# Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants (Review)

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[Intervention Review]

# Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

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## ABSTRACT

### Background

Vitamin A is necessary for normal lung growth and the integrity of respiratory tract epithelial cells. Preterm infants have low vitamin A status at birth, and this has been associated with increased risk of developing chronic lung disease.

### Objectives

To evaluate vitamin A supplementation on the incidence of death and/or neonatal chronic lung disease and long-term neurodevelopmental disability in very low birthweight infants (VLBW); and to consider the effect of the supplementation route, dose, and timing.

### Search methods

In August 2011, the Cochrane Central Regsiter of Controlled Trials (Central, *The Cochrane Library*), MEDLINE, Science Citation Index and the Oxford Database of Perinatal Trials were searched. The reference lists of relevant trials, paediatric and nutrition journals, and conference abstracts and proceedings were handsearched up to 2007.

### Selection criteria

Randomised controlled trials comparing vitamin A supplementation with a control (placebo or no supplementation) or other dosage regimens in VLBW infants (birthweight $\leq$ 1500 g or < 32 weeks' gestation).

### Data collection and analysis

Both review authors screened the search results, extracted data, and assessed the trials' risk of bias. Results were reported as risk ratios (RR), risk differences (RD), and number needed to treat to benefit (NNTB), all with 95% confidence intervals (CI). Trialists were contacted for additional data.

### Main results

Nine trials met the inclusion criteria, eight compared vitamin A supplementation with a control (1291 infants), and one compared different regimens (120 infants). Compared to the control group, vitamin A appears to be beneficial in reducing death or oxygen requirement at one month of age (RR 0.93, 95% CI 0.88 to 0.99; RD -0.05, 95% CI -0.10 to -0.01; NNTB 20, 95% CI 10 to

100; 1165 infants) and oxygen requirement at 36 weeks' postmenstrual age (RR 0.87, 95% CI 0.77 to 0.98; RD -0.08, 95% CI -0.14 to -0.01; NNTB 13, 95% CI 7 to 100; 824 infants). A trend towards a reduction in death or oxygen requirement at 36 weeks' postmenstrual age was also noted (RR 0.91, 95% CI 0.82 to 1.00; 1001 infants). Neurodevelopmental assessment of 88% of surviving infants in the largest trial showed no differences between the groups at 18 to 22 months of age, corrected for prematurity. The different dosage vitamin A regimens showed similar results.

**Authors' conclusions**

Whether clinicians decide to utilise repeat intramuscular doses of vitamin A to prevent chronic lung disease may depend upon the local incidence of this outcome and the value attached to achieving a modest reduction in this outcome, balanced against the lack of other proven benefits and the acceptability of treatment. Information on long-term neurodevelopmental status suggests no evidence of either benefit or harm from the intervention.

## PLAIN LANGUAGE SUMMARY

**Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants**

Vitamin A is a group of fat-soluble compounds used by the body for regulation and promotion of growth and differentiation of many cells, including cells in the retina of the eye and the cells that line the lung. Preterm infants have low vitamin A levels at birth. This may contribute to an increased risk of developing chronic lung disease, and hence a requirement for oxygen. It is possible that additional vitamin A supplement may reduce complications of prematurity, including abnormal development of the retina (retinopathy), bleeding in the brain (intraventricular haemorrhage), and damage to the gut from inflammation (necrotising enterocolitis) as well as reducing respiratory infections. Too much vitamin A is potentially harmful as it can raise intracranial pressure and cause skin and mucous membrane changes (injury or lesions), and vomiting. Nine trials were included in this review, eight comparing vitamin A with a control (placebo or no supplementation) and one comparing different vitamin A regimens. Supplementing very low birthweight infants with vitamin A by intramuscular injection or in the milk formula was associated with a trend toward a reduced number of deaths or oxygen requirement at one month of age compared to placebo. For surviving infants with birthweight less than 1000 g (three trials, 824 infants of which at least 96% had a birthweight < 1000 g), fewer infants required oxygen at 36 weeks' postmenstrual age compared to the control; the number needed to treat for one to benefit was 13 (95% confidence interval 7 to 100). Three trials with information on retinopathy of prematurity suggested a trend towards reduced incidence in infants receiving vitamin A supplementation. The one trial that investigated neurodevelopmental status at 18 to 22 months of age correcting for prematurity found no evidence of benefit or harm associated with vitamin A supplementation compared to control. No adverse effects of vitamin A supplementation were reported, but it was noted that intramuscular injections of vitamin A were painful.

## BACKGROUND

### Description of the condition

Vitamin A is the generic name for a group of fat-soluble compounds which have the biological activity of the primary alcohol retinol. Vitamin A is involved in the regulation and promotion of growth and differentiation of many cells and in maintaining the integrity of the epithelial cells of the respiratory tract. Vitamin A is also necessary for formation of photosensitive visual pigment in the retina, reproductive functions, and immuno-competence. Caretenoids, dietary precursors of vitamin A, have antioxidant properties.

The fetus accumulates vitamin A in the third trimester. The transport mechanism of vitamin A across the placenta and its regulation are not fully established. Premature infants have reduced hepatic stores (of retinyl ester). In the plasma, vitamin A is bound to a specific carrier protein, retinol-binding protein (RBP), and the resulting complex is further complexed with transthyretin (formerly prealbumin) (Mactier 2005). Premature infants have lower concentrations of plasma RBP than term infants, and most preterm infants have low plasma vitamin A concentrations and low plasma retinol/RBP molar ratios, suggesting they are vitamin A deficient (Shenai 1993). Inadequate provision and delivery of vitamin A postnatally may exacerbate the problem.

