Cochrane Library

Cochrane Database of Systematic Reviews

Vitamin A supplementation for postpartum women (Review)

Oliveira-Menegozzo JM, Bergamaschi DP, Middleton P, East CE

Oliveira-Menegozzo JM, Bergamaschi DP, Middleton P, East CE.
Vitamin A supplementation for postpartum women.
Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD005944.
DOI: 10.1002/14651858.CD005944.pub2.

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER . . . 1
ABSTRACT . . . 1
PLAIN LANGUAGE SUMMARY . . . 2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON . . . 3
BACKGROUND . . . 6
OBJECTIVES . . . 8
METHODS . . . 8
RESULTS . . . 11
Figure 1. . . . 12
Figure 2. . . . 13
DISCUSSION . . . 17
AUTHORS' CONCLUSIONS . . . 19
ACKNOWLEDGEMENTS . . . 19
REFERENCES . . . 19
CHARACTERISTICS OF STUDIES . . . 23
DATA AND ANALYSES . . . 41
Analysis 1.1. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 1 Maternal mortality to six months. . . . 47
Analysis 1.5. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 5 Maternal adverse effects of supplementation. . . . 48
Analysis 1.6. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 6 Maternal serum retinol (μmol/L) at 1.5 months postpartum. . . . 50
Analysis 1.7. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 7 Maternal serum retinol (mcmol/L) at 3 - 3.5 months postpartum. . . . 51
Analysis 1.8. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 8 Maternal serum retinol (mcmol/L) at 6 - 6.5 months postpartum. . . . 52
Analysis 1.9. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 9 Maternal serum retinol (mcmol/L) at 9 months postpartum. . . . 53
Analysis 1.10. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 10 Maternal low hepatic vitamin A stores 3 months postpartum (MRDR $\geq$ 0.06). . . 54
Analysis 1.11. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 11 Maternal low hepatic vitamin A stores 5 - 6 months postpartum (MRDR $\geq$ 0.06). 55
Analysis 1.12. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 12 Maternal low hepatic vitamin A stores 9 months postpartum (MRDR $\geq$ 0.06). . 56
Analysis 1.13. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 13 Maternal low hepatic vitamin A stores 3 months postpartum (RDR > 20%). . . 57
Analysis 1.14. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 14 Maternal low hepatic vitamin A stores 6 months postpartum (RDR > 20%). . . 57
Analysis 1.15. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 15 Breast milk retinol (mcmol/L) at 3 - 3.5 months postpartum. . . . 58
Analysis 1.16. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 16 Breast milk retinol (mcmol/L) at 6 - 6.5 months postpartum. . . . 59
Analysis 1.17. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 17 Breast milk retinol (mcmol/L) at 8 - 9 months postpartum. . . . 60
Analysis 1.18. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 18 Breast milk retinol (< 1.05 mcmol/L) at 3 months postpartum. . . . 61
Analysis 1.19. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 19 Breast milk retinol (< 1.05 mcmol/L) at 6 months postpartum. . . . 62
Analysis 1.20. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 20 Breast milk retinol (< 1.05 mcmol/L) at 8-9 months postpartum. . . . 63

Analysis 1.21. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 21 Breast milk retinol (< 0.28 mcmol/g of fat) at 3 months postpartum. 64
Analysis 1.22. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 22 Breast milk retinol (< 0.28 mcmol/g of fat) at 6 months postpartum. 65
Analysis 1.23. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 23 Breast milk retinol (< 0.28 mcmol/g of fat) at 9 months postpartum. 66
Analysis 1.24. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 24 Maternal abnormal conjunctival impression cytology 3 months postpartum. . . 67
Analysis 1.25. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 25 Maternal abnormal conjunctival impression cytology 6 months postpartum. . . 67
Analysis 1.26. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 26 Infant mortality. 68
Analysis 1.27. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 27 Infant diarrhoea (one or more episodes) to 12 months. 69
Analysis 1.29. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 29 Infant gastroenteritis to 3 months. 70
Analysis 1.30. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 30 Infant acute respiratory infection (one or more episodes) to 12 months. 70
Analysis 1.31. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 31 Infant upper respiratory tract infection to 3 months. 71
Analysis 1.34. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 34 Infant adverse effects of supplementation. 72
Analysis 1.35. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 35 Infant serum retinol (μmol/L) at 2 - 3.5 months postpartum. 73
Analysis 1.36. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 36 Infant serum retinol (μmol/L) at 5 - 6 months postpartum. 74
Analysis 1.37. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 37 Infant low hepatic vitamin A stores 1.5 months postpartum (MRDR ≥ 0.06). . . 75
Analysis 1.38. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 38 Infant low hepatic vitamin A stores at 5 - 6.5 months postpartum. 76
Analysis 2.1. Comparison 2 Supplement (vitamin A as retinyl) high dose versus low dose, Outcome 1 Infant mortality. 77
Analysis 2.2. Comparison 2 Supplement (vitamin A as retinyl) high dose versus low dose, Outcome 2 Maternal serum retinol (mol/L). 78
Analysis 2.3. Comparison 2 Supplement (vitamin A as retinyl) high dose versus low dose, Outcome 3 Breast milk retinol (< 1.05 mol/L). 79
Analysis 2.4. Comparison 2 Supplement (vitamin A as retinyl) high dose versus low dose, Outcome 4 Infant serum retinol (mol/L) at 2 months postpartum. 80
APPENDICES 80
HISTORY 81
CONTRIBUTIONS OF AUTHORS 81
DECLARATIONS OF INTEREST 81
SOURCES OF SUPPORT 81
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 82
INDEX TERMS 82

[Intervention Review]

Vitamin A supplementation for postpartum women

Julicristie M Oliveira-Menegozzo[1], Denise P Bergamaschi[2], Philippa Middleton[3], Christine E East[4]

[1]Department of Nutrition, School of Public Health, University of Sao Paulo, São Paulo, Brazil. [2]Departamento de Epidemiologia-Estatistica, University of Sao Paulo, Sao Paulo, Brazil. [3]ARCH: Australian Research Centre for Health of Women and Babies, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, Australia. [4] Department of Obstetrics and Gynaecology, University of Melbourne, Pregnancy Research Centre, Department of Perinatal Medicine, Royal Women's Hospital, Parkville, Australia

Contact address: Julicristie M Oliveira-Menegozzo, Department of Nutrition, School of Public Health, University of Sao Paulo, Av Dr Arnaldo, 715, São Paulo, SP, Cep 01246-904, Brazil. julicristie@yahoo.com. cristie@usp.br.

Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New, published in Issue 10, 2010.
Review content assessed as up-to-date: 26 August 2010.

Citation: Oliveira-Menegozzo JM, Bergamaschi DP, Middleton P, East CE. Vitamin A supplementation for postpartum women. *Cochrane Database of Systematic Reviews* 2010, Issue 10. Art. No.: CD005944. DOI: 10.1002/14651858.CD005944.pub2.

ABSTRACT

Background

In vitamin A deficient populations, the amount of vitamin A may be insufficient for maintenance of maternal health and levels in breast milk may be insufficient for breastfeeding infants' needs.

Objectives

To assess the effects of postpartum maternal vitamin A supplementation on maternal and infant health.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 July 2010), LILACS (1982 to July 2010), Web of Science (1945 to July 2010) and Biological Abstracts (1998 to July 2010).

Selection criteria

Randomised controlled trials evaluating the effects of postpartum maternal vitamin A supplementation.

Data collection and analysis

Two review authors assessed the studies independently.

Main results

We included 12 trials at moderate risk of bias, enrolling 25,465 mother-baby pairs and comparing several postpartum doses (200,000-400,000 IU) of vitamin A or 7.8 mg daily beta-carotene, with placebo, iron or no supplement; or higher (400,000 IU) versus lower dose (200,000 IU). The majority of infants in all studies were at least partially breastfed for six months.

Maternal: we observed no impact of vitamin A on maternal mortality (two trials of 9,126 women), morbidity (one trial of 50 women) or adverse effects (subset of 786 women in one trial). Vitamin A enhanced serum and breast milk retinol at three months in five trials, but these improvements were generally not sustained.

Infant: we observed no significant differences for infant mortality RR 1.14 95% CI 0.84 to 1.57 (five trials (6,170 infants) or morbidity (three trials) except for fewer episodes of fever with vitamin A in one small trial. No significant differences in infant vitamin A status were seen with maternal vitamin A supplementation (five trials).

No beneficial effects for maternal or infant health were associated with higher compared to lower doses of vitamin A in two trials.

Authors' conclusions

The lack of effect on maternal and infant mortality and morbidity, with exception of some improved infant morbidity in one small study, and the improvement in maternal vitamin A status, suggest that maternal postpartum vitamin A supplementation offers limited benefits.

PLAIN LANGUAGE SUMMARY

Vitamin A supplementation for breastfeeding mothers

While the amount of vitamin A in well-nourished mothers' breast milk is sufficient to meet the needs of their infants, this may not be the case for mothers from populations with vitamin A deficiency. Therefore, trials have tested whether giving mothers vitamin A supplements as single doses soon after birth or beta-carotene for long periods can improve the health and survival of these mothers and their babies. Ten of the 12 trials in this review compared a single dose of vitamin A and placebo, with one trial supplementing women with beta-carotene for nine months after birth. Two studies compared a higher dose with a lower dose of vitamin A. None of the trials was able to show an effect on infant death and only one small study showed improved infant health. None of the trials was able to show an effect on maternal death or morbidity. A significant improvement was seen for maternal serum retinol, breast milk retinol and vitamin A liver stores after single dose of vitamin A supplementation. Vitamin A did not show any adverse effects in these trials, but this may not apply for women and babies from well nourished populations.

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

Vitamin A supplementation compared to placebo for postpartum mothers

Patient or population: postpartum mothers
Settings:
Intervention: Vitamin A supplementation
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	Vitamin A supplementation				
Maternal mortality Follow-up: mean 12 months	**3 per 1000**[1]	**3 per 1000** (2 to 5)[2]	**HR 1.11** (0.81 to 1.51)	8577 (1 study)	⊕⊕◯◯ **low**[3,4,5,6,7]	
Maternal morbidity: Infections (total days of illness per days of follow-up) Follow-up: mean 3 months	See comment	See comment		50 (1 study)	⊕◯◯◯ **very low**[8,9,10,11,12]	30/2281 with vitamin A versus 28/2281 with placebo; no statistical comparison performed[13]
Maternal adverse effects after administration: vomiting	**8 per 1000**	**3 per 1000** (0 to 25)	**RR 0.33** (0.03 to 3.14)	786 (1 study)	⊕⊕◯◯ **low**[4,7,14]	
Maternal serum retinol (mcmol/L) mcmol/L Follow-up: 3-3.5 months	The mean maternal serum retinol (mcmol/l) in the control groups was **1.28 mcmol/L**	The mean Maternal serum retinol (mcmol/L) in the intervention groups was **0.17 higher** (0.06 to 0.28 higher)		258 (3 studies)	⊕⊕◯◯ **low**[15]	

Maternal low hepatic vitamin A stores (MRDR greater than or equal to 0.06) Follow-up: 3 months	**543 per 1000**	**179 per 1000** (81 to 386)	**RR 0.33** (0.15 to 0.71)	69 (1 study)	⊕⊕⊕○ **moderate**[16,17,18]
Maternal low hepatic vitamin A stores (RDR > 20%) Follow-up: 3 months	**87 per 1000**	**100 per 1000** (36 to 283)	**RR 1.15** (0.41 to 3.25)	139 (1 study)	⊕⊕⊕○ **moderate**[19,20,21]

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

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

[1] ZVITAMBO Study Group: The data for the number of deaths in the placebo group have been estimated from the original reference. The study did not report the number of deaths in the placebo group; we have estimated the figure using the reported number of participants in the placebo group, the total number of participants in both groups, the total number of deaths in both groups, and the hazard ratio of 1.11.

[2] ZVITAMBO Study Group: The data for the number of deaths in the intervention group have been estimated from the original reference. The study did not report the number of deaths in the vitamin A group; we have estimated the figure using the reported number of participants in the vitamin A group, the total number of participants in both groups, the total number of deaths in both groups, and the hazard ratio of 1.11.

[3] ZVITAMBO Study Group: The analysis was not by ITT, but the attrition rate was low (11%), and therefore a point has not been deducted for limitations in design

[4] ZVITAMBO Study Group: One study only, therefore no inconsistency.

[5] ZVITAMBO Study Group: Estimated rather than actual figures of mortality.

[6] ZVITAMBO Study Group: Wide 95% confidence intervals that cross the line of no effect, which therefore does not exclude benefit or harm of vitamin A.

[7] ZVITAMBO Study Group: Few events in trial.

[8] Roy 1997: Unclear allocation concealment and unblinded control group (no placebo).

[9] Roy 1997: No statistical analysis for comparison of vitamin A versus placebo.
[10] Roy 1997: One study only, therefore no inconsistency.
[11] Roy 1997: Maternal fever a proxy outcome for infectious morbidity.
[12] Roy 1997: Few events in trial.
[13] Roy 1997: Number of cumulative days of illness (numerator) and number of people days' follow-up (denominator). The number of people days has been extracted from the original reference.
[14] ZVITAMBO Study Group: Unclear why only 766 women out of the 14,110 women randomised were included in the assessment of adverse effects.
[15] RETIBETA, Roy 1997, Stoltzfus 1993a: Reasons for attrition were not reported, and no ITT analyses were performed, in RETIBETA and Stoltzfus 1993a. Unclear allocation concealment and unblinded control group (no placebo) in Roy 1997.
[16] RETIBETA: Reasons for attrition were not reported, and no ITT analysis was performed; however, follow-up rates were greater than 90%, and therefore no point has been deducted.
[17] RETIBETA: One study only, therefore no inconsistency.
[18] RETIBETA: Few events in trial.
[19] Stoltzfus 1993a: Reasons for attrition were not reported, and no ITT analysis was performed; however, follow-up rates were 89% at 6 months, and therefore no point has been deducted.
[20] Stoltzfus 1993a: One study only, therefore no inconsistency.
[21] Stoltzfus 1993a: Wide 95% confidence intervals that cross the line of no effect, which therefore does not exclude benefit or harm of vitamin A.

BACKGROUND

Description of the condition

Importance of vitamin A

Vitamin A is a generic term for a group of fat-soluble substances that carry out similar biological activity in human metabolism. It plays an important role in normal vision, gene expression, growth and physical development, maintenance and proliferation of epithelial cells, and immune function, at all stages of life, particularly during pregnancy and lactation, given maternal, fetal and newborn requirements (Butte 2002; FNB 2000; WHO 1996; WHO 1998). The dietary sources of pro-vitamin A (alfa- and beta-carotene, alfa-cryptoxanthin) are vegetables such as carrot, pumpkin, papaya, buriti, and red palm oil; and animal foods rich in pre-formed vitamin A, such as dairy products (whole milk, yogurt, cheese), liver, fish oils and human milk (FAO/WHO 2001; FNB 2000). In most cultures, young infants depend on breast milk to obtain adequate amounts of vitamin A (WHO 1998), which is highly dependent upon maternal diet and nutritional status. In well-nourished populations the breast milk amounts of vitamin A are adequate to meet the infants' requirements during the first six months of life. In populations deficient in vitamin A, the amount in breast milk will be suboptimal and insufficient to build or maintain stores of this micronutrient in nursing infants (Butte 2002; WHO 1998).

Biological Indicators

Specific biological indicators of vitamin A deficiency (VAD) can be divided into two types: clinical and subclinical. Among the clinical indicators is xerophthalmia, which includes all ocular manifestations of VAD from night blindness to corneal ulceration, and resultant blindness (Sommer 1993). Subclinical indicators can include measurement of serum retinol (less than 0.7 µmol/L), breast milk retinol (less than 1.05 µmol/L or 0.28 µmol/g milk fat), relative dose response (RDR), and modified relative dose response (MRDR) (WHO 1996). Although there is not consensus, serum retinol less than 1.05 μmol/l has been proposed to reflect low vitamin A status among pregnant and lactating women (WHO 2009, West 2002). RDR and MRDR are indirect methods to assess the level of vitamin A in the liver. Other non-specific symptoms, such as increased maternal and infant morbidity and mortality, increased risk of anaemia, slowed infant growth and development can be related to VAD (FAO/WHO 2001, WHO 2009). RDR and MRDR are indirect methods to assess the level of vitamin A in the liver. Other non-specific symptoms, such as increased maternal and infant morbidity and mortality, increased risk of anaemia, slowed infant growth and development can be related to VAD (FAO/WHO 2001).

Vitamin A and adverse effects

There are limited human data on the potential teratogenicity of high doses of vitamin A in women exposed during early pregnancy. However, teratogenic effects from natural metabolites of vitamin A (like trans retinoic acids and 13-cis retinoic acids) are well documented from case studies of women exposed to high doses of retinoic acid derivatives within the first six weeks of pregnancy. Extensive epidemiologic studies have produced no evidence of teratogenicity in the human fetus after six weeks of pregnancy (Rasmussen 1998). Maternal or infant supplementation with high doses of vitamin A (more than 50,000 IU) can produce adverse effects including nausea, headache, fever, vomiting, transient diarrhoea, increased cerebrospinal fluid pressure, blurred vision and lack of muscular co-ordination (Allen 2002).

Vitamin A interaction with other micronutrients

It is believed that zinc status may influence vitamin A metabolism, including its absorption, transport and utilisation, probably through regulation of vitamin A transport and oxidative conversion of retinol to retinal. However, randomised trials have failed to show a consistent effect of zinc supplementation on vitamin A status (Christian 1998).

There is evidence that VAD impairs iron mobilisation from stores and its transportation, resulting in anaemia (Lynch 1997). The role of vitamin A in iron absorption is unconfirmed; according to Garcia-Casal 1998, vitamin A forms a complex with iron, increasing its absorption, but Walczyk 2003 found a slightly negative effect of this vitamin.

Some studies have shown that iron deficiency may influence vitamin A metabolism (Oliveira 2008a), decreasing liver mobilisation and serum retinol concentration (Rosales 1999; Jang 2000; Strube 2002). Munoz 2000 conducted a clinical trial and found that iron supplementation improved the indicators of vitamin A status in preschoolers from Mexico.

Vitamin A deficiency around the world

The global distribution of VAD, presented by the World Health Organization (WHO) (WHO 1995), classifies countries by the significance of VAD as a public health problem, based on clinical and subclinical (serum retinol) indicators. The most widely affected areas are in Africa, Asia and Latin America. The recent prevalence presented by WHO (WHO 2009), including data from 1995 to 2005, indicates that Africa and South-East Asia have the highest burden of VAD. Although these estimations were produced by different methodologies, there is some indication that the prevalence of xerophthalmia among pre-school children decreased, but the subclinical VAD (serum retinol concentration) in pre-school children and pregnant women increased, possibly due to improved methods of assessing, and a wider population being assessed (WHO 2009). Results relating to lactating women were not considered in these publications. A study carried out in Nepal

showed that 27% of postpartum women were vitamin A deficient (West 1997). Another study in Bangladesh found that 13.3% of lactating women presented with VAD (Ahmed 2003).

Vitamin A supplementation during pregnancy

A Cochrane systematic review (Van den Broek 2002) of five trials with a total of 23,426 pregnant women, mostly from countries with significant levels of VAD, noted a possible beneficial effect on maternal mortality after weekly supplementation, a reduction in maternal night-blindness and a reduction in maternal anaemia in some, but not all studies.

Breastfeeding around the world

According to the WHO (WHO 2010), 36% of infants are exclusively breast fed for the first six months of life. South-East Asia presents the highest prevalence (48%) and Europe the lowest (23%). The prevalence in Africa and America is the same (31%). Considering income, the low and lower middle income groups showed the highest proportion (around 38%). In Bangladesh, India, Indonesia and Nepal 43%, 46%, 32% and 53% of infants are exclusively breast fed during the first six months. The prevalences in Africa vary by the specific country. In Ghana the proportion is 63%, followed by Gambia (41%), Tanzania (41%), Kenya (32%), and Zimbabwe (22%). In South America these differences are also observed. For example, in Brazil the prevalence is 40% and in Peru 73%.

Maternal mortality around the world

In Africa and South-East Asia the maternal mortality ratios (MMR) average 900/100,000 and 450/100,000 live births, respectively. Although these areas present the highest maternal mortality around the world, the ratios are not homogenous when considering different countries within continents. The MMR is higher in Nepal (830/100,000) than in Bangladesh (570/100,000), India (450/100,000) or Indonesia (420/100,000). The differences among African countries are also evident. In Tanzania the MMR is 950/100,000; followed by Zimbabwe (880/100,000); Gambia (690/100,000); Ghana and Kenya (both 560/100,000 live births). In North America and Europe, these ratios are below 100/100,000 live births, but the rates are relatively high in Brazil (110/100,000) and Peru (240/100,000 live births) (WHO 2010).

Description of the intervention

Vitamin A supplementation for postpartum mothers

Vitamin A supplementation may take a number of forms: for example, as Vitamin A, measured in international units (IU) of Retinyl palmitate (3.33 IU or 0.003491 micromol of retinol = 1 microgram or 1 Retinol Equivalent (RE) (IVACG 2004), water miscible formulation, or as beta-carotene. Synthetic beta-carotene supplements result in improved breast milk vitamin A concentrations compared with dietary sources of beta-carotene (De Pee 1995).

WHO, UNICEF and the International Vitamin A Consultative Group recommend that in areas of endemic VAD, high doses of supplementary vitamin A should be given to breastfeeding women during the postpartum period (to six weeks after childbirth), as a strategy to improve mothers' and infants' stores of this micronutrient (Ross 2002; WHO 1996).

Four scenarios in which vitamin A supplements could be given in VAD countries, considering safe dosage and frequency of administration, are: (1) maternal supplementation during pregnancy; (2) supplementation for mothers in the first six months postpartum; (3) supplementation of infants before six months of age; and (4) supplementation of both the mothers during the safe infertile postpartum period and infants under six months of age (WHO 1998).

At the population level, for mothers from VAD countries who are not breastfeeding, a high dose of vitamin A (over 25,000 IU and usually 200,000 IU) during the first four weeks after delivery could be beneficial. Beyond six months, for these mothers no more than 10,000 IU daily should be given. Non-breast-fed infants (less than six months of age) could receive a single high dose of 50,000 IU of vitamin A or two doses of 25,000 IU approximately a month apart, to meet their needs if they are not receiving a fortified breast-milk substitute. However, for mothers who are breastfeeding, a high dose given up until 60 days postpartum could be beneficial for them and as well as for their infants through higher concentration of vitamin A in breast milk (WHO 1998).

According to WHO's recommendations (WHO 1998), research that considers the supplementation of mothers up to eight weeks postpartum should include an evaluation of maternal outcomes, such as morbidity, mortality, serum retinol and breast milk retinol and its metabolites; long-term effects on morbidity, mortality and vitamin A status in infancy up to three years of age; as well as effects on partial weaning/cessation of breastfeeding on morbidity, mortality, vitamin A status and return to fertility.

Other integrated approaches to control VAD are the improvement of dietary quality, quantity and food fortification (WHO 1998).

Why it is important to do this review

Numerous studies and programs have involved postpartum supplementation that aims to improve women's and infants' health in regions of vitamin A deficiency. However, there are no consistent practices or recommendations. A systematic review of the relevant randomised controlled trials is therefore warranted.

OBJECTIVES

To assess the effects of vitamin A supplementation, alone or in combination with other micronutrients (e.g. iron, folic acid, vitamin E), in mothers during the postpartum period, on maternal and infant health.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials evaluating the effects of vitamin A supplementation in mothers during the postpartum period, including cluster-randomised studies and excluding quasi-randomised studies.

Types of participants

Mothers in the postpartum period, breastfeeding or not, from vitamin A deficiency areas, without confirmed chronic diseases (e.g. HIV). We included maternal data from studies conducted in areas with high prevalence of HIV without individual diagnostics at baseline. We considered only data of HIV-negative mothers in studies conducted with both HIV-positive and -negative mothers.

Types of interventions

Maternal vitamin A supplementation (beta-carotene or retinyl palmitate or water miscible formulation) alone or in combination with other micronutrients (examples: iron, folic acid, vitamin E) compared with placebo, no intervention, other micronutrient, or a lower dose of vitamin A, commenced at any time during the postpartum period, that is, within 24 hours of birthing until six weeks after giving birth.

Studies included maternal administration of high doses (given as a single dose of 200,000, 300,000, or 400,000 IU) or two doses (for a total of 400,000 IU), daily (7.8 mg or 4,327 IU) doses or a combination of high or lower doses.

Studies that involved continuous daily/weekly supplementation for mothers during reproductive age (pre-pregnancy or during pregnancy) are addressed in a separate systematic review (Van den Broek 2002).

Several studies included infant supplementation, in addition to maternal postpartum supplementation. We considered maternal outcomes from these studies. We included infant outcomes only when they had been measured prior to commencement of infant supplementation.

Types of outcome measures

When studies involved both maternal and infant supplementation, we reviewed them for maternal outcomes and limited the infant outcomes to those measured prior to commencement of infant supplementation. In this way, we only included results related to a comparison of maternal supplementation or no treatment/placebo; or different maternal supplementation regimens. With the exception of adverse effects of vitamin supplementation, we reviewed outcomes for up to 12 months postpartum.

Primary outcomes

Primary maternal outcomes

1. Mortality;
2. morbidity (febrile illness, respiratory tract infection, diarrhoea);
3. adverse effects of vitamin A within three days after receiving supplement.

Primary infant outcomes

1. Mortality;
2. morbidity episodes (febrile illness, respiratory tract infection, diarrhoea, and others);
3. adverse effects of vitamin A supplementation within three days after receiving supplement.

Secondary outcomes

Secondary maternal outcomes

1. Serum retinol concentration;
2. vitamin A hepatic stores (MRDR or RDR);
3. breast milk retinol concentration;
4. vitamin A deficiency (clinical: impaired visual adaptation to darkness, night blindness, xerophthalmia; and subclinical: abnormal conjunctival impression cytology);
5. anaemia.

Secondary infant outcomes

1. Serum retinol concentration;
2. vitamin A hepatic stores (RDR or MRDR);
3. clinical vitamin A deficiency.

Search methods for identification of studies

Electronic searches

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (31 July 2010).

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

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

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

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

In addition, we searched LILACS - Latin American and Caribbean Health Sciences by Bireme (1982 to July 2010), Web of Science (1945 to July 2010), Biological Abstracts (1998 to July 2010) using the search strategies detailed in Appendix 1.

We also searched Human Nutrition (1982 to October 2007), Food Sciences & Tech Abstracts (1969 to November 2008), Food and Human Nutrition (1975 to October 2007), and AGRIS (1975 to October 2007). *See* Appendix 1 for details.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

At least two review authors (JM Oliveira-Menegozzo, DP Bergamaschi, CE East, P Middleton) assessed potentially eligible trials identified by the literature search to determine if they met the inclusion criteria for the review. We made decisions regarding inclusion independently and compared results. We resolved any disagreement through discussion.

Data extraction and management

For eligible studies, at least two authors (JM Oliveira-Menegozzo, CE East, P Middleton) independently extracted data and compared the results. We resolved discrepancies through discussion. We double-checked data against printouts of data entered into Review Manager software (RevMan 2008).

We carried out the meta-analysis using the Review Manager software (RevMan 2008).

Assessment of risk of bias in included studies

At least two authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). We resolved any disagreements by discussion.

