Vit A with micronutrients), 4 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
2 High prevalence of vitamin A deficiency					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vit A with micronutrients), 0 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**89**	**90**		**100.0 %**	**0.51 [0.10, 2.69]**
Total events: 2 (Vit A with micronutrients), 4 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
Test for subgroup differences: Not applicable					

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Analysis 6.8. Comparison 6 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A (subgroups), Outcome 8 Perinatal mortality (prevalence of HIV in the general population).

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

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

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

Study or subgroup	Vit A with micronutri-ents n/N	micronutrients without A n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Countries with low HIV prevalence					
Dijkhuizen 2004	2/89	4/90		100.0 %	0.51 [0.10, 2.69]
Subtotal (95% CI)	**89**	**90**		**100.0 %**	**0.51 [0.10, 2.69]**
Total events: 2 (Vit A with micronutrients), 4 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
2 Countries with high HIV prevalence					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vit A with micronutrients), 0 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**89**	**90**		**100.0 %**	**0.51 [0.10, 2.69]**
Total events: 2 (Vit A with micronutrients), 4 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
Test for subgroup differences: Not applicable					

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Analysis 6.10. Comparison 6 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A (subgroups), Outcome 10 Perinatal mortality (dose).

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

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

Outcome: 10 Perinatal mortality (dose)

Study or subgroup	Vit A with micronutri-ents n/N	micronutrients without A 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**			**Not estimable**
Total events: 0 (Vit A with micronutrients), 0 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Others					
Dijkhuizen 2004	2/89	4/90		100.0 %	0.51 [0.10, 2.69]
Subtotal (95% CI)	**89**	**90**		**100.0 %**	**0.51 [0.10, 2.69]**
Total events: 2 (Vit A with micronutrients), 4 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
Total (95% CI)	**89**	**90**		**100.0 %**	**0.51 [0.10, 2.69]**
Total events: 2 (Vit A with micronutrients), 4 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
Test for subgroup differences: Not applicable					

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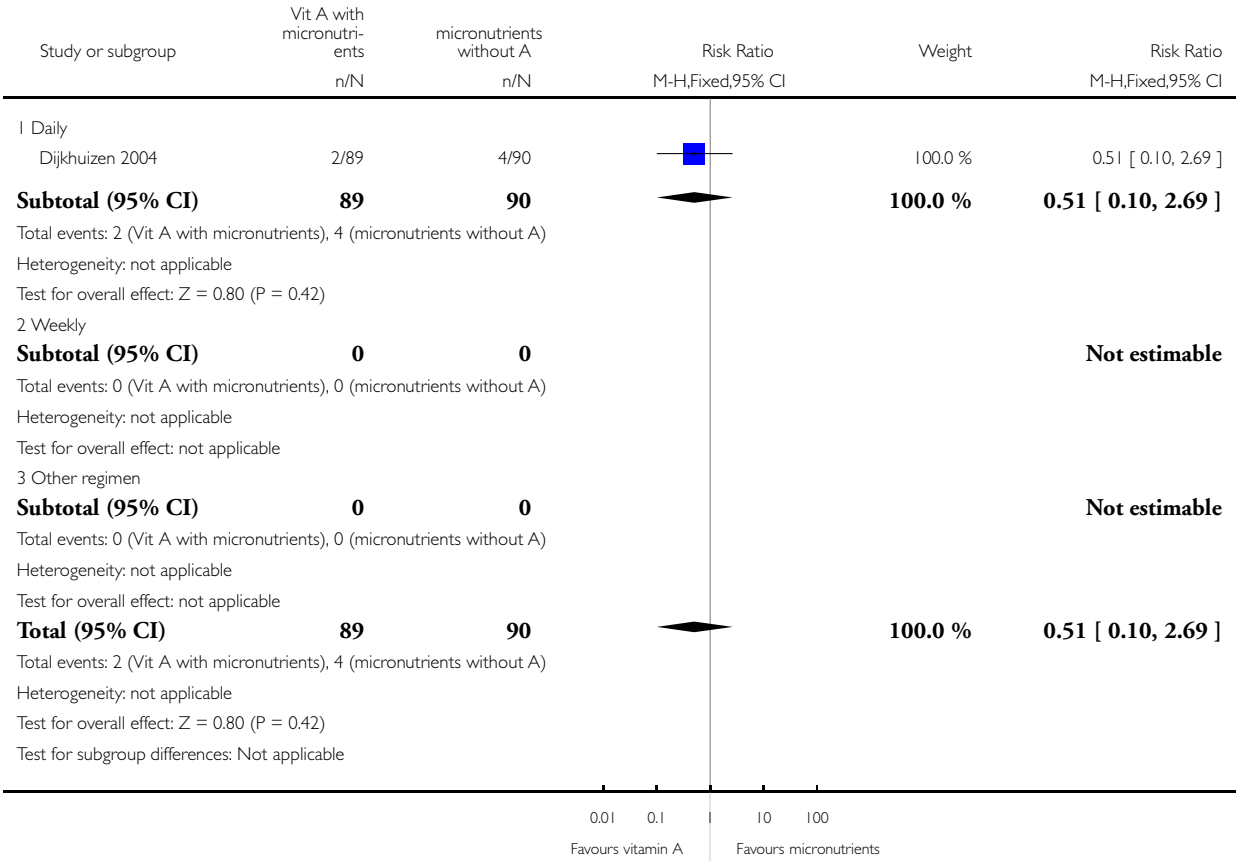
Analysis 6.12. Comparison 6 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A (subgroups), Outcome 12 Perinatal mortality (regimen).