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

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

We assessed the method as:

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

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

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

We assessed the methods as:

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

(3) Blinding (checking for possible performance bias)

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

We assessed the methods as:

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

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

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we would have re-included missing data in the analyses which we undertook. However, this did not apply to any of the included studies. We did not specify a level of missing data to assess that a study was adequate. We assessed methods as:

- adequate;
- inadequate;
- unclear.

(5) Selective reporting bias

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

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

(6) Other sources of bias

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

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

- yes;
- no;
- unclear.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2009). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We planned to explore the impact of the level of bias through undertaking sensitivity analyses - *see* 'Sensitivity analysis'.

Measures of treatment effect

Dichotomous data

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

Continuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials.

Where data were reported in a format that did not allow for entry into the RevMan software, we have reported the published results in tables or in text.

Unit of analysis issues

Cluster-randomised trials

We planned to include cluster-randomised trials in the analyses along with individually randomised trials. If we had identified cluster trials, we planned to adjust their sample sizes using the methods described in the *Handbook* (Secion 16.3.4) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population.

If cluster studies are in included in future review updates, we will use ICCs from other sources; we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Dealing with missing data

For included studies, we noted levels of attrition. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis if we identified such studies.

Although not ultimately required for the included studies, for all outcomes, we planned to carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we planned to attempt to include all participants randomised to each group in the analyses, and all participants would have been analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. If studies requiring this are identified in future review updates, the denominator for each outcome in each

trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

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

Assessment of reporting biases

If 10 or more studies were meta-analysed we would have investigated reporting biases (such as publication bias) using funnel plots. However, no outcomes had results from 10 or more studies. If this becomes necessary in future review updates, we will assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes we will use the test proposed by Egger 1997, and for dichotomous outcomes we will use the test proposed by Harbord 2006. If we detect asymmetry in any of these tests or by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using RevMan software (RevMan 2008). We use 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. We treated the random-effects summary as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials.

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

Subgroup analysis and investigation of heterogeneity

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

We planned to conduct the following sub-groups analyses of primary outcomes, if sufficient data were available:

1. type of supplement (vitamin A (retinyl palmitate or water miscible formulation) or beta-carotene);
2. duration of supplementation (daily, single or double dose);
3. dose of supplement (200,000-300,000 IU or 400,000 IU);
4. type of control group (supplementation versus placebo/no supplement, or higher versus lower supplementation dose);
5. duration of breastfeeding.

Sensitivity analysis

If we identified substantial heterogeneity, we investigated it using sensitivity analyses.

RESULTS

Description of studies

Included studies

We included 12 studies enrolling 25,465 mother-baby pairs residing in low-income settings in India, Bangladesh, Indonesia, Tanzania, Gambia, Zimbabwe, Kenya, Ghana and Peru, countries in which women in the studies were likely to have low vitamin A levels and low nutritional status. The 'Characteristics of included studies' table provides further information on these trials. Although all studies reported or implied that postpartum women breastfed their infants, the available details made it impractical to perform subgroup analysis by duration of breastfeeding. Moreover, there were insufficient data to perform sensitivity analyses.

Dosage and duration of vitamin A supplementation

Nine studies (Ayah 2007; Bhaskaram 2000; Newton 2005; Roy 1997; Stoltzfus 1993a; Venkatarao 1996; Vinutha 2000; WHO/CHD IVASSG; ZVITAMBO Study Group) administered a single dose of vitamin A in the form of retinyl palmitate or water miscible formulation (200,000; 300,000 or 400,000 IU) supplementation for mothers within the first days or weeks postpartum. Eight of the trials compared vitamin A supplementation with placebo (Ayah 2007; Bhaskaram 2000; RETIBETA Project; Stoltzfus 1993a; Venkatarao 1996; ZVITAMBO Study Group; WHO/CHD IVASSG; Newton 2005). In two studies, women in the control group received no intervention (Vinutha 2000) or were given iron supplementation (as were those in that study's intervention group) (Roy 1997). The RETIBETA Project used a three-group approach of single postpartum dose of vitamin A (as retinyl palmitate) followed by placebo for nine months, placebo at enrolment followed by daily beta-carotene supplementation for nine months, or placebo at enrolment and daily for nine months.

Two trials compared a lower dose of vitamin A (200,000 IU) with a higher dose (400,000 IU) (Darboe 2007; Idindili 2007).

The studies reported the dosage in a variety of units: for the purpose of this review, dosages have generally been presented as international units (IU), based on the calculation of 3.33 IU or 0.003491 micromol of retinol = 1 microgram or 1 Retinol Equivalent (RE).

Breastfeeding patterns

Eight of the included studies reported that women breastfed their infants, with several studies noting that infants were exclusively breastfed (Vinutha 2000 for the duration of the study and Idindili 2007 for the first month) and others indicating that infants were at least partially breast fed to six months (Bhaskaram 2000; RETIBETA Project; Roy 1997; Venkatarao 1996; WHO/CHD IVASSG; ZVITAMBO Study Group). All four studies that did not specify details of breastfeeding provided strong surrogate evidence to support the likelihood of at least partial breastfeeding. The studies by Ayah 2007 and Darboe 2007 reported breast milk retinol levels at six months postpartum, whilst the study title, background and/or discussion material suggested that the reports from Newton 2005 and Stoltzfus 1993a related to breastfeeding, although the duration or extent cannot be estimated.

Excluded studies

We excluded four trials because they used alternate, rather than randomised allocation (Ala-Houhala 1988; Basu 2003, Bezerra 2010; Tchum 2006). We excluded eight trials that involved provision of vitamin A rich foods, rather than vitamin A supplementation (Canfield 2001; De Pee 1995; Filteau 1999; Gossage 2000; Khan 2007; Lietz 2001; Lietz 2006; Ncube 2001). We also excluded two studies involving long-term supplementation for women of reproductive age (NNIPS-2; ObaapaVitA). (*See* 'Characteristics of excluded studies').

Risk of bias in included studies

We assessed the overall risk of bias in the 12 included trials as being moderate (Figure 1; Figure 2)

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

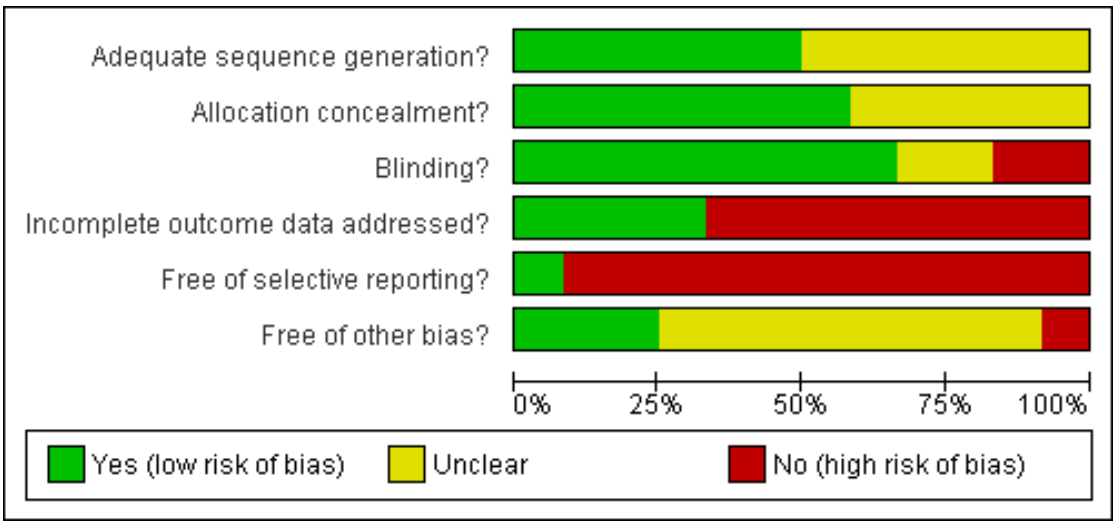
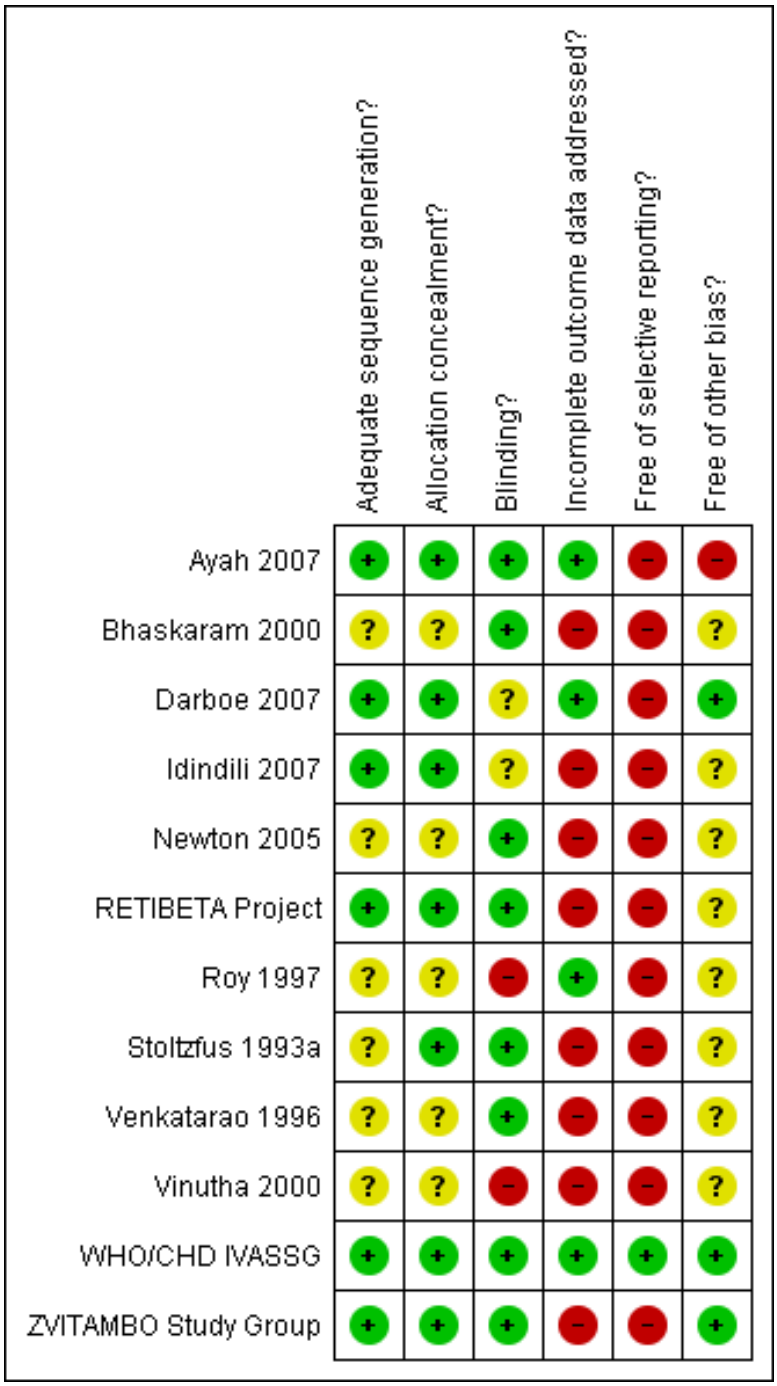


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

In the WHO CHD Immunization Linked Vitamin A supplementation multi-centre trial (WHO/CHD IVASSG), mother and infant pairs were individually randomised to one of four treatment groups. Randomisation was carried out by identification numbers generated by computer and assigned as random permuted blocks of size eight. The codes were kept by WHO in Geneva.

Participants in the RETIBETA Project were individually randomised. Before beginning the study, treatment codes and follow-up schedules were assigned to a sequence of identification numbers in blocks of 18 using a random number table. During enrolment, the women were randomly allocated to one of three treatment groups and to a follow-up schedule.

In the Ayah 2007 trial, two random sequences were prepared for mothers and infants. The randomisation code was concealed for the entire trial duration and only revealed after completion of data analysis. In the ZVITAMBO trial (ZVITAMBO Study Group) randomisation was done by computer generation of identification numbers in blocks of 12.

Subjects from the Gambia trial (Darboe 2007) were randomised by a senior scientist, who then packed and labelled the supplements, by blocks (16 per block) to allow for possible effects of season of birth. In the Idindili 2007 trial, individual randomisation was achieved by using a list of study numbers that had been randomly assigned to an intervention arm in blocks of ten, generated by the Data and Safety Monitoring Board. The Stoltzfus 1993a trial used individual randomisation to treatment codes in blocks of eight.

The reports from the trials by Venkatarao 1996, Roy 1997, Bhaskaram 2000 and Vinutha 2000 provided no information about the method of randomisation and concealment.

Blinding

For most studies, the vitamin A and placebo capsules were identical in appearance (see Risk of bias tables in Characteristics of included studies. In one study (RETIBETA Project) the capsules differed slightly in colour, but they were individually wrapped in foil, making the direct comparisons between groups unlikely.

In the study by Idindili 2007, there was not enough detail to judge whether participants were blinded, while the Vinutha 2000 study did not provide detail on blinding. Stoltzfus 1993a noted that all investigators, field, and laboratory staff were blinded to the randomisation code until field work was completed.

Incomplete outcome data

In the Venkatarao 1996 trial study there was a 24.2% overall loss of follow-up, distributed similarly between the three groups and attributed to post-randomisation exclusions for medical reasons such as congenital abnormalities or jaundice, migration and miscellaneous. In the study by Roy et al (Roy 1997) no losses to follow-up were discussed, but data from the tables indicate 100% of follow-up. In the Vinutha et al (Vinutha 2000) clinical trial the loss of follow-up rate was 22.9%. In the trial by Bhaskaram et al (Bhaskaram 2000) the rates of loss to follow-up were 13% and 54% until three and six months postpartum, respectively. Ayah 2007 reported a 12.6% loss to follow-up by 14 weeks' postpartum and a 22.9% loss by six months. In the trial from Gambia (Darboe 2007) 89.5% of mothers and infants were followed up until 12 months. Idindili 2007 reported 19%, 20.5%, 22.8% of loss by three, six, and nine months, respectively. Attrition was 11.3% (in both the vitamin A and placebo groups) for HIV-negative women (985/9562) in the report from the ZVITAMBO Study Group.

Twenty-three of the total 220 women in the RETIBETA Project missed one or more visits, resulting in follow-up rates of 98%, 95%, and 92% at three, six, and nine months postpartum, respectively, with data reported for these participants in most outcomes. The exception was for maternal hepatic stores of vitamin A and serum retinol concentrations, for which approximately 50% of women were sampled: the report does not specify why all women were not tested. The study by Stoltzfus 1993a had a 9% loss to follow-up in each group by three months and 13% and 5% losses in the vitamin A and control groups respectively by six months.

Loss of follow-up at nine months for the WHO/CHD IVASSG study was 783 (17%) in the intervention group and 770 (16%) in the placebo group. This increased to 25% and 24.5% in the intervention and control groups respectively by 12 months. Infant death was the only outcome of interest for this review at this time, therefore it was recorded in this review for the nine month follow-up time, rather than at 12 months. Biochemical markers had been measured in a subgroup of approximately 100 mothers and their infants from each of the three participating countries: the exact number sampled increased from the first to the second timeframe, which meant we were unable to determine loss to follow up from the report.

Selective reporting

We judged all but one trial to be at risk of selective reporting; for example only five of the 12 trials reported infant mortality and only two reported maternal mortality.

Other potential sources of bias

We judged most trials as unclear for risk of other bias, mostly due to a lack of clarity about any influence of funding bodies.

Effects of interventions

See: **Summary of findings for the main comparison** Vitamin A supplementation compared to placebo for postpartum mothers

Primary maternal outcomes

Maternal mortality

Two studies evaluated maternal mortality for a total of 9126 women (Ayah 2007; ZVITAMBO Study Group). The study by Ayah 2007 reported no statistically significant difference in maternal mortality to six months (n = 564, RR 0.50, 95% CI 0.09 to 2.71) - Analysis 1.1. There were no reported differences in maternal deaths following vitamin A supplementation or placebo in HIV-negative women (n = 8562) followed to six months (Hazard Ratio (HR) 1.40, 95% CI 0.4, 5.0) or 12 months (HR 1.11, 95% CI 0.81, 1.51) in the report by Zvandasara (ZVITAMBO Study Group): we report here the adjusted HR and confidence intervals for maternal mortality, as there was insufficient detail to re-analyse using RevMan software (RevMan 2008).

Maternal morbidity

One small study of 50 women (Roy 1997) reported no significant difference in cumulative episodes of diarrhoea, respiratory infection or fever - Analysis 1.2, Analysis 1.3, Analysis 1.4).

Adverse effects of vitamin A supplementation

In a subset of 788 mother-infant pairs in the ZVITAMBO Study Group, no statistically significant differences were seen in adverse effects within 30 hours of supplementation, including headache, blurred vision, drowsiness, vomiting, poor appetite or abdominal pain following a single dose of 400,000 IU vitamin A or placebo - Analysis 1.5.

Secondary maternal outcomes

Maternal serum retinol

Six studies reported maternal serum retinol values, measured between six weeks and nine months after birth, for a total of 1418 women (Analysis 1.6; Analysis 1.7; Analysis 1.8; Analysis 1.9). Few analyses included meta-analysis of more than three of these studies at a time, due to the clinical and statistical heterogeneity of reported data.

Maternal serum retinol concentrations were not enhanced by the largest single dose (400,000 IU), when measured at one and a half months (260 HIV-negative women, mean difference (MD) 0.09 µmol/L, 95% CI -0.02 to 0.20) (ZVITAMBO Study Group); nor at three and a half months (n = 402, MD 0.04 µmol/L, 95% CI -0.01 to 0.09) or six months postpartum (n = 291, MD -0.02 µmol/L, 95% CI -0.08 to 0.04) in a study that had substantial losses to follow-up (Ayah 2007). However, other smaller studies that administered a single dose (200,000-300,000 IU) within three weeks postpartum reported a statistically significant improvement in serum retinol at three months compared with placebo (three studies, n = 258, MD 0.17 µmol/L, 95% CI 0.06 to 0.28), but not at six months (three studies, n = 260, MD 0.10 µmol/L, 95% CI -0.02 to 0.23). Daily postpartum administration of 7.8 mg beta-carotene did not improve maternal serum retinol concentrations three, six or nine months after delivery in one small study (n = 71, RETIBETA Project).

Vitamin A hepatic stores

Three studies analysed low vitamin A hepatic stores (reported as relative dose response (RDR) greater than 20% or modified relative dose response (MRDR) $\geq$ 0.06) at three, six, and nine months postpartum (n = 315) - Analysis 1.10, Analysis 1.11, Analysis 1.12, Analysis 1.13, Analysis 1.14. The RETIBETA Project reported an improvement in the proportion of women with low hepatic stores at three months (n = 69, MRDR $\geq$ 0.06; RR 0.33, 95% CI 0.15 to 0.71) following a single 200,000 IU dose of vitamin A, compared with placebo. In contrast, another small study (Stoltzfus 1993a) did not report any difference in RDR greater than 20% three months postpartum (n = 139, RR 1.15, 95% CI 0.41, 3.25). Neither study reported statistically significant differences when measuring at six or months postpartum. No differences were reported in the RETIBETA Project for this outcome between daily beta-carotene supplementation (for nine months) and placebo at any times, for example, when measured at nine months (n = 66, RR 0.61, 95% CI 0.30,1.23).

Breast milk retinol

Breast milk retinol levels were reported in several formats (retinol concentration, proportion of milk retinol <1.05µmol/L or <0.28 µmol/gram of fat) in seven studies for a total of 1075 women (Analysis 1.15 to Analysis 1.23 and Analysis 2.3). Vitamin A supplementation (200,000-300,000 IU) was associated with an increased breast milk retinol concentration at three to three and a half months (four studies, n = 390, MD 0.27µmol/L, 95% CI 0.11 to 0.43) but this improvement was not sustained by six to six and a half months postpartum. Supplementation with a single dose of vitamin A (200,000-300,000 IU) significantly reduced the proportion of women with low retinol concentration (<1.05µmol/L) in human milk at three months (three studies, n = 373, RR 0.42, 95% CI 0.19 to 0.91), but not at six months after delivery (two studies, n = 275, RR 0.65, 95% CI 0.23 to 1.90), compared with placebo. Daily doses of beta-carotene to nine months postpartum did not improve breast milk retinol at three or six months but

did demonstrate improvement for this outcome by nine months postpartum (n=135, MD 0.21µmol/L, 95% CI 0.04 to 0.38) in the RETIBETA Project, compared with placebo.

Two studies (RETIBETA Project; WHO/CHD IVASSG) reported the proportion of women with low breast milk retinol levels (< 0.28 µmol/gram of fat; n = 479). Supplementation with a single dose of vitamin A (200,000 IU) or daily beta-carotene 7.8mg daily for nine months did not improve this measure at three months postpartum. Following supplementation with 200,000 IU demonstrated an improvement (two studies, n = 813, RR 0.84, 95% CI 0.71 to 0.99) at six months, which did not persist to nine months (two studies, n = 699, RR 0.87, 95% 0.74 to 1.02). Although no improvements were noted at three and six months following daily administration of beta-carotene, an improvement was noted by nine months (n = 134, RR 0.76, 95% CI 0.62 to 0.95).

Clinical and subclinical vitamin A deficiency

Stoltzfus 1993a measured abnormal conjunctival impression cytology (CIC) in one or both eyes as the criterion for vitamin A deficiency. There was no significant difference in the proportion of women with abnormal CIC at six months postpartum, following supplementation with vitamin A or placebo (n = 148, RR 0.56, 95% CI 0.27 to 1.17). However, they did reported a decline in abnormal CIC from baseline (32.5%) to six months postpartum (23.3%) following vitamin A supplementation (P < 0.006). No such decline was recorded in the placebo group (27.6% at baseline; 23.3% at six months) - Analysis 1.24, Analysis 1.25.

Anaemia

No studies addressed maternal anaemia.

Primary infant outcomes

Infant mortality

Infant mortality was assessed in four trials (Ayah 2007; Newton 2005; Venkatarao 1996; ZVITAMBO Study Group), with no differences for vitamin A compared with placebo (RR 1.14 95% CI 0.84 to 1.57; 6170 infants - Analysis 1.26) or between different dosing regimens (Analysis 2.1).

Infant morbidity

Three studies (Roy 1997; Venkatarao 1996; Vinutha 2000) evaluated infant morbidity in a total of 590 infants - Analysis 1.27 to Analysis 1.33.

Diarrhoea

None of the three studies that considered diarrhoea or gastroenteritis reported any significant differences between the vitamin A supplementation or control groups (Roy 1997 (n = 50, diarrhoea episodes, P = 0.59), Venkatarao 1996 (n = 456, RR 1.02, 95% CI 0.98 to 1.06) and Vinutha 2000 (n = 84, RR 8.44, 95% CI 0.45, 158.4).

Respiratory illnesses

The reduction in observed reduced mean duration of acute respiratory tract infection (n = 50, 3.1 versus 3.7; P < 0.03) in the treatment group reported by Roy 1997 was not noted in the larger study by Venkatarao 1996, which reported no significant statistical difference in overall incidence of one or more episodes to 12 months of age of acute respiratory infection (n = 456, RR 1.00, 95% CI 0.96 to 1.03) between the supplemented and placebo groups.

Febrile illness

One small study (Roy 1997) reported a lower mean number of febrile illness episodes (n = 50, 0.1 versus 0.3, P < 0.002) in the vitamin A group compared to the control group.

Adverse effects of vitamin A supplementation

No statistically significant differences were detected in the potential for developing the adverse effect of bulging fontanelle following vitamin A supplementation, including bulging fontanelle (200,000 or 400,000 IU; n = 9622; RR 2.22 95% CI 1.01, 4.86) - Analysis 1.34.

Secondary infant outcomes

Infant serum retinol

Four studies reported infant serum retinol between two and three and a half months after birth (n = 454), with none demonstrating a beneficial effect from any of the variety of dosing regimens used - Analysis 1.35, Analysis 1.36. For example, the use of 400,000 IU versus placebo resulted in a MD of 0.02 µmol/L (n = 164, 95% CI -0.03 to 0.07) (Ayah 2007); or 400,000 versus 200,000 IU resulted in MD -0.02µmol/L (n = 134, 95% CI -0.05 to 0.09) (Darboe 2007). There were no differences at five to six months by any of the four studies that reported this outcome (Analysis 1.36, n = 604), for example, the subgroup analysis of 200,000-300,000 IU versus placebo yielded a MD 0.04µmol/L (three studies, n = 324, 95% CI -0.01 to 0.09).

Vitamin A hepatic stores

Four studies reported low hepatic vitamin A stores (MRDR; n = 1128; Analysis 1.37, Analysis 1.38).

Vitamin A hepatic stores analysed at six weeks, or five to six months of infancy were not enhanced by any vitamin A dosing regimens, compared with placebo, for example, 200,000 IU versus placebo, measured at six weeks of age (n = 600, RR 1.11, 95% CI 1.02 to1.21) (WHO/CHD IVASSG).

Clinical vitamin A deficiency

No studies addressed infant clinical vitamin A deficiency.

DISCUSSION

Summary of main results

Maternal mortality was not influenced by single high-dose vitamin A supplementation (400,000 IU) in two studies (Ayah 2007; ZVITAMBO Study Group) conducted in areas of high maternal mortality ratios (MMR): Zimbabwe (880/100,000) and Kenya (560/100,000 live births). In contrast to our findings, one large study carried out in Nepal that evaluated weekly long-term low-dose supplementation with vitamin A or beta carotene (23,300 IU) for women during pregnancy and postpartum period demonstrated a protective effect of vitamin A for maternal mortality (NNIPS-2). However, more recently, other large studies from Bangladesh (JivitA-1 Trial) and Ghana (ObaapaVitA) have not been able to replicate this effect, which may relate to the different maternal mortality ratios in these countries (Nepal 830/100,000; Bangladesh 570/100,000 and Ghana 560/100,000 live births).

Infant mortality was not influenced by postpartum maternal vitamin A supplementation (Ayah 2007; Darboe 2007; Newton 2005; ZVITAMBO Study Group).

Several maternal morbidities are more prevalent in populations known to be vitamin A deficient than in industrialised countries. However, we did not observe a reduction in maternal morbidity after supplementation. Only a protective effect of vitamin A (300,000 IU) supplementation was observed in the prevalence of abnormal conjunctival impression cytology, a measure that is useful when there is restricted access to laboratory estimation of vitamin A status, although not an ideal stand-alone indicator of vitamin A deficiency (VAD) (Stoltzfus 1993b).

Maternal supplementation with a single postpartum dose of 200,000 IU vitamin A improved the proportion of women with breast milk retinol content < 0.28 µmol/g of fat, compared with placebo at six months after giving birth. This protective effect was not observed in the pooled analysis including studies of mean breast milk retinol (µmol/L).

Methodological studies suggest that the breast milk vitamin A content expressed per gram of fat is a more responsive indicator compared with serum retinol (Rice 2000; Stoltzfus 1993c). Moreover, serum retinol has some limitations as an indicator of vitamin A status, because retinol binding protein is a negative acute phase reactant protein (Filteau 1993; WHO 1996). Dancheck 2005 investigated the influence of acute phase reaction in breast milk retinol concentration in women from Malawi. The authors observed no significant differences in retinol breast milk concentration between lactating women with or without signs of inflammation. Thus, the meta-analysis results for breast milk retinol in this review were probably more informative than serum retinol in assessing the impact of vitamin A supplementation.

Although serum retinol concentration has some limitations as an indicator, the Global WHO database on Vitamin A Deficiency, a part of the Vitamin and Mineral Nutrition Information System (VMNIS), compiles data on the prevalence of clinical VAD (night blindness and ocular manifestation) and blood retinol concentration regularly from scientific literature and collaborators to estimates the prevalence of VAD around the world. These estimates provide valuable information for monitoring global progress and for evaluating current strategies to reduce VAD (WHO 2009). The pooled analysis of the reviewed studies showed that maternal supplementation (200,000-300,000 IU) is associated with reduced proportions of low vitamin A hepatic stores and significantly higher serum retinol concentration only until three months postpartum.

There is a concern that maternal administration of 400,000 IU within a single day might result in transient increases in breast milk retinoic acids to toxic levels. For this reason, the International Vitamin A Consultative Group (Ross 2002) recommends an interval of at least 24 hours between the two doses (200,000 IU each) for a total 400,000 IU vitamin A. Despite this recommendation, the full 400,000 IU was administered as one dose in two studies (ZVITAMBO Study Group; Ayah 2007), with no reports of breast milk retinoic acid concentration immediately after supplementation. Although Darboe 2007 and Idindili 2007 supplemented the mothers with two doses of 200,000 IU with an interval of 24 hours or one month, respectively, no data regarding breast milk retinoic acid concentration were described. Studies of VAD populations included in this review reported no increase in signs and symptoms likely to be associated with raised intracranial pressure among lactating women supplemented with high doses of vitamin A, compared with placebo, including headaches, drowsiness, nausea, vomiting or blurred vision.

This review did not find evidence of a protective effect in respect of infant mortality. Only one small study reviewed observed significant impact on infant morbidity (duration of acute respiratory illness, number of febrile illnesses) (Roy 1997). In spite of the lack of impact observed in this current review, other published meta-analyses provide evidence that vitamin A supplementation in children over six months of age may be associated with reduced risk

of mortality from measles (Fawzi 1993; Yang 2005) and diarrhoea (Glasziou 1993). The coexistence of multiple micronutrient deficiencies could also be a factor that influenced the results. According to Rahman 2001, supplementation with zinc and vitamin A is more effective than vitamin A supplementation alone in reduction of persistent diarrhoea and dysentery in children (one to three years). Multiple-micronutrient supplementation to women during pregnancy may improve outcomes such as fetal growth, but infant outcomes including neurodevelopmental delay had not been reported at the time of a systematic review by Haider 2006. Further studies that consider fetal/neonatal/infant outcomes following maternal multiple-micronutrient supplementation during pregnancy, breastfeeding, or both, may therefore be of interest.

A case-control study by Rondó 1997 conducted with Brazilian infants observed that cord blood retinol concentration was higher in infants with adequate growth for gestational age at delivery compared with infants with intrauterine growth restriction. According to the authors, one possible explanation for this result is maternal VAD. In our review, we included one study (Ayah 2007) that investigated the interaction of birthweight in the response to the vitamin A supplementation, but the authors found no significant effect. The studies included in this present systematic review did not provide data in a format that would allow us to perform subgroup analysis considering birthweight, although future studies may consider this.

Co-existing vitamin A, iron and zinc deficiencies are important and common nutritional problems. There is evidence that zinc status influences several aspects of vitamin A metabolism, including absorption, transport and use (Christian 1998). Studies conducted in rats noted that vitamin A metabolism is also altered with iron deficiency, characterised by low serum retinol concentration and increased vitamin A hepatic stores, probably associated with reduced retinyl ester hydrolase's activity (Jang 2000; Oliveira 2008a; Rosales 1999; Strube 2002). Clinical trials that combine two or more micronutrients may be more effective in improving the nutritional parameters compared to studies that use only one micronutrient (Dijkhuizen 2004; Rahman 2001; Suharno 1993). In the present review, one trial supplemented the postpartum women with vitamin A plus iron, compared to iron alone. In the vitamin A plus iron group, the improvement on vitamin A status was evident only until three months postpartum. Although the maternal serum retinol and breast milk concentration demonstrated a trend toward improvement in the iron alone group at nine months, it did not reach statistical significance (Roy 1997). In the trial by Ayah 2007 a significant interaction between vitamin A supplementation and serum ferritin was found. The authors observed higher serum retinol among women with serum ferritin above 12 µg/L, suggesting that an improved iron status could influence the response to vitamin A supplementation.

Regarding the infant hepatic vitamin A estimated stores, no protective effect of maternal vitamin A supplementation (200,000-400,000 IU) was observed (Ayah 2007, RETIBETA Project; Stoltzfus 1993a; WHO/CHD IVASSG).

Concern has been expressed about adverse effects from infant supplementation with high doses of vitamin A (more than 50,000 IU; Allen 2002). Studies included in this review did not report increased adverse signs and symptoms among infants supplemented with doses ranging from 25,000-200,000 IU vitamin A, or whose mothers received supplements. The lack of adverse effects in women and babies following maternal vitamin A supplementation is reassuring in the VAD populations studied. Such reassurance cannot be assumed for other populations, including many industrialised nations, where adequate vitamin A dietary intake is achieved.

Only one study monitored the vitamin A content in the capsules during the trial and demonstrated that the vitamin content was stable in the capsules administered to the women. However, the lower dose capsules administered to infants (results not included in this review) were subject to deterioration over time by up to 32% of expected content (Idindili 2007). Thus, the stability of vitamin A capsules should be considered in further studies and routine supplementation programmes (Idindili 2007; Newton 2008).

Four studies (Ayah 2007; Darboe 2007; Idindili 2007; ZVITAMBO Study Group) assessed the effects of a higher dose of vitamin A (400,000 IU). Two of them evaluated the effects of two high doses of 200,000 IU vitamin A (400,000 IU) versus one dose (200,000 IU) and no improvement in maternal and infant health were observed. The remaining studies compared the higher dose (400,000 IU) with placebo and did not report a significant impact on maternal health.

Overall completeness and applicability of evidence

Although included studies were conducted in areas of VAD (WHO 2009), in most of the studies the baseline mean maternal serum concentrations were above the cutoff point proposed by WHO (WHO 1996). Despite this, our findings may be interpreted to represent chronic inadequate vitamin A stores for mothers' health needs, which translated to infants born with inadequate stores. This sub-optimal 'starting point' could not be corrected by postpartum administration of vitamin A to mothers, specifically when breastfeeding. Other systematic reviews of long-term supplementation to women during their reproductive years (including the postpartum period) and of infant supplementation may examine whether long-term preventive supplementation confers greater benefits than postpartum supplementation, that is, after the time when the infant has already received inadequate provision of vitamin A during pregnancy (Haider 2006; Van den Broek 2002).

Quality of the evidence

We judged the included trials to have an overall moderate risk of bias. However we also judged that any bias was unlikely to have obscured a true effect of vitamin A (should it have existed).

Potential biases in the review process

We used several approaches in an attempt to minimise bias. The search strategy incorporated both the trials register of the Cochrane Pregnancy and Childbirth Group and other databases that were likely to included publications from less well developed countries that may not be identified through standard searches. The review authors independently assessed eligibility for conclusion, conducted data extraction and negotiated on areas of concern or uncertainty. Considering the high number of meta-analyses, there is a risk of spuriously significant results.

No vitamin A supplementation regimens report adverse effects for infants or their mothers, in regions of vitamin A deficiency.

This review has not evaluated vitamin A supplementation in non-deficient populations.

Implications for research

This review's focus on postpartum supplementation needs to be considered as part of a wider focus on vitamin A status during infancy and for women, across their reproductive years, including the ideal dosing regimen to achieve improved maternal and infant health for those residing in countries of vitamin A deficiency, where there are also high rates of maternal and infant mortality. Moreover, the stability of vitamin A content in capsules needs consideration.

Further research may consider the potential interaction between vitamin A and other micronutrients, including iron and zinc. Other sustainable long-term strategies to achieve food security, as increased access to local vitamin A rich foods and nutritional education, are also recommended.

AUTHORS' CONCLUSIONS

Implications for practice

In countries with widespread breastfeeding practices and high prevalences of vitamin A deficiency, the transient improvement in maternal serum retinol concentration and milk retinol represent at least a limited benefit of vitamin A supplementation for postpartum women. These findings need to be considered in the context of the potential for follow up with longer term supplementation to ultimately improve maternal and infant health outcomes.

ACKNOWLEDGEMENTS

Staff at the Cochrane Editorial Unit who helped finalise the review.

As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

REFERENCES

References to studies included in this review

Ayah 2007 *{published data only}*

Ayah RA, Mwaniki DL, Magnussen P, Tedstone AE, Marshall T, Alusala D, et al. The effects of maternal and infant supplementation on vitamin A status: a randomised trial in Kenya. *British Journal of Nutrition* 2007;**98**:422–30.

Bhaskaram 2000 *{published data only}*

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

* Bhaskaram P, Balakrishna N, Nair M, Sivakumar B. Vitamin A deficiency in infants: effects of postnatal maternal vitamin A supplementation on the growth and vitamin A status. *Nutrition Research* 2000;**20**:769–78.

Darboe 2007 *{published data only}*

Darboe MK, Thurnham DI, Morgan G, Adegbola RA, Secka O, Solon JA, et al. Effectiveness of an early supplementation scheme of high-dose vitamin A versus standard WHO protocol in Gambian mothers and infants: a randomised controlled trial. *Lancet* 2007;**369**:2088–96.

Idindili 2007 *{published data only}*

Idindili B, Masanja H, Urassa H, Bunini W, Van Jaarsveld P, Aponte JJ, et al. Randomized controlled safety and efficacy trial of 2 vitamin A supplementation schedules in Tanzania infants. *American Journal of Clinical Nutrition* 2007;**85**: 1312–9.

Newton 2005 *{published data only}*

Newton S, Cousens S, Owusu-Agyei S, Filteau S, Stanley C, Linsell L, et al. Vitamin A supplementation does not affect infants' immune responses to polio and tetanus vaccines. *Journal of Nutrition* 2005;**135**:2669–73.

RETIBETA Project *{published data only}*

Filteau SM, Rice AL, Ball JJ, Chakraborty J, Stoltzfus R, De Francisco A, et al. Breast milk immune factors in Bangladeshi women supplemented postpartum with retinol

or beta-carotene. *American Journal of Clinical Nutrition* 1999;**69**:953–8.

* Rice AL, Stoltzfus RJ, De Francisco A, Chakraborty J, Kjolhede CL, Wahed MA. Maternal vitamin A or beta-carotene supplementation in lactating Bangladeshi women benefits mothers and infants but does not prevent subclinical deficiency. *Journal of Nutrition* 1999;**129**:356–65.

Rice AL, Stoltzfus RJ, De Francisco A, Kjolhede CL. Evaluation of serum retinol, the modified-relative-dose-response ratio, and breast-milk vitamin A as indicators of response to postpartum maternal vitamin A supplementation [see comments]. *American Journal of Clinical Nutrition* 2000;**71**:799–806.

Rice AL, Stoltztus RJ, De Francisco A, Kjolhede CL. Low breast milk vitamin A concentration reflects an increased risk of low liver vitamin A stores in women. *Advances in Experimental Medicine and Biology* 2000;**478**:375–6.

Roy 1997 ***{published data only}***

Roy SK, Islam A, Molla A, Akramuzzaman SM, Jahan F, Fuchs G. Impact of single megadose of vitamin A at delivery on breastmilk of mothers and morbidity of their infants. *European Journal of Clinical Nutrition* 1997;**51**(5):302–7.

Stoltzfus 1993a ***{published data only}***

* Stoltzfus RJ, Hakimi M, Miller KW, Rasmussen KM, Dawiesh S, Habicht J, et al. High dose vitamin A supplementation of breast-feeding Indonesian mothers: effects on the vitamin A status of mother and infant. *Journal of Nutrition* 1993;**123**:666–75.

Stoltzfus RJ, Miller KW, Hakimi M, Rasmussen KM. Conjunctival impression cytology as an indicator of vitamin A status in lactating Indonesian women. *American Journal of Clinical Nutrition* 1993;**58**:167–73.

Venkatarao 1996 ***{published data only}***

Venkatarao T, Ramakrishnan R, Nair NGK, Radhakrishnan S, Sundaramoorthy L, Koya PKM, et al. Effect of vitamin A supplementation to mother and infant on morbidity in infancy. *Indian Pediatrics* 1996;**33**(4):279–86.

Vinutha 2000 ***{published data only}***

Vinutha B, Mehta MN, Shanbag P. Vitamin A status of pregnant women and effect of post partum vitamin A supplementation. *Indian Pediatrics* 2000;**37**:1188–93.

WHO/CHD IVASSG ***{published data only}***

Bahl R, Bhandari N, Kant S, Molbak K, Ostergaard E, Bhan MK. Effect of vitamin A administered at expanded program on immunization contacts on antibody response to oral polio vaccine. *European Journal of Clinical Nutrition* 2002;**56**(4):321–5.

Bahl R, Bhandari N, Wahed MA, Kumar GT, Bhan MK. Vitamin A supplementation of women postpartum and their infants at immunization alters breast milk retinol and infant vitamin A status. *Journal of Nutrition* 2002;**132**: 3243–8.

Bahl R, Frost C, Kirkwood BR, Edmond K, Martines J, Bhandari N, et al. Infant feeding patterns and risks of death and hospitalization in the first half of infancy multicentre cohort study. *Bulletin of the World Health Organization* 2005;**83**(6):1–13.

* WHO/CDC IVASSG. Randomised trial to assess benefits and safety of vitamin A supplementation linked to immunisation in early infancy. WHO/CHD Immunisation-Linked Vitamin A Supplementation Study Group. *Lancet* 1998;**352**(9136):1257–63.

ZVITAMBO Study Group ***{published data only}***

Humphrey JH, Hargrove JW, Malaba LC, Iliff PJ, Moulton LH, Mutasa K, et al. HIV incidence among post-partum women in Zimbabwe: risk factors and effect of vitamin A supplementation. *AIDS* 2006;**20**(10):1437–46.

Iliff PJ, Humphrey JH, Mahomva AI, Zvandasara P, Bonduelle M, Malaba L, et al. Tolerance of large doses of vitamin A given to mothers and their babies shortly after delivery. *Nutrition Research* 1999;**19**:1437–46.

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

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

Zvandasara P, Hargrove JW, Ntozini R, Chidawanyika H, Mutasa K, Iliff PJ, et al. Mortality and morbidity among postpartum HIV-positive and HIV-negative women in Zimbabwe: risk factors, causes, and impact of single-dose postpartum vitamin A supplementation. *Journal of Acquired Immune Deficiency Syndromes* 2006;**43**:107–16.

References to studies excluded from this review

Ala-Houhala 1988 ***{published data only}***

Ala-Houhala M, Koskinen T, Mäki R, Rinkari S. Serum vitamin A levels in mothers and their breast-fed term infants with or without supplemental vitamin A. *Acta Paediatrica Scandinavica* 1988;**77**:198–201.

Basu 2003 ***{published data only}***

Basu S, Sengupta B, Paladhi PK. Single megadose vitamin A supplementation of Indian mothers and morbidity in breastfed young infants. *Postgraduate Medical Journal* 2003; **79**:397–402.

Bezerra 2010 ***{published data only}***

* Bezerra DS, Araujo KF, Azevedo GM, Dimenstein R. Maternal supplementation with retinyl palmitate during immediate postpartum period: potential consumption by infants. *Revista de Saude Publica* 2009;**43**(4):572–9.

Bezerra DS, de Araujo KF, Azevedo GM, Dimenstein R. A randomized trial evaluating the effect of 2 regimens of maternal vitamin a supplementation on breast milk retinol levels. *Journal of Human Lactation* 2010;**26**(2):148–56.

Ribeiro KDS, Araújo KF, Dimenstein R. The effect of vitamin A supplementation upon retinol concentration in

the colostrum of women in a public maternity hospital. *Revista da Associação Médica Brasileira* 2009;**55**(4):452–7.

Canfield 2001 *{published data only}*
Canfield LM, Kaminsky RG, Taren DL, Shaw E, Sander JK. Red palm oil in the maternal diet increases provitamin A carotenoids in breastmilk and serum of the mother-infant dyad. *European Journal of Clinical Nutrition* 2001;**40**:30–8.

De Pee 1995 *{published data only}*
De Pee S, West CE, Muhilal Karyadi D, Hautvast JG. Lack of improvement in vitamin A status with increased consumption of dark-green leafy vegetables. *Lancet* 1995; **346**(8967):75–81.

Filteau 1999 *{published data only}*
Filteau SM, Lietz G, Mulokozi G, Bilotta S, Henry CJ, Tomkins AM. Milk cytokines and subclinical breast inflammation in Tanzanian women: effects of dietary red palm oil or sunflower oil supplementation. *Immunology* 1999;**97**:595–600.

Gossage 2000 *{published data only}*
Gossage C, Deyhim M, Moser-Veillon PB, Douglas LW, Kramer TR. Effect of beta-carotene supplementation and lactation on carotenoid metabolism and mitogenic t lymphocyte proliferation. *American Journal of Clinical Nutrition* 2000;**71**(4):950–5.

Khan 2007 *{published data only}*
Khan NC, West CE, De Pee S, Bosch D, Phuong HD, Hulshof PJ, et al. The contribution of plant foods to the vitamin A supply of lactating women in Vietnam: a randomized controlled trial. *American Journal of Clinical Nutrition* 2007;**85**(4):1112–20.

Lietz 2001 *{published data only}*
Lietz G, Henry CJK, Mulokozi G, Mugyabuso JKL, Ballart A, Ndossi GD, et al. Comparison of the effects of supplemental red palm oil and sunflower oil on maternal vitamin A status. *American Journal of Clinical Nutrition* 2001;**74**(4):501–9.

Lietz 2006 *{published data only}*
Lietz G, Mulokozi G, Henry JC, Tomkins AM. Xanthophyll and hydrocarbon carotenoid patterns differ in plasma and breast milk of women supplemented with red palm oil during pregnancy and lactation. *Journal of Nutrition* 2006; **136**(7):1821–7.

Ncube 2001 *{published data only}*
Ncube TN, Greiner T, Malaba LC, Gebre-Medhin M. Supplementing lactating women with pureed papaya and grated carrots improved vitamin A status in a placebo-controlled trial. *Journal of Nutrition* 2001;**131**:1497–1502.

NNIPS-2 *{published data only}*
Christian P. Effects of prenatal micronutrient supplementation on complications of labor and delivery and puerperal morbidity in rural Nepal. *International Journal of Gynecology and Obstetrics* 2009;**106**(1):3–7.
Christian P, West KP Jr, Khatry SK, Katz J, LeClerq S, Pradhan EK, et al. Vitamin A or beta-carotene supplementation reduces but does not eliminate maternal night blindness in Nepal. *Journal of Nutrition* 1998;**128**: 1458–63.
Christian P, West KP Jr, Khatry SK, Katz J, LeClerq SC, Pradhan EK, et al. Vitamin A or beta-carotene supplementation reduces symptoms of illness in pregnant and lactating Nepali women. *Journal of Nutrition* 2000; **130**:2675–82.
Congdon NG, Dreyfuss ML, Christian P, Navitsky RC, Sanchez AM, Wu LSF, et al. Responsiveness of dark adaptation threshold to vitamin A and beta-carotene supplementation in pregnant and lactating women in Nepal. *American Journal of Clinical Nutrition* 2000;**72**:1004–9.
Katz J, West KP Jr, Khatry SK, Pradhan EK, LeClerq SC, Christian P, et al. Maternal low-dose vitamin A or beta-carotene supplementation has no effect on fetal loss and early infant mortality: a randomized cluster trial in Nepal. *American Journal of Clinical Nutrition* 2000;**71**:1570–6.
* West JP Jr, Katz J, Khatry SK, LeClerq S, Pradhan EK, Shrestha SR, et al. Double blind, cluster randomised trial of low dose supplementation with vitamin a or beta carotene on mortality related to pregnancy in Nepal The NNIPS-2 Study Group. *BMJ* 1999;**317**(7183):570–5.
Yamini S, West KP Jr, Wu L, Dreyfuss ML, Yang DX, Khatry SK. Circulating levels of retinol, tocopherol and carotenoid in Nepali pregnant and postpartum women following long-term beta-carotene and vitamin A supplementation. *European Journal of Clinical Nutrition* 2001;**55**:252–9.

ObaapaVitA *{published data only}*
Kirkwood BR, Hurt L, Amenga-Etego S, Tawiah C, Zandoh C, Danso S, et al. Effect of vitamin A supplementation in women of reproductive age on maternal survival in Ghana (ObaapaVitA): a cluster-randomised, placebo-controlled trial. *Lancet* 2010;**375**:1640–9.

Tchum 2006 *{published data only}*
Tchum SK, Tanumihardjo SA, Newton S, Benoist B, Owusu-Agyei S, Arthur FKN, et al. Evaluation of vitamin A supplementation regimens in Ghanaian postpartum mothers with the use of modified-relative-dose-response test. *American Journal of Clinical Nutrition* 2006;**84**: 1344–9.

Additional references

Ahmed 2003
Ahmed F, Azim A, Akhtaruzzaman M. Vitamin A deficiency in poor, urban, lactating women in Bangladesh: factors influencing vitamin A status. *Public Health Nutrition* 2003; **6**(5):447–52.

Allen 2002
Allen LH, Haskell M. Estimating the potential for vitamin A toxicity in women and young children. *Journal of Nutrition* 2002;**132**(9 Suppl):2907S–2919S.

Butte 2002
Butte NF, Lopez-Alarcon MG, Garza C. *Nutrient adequacy of exclusive breastfeeding for the term infant during the first six months of life. Expert consultation on the optimal duration of exclusive breastfeeding*. Geneva: WHO, 2002.

Christian 1998
Christian P, West KP Jr. Interactions between zinc and vitamin A: an update. *American Journal of Clinical Nutrition* 1998;**68**(2S):435S–441S.

Dancheck 2005
Dancheck B, Nussenblatt V, Ricks MO, Kumwenda N, Neville MC, Moncrief DT, et al. Breast milk retinol concentrations are not associated with systemic inflammation among breast-feeding women in Malawi. *Journal of Nutrition* 2005;**135**(2):223–6.

De Pee 1995
De Pee S, West CE, Muhilal Karyadi D, Hautvast JG. Lack of improvement in vitamin A status with increased consumption of dark-green leafy vegetables. *Lancet* 1995; **346**:75–81.

Dijkhuizen 2004
Dijkhuizen MA, Wieringa FT, West CE, Muhilal. Zinc plus beta-carotene supplementation of pregnant women is superior to beta-carotene supplementation alone in improving vitamin A status in both mothers and infants. *American Journal of Clinical Nutrition* 2004;**80**(5): 1299–307.

Egger 1997
Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–34.

FAO/WHO 2001
Food and Agriculture Organization of United Nations/ World Health Organization. *Human vitamin and mineral requirements. Report of a joint FAO/WHO expert consultation, Bangkok, Thailand*. Bangkok: FAO, 2001.

Fawzi 1993
Fawzi WW, Chalmers TC, Herrera MG, Mosteller F. Vitamin A supplementation and child mortality. *JAMA* 1993;**269**(7):898–903.

Filteau 1993
Filteau SM, Morris SS, Abbott RA, Tomkins AM, Kirkwood BR, Arthur P, et al. Influence of morbidity on serum retinol of children in a community-based study in northern Ghana. *American Journal of Clinical Nutrition* 1993;**58**:192–7.

FNB 2000
Food, Nutrition Board. Vitamin A. *Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2000.

Garcia-Casal 1998
García-Casal MN, Layrisse M, Solano L, Baron MA, Arguello F, Llovera D, et al. Vitamin A and beta-carotene can improve nonheme iron absorption from rice, wheat and corn by humans. *Journal of Nutrition* 1998;**128**(3):646–50.

Glasziou 1993
Glasziou PP, Mackerras DEM. Vitamin A supplementation in infection diseases: a meta-analysis. *BMJ* 1993;**306**: 366–70.

Haider 2006
Haider BA, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: 10.1002/14651858.CD004905.pub2]

Harbord 2006
Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine* 2006;**25**:3443–57.

Higgins 2009
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration, 2009. Available from www.cochrane-handbook.org.

IVACG 2004
International Vitamin A Consultative Group (IVACG). *Conversion factors for vitamin A and carotenoids*. Washington: IVACG Secretariat, 2004.

Jang 2000
Jang JT, Green JB, Beard JL, Green MH. Kinetic analysis shows that iron deficiency decreases liver vitamin A mobilization in rats. *Journal of Nutrition* 2000;**130**:1291–6.

JivitA-1 Trial
Christian P, West Jr KP, Labrique A, Klemm R, Rashid M, Shamim AA, et al. Effects of maternal vitamin A or beta-carotene supplementation on maternal and infant mortality in rural Bangladesh: The JivitA-1 Trial. Micronutrient Forum; 2007 April 16-18; Istanbul, Turkey. 2007:Abstract No: W121.

Lynch 1997
Lynch SR. Interactions of iron with other nutrients. *Nutrition Reviews* 1997;**55**(4):102–10.

Munoz 2000
Muñoz EC, Rosado JL, Lopez P, Furr HC, Allen LH. Iron and zinc supplementation improves indicators of vitamin A status of Mexican preschoolers. *American Journal of Clinical Nutrition* 2000;**71**(3):789–94.

Newton 2008
Newton S, Owusu-Agyei S, Kirkwood B. Is there any monitoring of the quality of vitamin A capsules used in supplementation programs?. *American Journal of Clinical Nutrition* 2007;**86**(4):1254.

Oliveira 2008a
Oliveira JM, Michelazzo F, Stefanello J, Rondó PH. Influence of iron on vitamin A nutritional status. *Nutrition Reviews* 2008;**66**:141–7.

Rahman 2001
Rahman MM, Vermund SH, Wahed MA, Fuchs GJ, Baqui AH, Alvarez JO. Simultaneous zinc and vitamin A supplementation in Bangladeshi children: randomised double blind controlled trial. *BMJ* 2001;**323**:314–8.

Rasmussen 1998
Rasmussen K. Vitamin A needs during pregnancy and lactation for the health of the mother and her fetus or infant. *Safe vitamin A dosage during pregnancy and lactation:*

recommendations and report of a consultation. Micronutrient Initiative. Geneva: WHO, 1998:8–12.

RevMan 2008 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5 for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

Rice 2000
Rice AL, Stoltzfus RJ, De Francisco A, Kjolhede CL. Evaluation of serum retinol, the modified-relative-dose-response ratio, and breast-milk vitamin A as indicators of response to postpartum maternal vitamin A supplementation. *American Journal of Clinical Nutrition* 2000;**71**(3):799–806.

Rondó 1997
Rondó PH, Abbott R, Tomkins AM. Vitamin A and intrauterine growth retardation. *Journal of Pediatrics* 1997; **73**:335–9.

Rosales 1999
Rosales FJ, Jang JT, Pinero DJ, Erikson KM, Beard JL, Ross AC. Iron deficiency in young rats alters the distribution of vitamin A between plasma and liver and between hepatic retinol and retinyl esters. *Journal of Nutrition* 1999;**129**: 1223–8.

Ross 2002
Ross DA. Recommendations for vitamin A supplementation. *Journal of Nutrition* 2002;**131**:2902S–2906S.

Sommer 1993
Sommer A. Clinical signs of xerophthalmia. *IVACG. A brief guide to current methods of assessing vitamin A status*. Washington DC: The Nutrition Foundation, 1993:37.

Stoltzfus 1993b
Stoltzfus RJ, Habicht JP, Rasmussen KM, Hakimi M. Evaluation of indicators for use in vitamin A intervention trials targeted at women. *International Journal of Epidemiology* 1993;**123**(4):666–75.