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

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

Outcome: 12 Perinatal mortality (regimen)

Study or subgroup	Vit A with micronutri-ents n/N	micronutrients without A n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Daily					
Dijkhuizen 2004	2/89	4/90		100.0 %	0.51 [0.10, 2.69]
Subtotal (95% CI)	**89**	**90**		**100.0 %**	**0.51 [0.10, 2.69]**
Total events: 2 (Vit A with micronutrients), 4 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
2 Weekly					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vit A with micronutrients), 0 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Other regimen					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vit A with micronutrients), 0 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**89**	**90**		**100.0 %**	**0.51 [0.10, 2.69]**
Total events: 2 (Vit A with micronutrients), 4 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
Test for subgroup differences: Not applicable					



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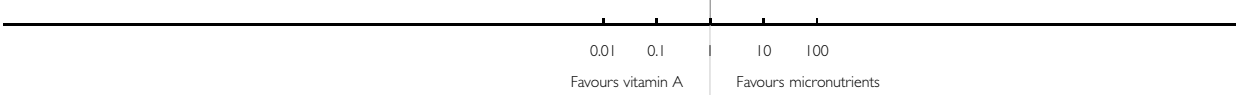
Analysis 6.16. Comparison 6 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A (subgroups), Outcome 16 Perinatal mortality (trimester of pregnancy).

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

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

Outcome: 16 Perinatal mortality (trimester of pregnancy)

Study or subgroup	Vit A with micronutri-ents n/N	micronutrients without A n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Pre-pregnancy					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vit A with micronutrients), 0 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 First trimester					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vit A with micronutrients), 0 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Second trimester					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vit A with micronutrients), 0 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Third trimester					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vit A with micronutrients), 0 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
5 Mixed					
Dijkhuizen 2004	2/89	4/90		100.0 %	0.51 [0.10, 2.69]
Subtotal (95% CI)	**89**	**90**		**100.0 %**	**0.51 [0.10, 2.69]**
Total events: 2 (Vit A with micronutrients), 4 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
Total (95% CI)	**89**	**90**		**100.0 %**	**0.51 [0.10, 2.69]**
Total events: 2 (Vit A with micronutrients), 4 (micronutrients without A)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
Test for subgroup differences: Not applicable					