Stoltzfus 1993c
Stoltzfus RJ, Miller KW, Hakimi M, Rasmussen KM. Conjunctival impression cytology as an indicator of vitamin A status in lactating Indonesian women. *American Journal of Clinical Nutrition* 1993;**58**(2):167–73.

Strube 2002
Strube YNJ, Beard JL, Ross AC. Iron deficiency and marginal vitamin A deficiency affect growth, hematological indices and the regulation of iron metabolism genes in rats. *Journal of Nutrition* 2002;**132**:3607–15.

Suharno 1993
Suharno D, West CE, Muhilal, Karyadi D, Hautvast JG. Supplementation with vitamin A and iron for nutritional anaemia in pregnant women in West Java, Indonesia. *Lancet* 1993;**342**(8883):1235–8.

Van den Broek 2002
Van den Broek N, Kulier R, Gülmezoglu AM, Villar J. Vitamin A supplementation during pregnancy. *Cochrane Database of Systematic Reviews* 2002, Issue 4. [DOI: 10.1002/14651858.CD001996]

Walczyk 2003
Walczyk T, Davidsson L, Rossander-Hulthen L, Hallberg L, Hurrell RF. No enhancing effect of vitamin A on iron absorption in humans. *American Journal of Clinical Nutrition* 2003;**77**(1):144–9.

West 1997
West KP, LeClerq SC, Shrestha SR, Wu LS, Pradhan EK, Khatry SK, et al. Effects of vitamin A on growth of vitamin A-deficient children: field studies in Nepal. *Journal of Nutrition* 1997;**127**(10):1957–65.

West 2002
West KP Jr. Extent of vitamin A deficiency among preschool children and women of reproductive age. *Journal of Nutrition* 2002;**132**:285S–2866S.

WHO 1995
World Health Organization. *Global prevalence of vitamin A deficiency. Micronutrient Deficiency Information System, No 2 (WHO/NUT/95.3)*. Vol. **2**, Geneva: WHO, 1995.

WHO 1996
World Health Organization. *Indicators for assessing vitamin A deficiency and their application in monitoring and evaluating intervention programmes. (WHO/NUT/96.1)*. Geneva: WHO, 1996.

WHO 1998
World Health Organization. *Safe vitamin A dosage during pregnancy and lactation: recommendations and report of a consultation. Micronutrient Initiative*. Geneva: WHO, 1998.

WHO 2009
World Health Organization. Global prevalence of vitamin A deficiency in population at risk 1995-2005: WHO database of vitamin A deficiency. Geneva: WHO, 2009.

WHO 2010
World Health Organization. *World health statistics 2010*. Geneva: WHO, 2010.

Yang 2005
Yang HM, Mao M, Wan CM. Vitamin A for treating measles in children. *Cochrane Database of Systematic Reviews* 2005, Issue 4. [DOI: 10.1002/14651858.CD001479]

References to other published versions of this review

Oliveira 2008b
Oliveira JM, East CE, Bergamashi DP. Vitamin A supplementation for breastfeeding mothers: a systematic review. *Journal of Paediatrics and Child Health* 2008;**44** (Suppl 1):A88.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Ayah 2007

Methods	Randomised, double blind, placebo controlled, 2 by 2 factorial trial
Participants	Women giving birth to a live single baby and their infants. Bondo, Kenya. N = 564 mothers and their infants.
Interventions	Single dosage administered to mother within 24 hours of birth; single dosage to infant at 1-4 weeks of age All infants received 100,000 IU vitamin A at 8 months of age (after trial) 4 intervention groups: 1. Mother received 400,000 IU vitamin A and infant received 100,000 IU vitamin A as retinyl palmitate (n = 142). 2. Mother received 400,000 IU vitamin A and infant received placebo (n = 140). 3. Mother received placebo and infant received 100,000 IU vitamin A (n = 143). 4. Mother received placebo and infant received placebo (n = 139)
Outcomes	Maternal serum retinol concentration, breast milk retinol concentration. Infant serum retinol concentration, vitamin A hepatic stores (MRDR)
Notes	No information regarding breastfeeding pattern was provided. However, at least some breastfeeding is implied by the analysis of breast milk retinol at 6 months for 63% of the women originally enrolled 87.4% of follow up until 14 weeks, 77.1% of follow up until 26 weeks postpartum The prevalence of HIV infection among antenatal attendees was above 28% at the time of the study. However, the trial was conducted prior to availability of HIV testing and antiretrovirals for antenatal women in western Kenya. Thus, it was not possible to know the prevalence of HIV among recruited women Sample size calculation reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	"Two random sequences of X and Y were prepared, one for the mothers and one for the infants. Identification numbers from 1 to 700 were assigned consecutively to each of the two lists and mother-infant pairs of capsules were packaged in zip-lock bags numbered from 1 to 700 and kept in batches of ten."

Ayah 2007 (*Continued*)

Allocation concealment?	Low risk	"The randomisation codes were concealed for the entire trial duration and only revealed after completion of data analysis."
Blinding? All outcomes	Low risk	"...prepared and supplied the vitamin A and identical-looking placebo supplements as oily capsules in brown bottles coded as X or Y."
Incomplete outcome data addressed? All outcomes	Low risk	All analyses were by intention-to-treat.
Free of selective reporting?	High risk	Not all clinically relevant outcomes reported.
Free of other bias?	High risk	Supported by Hoffmann-La Roche Ltd (Basel Switzerland).

Bhaskaram 2000

Methods	Randomised, double blind, placebo controlled trial.
Participants	Hospital based study with postpartum women who did not receive any vitamin A supplements during pregnancy and had uncomplicated full term births Hyderabad, India. 102 mothers and their infants.
Interventions	Single high dose to mother within 24 hours after birth. 2 intervention groups: 1. Mother received 200,000 IU vitamin A as retinyl palmitate (n = 50). 2. Mother received placebo (n = 52).
Outcomes	Infant serum retinol concentration, breast milk retinol concentration, and corneal lesions
Notes	All babies given oral polio vaccine within 72 hours after birth. All infants breastfed, followed up at 6 months. 100% of follow up until 6 weeks, 87% followed up until 3 months, 46% followed up until 6 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Randomised, no detail provided.
Allocation concealment?	Unclear risk	No detail provided.

Bhaskaram 2000 (*Continued*)

Blinding? All outcomes	Low risk	Blinding: vitamin A and placebo coded by person not connected with the investigation. Nurse administering dose unaware of code.
Incomplete outcome data addressed? All outcomes	High risk	Reasons for attrition and exclusions not reported. Intention-to-treat analyses not performed
Free of selective reporting?	High risk	Not all clinically relevant outcomes reported.
Free of other bias?	Unclear risk	Source of funding not mentioned. No mention of any research protocol published a priori

Darboe 2007

Methods	Randomised, double blind, placebo controlled trial.
Participants	Postpartum women without severe peripartum difficulties or preterm birth, with newborns $\geq$ 2200 g with no congenital defects at birth Keneba and West Kiang, Gambia. 220 mothers and their infants.
Interventions	Single or double high dose to mother at delivery (first dose) and within a week (second dose); and 3 high doses to infant at 2, 3 or 4 months All infants received 100,000 IU vitamin A at 9 months and 200,000 IU at 12 months postpartum 2 intervention groups: 1. Mother received 400,000 IU vitamin A as retinyl palmitate and infant received 150,000 IU vitamin A (3 doses of 50,000 IU) (n = 110); 2. Mother received 200,000 IU and infant received placebo (3 doses) (n = 110)
Outcomes	Maternal morbidity, and serum retinol and breast milk retinol concentration. Infant morbidity, haemoglobin concentration, and serum retinol concentration
Notes	No information regarding breastfeeding pattern was provided. However, at least partial breastfeeding is implied by the reported analysis of breast milk retinol to 6 months in 88% of those enrolled 89.5% of follow up until 12 months.

Risk of bias

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

Darboe 2007 (*Continued*)

Adequate sequence generation?	Low risk	"An independent senior scientist packed and labelled the supplements, and did a block randomisation procedure (16 per block) to allow for possible effects of season of birth."
Allocation concealment?	Low risk	"All members of the trial team were unaware of allocation until the data had been cleaned and locked."
Blinding? All outcomes	Unclear risk	"Vitamin A in vegetable oil and vegetable oil placebo were prepared by Hoffmann La Roche (Basel, Switzerland)."
Incomplete outcome data addressed? All outcomes	Low risk	Reasons for attrition and exclusions were reported in detail, although intention-to-treat analysis was not performed
Free of selective reporting?	High risk	Not all clinically relevant outcomes reported
Free of other bias?	Low risk	Trial registered a priori (No. ISRCTN 98554309). The UK Medical Research Council funded the study, and laboratory analyses in Coleraine were supported by BASF Aktiengesellschaft (Ludwigshafen, Germany).

Idindili 2007

Methods	Randomised, double blind, placebo controlled trial.
Participants	Mothers resident in the study area that brought their infants for vaccination Ifakara, Tanzania. 780 mothers and their infants.
Interventions	Single or double high dose to mother within 1 week after delivery; and 3 standard or higher doses to infant at 1, 2 or 3 months (DPT/OPV vaccination) All infants received 100,000 IU vitamin A at measles vaccination (9 months) 2 intervention groups: 1. Mother received 200,000 IU vitamin A as retinyl palmitate and infant received 75,000 IU vitamin A (3 doses of 25,000 IU) (n = 390). 2. Mother received 400,000 IU vitamin A and infant received 150,000 IU vitamin A (3 doses of 50,000 IU) (n = 390)

Outcomes	Infant morbidity, anaemia (packed cell volume), serum retinol concentration, vitamin A hepatic stores (MRDR), and breast milk retinol concentration
Notes	At least 86% of infants were exclusively breastfed until 1 month 81% of follow up until 3 months; 79.5% until 6 months; and 77.2% until 9 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	"Individual randomization was achieved by using a list of study numbers that had been randomly assigned to an intervention arm in blocks of 10, generated by the Data and Safety Monitoring Board."
Allocation concealment?	Low risk	"A compact disk containing the cleaned and locked database files was exchanged for the treatment randomization code, held by the Data and Safety Monitoring Board." All members of the trial team were unaware of allocation until the data had been cleaned and locked
Blinding? All outcomes	Unclear risk	"Vitamin A capsules providing different doses were manufactured by Accucaps Industries (Windsor, Canada) (25,000 and 50,000 IU) and RpScherer (Aprilia, Italy) (200,000 IU), and were supplied to the project by the WHO." Not enough detail to judge whether participants were blinded
Incomplete outcome data addressed? All outcomes	High risk	Reasons for attrition and exclusions not reported. Intention-to-treat analyses not performed
Free of selective reporting?	High risk	Not all clinically relevant outcomes reported.
Free of other bias?	Unclear risk	Post hoc analyses were conducted because of concerns that the capsules did not contain the necessary amount of vitamin A (in a sample of capsules vitamin degraded) Supported by Immunization Vaccines & Biologicals (the World Health Organization and the United Nations Foundation), Sight&Life (Hoffman-la Roche

		Ltd), Micronutrient Initiative, the Canadian International Development Agency, and the United Nations Children's Fund (UNICEF)

Newton 2005

Methods	Randomised, double blind, placebo controlled 2 x 2 factorial design trial
Participants	Women 3-4 weeks postpartum and their infants. Kintampo, Brong Ahafo Region, Ghana. N = 1085 mothers and their infants.
Interventions	4 intervention groups. 1. Mother received 200,000 IU of vitamin A as retinyl palmitate at 3-4 weeks and infant received total of 75,000 IU (25,000 IU at 6, 10 and 14 weeks) (n = 274) 2. Mother received placebo at 3-4 weeks and infant received total of 75,000 IU (25,000 IU at 6, 10 and 14 weeks) (n = 265) 3. Mother received 200,000 IU of vitamin A as retinyl palmitate and infant received total of placebo (n = 269) 4. Mother received placebo and infant received placebo at 6, 10 and 14 weeks (n = 277)
Outcomes	Infant serum antibody titers for polio and tetanus at 6 months of age, and infant mortality
Notes	No information supplied regarding breastfeeding rates. The report's background outlined the evaluation of whether maternal supplementation alone could achieve adequate vitamin A status, without the need for infant supplementation. This suggests that women were breastfeeding Infant supplementation linked to time of administration of diphtheria pertussis tetanus and polio vaccinations It was confirmed with the first author that the mortality data in the study referred to infants

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	"Mothers and infants were allocated to 1 of 4 treatment groups, using a blocked randomization scheme."
Allocation concealment?	Unclear risk	Details not provided.
Blinding? All outcomes	Low risk	"The test and placebo capsules were identical in size colour and shape."
Incomplete outcome data addressed? All outcomes	High risk	Only infants of mothers for which blood sample was obtained in the end of the study

		were included in the analysis. Attrition was 34.6%
Free of selective reporting?	High risk	Not all clinically relevant outcomes were reported.
Free of other bias?	Unclear risk	Enrolment of participants was extended to higher than planned lost to follow-up. Sample size calculation provided, but unclear whether a protocol was published a priori. Supported by a grant from the Wellcome Trust

RETIBETA Project

Methods	Randomised, double blind, placebo controlled trial.
Participants	Community-based study with women at 1-3 weeks after birth. Matlab, Bangladesh. 220 mothers and their infants.
Interventions	Single high dose to mother within 1-3 weeks after delivery of beta-carotene daily for 9 months 3 intervention groups: 1. Mother received 200,000 IU of vitamin A as retinyl palmitate and placebo daily for 9 months postpartum (n = 74). 2. Mother received placebo and 7.8 mg (1,300 µg RE or 4,327 IU) of beta-carotene daily until 9 months postpartum (n = 73). 3. Mother received placebo and placebo daily until 9 months postpartum (n = 73)
Outcomes	Maternal serum retinol, vitamin A hepatic stores (MRDR), and breast milk retinol concentration. Infant serum retinol concentrations, and vitamin A hepatic stores (MRDR) in a subsample of mothers and infants
Notes	All Infants at least partially breastfed to 6 months of age. 87% ate complementary food during this period. 98% follow-up rates until 3 months, 95% until 6 months, and 92% until 9 months postpartum

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	"Before beginning the study, individual treatment codes and follow-up schedules were assigned to a sequence of identification numbers in blocks of 18 using a random number table"..."Each block con-

RETIBETA Project (*Continued*)

		tained all possible combinations of three treatment groups."
Allocation concealment?	Low risk	"The study capsules were manufactured by Tischon Corporation (Salisbury, MD) and delivered to the field and to study participants coded as type A, B or C."
Blinding? All outcomes	Low risk	Capsules: packaged in blister pack strips. Vitamin A and placebo capsules differed in colour slightly - authors considered that foil packaging would reduce direct comparisons between groups. Beta-carotene and placebo capsules identical in colour
Incomplete outcome data addressed? All outcomes	High risk	Reasons for attrition and exclusions not reported. Intention-to-treat analyses not performed
Free of selective reporting?	High risk	Not all clinically relevant outcomes were reported.
Free of other bias?	Unclear risk	Supported by cooperative agreements between The Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD, USA and the Office of Health and Nutrition, U.S. Agency for International Development, Washington, DC (DAN-5116-1-00-8051-00 and HRN-A-00-97-00015-00). Research protocol not published a priori

Roy 1997

Methods	Randomised controlled trial.
Participants	Postpartum women. Dhaka, Bangladesh. 50 mothers and their infants.
Interventions	Single high dose to mother within 24 hours after birth. 2 intervention groups: 1. Mother received 200,000 IU vitamin A as retinyl palmitate plus 60 mg of iron daily for 9 months (n = 25). 2. Mother received 60 mg of iron daily for 9 months (n = 25)
Outcomes	Maternal serum retinol, and breast milk retinol concentration. Infant morbidity

Roy 1997 (*Continued*)

Notes	All babies were breastfed until 6 months postpartum. No information regarding breastfeeding pattern was provided.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Women were randomly allocated to either the intervention or control group. No further details provided
Allocation concealment?	Unclear risk	No details provided.
Blinding? All outcomes	High risk	Women in the control group did not receive a placebo. No details provided about blinding of field workers, laboratory staff or investigators
Incomplete outcome data addressed? All outcomes	Low risk	All randomised participants were accounted for in the analysis
Free of selective reporting?	High risk	Not all clinically relevant outcomes were reported.
Free of other bias?	Unclear risk	Study supported by the International Centre for Diarrhoeal Disease Research and the United States Agency for International Development. Research protocol not published a priori

Stoltzfus 1993a

Methods	Randomised, double blind, placebo controlled trial.
Participants	Women at 1-3 weeks postpartum. Java, Indonesia. 153 mothers and their infants.
Interventions	Single high dose to mother within 1-3 weeks after birth. 2 intervention groups: 1. Mother received 300,000 IU vitamin A as retinyl palmitate (n = 77) 2. Mother received placebo (n = 76).
Outcomes	Maternal abnormal conjunctival impression cytology (CIC), breast milk retinol concentration, maternal serum retinol concentration. Infant serum retinol concentration, vitamin A hepatic stores (RDR)
Notes	No specific information regarding breastfeeding pattern was provided. However, the report's title, background and analysis of breast milk retinol to 8 months postpartum strongly suggest that infants received at least some breast milk for the duration of the study. Additionally, it is noted that the 3 women who stopped breastfeeding were not

Stoltzfus 1993a (*Continued*)

	included in the 6 month follow-up 88.9% follow-up rate until 6 months postpartum.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	"Individual randomization to treatment codes A and B was done in blocks of eight according to the Moses-Oakford assignment algorithm."
Allocation concealment?	Low risk	"The allocation of treatment codes A and B to vitamin A or placebo capsules was done by the Sight and Life Task Force, Hoffmann-LaRoche (Basel, Switzerland), who prepared the capsules."
Blinding? All outcomes	Low risk	Vitamin A and placebo capsules "looked practically identical" and were prepared by "Sight and Life Task Force, Hoffmann-LaRoche" - in labelled foil packs. Participants, field workers, investigators and laboratory staff blinded to randomisation sequence until after field work complete
Incomplete outcome data addressed? All outcomes	High risk	Reasons for attrition and exclusions not reported. Intention-to-treat analyses not performed
Free of selective reporting?	High risk	Not all clinically relevant outcomes were reported.
Free of other bias?	Unclear risk	Supported by a grant from the Thrasher Research Fund and a National Science Foundation Graduate Fellowship to Rebecca I. Stoltzfus. Study protocol not published a priori

Venkatarao 1996

Methods	Randomised, double blind, placebo controlled trial.
Participants	Women at 1-2 weeks after birth. Tamil Nadu, India. 909 mothers and their infants.

Venkatarao 1996 (*Continued*)

Interventions	Single high dose to mother within 1-2 weeks after birth; and high dose to infant at 6 months 3 intervention groups: 1. Mother received 300,000 IU vitamin A as retinyl palmitate and Infant received 200, 000 IU vitamin A (n = 301) 2. Mother received 300,000 IU vitamin A and Infant received placebo (n = 297) 3. Mother received placebo and Infant received placebo at 6 months of age (n = 311)
Outcomes	Infant morbidity, and adverse effects.
Notes	99.7% of infants were breast fed for at least 6 months. No information regarding breast-feeding pattern was provided 75.8% follow-up rate until 12 months postpartum.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	"...randomly allocated". No further details given.
Allocation concealment?	Unclear risk	" the Medical Officer...administered the appropriate capsules to the mother from the sealed envelope supplied by the Statistical Section at the Camp Office."
Blinding? All outcomes	Low risk	Capsules were "similar in colour". Infant syrup matched for colour and consistency
Incomplete outcome data addressed? All outcomes	High risk	Exclusions and attrition were 23%. Intention-to-treat analyses not performed
Free of selective reporting?	High risk	Not all expected outcomes reported.
Free of other bias?	Unclear risk	Source of funding not provided. No mention of research protocol

Vinutha 2000

Methods	Randomised, controlled trial.
Participants	Postpartum women (primigravid and second-gravid). Mumbai, India. 109 mothers and their infants.
Interventions	Single high dose to mother within 48 hours after delivery. 2 intervention groups:

Vinutha 2000 (*Continued*)

	1. Mother received 200,000 IU vitamin A as aquasol water miscible (n = 53) 2. Mother did not receive vitamin A or placebo (n = 56).
Outcomes	Maternal serum retinol, breast milk retinol concentration. Infant serum retinol concentration
Notes	All babies were exclusively breastfed. 77.1% follow-up rate until 3 months postpartum.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Randomised. No further details provided.
Allocation concealment?	Unclear risk	No details provided.
Blinding? All outcomes	High risk	Women in the control group did not receive a placebo. No other details provided on blinding
Incomplete outcome data addressed? All outcomes	High risk	Reasons for attrition and exclusions not reported. Intention-to-treat analyses not performed
Free of selective reporting?	High risk	Not all clinically relevant outcomes were reported.
Free of other bias?	Unclear risk	Funded by the Lokmanya Tilak Municipal Medical College and Hospital in Mumbai. Study protocol not published a priori

WHO/CHD IVASSG

Methods	Randomised, double blind, placebo controlled, multicentre trial (India, Ghana, and Peru)
Participants	Postpartum women and their infants. New Delhi, India; Brong Ahafo, Ghana; Lima, Peru. 7078 mothers and their infants.
Interventions	Single high dose to mother within 21-42 days after birth in Ghana and 18-28 days after birth in Peru and India 3 doses to infant during their DPT or OPV immunization (6, 10, 14 weeks) in Ghana, India and (2, 3 and 4 months) in Peru Multicentre trial - At 9 months, infants received 25,000 IU vitamin A with measles immunisation and infants from the control group received single high dose 100,000 IU vitamin A Ghana trial - At 6 months, infants received 25,000 IU vitamin A and infants from the control group received single high dose 100,000 IU vitamin A Multicentre trial - 2 intervention groups:

	1. Mother received 200,000 IU vitamin A as retinyl palmitate and Infants received 100, 000 IU vitamin A (4 doses 25,000 IU) (n = 3,522) 2. Mothers received placebo and Infants received placebo (3 doses) plus 100,000 IU vitamin A at 9 months (equivalent total dose received by group 1) (n = 3,556) Ghana - 4 intervention groups: 1. Mother received 200,000 IU vitamin A as retinyl palmitate and Infants received 100, 000 IU vitamin A (4 doses 25,000 IU) (n = 196). 2. Mother received placebo and Infants received vitamin A as per group 1 (n = 192). 3. Mother received vitamin A as per group 1 and Infants received placebo at times of immunisation, plus 100,000 IU vitamin A at 6 months (equivalent total dose received by groups 1 and 2) (n = 185). 4. Mothers received placebo and Infants received placebo (3 doses), plus 100,000 IU vitamin A at 6 months (equivalent total dose received by groups 1 and 2) (n = 194)
Outcomes	Maternal serum retinol, breast milk retinol concentration. Infant mortality, morbidity, acute toxic effects, serum retinol concentration, vitamin A hepatic stores (MRDR)
Notes	At least 99.4% of infants were breastfed at enrolment. The sub-study that reported breast milk retinol gave these findings for 570 women, compared with 631 at 2 months, suggesting that the majority of infants were at least partially breast fed to 9 months 74.9% follow-up rate until 12 months postpartum. Before and periodically during the study standardisation exercises to assess agreement within and between observers were conducted for the main outcome variables Standardisation across sites (Ghana, India and Peru) was ensured by exchange visits

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	"Identification numbers were generated by computer at the data management centre at John Hopkins University in Baltimore, and assigned as random permuted blocks of size eight."
Allocation concealment?	Low risk	"Three sealed copies of study codes were prepared and kept at WHO in Geneva, with the ethics committee of the All India Institute of Medical Sciences in New Delhi, and at the data management centre in Baltimore. Access was limited to one data manager, who had no direct involvement in the data analysis, and who prepared information requested by the treatment effects monitoring committee."
Blinding? All outcomes	Low risk	"The supplements and placebo, in identical opaque gelatin capsules, were packaged in individually coded blister packs in Bal-

WHO/CHD IVASSG (*Continued*)

		timore."
Incomplete outcome data addressed? All outcomes	Low risk	"All analyses were by intent to treat from the time of first administration of study capsule to the mother."
Free of selective reporting?	Low risk	All expected clinically relevant outcomes were reported.
Free of other bias?	Low risk	Trial supported by the Child Health and Development Division of WHO, the Johns Hopkins Family Health and Child Survival Cooperative Agreement (HRN 5986-A-00-6006-00) with funding from the United States Agency for International Development, and the Indian Council of Medical Research. A study protocol was not mentioned but study described in detail

ZVITAMBO Study Group

Methods	Randomised, double blind, placebo controlled, 2 by 2 factorial trial
Participants	Postpartum women without a life-threatening condition and their infants with birthweight $\geq$ 1500 g from urban maternity centres. Harare, Zimbabwe. N = 14,110 mothers and their infants.
Interventions	Double high dose to mother within 96 hours of birth and single high dose to infant 4 treatment groups: 1. Mother received 400,000 IU vitamin A as retinyl palmitate and infant received 50,000 IU vitamin A (n = 3529) 2. Mother received 400,000 IU vitamin A and infant received placebo (n = 3529) 3. Mother received placebo and infant received 50,000 IU vitamin A (n = 3530) 4. Mother received placebo and infant received placebo (n = 3522)
Outcomes	Maternal mortality, morbidity, serum retinol concentration, haemoglobin concentration. Infant mortality, acute adverse effects (for 788 mother-infant pairs only), and serum retinol concentration Infant cause of death was determined from medical records when the death occurred in the hospital, or from a review of verbal autopsy information by study paediatrician
Notes	All women initiated breastfeeding (97% started breastfeeding within 12 hours postpartum). 99.5% were still breastfeeding at 6 months and 85.8% at 12 months postpartum

Risk of bias

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

Adequate sequence generation?	Low risk	"A separate team at Johns Hopkins University prepared the study capsule packets. Study identification numbers were randomly allocated to the treatment groups by computer in blocks of 12. The numbers were printed on adhesive labels and affixed to amber-colored zip-lock plastic bags that were packed with the assigned capsules. Capsule packets were prepared separately for each of the 4 treatment groups and were then merged into numeric order before shipping to Zimbabwe, where a series of packets were distributed to each recruitment site. As each mother-infant pair was recruited, the capsules in the next sequential bag were administered, and the associated study number was assigned to the pair."
Allocation concealment?	Low risk	"Lists linking the study number to the treatment were kept in sealed envelopes and encrypted computer files."
Blinding? All outcomes	Low risk	"Treatment and placebo capsules appeared identical." "separate team at Johns Hopkins University prepared the study capsule packets" and "neither participants nor nurses who administered the capsules or assessed outcomes were aware of treatment group assignment."
Incomplete outcome data addressed? All outcomes	High risk	"Only infants of mothers who remained HIV-negative to 12 months postpartum were included in the current analysis." Attrition was 11.3% (in both the vitamin A and placebo groups) for HIV-negative women (985/9562) Adverse event data was only available for a subset of 788 mother-infant pairs The analyses were not by ITT.
Free of selective reporting?	High risk	Not all clinically relevant outcomes were reported.
Free of other bias?	Low risk	"The ZVITAMBO Project was primarily supported by the Canadian International Development Agency (R/C Project 690/

ZVITAMBO Study Group (*Continued*)

		M3688), the US Agency for International Development (cooperative agreement no. HRN-A-00-97-00015-00 between Johns Hopkins University and the Office of Health and Nutrition of the USAID), and a grant from the Bill and Melinda Gates Foundation (Seattle); additional support was provided by the Rockefeller Foundation (New York) and BASF (Ludwigshafen, Germany)."

CIC: conjunctival impression cytology
DPT: diphtheria, pertussis, tetanus vaccine
h: hour
IU: international unit
MRDR: modified relative dose response
OPV: oral polio vaccine
RE: Retinol equivalent

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

Study	Reason for exclusion
Ala-Houhala 1988	Alternate allocation to the control or test group.
Basu 2003	Alternate allocation to the control or test group.
Bezerra 2010	Alternate allocation to the control or test group.
Canfield 2001	Provision of vitamin A rich foods rather than vitamin A supplements
De Pee 1995	Provision of vitamin A rich foods rather than vitamin A supplements
Filteau 1999	Provision of vitamin A rich foods rather than vitamin A supplements
Gossage 2000	Provision of vitamin A rich foods rather than vitamin A supplements
Khan 2007	Provision of vitamin A rich foods rather than vitamin A supplements
Lietz 2001	Provision of vitamin A rich foods rather than vitamin A supplements
Lietz 2006	Provision of vitamin A rich foods rather than vitamin A supplements
Ncube 2001	Provision of vitamin A rich foods rather than vitamin A supplements

(*Continued*)

NNIPS-2	Long-term supplementation for women of reproductive age.
ObaapaVitA	Long-term supplementation for women of reproductive age.
Tchum 2006	Alternate allocation to the control or test group.

DATA AND ANALYSES

Comparison 1. Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal mortality to six months	1	564	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.09, 2.71]
1.1 400,000 IU versus placebo	1	564	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.09, 2.71]
2 Maternal fever at 3 months postpartum			Other data	No numeric data
2.1 200,000 IU versus no treatment			Other data	No numeric data
3 Maternal respiratory tract infection at 3 months postpartum			Other data	No numeric data
3.1 200,000 IU versus no treatment			Other data	No numeric data
4 Maternal diarrhoea at 3 months postpartum			Other data	No numeric data
4.1 200,000 IU versus no treatment			Other data	No numeric data
5 Maternal adverse effects of supplementation	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Headache within 30 hours of dosing: 400,000 IU versus placebo	1	786	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.74, 1.99]
5.2 Blurred vision within 30 hours of dosing: 400,000 IU versus placebo	1	786	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.39, 6.82]
5.3 Drowsiness within 30 hours of dosing: 400,000 IU versus placebo	1	786	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [0.91, 4.79]
5.4 Nausea within 30 hours of dosing: 400,000 IU versus placebo	1	786	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.44, 4.31]
5.5 Vomiting within 30 hours of dosing: 400,000 IU versus placebo	1	786	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.14]
5.6 Poor appetite within 30 hours of dosing: 400,000 IU versus placebo	1	786	Risk Ratio (M-H, Fixed, 95% CI)	2.22 [0.69, 7.14]
5.7 Abdominal pain within 30 hours of dosing: 400,000 IU versus placebo	1	786	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.95, 1.73]
6 Maternal serum retinol (μmol/L) at 1.5 months postpartum	1	260	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.02, 0.20]

6.1 HIV negative women: 400,000 IU versus placebo	1	260	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.02, 0.20]
7 Maternal serum retinol (mcmol/L) at 3 - 3.5 months postpartum	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 200,000-400,000 IU versus placebo or no treatment	4	660	Mean Difference (IV, Random, 95% CI)	0.11 [0.01, 0.20]
7.2 200,000-300,000 IU versus placebo or no treatment	3	258	Mean Difference (IV, Random, 95% CI)	0.17 [0.06, 0.28]
7.3 400,000 IU versus placebo	1	402	Mean Difference (IV, Random, 95% CI)	0.04 [-0.01, 0.09]
7.4 Beta-carotene: 7.8 mg daily versus placebo	1	71	Mean Difference (IV, Random, 95% CI)	0.10 [-0.10, 0.30]
8 Maternal serum retinol (mcmol/L) at 6 - 6.5 months postpartum	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 200,000-400,000 IU versus placebo or no treatment	4	551	Mean Difference (IV, Random, 95% CI)	0.05 [-0.07, 0.17]
8.2 200,000-300,000 IU versus placebo or no treatment	3	260	Mean Difference (IV, Random, 95% CI)	0.10 [-0.02, 0.23]
8.3 400,000 IU versus placebo	1	291	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.08, 0.04]
8.4 beta-carotene: 7.8mg daily versus placebo	1	68	Mean Difference (IV, Random, 95% CI)	0.05 [-0.22, 0.32]
9 Maternal serum retinol (mcmol/L) at 9 months postpartum	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 200,000-300,000 IU versus placebo or no treatment	2	113	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.13, 0.17]
9.2 beta-carotene: 7.8mg daily versus placebo	1	66	Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.03, 0.41]
10 Maternal low hepatic vitamin A stores 3 months postpartum (MRDR ≥ 0.06)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 200,000 IU versus placebo	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.15, 0.71]
10.2 beta-carotene: 7.8 mg daily versus placebo	1	71	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.47, 1.26]
11 Maternal low hepatic vitamin A stores 5 - 6 months postpartum (MRDR ≥ 0.06)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 200,000 IU versus placebo	1	71	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.48, 1.85]
11.2 beta-carotene: 7.8 mg daily versus placebo	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.24, 1.32]
12 Maternal low hepatic vitamin A stores 9 months postpartum (MRDR ≥ 0.06)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 200,000 IU versus placebo	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.34, 1.34]
12.2 beta-carotene: 7.8 mg daily versus placebo	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.30, 1.23]

13 Maternal low hepatic vitamin A stores 3 months postpartum (RDR > 20%)	1	139	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.41, 3.25]
13.1 300,000 IU versus placebo	1	139	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.41, 3.25]
14 Maternal low hepatic vitamin A stores 6 months postpartum (RDR > 20%)	1	139	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [0.20, 23.16]
14.1 300,000 IU versus placebo	1	139	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [0.20, 23.16]
15 Breast milk retinol (mcmol/L) at 3 - 3.5 months postpartum	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
15.1 200,000-400,000 IU versus placebo no treatment	5	812	Mean Difference (IV, Random, 95% CI)	0.20 [0.08, 0.33]
15.2 200,000-300,000 IU versus placebo no treatment	4	390	Mean Difference (IV, Random, 95% CI)	0.27 [0.11, 0.43]
15.3 400,000 IU versus placebo	1	422	Mean Difference (IV, Random, 95% CI)	0.08 [0.03, 0.13]
15.4 beta-carotene: 7.8 mg daily versus placebo	1	145	Mean Difference (IV, Random, 95% CI)	0.02 [-0.14, 0.18]
16 Breast milk retinol (mcmol/L) at 6 - 6.5 months postpartum	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
16.1 200,000-400,000 IU versus placebo or no treatment	4	679	Mean Difference (IV, Random, 95% CI)	0.19 [-0.01, 0.39]
16.2 200,000-300,000 IU versus placebo or no treatment	3	325	Mean Difference (IV, Random, 95% CI)	0.27 [-0.05, 0.60]
16.3 400,000 IU versus placebo	1	354	Mean Difference (IV, Random, 95% CI)	0.06 [0.01, 0.11]
16.4 beta-carotene: 7.8 mg daily versus placebo	1	138	Mean Difference (IV, Random, 95% CI)	0.12 [-0.09, 0.33]
17 Breast milk retinol (mcmol/L) at 8 - 9 months postpartum	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
17.1 200,000-300,000 IU versus placebo or no treatment	3	307	Mean Difference (IV, Random, 95% CI)	0.15 [-0.15, 0.44]
17.2 beta-carotene: 7.8 mg daily versus placebo	1	135	Mean Difference (IV, Random, 95% CI)	0.21 [0.04, 0.38]
18 Breast milk retinol (< 1.05 mcmol/L) at 3 months postpartum	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
18.1 200,000-300,000 IU versus placebo or no treatment	3	373	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.19, 0.91]
18.2 beta-carotene: 7.8 mg daily versus placebo	1	145	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.80, 1.14]
19 Breast milk retinol (< 1.05 mcmol/L) at 6 months postpartum	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19.1 200,000-300,000 IU versus placebo	2	275	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.23, 1.90]
19.2 beta-carotene: 7.8 mg daily versus placebo	1	138	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.67, 1.06]

20 Breast milk retinol (< 1.05 mcmol/L) at 8-9 months postpartum	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.1 200,000-300,000 IU versus placebo	2	257	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.48, 1.35]
20.2 beta-carotene: 7.8mg daily versus placebo	1	135	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.63, 0.98]
21 Breast milk retinol (< 0.28 mcmol/g of fat) at 3 months postpartum	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 200,000 IU versus placebo	1	141	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.63, 1.03]
21.2 beta-carotene: 7.8mg daily versus placebo	1	145	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.82, 1.23]
22 Breast milk retinol (< 0.28 mcmol/g of fat) at 6 months postpartum	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 200,000 IU versus placebo	2	813	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.71, 0.99]
22.2 beta-carotene: 7.8mg daily versus placebo	1	138	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.71, 1.07]
23 Breast milk retinol (< 0.28 mcmol/g of fat) at 9 months postpartum	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
23.1 200,000 IU versus placebo	2	699	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.74, 1.02]
23.2 beta-carotene: 7.8 mg daily versus placebo	1	134	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.62, 0.95]
24 Maternal abnormal conjunctival impression cytology 3 months postpartum	1	148	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.55, 1.80]
24.1 300,000 IU versus placebo	1	148	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.55, 1.80]
25 Maternal abnormal conjunctival impression cytology 6 months postpartum	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
25.1 300,000 IU versus placebo	1	142	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.27, 1.17]
26 Infant mortality	4	6170	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.84, 1.57]
26.1 deaths to 14 weeks: 400,000 IU versus placebo	1	564	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.57, 1.74]
26.2 deaths to 12 months: 300,000 IU versus placebo	1	598	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.34, 2.24]
26.3 death to 6 months: 200,000 IU versus placebo	1	407	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.26, 9.10]
26.4 deaths to 12 months: 400,000 IU versus placebo	1	4601	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.83, 1.98]
27 Infant diarrhoea (one or more episodes) to 12 months	1	456	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.98, 1.06]
27.1 300,000 IU versus placebo	1	456	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.98, 1.06]

28 Infant diarrhoea episodes and duration			Other data	No numeric data
28.1 200,000 IU versus no treatment			Other data	No numeric data
29 Infant gastroenteritis to 3 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
29.1 200,000 IU versus no treatment	1	84	Risk Ratio (M-H, Fixed, 95% CI)	8.44 [0.45, 158.40]
30 Infant acute respiratory infection (one or more episodes) to 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
30.1 300,000 IU versus placebo	1	456	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.96, 1.03]
31 Infant upper respiratory tract infection to 3 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
31.1 200,000 IU versus treatment	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.22, 3.81]
32 Infant acute respiratory tract infection episodes and duration			Other data	No numeric data
32.1 200,000 IU versus no treatment			Other data	No numeric data
33 Infant febrile illness episodes			Other data	No numeric data
33.1 200,000 IU versus no treatment			Other data	No numeric data
34 Infant adverse effects of supplementation	2	9622	Risk Ratio (M-H, Random, 95% CI)	2.22 [1.01, 4.86]
34.1 Bulging fontanelle: 200,000 IU versus placebo	1	9178	Risk Ratio (M-H, Random, 95% CI)	2.41 [0.85, 6.83]
34.2 Bulging fontanelle: 400,000 IU versus placebo	1	444	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.61, 6.55]
35 Infant serum retinol (µmol/L) at 2 - 3.5 months postpartum	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
35.1 200,000-400,000 IU versus no treatment	3	320	Mean Difference (IV, Random, 95% CI)	0.12 [-0.08, 0.33]
35.2 200,000 IU versus placebo or no treatment	2	156	Mean Difference (IV, Random, 95% CI)	0.19 [-0.04, 0.42]
35.3 400,000 IU versus placebo	1	164	Mean Difference (IV, Random, 95% CI)	0.02 [-0.03, 0.07]
36 Infant serum retinol (µmol/L) at 5 - 6 months postpartum	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
36.1 200,000-400,000 IU versus placebo	4	465	Mean Difference (IV, Fixed, 95% CI)	0.04 [0.00, 0.09]
36.2 200,000-300,000 IU versus placebo	3	324	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.01, 0.09]
36.3 beta-carotene: 7.8 mg daily versus placebo	1	139	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.04, 0.10]
36.4 400,000 IU versus placebo	1	141	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.02, 0.14]
37 Infant low hepatic vitamin A stores 1.5 months postpartum (MRDR ≥ 0.06)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

37.1 200,000 IU versus placebo	1	600	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.02, 1.21]
38 Infant low hepatic vitamin A stores at 5 - 6.5 months postpartum	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
38.1 200,000-400,000 IU versus placebo	3	459	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.79, 1.15]
38.2 200,000-300,000 IU versus placebo	2	270	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.26, 1.84]
38.3 400,000 IU versus placebo	1	189	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.90, 1.22]
38.4 beta-carotene: 7.8 mg daily versus placebo	1	139	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.80, 1.02]

Comparison 2. Supplement (vitamin A as retinyl) high dose versus low dose

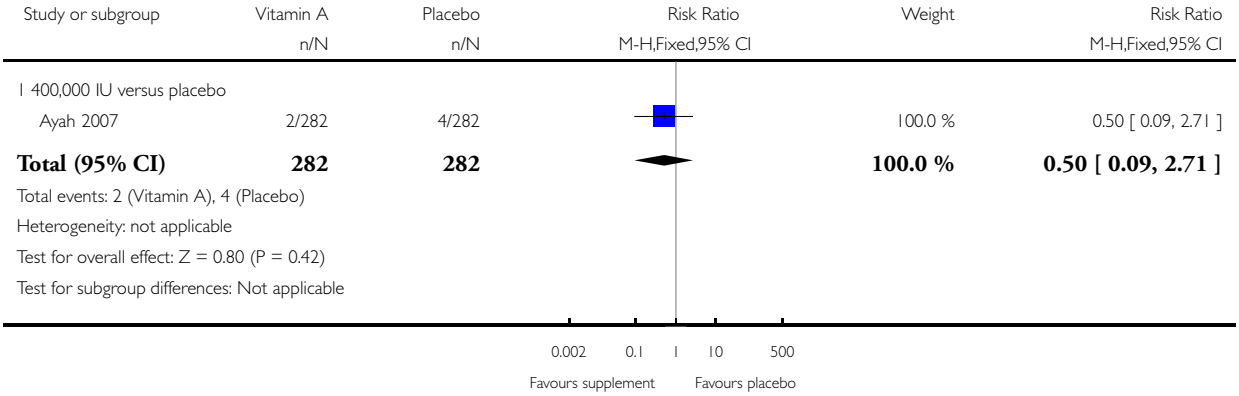
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Infant mortality	1	220	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.37, 10.70]
1.1 400,000 IU versus 200,000 IU	1	220	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.37, 10.70]
2 Maternal serum retinol (μ mol/L)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 400,000 IU versus 200,000 IU at 2 months postpartum	1	193	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.10, 0.14]
2.2 400,000 IU versus 200,000 IU at 3 months postpartum	1	190	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.28, 0.16]
2.3 400,000 IU versus 200,000 IU at 6 months postpartum	2	812	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.14, 0.13]
2.4 400,000 IU versus 200,000 IU at 9 months postpartum	1	602	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.26, 0.08]
3 Breast milk retinol (< 1.05 μ mol/L)	1	382	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.69, 1.36]
3.1 400,000 IU versus 200,000 IU at 3 months postpartum	1	190	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.72, 2.17]
3.2 400,000 IU versus 200,000 IU at 6 months postpartum	1	192	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.53, 1.25]
4 Infant serum retinol (μ mol/L) at 2 months postpartum	1	134	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.05, 0.09]
4.1 400,000 IU versus 200,000 IU	1	134	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.05, 0.09]

Analysis 1.1. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 1 Maternal mortality to six months.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 1 Maternal mortality to six months



Analysis 1.2. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 2 Maternal fever at 3 months postpartum.

Maternal fever at 3 months postpartum

Study	Outcome	Supplement	Control	P value
200,000 IU versus no treatment				
Roy 1997	Number of cumulative episodes; (cumulative duration of illness in days)	10 (30); n = 25	10 (28); n = 25	Report states no significant difference

Analysis 1.3. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 3 Maternal respiratory tract infection at 3 months postpartum.

Maternal respiratory tract infection at 3 months postpartum

Study	Outcome	Supplement	Control	P value
200,000 IU versus no treatment				
Roy 1997	Number of cumulative episodes; (cumulative duration of ill-	23 (82); n = 25	25 (125); n = 25	Report states no significant difference

Maternal respiratory tract infection at 3 months postpartum (*Continued*)

	ness in days)			
Roy 1997				

Analysis 1.4. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 4 Maternal diarrhoea at 3 months postpartum.

Maternal diarrhoea at 3 months postpartum

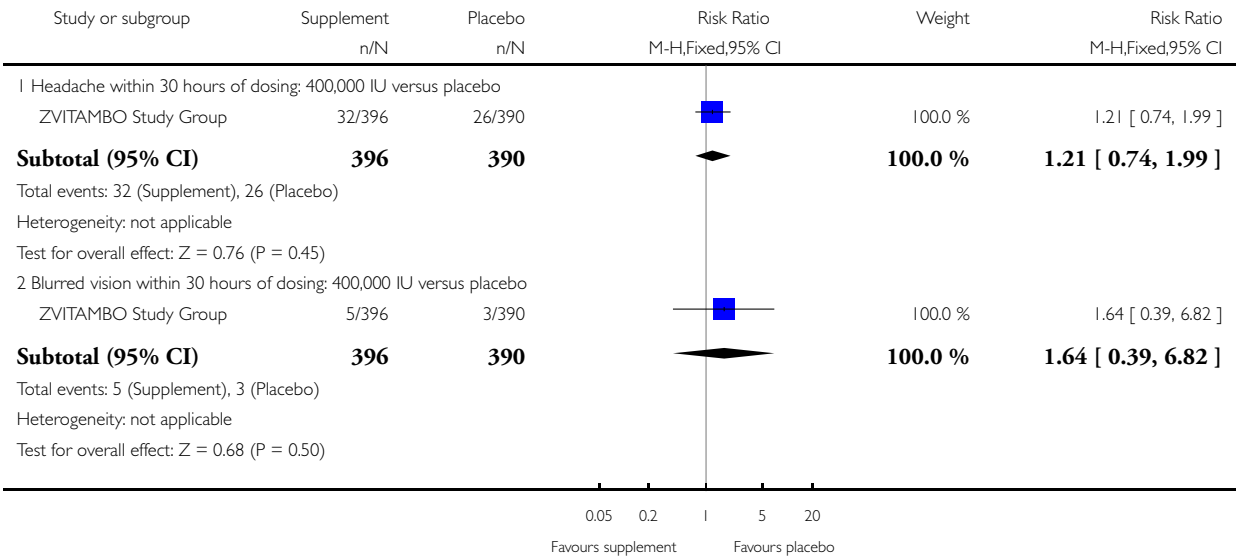
Study	Outcome	Vitamin A	Control	P value
200,000 IU versus no treatment				
Roy 1997	Number of cumulative episodes; (cumulative duration of illness in days)	10 (27); n = 25	2 (15); n = 25	Report states no significant difference

Analysis 1.5. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 5 Maternal adverse effects of supplementation.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

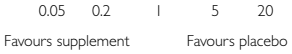
Outcome: 5 Maternal adverse effects of supplementation



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Supplement n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 Drowsiness within 30 hours of dosing: 400,000 IU versus placebo					
ZVITAMBO Study Group	17/396	8/390		100.0 %	2.09 [0.91, 4.79]
Subtotal (95% CI)	**396**	**390**		**100.0 %**	**2.09 [0.91, 4.79]**
Total events: 17 (Supplement), 8 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.75 (P = 0.081)					
4 Nausea within 30 hours of dosing: 400,000 IU versus placebo					
ZVITAMBO Study Group	7/396	5/390		100.0 %	1.38 [0.44, 4.31]
Subtotal (95% CI)	**396**	**390**		**100.0 %**	**1.38 [0.44, 4.31]**
Total events: 7 (Supplement), 5 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.55 (P = 0.58)					
5 Vomiting within 30 hours of dosing: 400,000 IU versus placebo					
ZVITAMBO Study Group	1/396	3/390		100.0 %	0.33 [0.03, 3.14]
Subtotal (95% CI)	**396**	**390**		**100.0 %**	**0.33 [0.03, 3.14]**
Total events: 1 (Supplement), 3 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.97 (P = 0.33)					
6 Poor appetite within 30 hours of dosing: 400,000 IU versus placebo					
ZVITAMBO Study Group	9/396	4/390		100.0 %	2.22 [0.69, 7.14]
Subtotal (95% CI)	**396**	**390**		**100.0 %**	**2.22 [0.69, 7.14]**
Total events: 9 (Supplement), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.33 (P = 0.18)					
7 Abdominal pain within 30 hours of dosing: 400,000 IU versus placebo					
ZVITAMBO Study Group	82/396	63/390		100.0 %	1.28 [0.95, 1.73]
Subtotal (95% CI)	**396**	**390**		**100.0 %**	**1.28 [0.95, 1.73]**
Total events: 82 (Supplement), 63 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.64 (P = 0.10)					



Analysis 1.6. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 6 Maternal serum retinol (μmol/L) at 1.5 months postpartum.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 6 Maternal serum retinol (μ mol/L) at 1.5 months postpartum

Study or subgroup	Vitamin A N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 HIV negative women: 400,000 IU versus placebo							
ZVITAMBO Study Group	128	1.74 (0.45)	132	1.65 (0.44)		100.0 %	0.09 [-0.02, 0.20]
Total (95% CI)	**128**		**132**			**100.0 %**	**0.09 [-0.02, 0.20]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.63 (P = 0.10)							
Test for subgroup differences: Not applicable							

Analysis 1.7. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 7 Maternal serum retinol (mcmol/L) at 3 - 3.5 months postpartum.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 7 Maternal serum retinol (mcmol/L) at 3 - 3.5 months postpartum

Study or subgroup	Supplement N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 200,000-400,000 IU versus placebo or no treatment							
Ayah 2007	205	1.05 (0.22)	197	1.01 (0.29)		47.8 %	0.04 [-0.01, 0.09]
RETIBETA Project	34	1.45 (0.47)	35	1.33 (0.42)		15.0 %	0.12 [-0.09, 0.33]
Roy 1997	25	1.59 (0.39)	25	1.33 (0.39)		14.4 %	0.26 [0.04, 0.48]
Stoltzfus 1993a	70	1.39 (0.49)	69	1.24 (0.43)		22.8 %	0.15 [0.00, 0.30]
Subtotal (95% CI)	**334**		**326**			**100.0 %**	**0.11 [0.01, 0.20]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.51$, df = 3 (P = 0.14); $I^2 = 46\%$							
Test for overall effect: Z = 2.23 (P = 0.026)							
2 200,000-300,000 IU versus placebo or no treatment							
RETIBETA Project	34	1.45 (0.47)	35	1.33 (0.42)		26.1 %	0.12 [-0.09, 0.33]
Roy 1997	25	1.59 (0.39)	25	1.33 (0.39)		24.7 %	0.26 [0.04, 0.48]
Stoltzfus 1993a	70	1.39 (0.49)	69	1.24 (0.43)		49.2 %	0.15 [0.00, 0.30]
Subtotal (95% CI)	**129**		**129**			**100.0 %**	**0.17 [0.06, 0.28]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.95$, df = 2 (P = 0.62); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.09 (P = 0.0020)							
3 400,000 IU versus placebo							
Ayah 2007	205	1.05 (0.22)	197	1.01 (0.29)		100.0 %	0.04 [-0.01, 0.09]
Subtotal (95% CI)	**205**		**197**			**100.0 %**	**0.04 [-0.01, 0.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.55 (P = 0.12)							
4 Beta-carotene: 7.8 mg daily versus placebo							
RETIBETA Project	36	1.43 (0.43)	35	1.33 (0.42)		100.0 %	0.10 [-0.10, 0.30]
Subtotal (95% CI)	**36**		**35**			**100.0 %**	**0.10 [-0.10, 0.30]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.99 (P = 0.32)							

Analysis 1.8. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 8 Maternal serum retinol (mcmol/L) at 6 - 6.5 months postpartum.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 8 Maternal serum retinol (mcmol/L) at 6 - 6.5 months postpartum

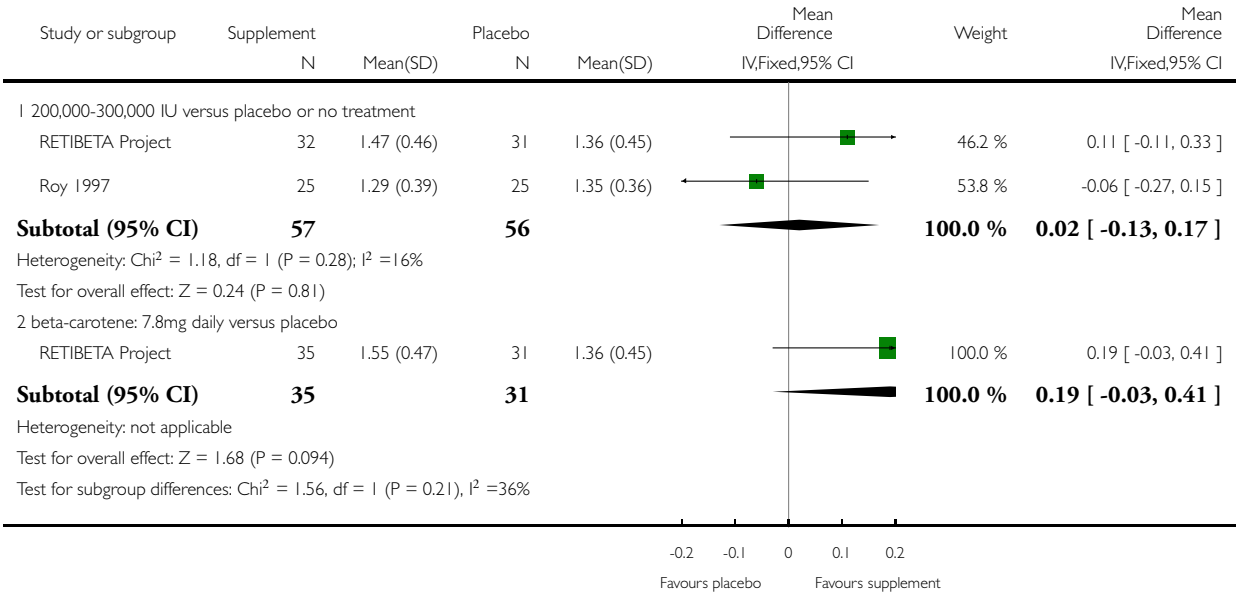
Study or subgroup	Supplement N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 200,000-400,000 IU versus placebo or no treatment							
Ayah 2007	148	0.96 (0.25)	143	0.98 (0.24)		40.5 %	-0.02 [-0.08, 0.04]
RETIBETA Project	35	1.47 (0.38)	36	1.52 (0.56)		17.0 %	-0.05 [-0.27, 0.17]
Roy 1997	25	1.54 (0.65)	25	1.36 (0.34)		12.0 %	0.18 [-0.11, 0.47]
Stoltzfus 1993a	67	1.23 (0.34)	72	1.08 (0.37)		30.6 %	0.15 [0.03, 0.27]
Subtotal (95% CI)	**275**		**276**			**100.0 %**	**0.05 [-0.07, 0.17]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 8.10$, df = 3 (P = 0.04); $I^2 = 63\%$							
Test for overall effect: Z = 0.86 (P = 0.39)							
2 200,000-300,000 IU versus placebo or no treatment							
RETIBETA Project	35	1.47 (0.38)	36	1.52 (0.56)		25.3 %	-0.05 [-0.27, 0.17]
Roy 1997	25	1.54 (0.65)	25	1.36 (0.34)		16.5 %	0.18 [-0.11, 0.47]
Stoltzfus 1993a	67	1.23 (0.34)	72	1.08 (0.37)		58.2 %	0.15 [0.03, 0.27]
Subtotal (95% CI)	**127**		**133**			**100.0 %**	**0.10 [-0.02, 0.23]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.65$, df = 2 (P = 0.27); $I^2 = 25\%$							
Test for overall effect: Z = 1.63 (P = 0.10)							
3 400,000 IU versus placebo							
Ayah 2007	148	0.96 (0.25)	143	0.98 (0.24)		100.0 %	-0.02 [-0.08, 0.04]
Subtotal (95% CI)	**148**		**143**			**100.0 %**	**-0.02 [-0.08, 0.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.70 (P = 0.49)							
4 beta-carotene: 7.8mg daily versus placebo							
RETIBETA Project	32	1.57 (0.59)	36	1.52 (0.56)		100.0 %	0.05 [-0.22, 0.32]
Subtotal (95% CI)	**32**		**36**			**100.0 %**	**0.05 [-0.22, 0.32]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.36 (P = 0.72)							

Analysis 1.9. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 9 Maternal serum retinol (mcmol/L) at 9 months postpartum.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 9 Maternal serum retinol (mcmol/L) at 9 months postpartum

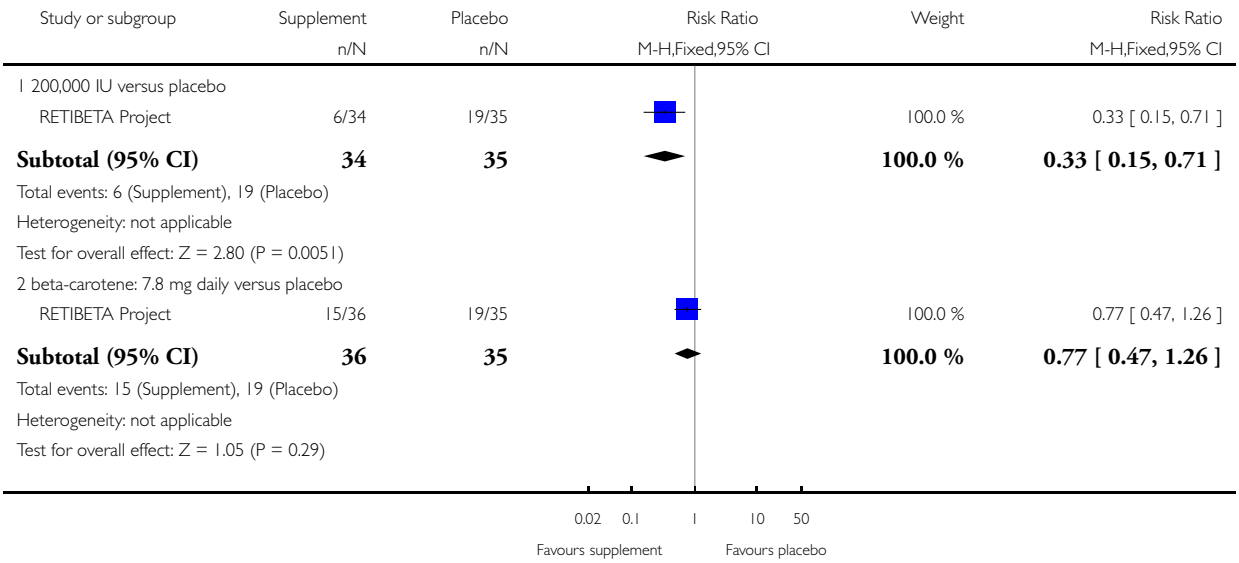


Analysis 1.10. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 10 Maternal low hepatic vitamin A stores 3 months postpartum (MRDR ≥ 0.06).