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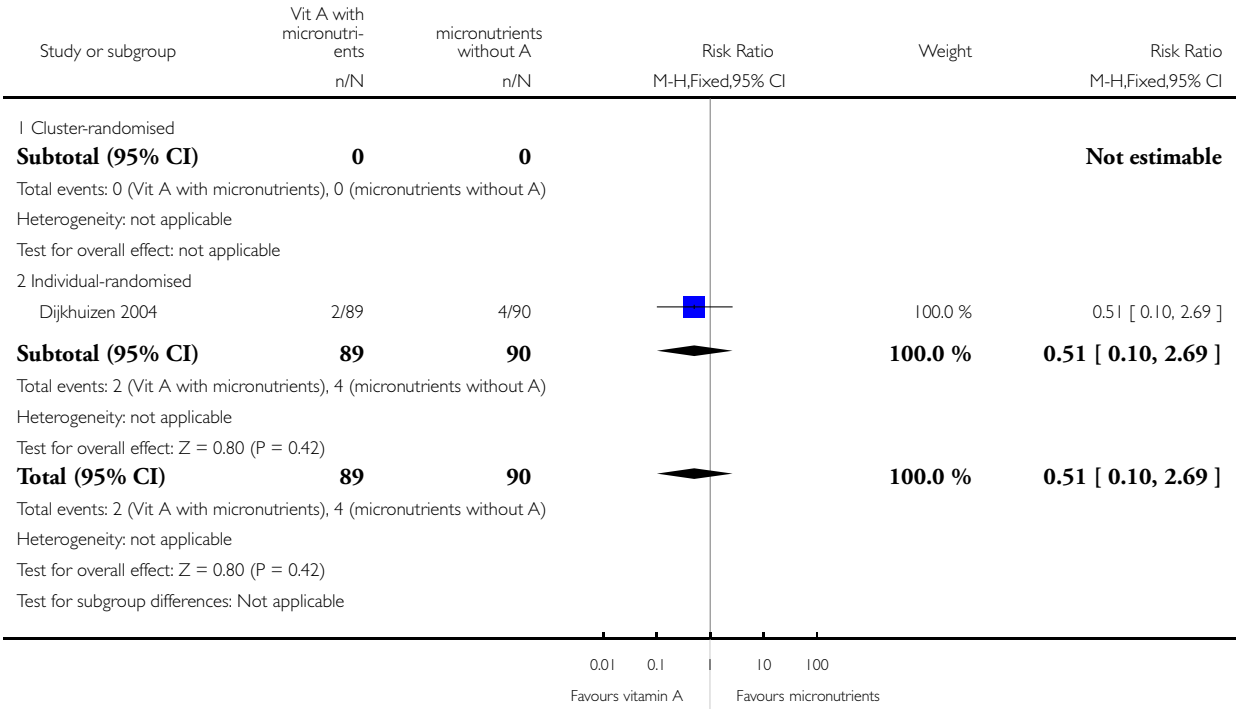
Analysis 6.18. Comparison 6 Vitamin A with other micronutrients versus micronutrient supplements without vitamin A (subgroups), Outcome 18 Perinatal mortality (randomisation).

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

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

Outcome: 18 Perinatal mortality (randomisation)



ADDITIONAL TABLES

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

IU: international units

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Table 2. Serum retinol conversion table

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

WHAT'S NEW

Last assessed as up-to-date: 30 March 2015.

Date	Event	Description
30 March 2015	New search has been performed	Search updated. Methods updated. 'Summary of findings' tables have been incorporated for this update
30 March 2015	New citation required but conclusions have not changed	Three new studies have been included in this update (Hakimi 1999; Sun 2010; West 2011). The review now includes a total of 19 studies. The conclusions remain the same

HISTORY

Protocol first published: Issue 9, 2010

Review first published: Issue 11, 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%

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CONTRIBUTIONS OF AUTHORS

M McCauley and M Othman carried out the data extraction, which was checked by N van den Broek and L Dou. L Dou performed the statistical analysis and contributed to the text of the review. This review was written by M McCauley, adapted from the original protocol for van den Broek 2010 and reviewed at draft and final manuscript by N van den Broek.

DECLARATIONS OF INTEREST

N van den Broek is an investigator in the included trial van den Broek 2006 and did not perform any assessment or data extraction for this trial.

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.

- UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Methods updated to current standard text of Cochrane Pregnancy and Childbirth. 'Summary of findings' tables have been incorporated for the 2015 update.

INDEX TERMS

Medical Subject Headings (MeSH)

Anemia [prevention & control]; Infant Mortality; 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; Infant, Newborn; Pregnancy

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