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 10 Maternal low hepatic vitamin A stores 3 months postpartum (MRDR ≥ 0.06)

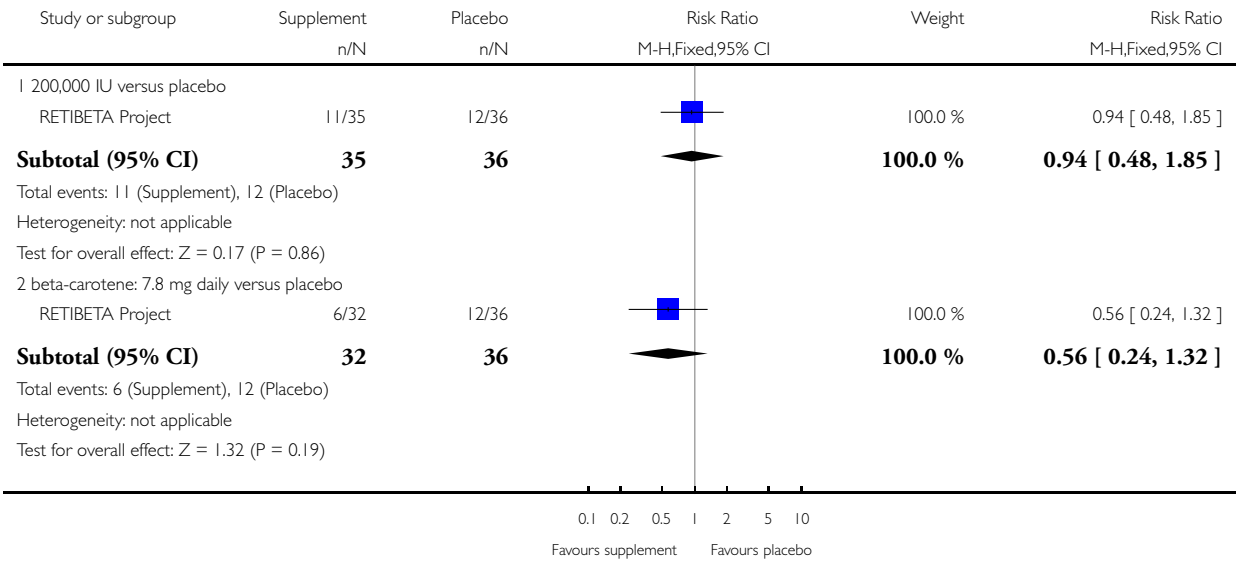


Analysis 1.11. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 11 Maternal low hepatic vitamin A stores 5 - 6 months postpartum (MRDR ≥ 0.06).

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 11 Maternal low hepatic vitamin A stores 5 - 6 months postpartum (MRDR ≥ 0.06)

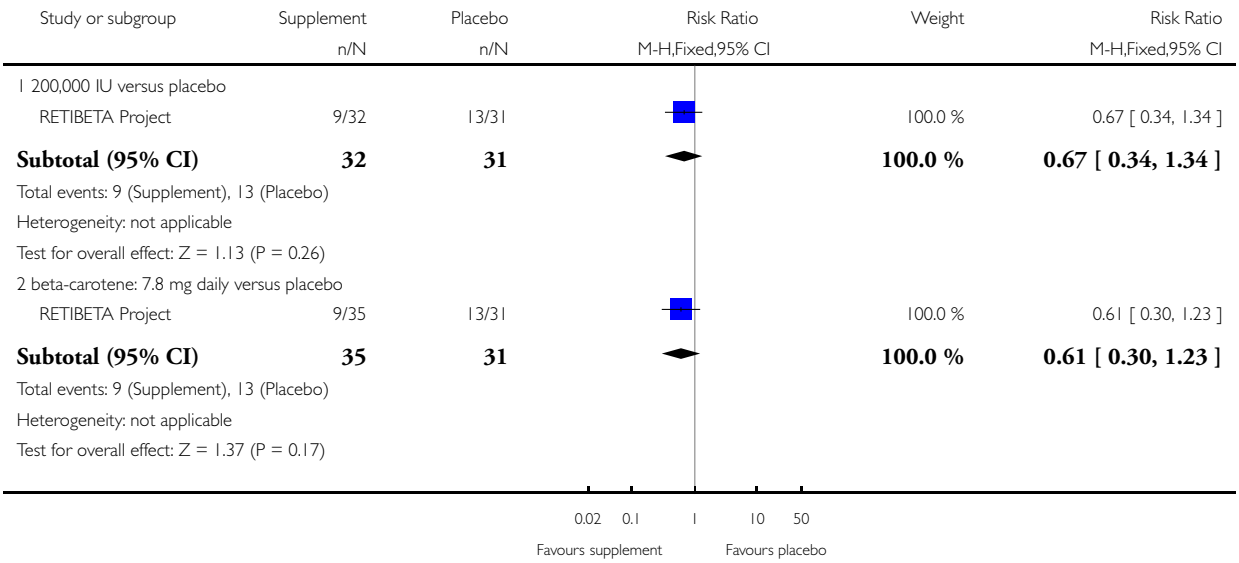


Analysis 1.12. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 12 Maternal low hepatic vitamin A stores 9 months postpartum (MRDR ≥ 0.06).

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 12 Maternal low hepatic vitamin A stores 9 months postpartum (MRDR ≥ 0.06)

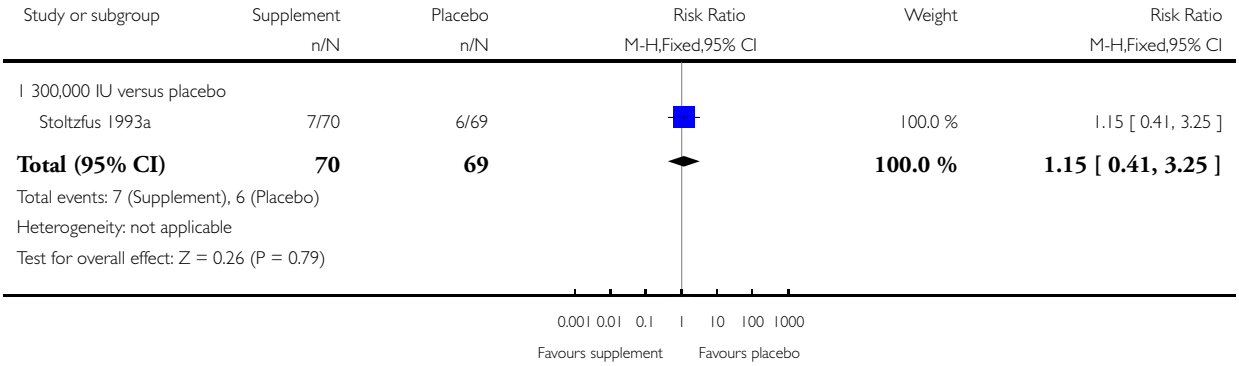


Analysis 1.13. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 13 Maternal low hepatic vitamin A stores 3 months postpartum (RDR > 20%).

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 13 Maternal low hepatic vitamin A stores 3 months postpartum (RDR > 20%)

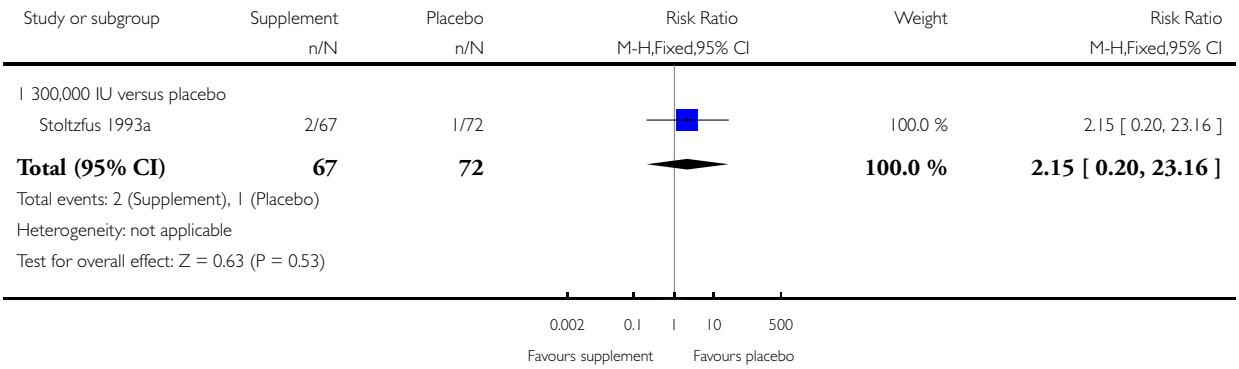


Analysis 1.14. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 14 Maternal low hepatic vitamin A stores 6 months postpartum (RDR > 20%).

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 14 Maternal low hepatic vitamin A stores 6 months postpartum (RDR > 20%)



Analysis 1.15. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 15 Breast milk retinol (mcmol/L) at 3 - 3.5 months postpartum.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 15 Breast milk retinol (mcmol/L) at 3 - 3.5 months postpartum

Study or subgroup	Supplement N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 200,000-400,000 IU versus placebo no treatment							
Ayah 2007	221	0.52 (0.23)	201	0.44 (0.28)		36.0 %	0.08 [0.03, 0.13]
RETIBETA Project	69	1.2 (1)	72	0.83 (0.43)		15.0 %	0.37 [0.11, 0.63]
Roy 1997	25	1.34 (0.53)	25	1.12 (0.51)		12.9 %	0.22 [-0.07, 0.51]
Stoltzfus 1993a	57	2.45 (1.23)	60	1.82 (1.28)		6.5 %	0.63 [0.18, 1.08]
Vinutha 2000	36	1.09 (0.26)	46	0.92 (0.24)		29.7 %	0.17 [0.06, 0.28]
Subtotal (95% CI)	**408**		**404**			**100.0 %**	**0.20 [0.08, 0.33]**
Heterogeneity: Tau² = 0.01; Chi² = 12.12, df = 4 (P = 0.02); I² =67%							
Test for overall effect: Z = 3.14 (P = 0.0017)							
2 200,000-300,000 IU versus placebo no treatment							
RETIBETA Project	69	1.2 (1)	72	0.83 (0.43)		23.4 %	0.37 [0.11, 0.63]
Roy 1997	25	1.34 (0.53)	25	1.12 (0.51)		20.2 %	0.22 [-0.07, 0.51]
Stoltzfus 1993a	57	2.45 (1.23)	60	1.82 (1.28)		10.2 %	0.63 [0.18, 1.08]
Vinutha 2000	36	1.09 (0.26)	46	0.92 (0.24)		46.2 %	0.17 [0.06, 0.28]
Subtotal (95% CI)	**187**		**203**			**100.0 %**	**0.27 [0.11, 0.43]**
Heterogeneity: Tau² = 0.01; Chi² = 5.24, df = 3 (P = 0.16); I² =43%							
Test for overall effect: Z = 3.36 (P = 0.00077)							
3 400,000 IU versus placebo							
Ayah 2007	221	0.52 (0.23)	201	0.44 (0.28)		100.0 %	0.08 [0.03, 0.13]
Subtotal (95% CI)	**221**		**201**			**100.0 %**	**0.08 [0.03, 0.13]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.19 (P = 0.0014)							
4 beta-carotene: 7.8 mg daily versus placebo							
RETIBETA Project	73	0.85 (0.55)	72	0.83 (0.43)		100.0 %	0.02 [-0.14, 0.18]
Subtotal (95% CI)	**73**		**72**			**100.0 %**	**0.02 [-0.14, 0.18]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.24 (P = 0.81)							

Analysis 1.16. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 16 Breast milk retinol (mcmol/L) at 6 - 6.5 months postpartum.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 16 Breast milk retinol (mcmol/L) at 6 - 6.5 months postpartum

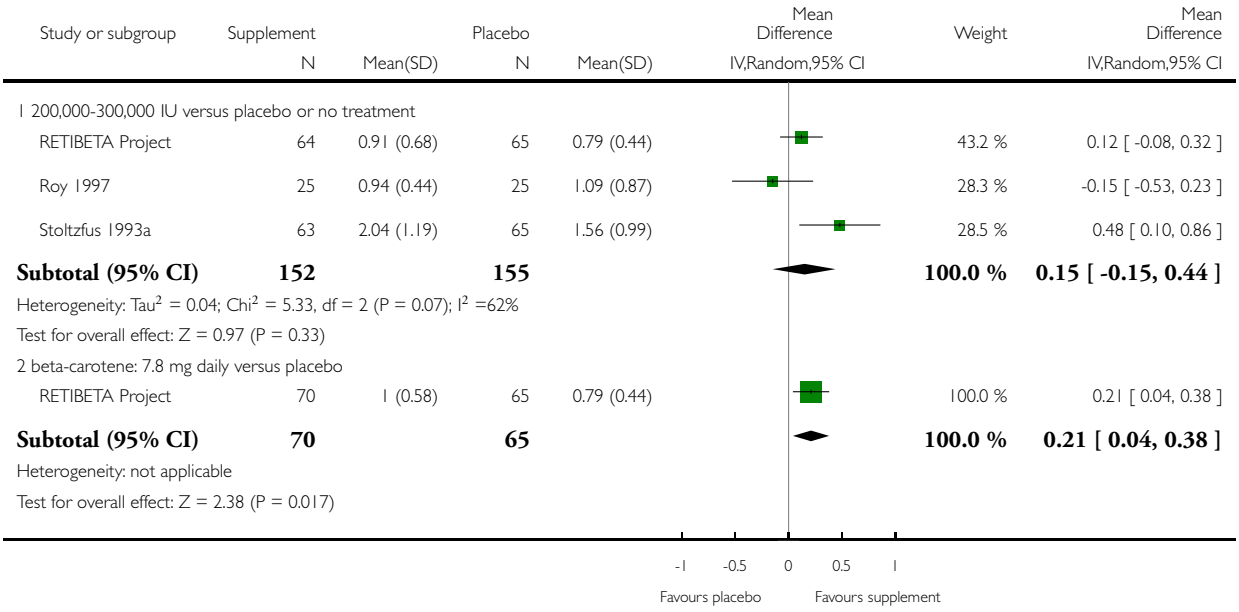
Study or subgroup	Supplement N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 200,000-400,000 IU versus placebo or no treatment							
Ayah 2007	184	0.5 (0.21)	170	0.44 (0.27)		33.3 %	0.06 [0.01, 0.11]
RETIBETA Project	70	0.85 (0.53)	69	0.87 (0.61)		25.8 %	-0.02 [-0.21, 0.17]
Roy 1997	25	1.06 (0.46)	25	0.73 (0.22)		25.2 %	0.33 [0.13, 0.53]
Stoltzfus 1993a	66	2.36 (1.17)	70	1.77 (0.97)		15.7 %	0.59 [0.23, 0.95]
Subtotal (95% CI)	**345**		**334**			**100.0 %**	**0.19 [-0.01, 0.39]**
Heterogeneity: Tau² = 0.03; Chi² = 15.28, df = 3 (P = 0.002); I² =80%							
Test for overall effect: Z = 1.91 (P = 0.056)							
2 200,000-300,000 IU versus placebo or no treatment							
RETIBETA Project	70	0.85 (0.53)	69	0.87 (0.61)		36.5 %	-0.02 [-0.21, 0.17]
Roy 1997	25	1.06 (0.46)	25	0.73 (0.22)		36.0 %	0.33 [0.13, 0.53]
Stoltzfus 1993a	66	2.36 (1.17)	70	1.77 (0.97)		27.5 %	0.59 [0.23, 0.95]
Subtotal (95% CI)	**161**		**164**			**100.0 %**	**0.27 [-0.05, 0.60]**
Heterogeneity: Tau² = 0.07; Chi² = 11.22, df = 2 (P = 0.004); I² =82%							
Test for overall effect: Z = 1.65 (P = 0.099)							
3 400,000 IU versus placebo							
Ayah 2007	184	0.5 (0.21)	170	0.44 (0.27)		100.0 %	0.06 [0.01, 0.11]
Subtotal (95% CI)	**184**		**170**			**100.0 %**	**0.06 [0.01, 0.11]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.32 (P = 0.020)							
4 beta-carotene: 7.8 mg daily versus placebo							
RETIBETA Project	69	0.99 (0.62)	69	0.87 (0.61)		100.0 %	0.12 [-0.09, 0.33]
Subtotal (95% CI)	**69**		**69**			**100.0 %**	**0.12 [-0.09, 0.33]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.15 (P = 0.25)							

Analysis 1.17. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 17 Breast milk retinol (mcmol/L) at 8 - 9 months postpartum.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 17 Breast milk retinol (mcmol/L) at 8 - 9 months postpartum

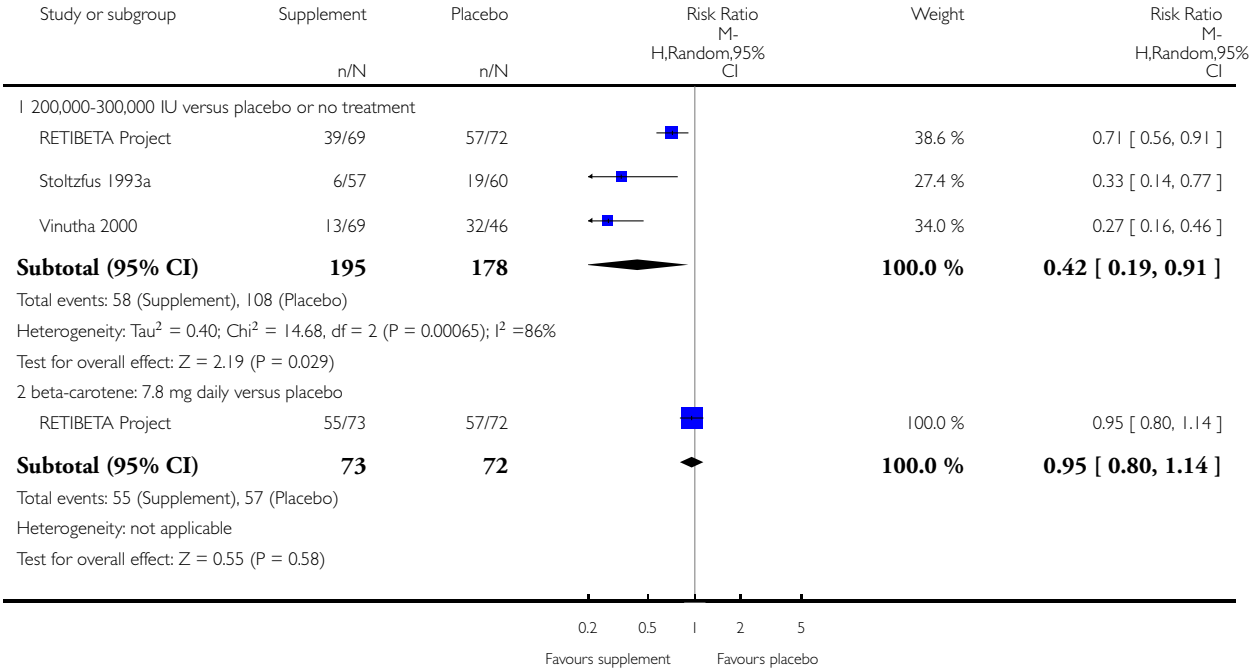


Analysis 1.18. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 18 Breast milk retinol (< 1.05 mcmol/L) at 3 months postpartum.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 18 Breast milk retinol (< 1.05 mcmol/L) at 3 months postpartum

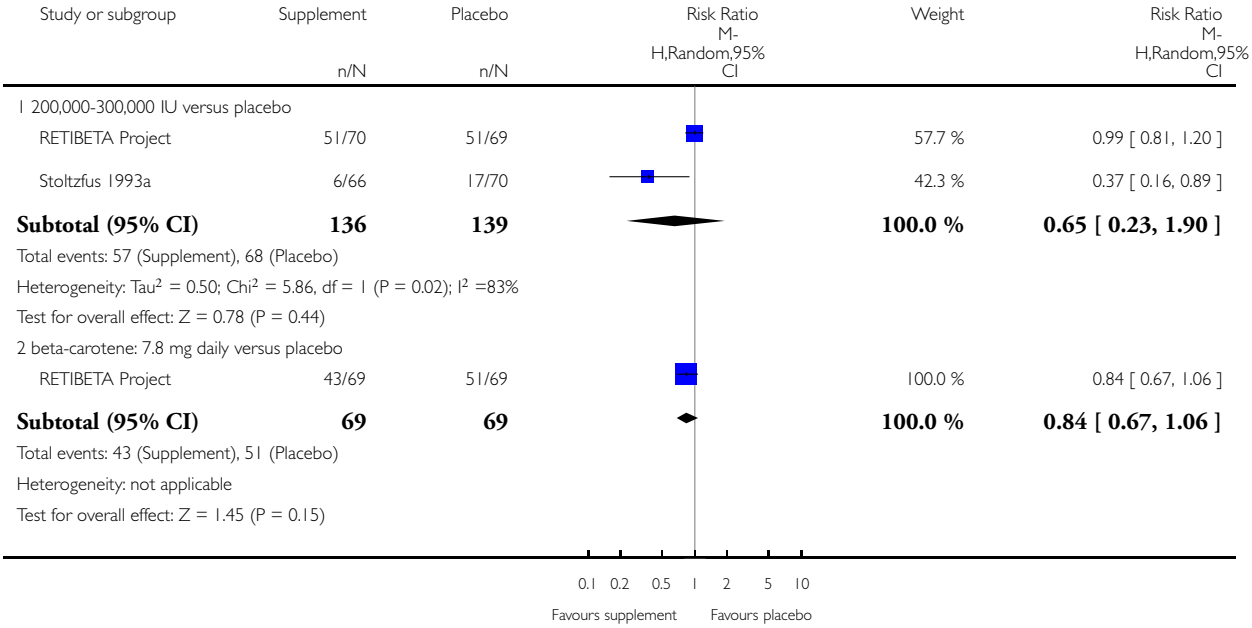


Analysis 1.19. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 19 Breast milk retinol (< 1.05 mcmol/L) at 6 months postpartum.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 19 Breast milk retinol (< 1.05 mcmol/L) at 6 months postpartum

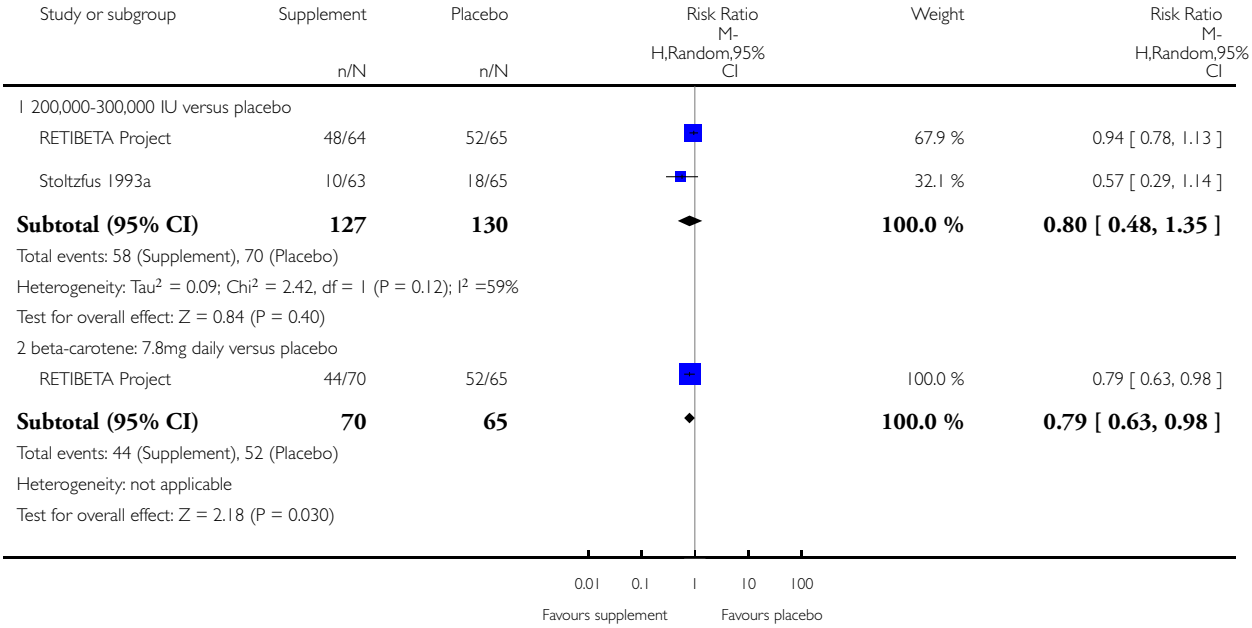


Analysis 1.20. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 20 Breast milk retinol (< 1.05 mcmol/L) at 8-9 months postpartum.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 20 Breast milk retinol (< 1.05 mcmol/L) at 8-9 months postpartum

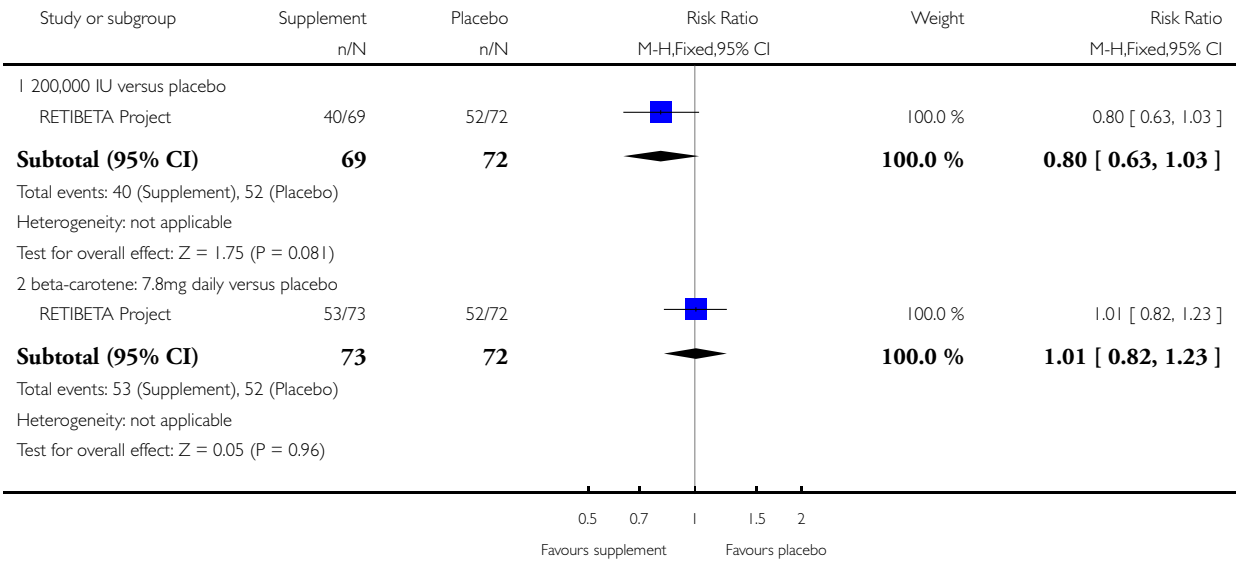


Analysis 1.21. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 21 Breast milk retinol (< 0.28 mcmol/g of fat) at 3 months postpartum.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 21 Breast milk retinol (< 0.28 mcmol/g of fat) at 3 months postpartum

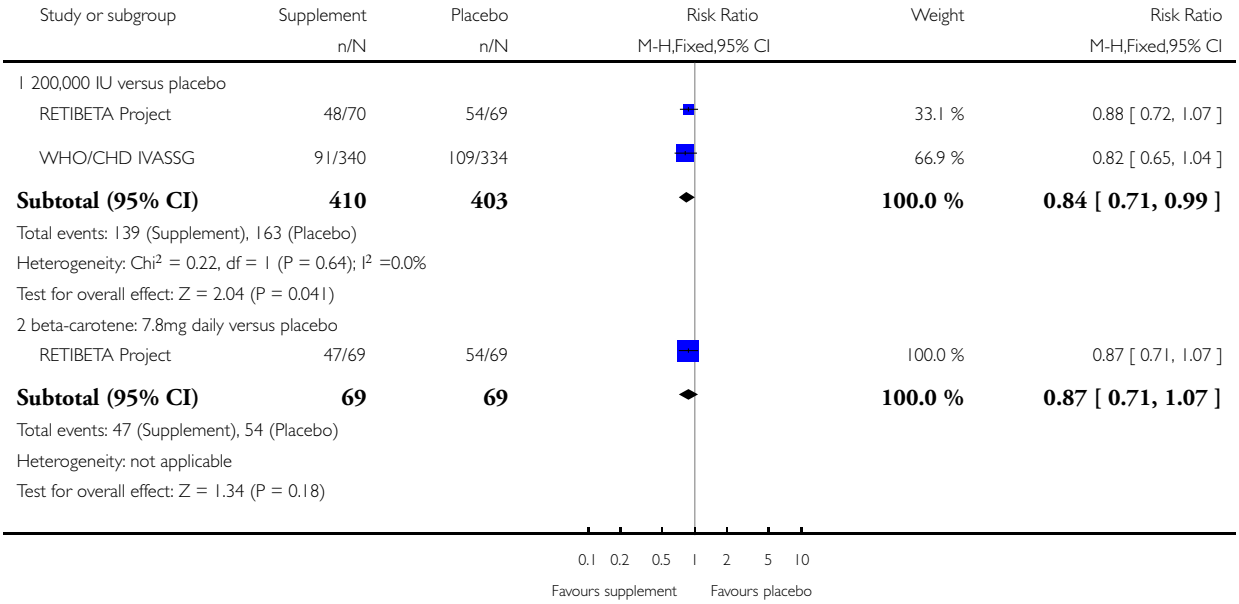


Analysis 1.22. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 22 Breast milk retinol (< 0.28 mcmol/g of fat) at 6 months postpartum.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 22 Breast milk retinol (< 0.28 mcmol/g of fat) at 6 months postpartum

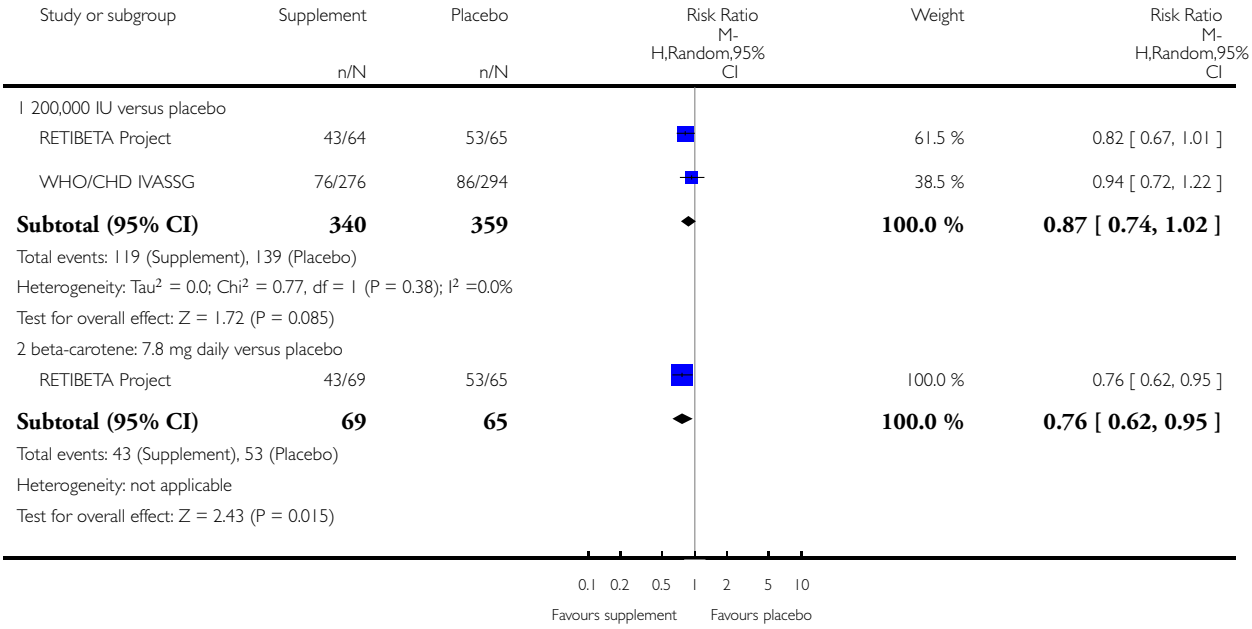


Analysis 1.23. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 23 Breast milk retinol (< 0.28 mcmol/g of fat) at 9 months postpartum.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 23 Breast milk retinol (< 0.28 mcmol/g of fat) at 9 months postpartum

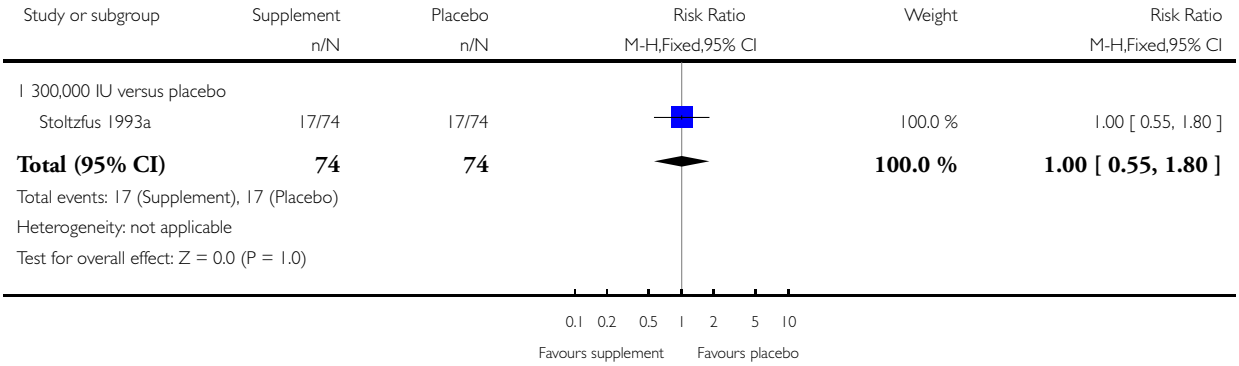


Analysis 1.24. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 24 Maternal abnormal conjunctival impression cytology 3 months postpartum.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 24 Maternal abnormal conjunctival impression cytology 3 months postpartum

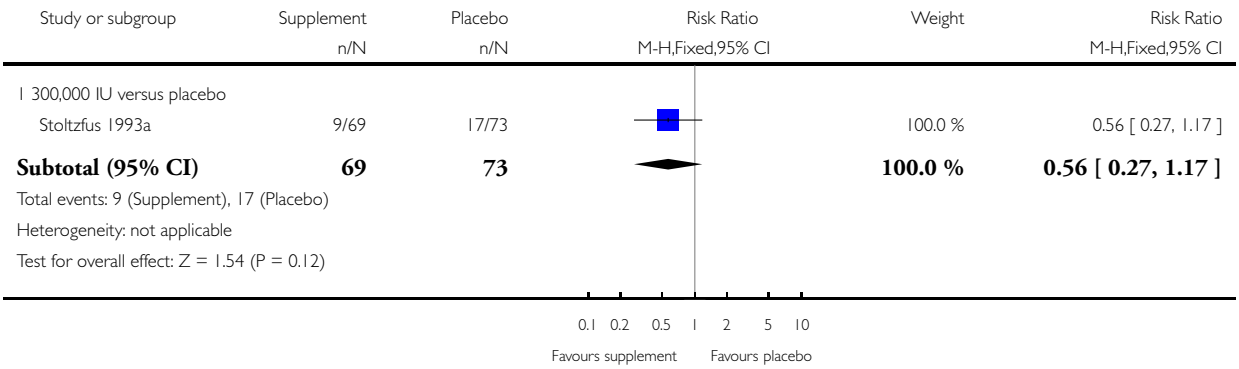


Analysis 1.25. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 25 Maternal abnormal conjunctival impression cytology 6 months postpartum.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 25 Maternal abnormal conjunctival impression cytology 6 months postpartum

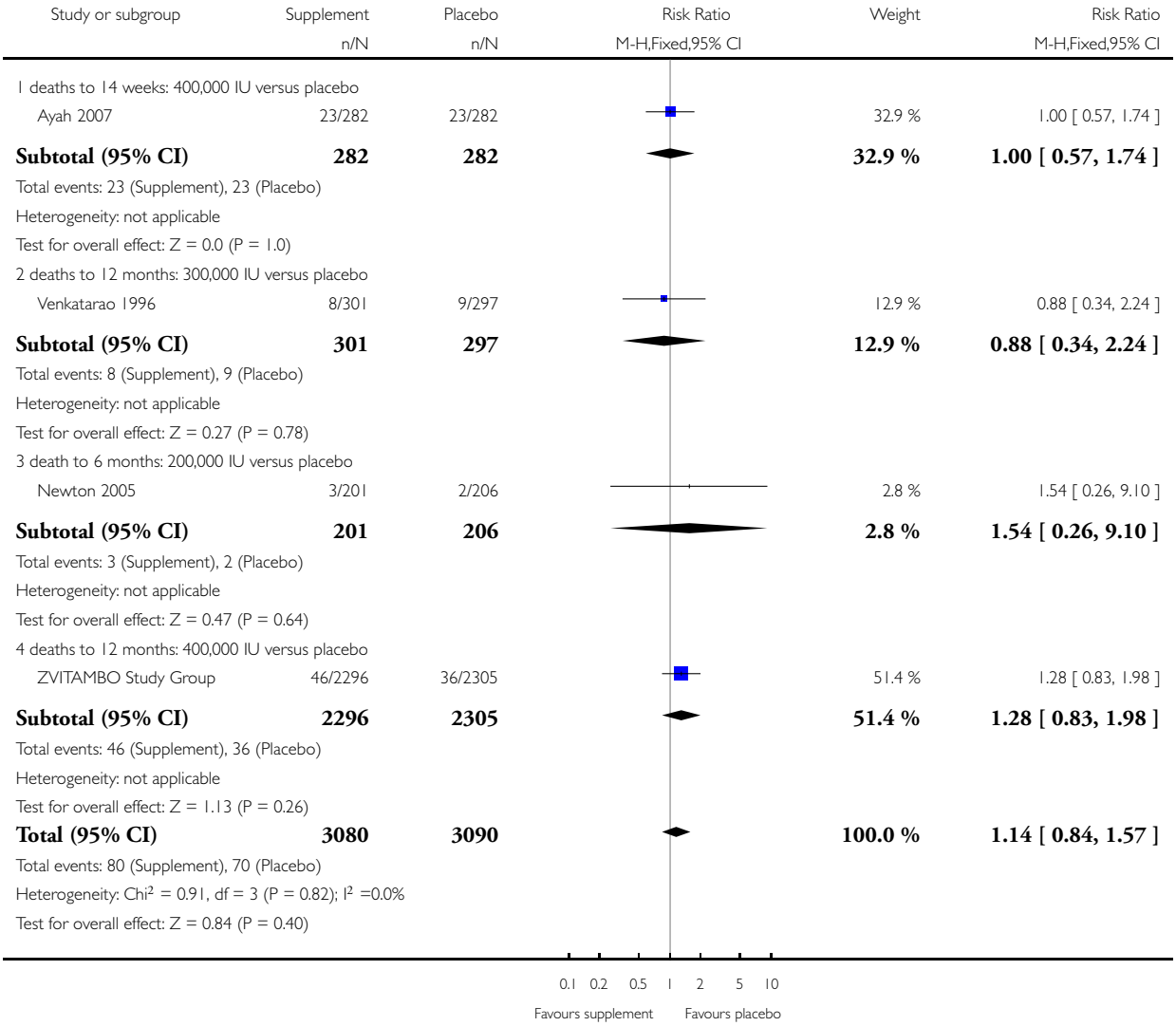


Analysis 1.26. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 26 Infant mortality.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 26 Infant mortality

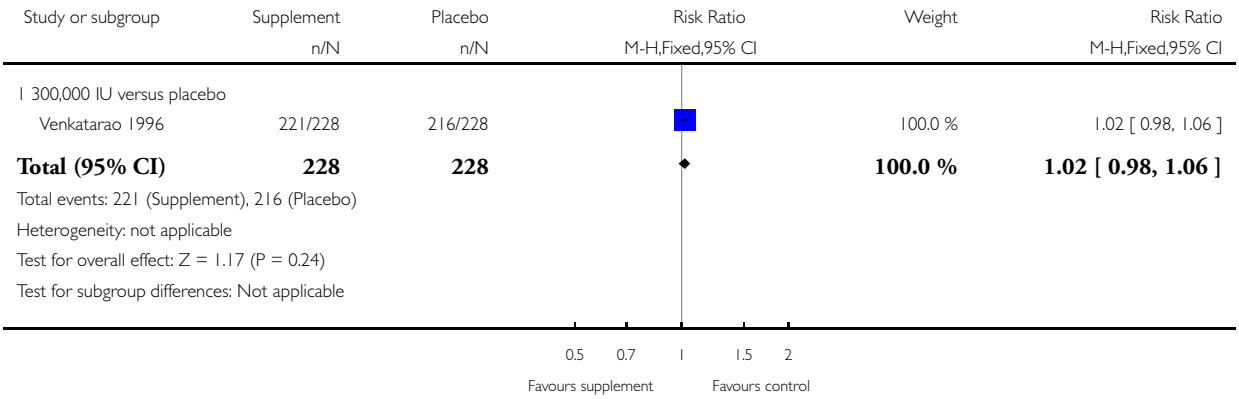


Analysis 1.27. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 27 Infant diarrhoea (one or more episodes) to 12 months.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 27 Infant diarrhoea (one or more episodes) to 12 months



Analysis 1.28. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 28 Infant diarrhoea episodes and duration.

Infant diarrhoea episodes and duration

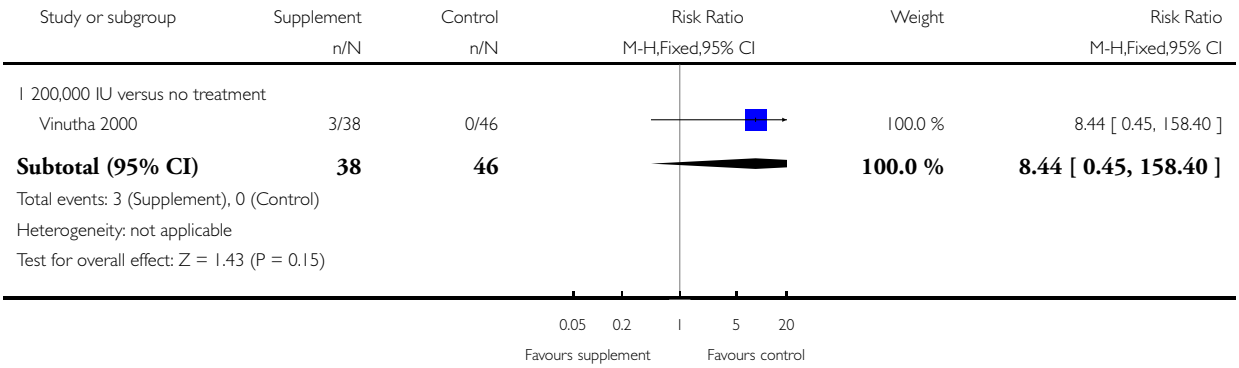
Study	Outcome	Supplement	No treatment	Significance
200,000 IU versus no treatment				
Roy 1997	Diarrhoea episodes	RR/OR?? 0.12 (95% CI 0.09 to 0.15)	0.11 (95% CI 0.08 to 0.14)	P = 0.59
Roy 1997	Diarrhoea duration	0.74 (95% CI 0.53 to 0.95)	0.71 (95% CI 0.50 to 0.92)	P = 0.78
Roy 1997	Child-weeks	515	522	

Analysis 1.29. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 29 Infant gastroenteritis to 3 months.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 29 Infant gastroenteritis to 3 months

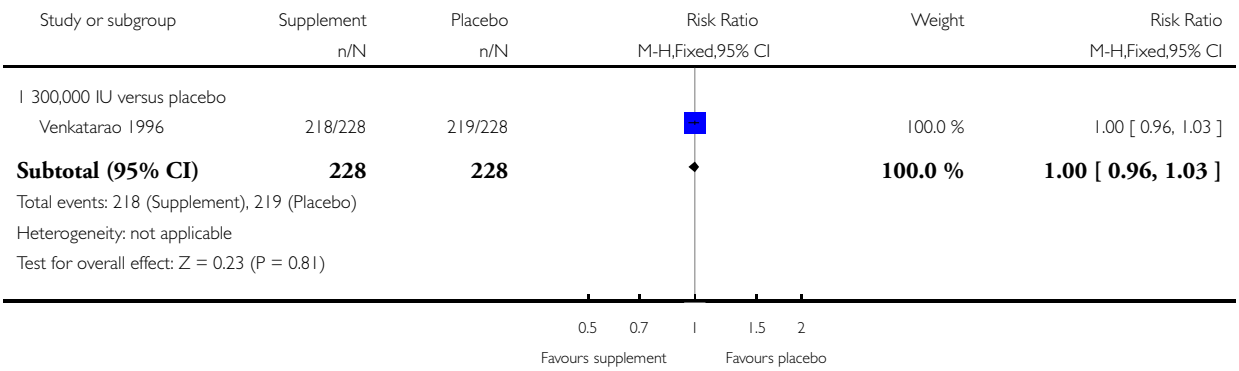


Analysis 1.30. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 30 Infant acute respiratory infection (one or more episodes) to 12 months.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 30 Infant acute respiratory infection (one or more episodes) to 12 months

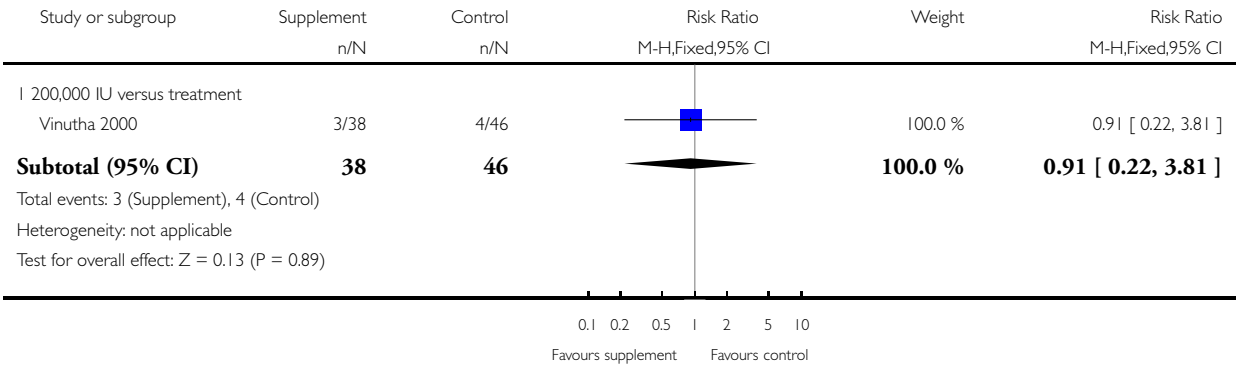


Analysis 1.31. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 31 Infant upper respiratory tract infection to 3 months.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 31 Infant upper respiratory tract infection to 3 months



Analysis 1.32. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 32 Infant acute respiratory tract infection episodes and duration.

Infant acute respiratory tract infection episodes and duration

Study	Outcome / Details	Vitamin A	Control	Significance
200,000 IU versus no treatment				
Roy 1997	Acute respiratory tract infection episodes (mean episodes per child-week of observation)	0.42 (95% CI 0.38 to 0.46)	0.45 (95% CI 0.41 to 0.49)	P = 0.51
Roy 1997	Acute respiratory tract infection duration (duration (days) per child-week of observation)	3.1 (95% CI 2.7 to 3.5)	3.7 (95% CI 3.25 to 4.15)	P = 0.03
Roy 1997	Child-weeks	515	522	

Analysis 1.33. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 33 Infant febrile illness episodes.

Infant febrile illness episodes

Study	Outcome / Details	Vitamin A	Control	Significance
200,000 IU versus no treatment				
Roy 1997	Febrile illness episodes (mean episodes per child-week of observation)	0.1 (95% CI 0.09 to 0.11)	0.3 (95% CI 0.27 to 0.30)	P < 0.002
Roy 1997	Child-weeks	515	522	

Analysis 1.34. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 34 Infant adverse effects of supplementation.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 34 Infant adverse effects of supplementation

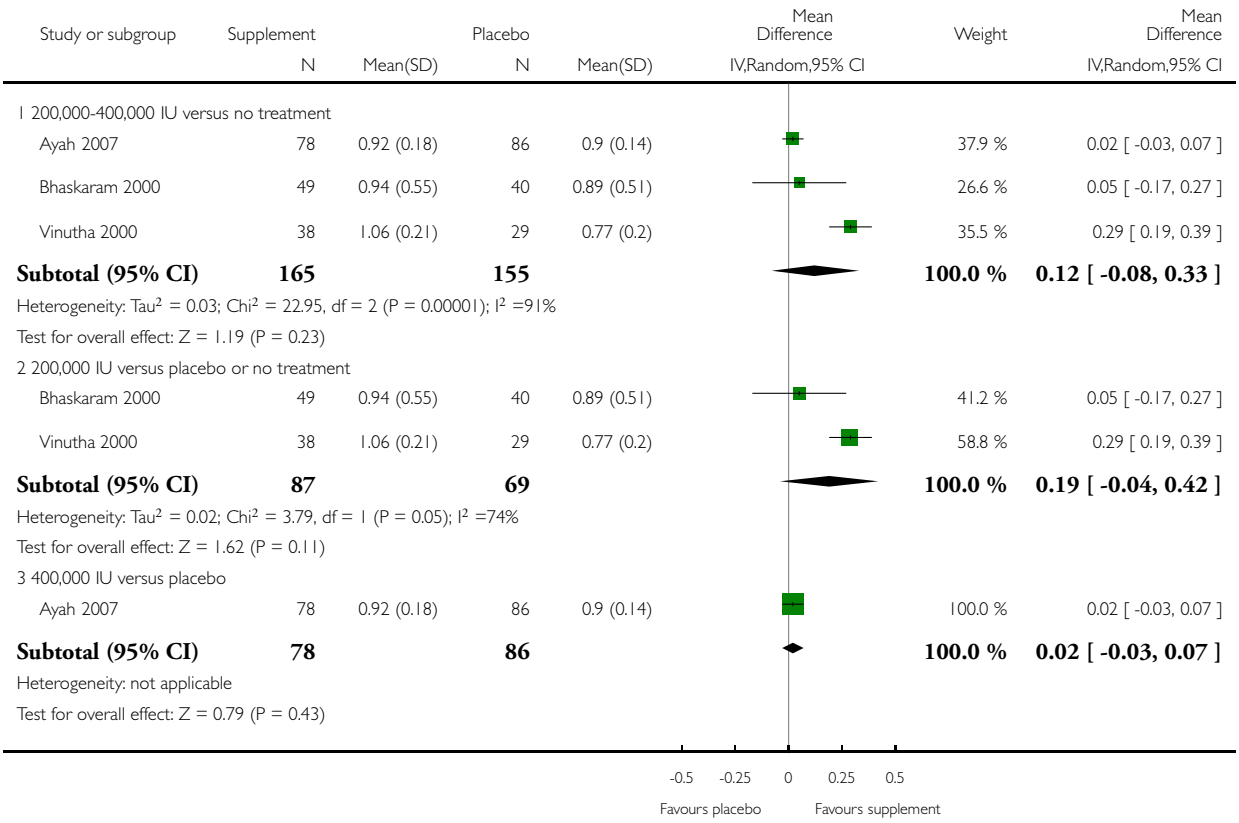
Study or subgroup	Supplement n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Bulging fontanelle: 200,000 IU versus placebo					
WHO/CHD IVASSG	12/4582	5/4596		56.4 %	2.41 [0.85, 6.83]
Subtotal (95% CI)	**4582**	**4596**		**56.4 %**	**2.41 [0.85, 6.83]**
Total events: 12 (Supplement), 5 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.65 (P = 0.099)					
2 Bulging fontanelle: 400,000 IU versus placebo					
Ayah 2007	8/222	4/222		43.6 %	2.00 [0.61, 6.55]
Subtotal (95% CI)	**222**	**222**		**43.6 %**	**2.00 [0.61, 6.55]**
Total events: 8 (Supplement), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.15 (P = 0.25)					
Total (95% CI)	**4804**	**4818**		**100.0 %**	**2.22 [1.01, 4.86]**
Total events: 20 (Supplement), 9 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.05, df = 1 (P = 0.82); I^2 =0.0%					
Test for overall effect: Z = 2.00 (P = 0.046)					

Analysis 1.35. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 35 Infant serum retinol (µmol/L) at 2 - 3.5 months postpartum.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 35 Infant serum retinol (mol/L) at 2 - 3.5 months postpartum



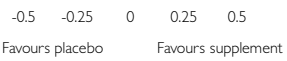
Analysis 1.36. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 36 Infant serum retinol (µmol/L) at 5 - 6 months postpartum.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 36 Infant serum retinol (mol/L) at 5 - 6 months postpartum

Study or subgroup	Supplement N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 200,000-400,000 IU versus placebo							
Ayah 2007	75	1.08 (0.31)	66	1.02 (0.17)		28.1 %	0.06 [-0.02, 0.14]
Bhaskaram 2000	22	0.81 (0.35)	25	0.88 (0.31)		5.1 %	-0.07 [-0.26, 0.12]
RETIBETA Project	69	0.84 (0.23)	70	0.77 (0.21)		34.6 %	0.07 [0.00, 0.14]
Stoltzfus 1993a	68	0.67 (0.19)	70	0.65 (0.26)		32.2 %	0.02 [-0.06, 0.10]
Subtotal (95% CI)	**234**		**231**			**100.0 %**	**0.04 [0.00, 0.09]**
Heterogeneity: Chi^2 = 2.40, df = 3 (P = 0.49); I^2 =0.0%							
Test for overall effect: Z = 2.00 (P = 0.046)							
2 200,000-300,000 IU versus placebo							
Bhaskaram 2000	22	0.81 (0.35)	25	0.88 (0.31)		7.1 %	-0.07 [-0.26, 0.12]
RETIBETA Project	69	0.84 (0.23)	70	0.77 (0.21)		48.0 %	0.07 [0.00, 0.14]
Stoltzfus 1993a	68	0.67 (0.19)	70	0.65 (0.26)		44.8 %	0.02 [-0.06, 0.10]
Subtotal (95% CI)	**159**		**165**			**100.0 %**	**0.04 [-0.01, 0.09]**
Heterogeneity: Chi^2 = 2.19, df = 2 (P = 0.33); I^2 =9%							
Test for overall effect: Z = 1.45 (P = 0.15)							
3 beta-carotene: 7.8 mg daily versus placebo							
RETIBETA Project	69	0.8 (0.22)	70	0.77 (0.21)		100.0 %	0.03 [-0.04, 0.10]
Subtotal (95% CI)	**69**		**70**			**100.0 %**	**0.03 [-0.04, 0.10]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.82 (P = 0.41)							
4 400,000 IU versus placebo							
Ayah 2007	75	1.08 (0.31)	66	1.02 (0.17)		100.0 %	0.06 [-0.02, 0.14]
Subtotal (95% CI)	**75**		**66**			**100.0 %**	**0.06 [-0.02, 0.14]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.45 (P = 0.15)							

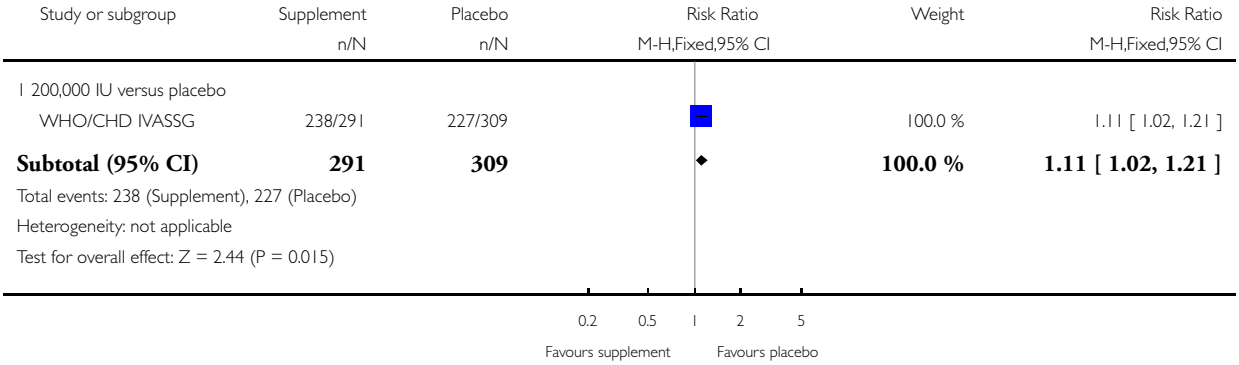


Analysis 1.37. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 37 Infant low hepatic vitamin A stores 1.5 months postpartum (MRDR ≥ 0.06).

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 37 Infant low hepatic vitamin A stores 1.5 months postpartum (MRDR ≥ 0.06)

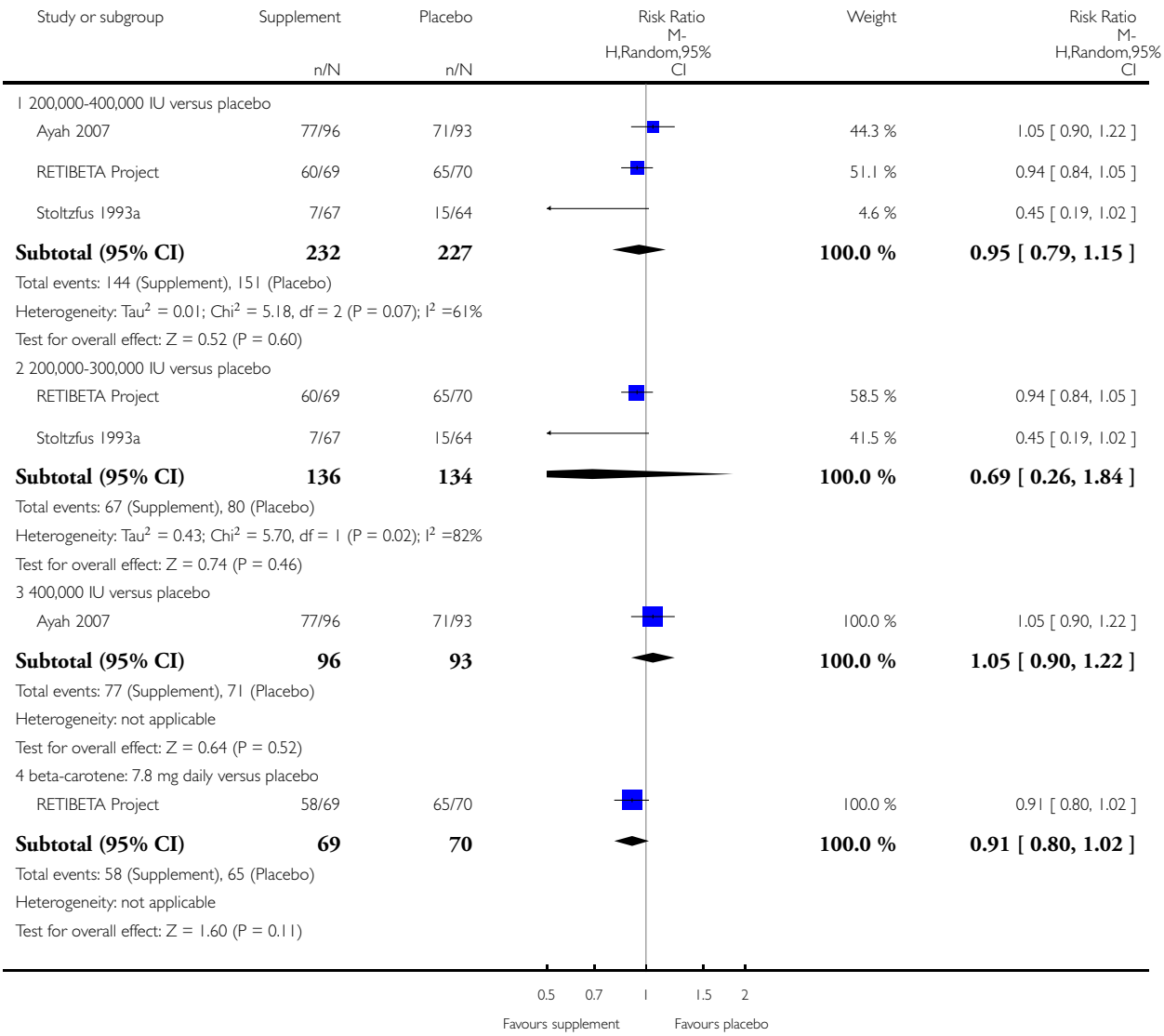


Analysis 1.38. Comparison 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment), Outcome 38 Infant low hepatic vitamin A stores at 5 - 6.5 months postpartum.

Review: Vitamin A supplementation for postpartum women

Comparison: 1 Supplement (vitamin A as retinyl, water miscible or beta-carotene) versus control (placebo, no treatment)

Outcome: 38 Infant low hepatic vitamin A stores at 5 - 6.5 months postpartum

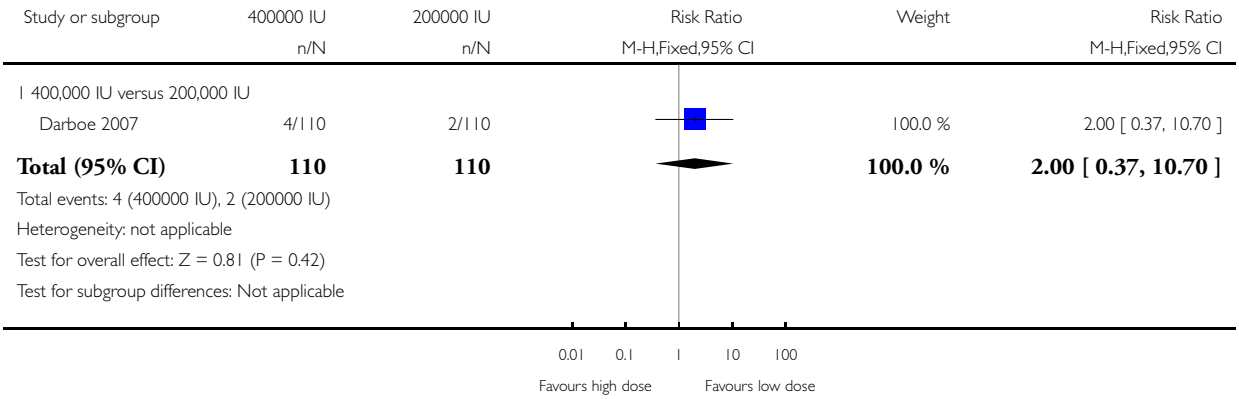


Analysis 2.1. Comparison 2 Supplement (vitamin A as retinyl) high dose versus low dose, Outcome 1 Infant mortality.

Review: Vitamin A supplementation for postpartum women

Comparison: 2 Supplement (vitamin A as retinyl) high dose versus low dose

Outcome: 1 Infant mortality

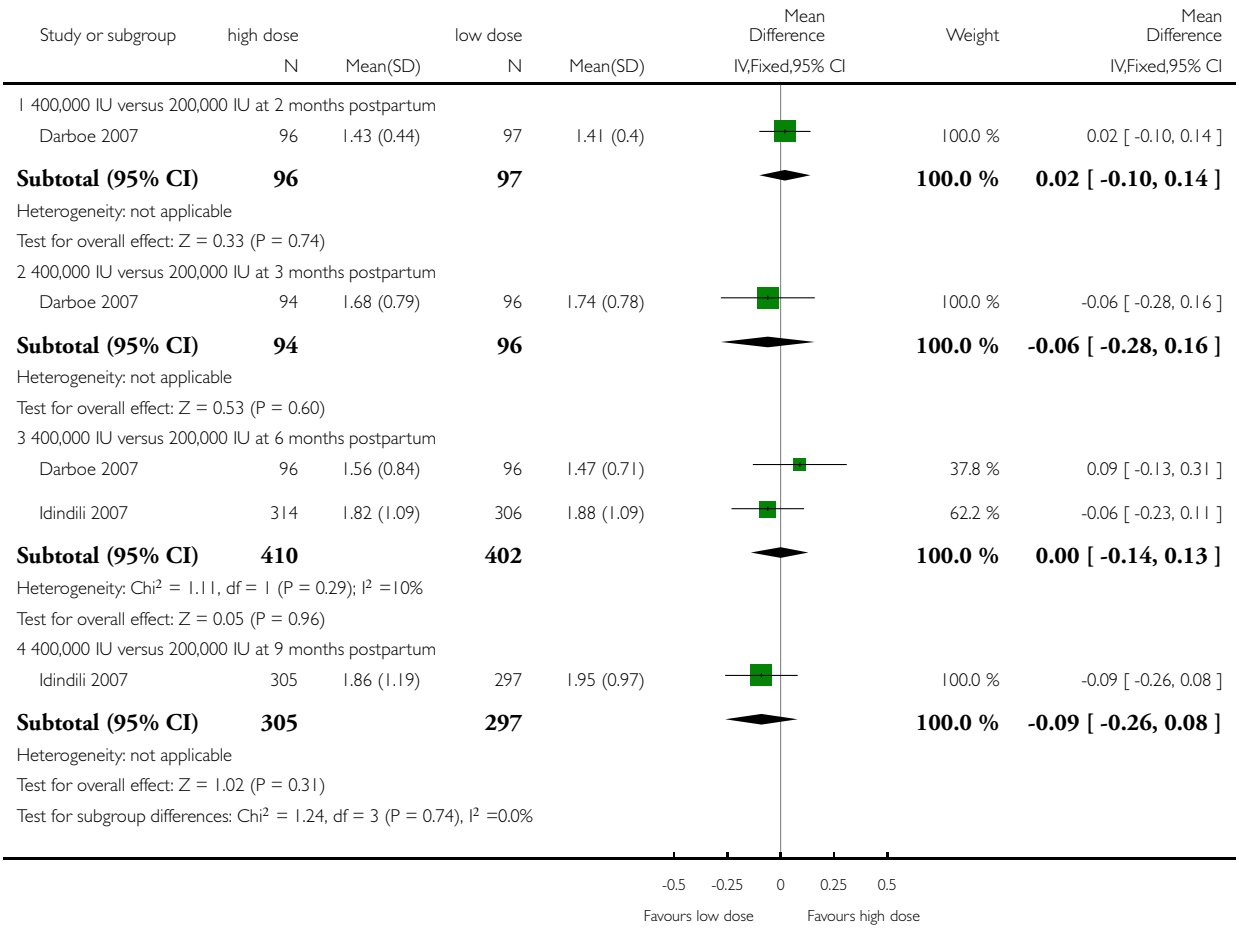


Analysis 2.2. Comparison 2 Supplement (vitamin A as retinyl) high dose versus low dose, Outcome 2 Maternal serum retinol (μ mol/L).

Review: Vitamin A supplementation for postpartum women

Comparison: 2 Supplement (vitamin A as retinyl) high dose versus low dose

Outcome: 2 Maternal serum retinol (μ mol/L)

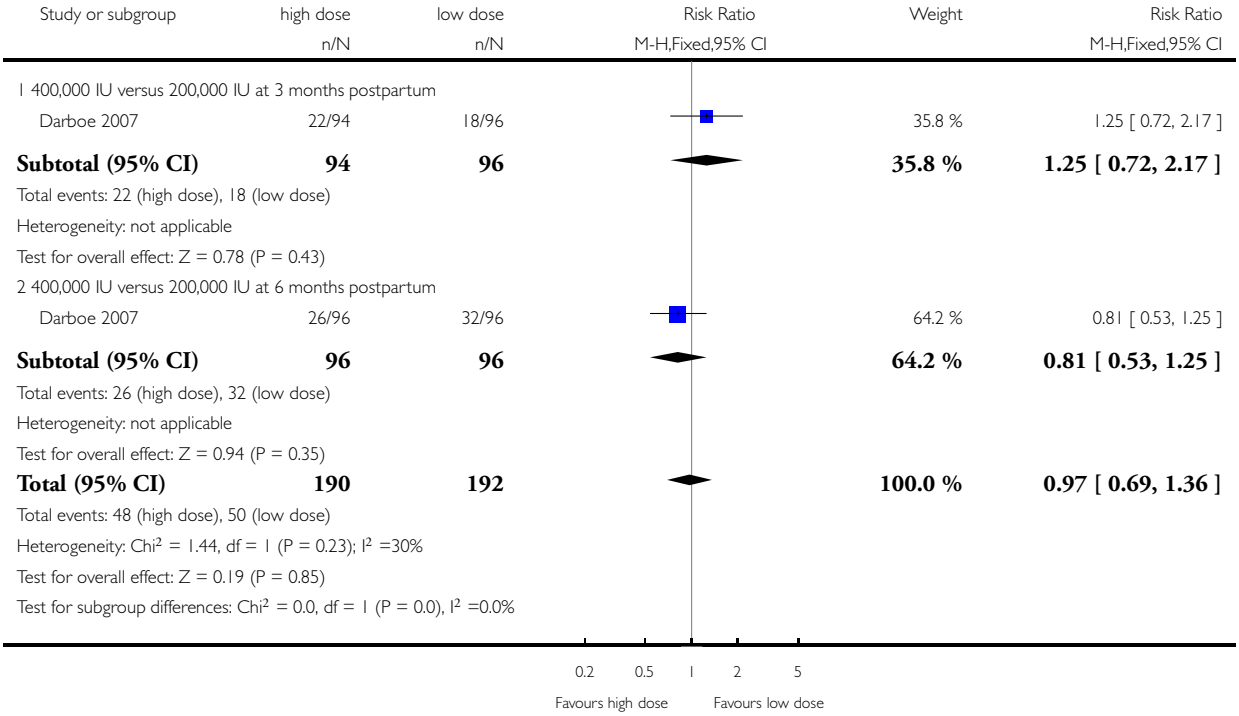


Analysis 2.3. Comparison 2 Supplement (vitamin A as retinyl) high dose versus low dose, Outcome 3 Breast milk retinol (< 1.05 μ mol/L).

Review: Vitamin A supplementation for postpartum women

Comparison: 2 Supplement (vitamin A as retinyl) high dose versus low dose

Outcome: 3 Breast milk retinol (< 1.05 μ mol/L)

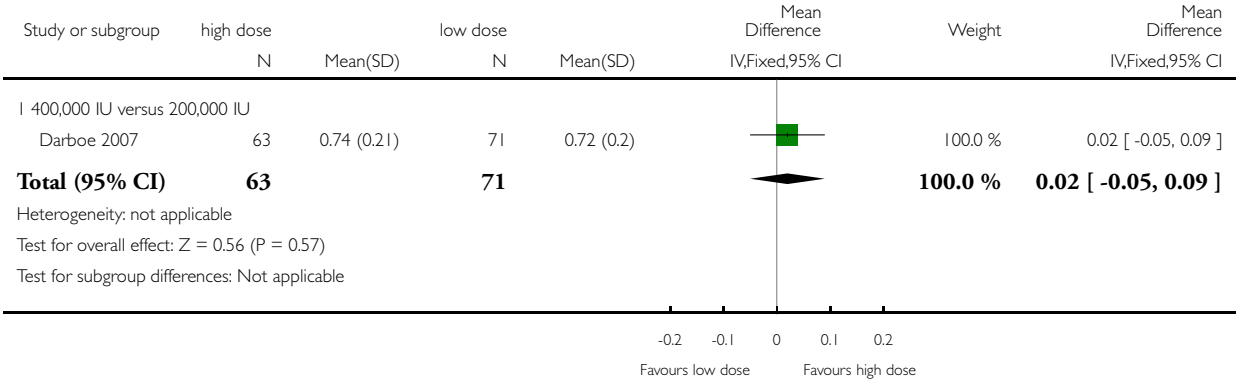


Analysis 2.4. Comparison 2 Supplement (vitamin A as retinyl) high dose versus low dose, Outcome 4 Infant serum retinol (μ mol/L) at 2 months postpartum.

Review: Vitamin A supplementation for postpartum women

Comparison: 2 Supplement (vitamin A as retinyl) high dose versus low dose

Outcome: 4 Infant serum retinol (μ mol/L) at 2 months postpartum



APPENDICES

Appendix 1. Additional search strategies

LILACS - Latin American and Caribbean Health Sciences by Bireme (1982 to July 2010)
#1: ((Pt ENSAIO CONTROLADO ALEATORIO OR Pt ENSAIO CLINICO CONTROLADO OR Mh ENSAIOS CONTROLADOS ALEATORIOS OR Mh DISTRIBUICAO ALEATORIA OR Mh MÉTODO DUPLO-CEGO OR Mh MÉTODO SIMPLES-CEGO) AND NOT (Ct ANIMAIS AND NOT (Ct HUMANO AND Ct ANIMAIS)) OR (Pt ENSAIO CLÍNICO OR Ex E05.318.760.535$) OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh PLACEBOS OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR (Mh PROJETOS DE PESQUISA) AND NOT (Ct ANIMAIS AND NOT (Ct HUMANO AND Ct ANIMAIS)) OR (Ct ESTUDO COMPARATIVO OR Ex E05.337$ OR Mh SEGUIMENTOS OR Mh ESTUDOS PROSPECTIVOS OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct ANIMAIS AND NOT (Ct HUMANO AND Ct ANIMAIS))) AND NOT Mh ANIMAIS [Palavras]
#2: retinol or "vitamin A" or caroten$ [Palavras]
#3: #1 AND #2
WEB OF SCIENCE by ISI (1945 to July 2010)
#1: TS=(randomised controlled trial) OR TS=(controlled clinical trial) OR TS=(randomised controlled trials) OR TS=(random allocation) OR TS=(double-blind method) OR TS=(single-blind method) OR TS=(clinical trial) OR TS=(clinical trials) OR TS=(clinical trial) OR ((TS=singl* OR TS=doubl* OR TS=trebl* OR TS=tripl*) AND (TS=mask* OR TS=blind*)) OR (TS=(latin square) OR TS=placebo* OR TS=random* OR TS=(research design) or TS=(comparative study) OR TS=(evaluation studies) OR TS=(follow-up studies) OR TS=(prospective studies) OR TS=(cross-over studies) OR TS=control* OR TS=prospectiv* OR TS=volunteer*)

#2: TS=puerp* or TS=matern* or TS=lacta* or TS=breastfe* or TS=(breast fee*) or TS=breast-fee* or TS=(human milk) or TS=postnatal or TS=postpart* or TS=newborn* or TS=infant* or TS=newborn
#3: TS=retinol* or TS=(vitamin A) or TS=caroten*
#4: #3 AND #2 AND #1
BIOLOGICAL ABSTRACTS (1998 to July 2010), HUMAN NUTRITION (1982 to October 2007), FOOD SCIENCES & TECH ABSTRACTS (1969 to November 2008), FOOD AND HUMAN NUTRITION (1975 to October 2007), AGRIS (1975 to October 2007) (By ERL - Electronic Reference Library): the latter database searches were not updated due to lack of access to them.
#1: (RANDOMIZED-CONTROLLED-TRIAL) or (CONTROLLED-CLINICAL-TRIAL) or RANDOMIZED-CONTROLLED-TRIALS or RANDOM-ALLOCATION or DOUBLE-BLIND-METHOD or SINGLE-BLIND-METHOD or (CLINICAL-TRIAL) or (CLINICAL-TRIALS) or ((clin* near trial*) in TI) or ((clin* near trial*) in AB) or ((singl* or doubl* or trebl* or tripl*) near (blind* or mask*)) or ((singl* or doubl* or trebl* or tripl*) near ((blind* or mask*) in TI)) or ((singl* or doubl* or trebl* or tripl*) near ((blind* or mask*) in AB)) or PLACEBOS or (placebo* in TI) or (placebo* in AB) or (random* in TI) or (random* in AB) or RESEARCH-DESIGN \
#2: (('POSTPARTUM PERIOD' or 'MATERNAL-CHILD NURSING' or 'MATERNAL NUTRITION' or 'LACTATION' or 'BREAST FEEDING' or 'MILK, HUMAN' or 'POSTNATAL CARE' or 'INFANT, NEWBORN' or 'INFANT') in DE) or PUERP* or MATERN* or LACTA* or BREASTFE* or 'BREAST FE*' or BREAST-FE* or 'HUMAN MILK' or MILK-HUMAN or POSTNATAL or POSTPART* or INFANT-NEWBORN* or NEWBORN* or INFANT*
#3: ('Vitamin A' in DE) or ('Vitamin A Deficiency' in DE) or ('Carotenoids' in DE) or caroten* or retinol* or 'vitamin A'
#4: #1 AND #2 AND #3

HISTORY

Protocol first published: Issue 2, 2006

Review first published: Issue 10, 2010

Date	Event	Description
22 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

JM Oliveira-Menegozzo, CE East and P Middleton wrote the review with input from DP Bergamaschi.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Brazilian Cochrane Center, Brazil.
- Coordenadoria de Aperfeiçoamento do Ensino Superior - CAPES, Brazil.
- Fundação de Amparo à Pesquisa do Estado de SP - FAPESP, Brazil.
- Pró-reitoria de Pesquisa da USP, Brazil.

External sources

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

Provided funding for the preparation of this review.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Considerable collaborative input from referees, authors and other Cochrane personnel resulted in a focus specifically on postpartum supplementation, rather than widening to include long-term supplementation during women's reproductive years.

Criteria for considering studies in this review: we added the potential for including cluster-randomised trials, which were considered important for the purpose of the review, although none were ultimately included.

INDEX TERMS

Medical Subject Headings (MeSH)

*Postpartum Period; Infant Mortality; Maternal Mortality; Milk, Human [chemistry]; Randomized Controlled Trials as Topic; Vitamin A [*administration & dosage; analysis]; Vitamin A Deficiency [drug therapy]; Vitamins [*administration & dosage]

MeSH check words

Female; Humans; Infant; Infant, Newborn; Pregnancy