### Description of the intervention

Preterm infants who are unable to tolerate oral feeds are routinely fed parenterally with both an amino-acid/dextrose mixture and a lipid emulsion. Multivitamin preparations containing retinol or an equivalent are commonly added to the amino-acid/dextrose mixture and infused over 24 to 48 hours, but significant losses in delivered vitamin A have been shown to result from light degradation and from adsorption to the tubing. Alternatively, the multivitamins may be added to the lipid infusate (Greene 1987). Kennedy 1997 demonstrated improved serum retinol concentrations following intramuscular injections given three days per week. This route of administration has been adopted in several recent studies. In preterm infants who are able to tolerate enteral feeds, the absorption of enteral vitamin A by the immature gut may be poor.

The 'adequate' concentration of plasma vitamin A in very low birthweight infants is not known. Concentrations below 200 $\mu$g/L (0.70 $\mu$mol/L) have been considered deficient in premature infants, and concentrations below 100 $\mu$g/L (0.35 $\mu$mol/L) indicate severe deficiency and depleted liver stores. Both the plasma RBP response (Shenai 1990) and the relative rise in serum retinal concentration (Zachman 1996) following intramuscular vitamin A administration have been described as useful tests to assess functional vitamin A status. However, in a recent review, Mactier 2005 concluded that the relationship between measures of vitamin A concentration and functional vitamin A status in preterm infants is not clear.

Vitamin A deficiency in laboratory animals produces a sequence of histopathological changes in the respiratory tract epithelium including necrotising tracheobronchiolitis and squamous metaplasia. These changes can be reversed by restoration of adequate vitamin A status. Similar changes are observed in ventilated infants with chronic neonatal lung injury, leading to the suggestion that vitamin A deficiency may contribute to such injury and supplementation with vitamin A may facilitate healing and recovery (Chytil 1992; Shenai 1993). Two earlier studies reported that very low birthweight infants who developed chronic lung disease had lower concentrations of vitamin A than similar infants without chronic lung disease (Hustead 1984; Shenai 1985), although other studies from an era when all infants received more adequate supplementation have given conflicting results (Chabra 1994; Spears 2004).

### How the intervention might work

In the 1920s, vitamin A was considered to be an anti-infective agent. There is increasing evidence that vitamin A does have a role in immune function (Bates 1995). Several studies in areas of the world where there is generally poor nutritional status have suggested vitamin A supplementation in infancy may be associated with decreased mortality and morbidity. In infants in Indonesia, Humphrey 1996 reported that a single dose of 52 $\mu$mol (50,000 IU) given orally to term infants at birth reduced infant mortality and the prevalence of severe respiratory infections compared with placebo. A Cochrane Review concluded that two oral doses of 200,000 IU in children under two years of age with measles are associated with a reduced risk of overall mortality and of pneumonia-specific mortality (Huiming 2005).

Vitamin A has a role early in gestation in the development of the cardiovascular system (Mactier 2005). Animal models suggest higher vitamin A concentrations may accelerate postnatal constriction of the ductus arteriosus. The possibility that vitamin A supplementation may ameliorate other complications of prematurity, including retinopathy, intraventricular haemorrhage, and necrotising enterocolitis, has been suggested by a number of authors, although the basis for any effect is not clearly established.

Vitamin A is potentially toxic, and raised intracranial pressure and vomiting have been described in infants receiving large doses. In children and adults, chronic hypervitaminosis A may include bone and joint pain, and mucocutaneous lesions and hepatic dysfunction, but the syndrome has not been recognised in preterm infants.

### Why it is important to do this review

Although a role for vitamin A in neonatal chronic lung disease is not in doubt, uncertainty exists regarding the efficacy of supplementation and whether additional benefit may be obtained by achieving concentrations beyond sufficiency.

This is an update of previous versions of this Cochrane Review (Darlow 1998; Darlow 2000; Darlow 2002; Darlow 2007).

## OBJECTIVES

To evaluate supplementation with vitamin A with a control (placebo or no supplementation) on the incidence of death and/or neonatal chronic lung disease and long-term neurodevelopmental disability in very low birthweight infants; and to consider the effect of the supplementation route, dose, and timing.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised and quasi-randomised controlled trials.

### Types of participants

Very low birthweight infants (defined as birthweight ≤ 1500 g or < 32 weeks' gestation).

### Types of interventions

- Vitamin A supplementation compared with control (placebo or no supplementation).
- Different vitamin A supplementation dosage regimens.

### Types of outcome measures

#### Primary outcomes

- Death (at 28 days and at hospital discharge).
- Chronic lung disease (defined as oxygen use at 28 days or at 36 weeks' postmenstrual age).
- Death or chronic lung disease (defined as oxygen use at 28 days or at 36 weeks' postmenstrual age).

#### Secondary outcomes

- Vitamin A concentration.
- Nosocomial infection.
- Patent ductus arteriosus.*
- Necrotizing enterocolitis.*
- Intraventricular haemorrhage.*
- Periventricular leukomalacia.*
- Retinopathy of prematurity.
- Neurodevelopment at 18 to 36 months.
- Adverse effects, including manifestations of hypervitaminosis A, particularly raised intracranial pressure and mucocutaneous lesions.

* *Additional secondary outcomes added in the 2010 update.*

## Search methods for identification of studies

### Electronic searches

The Cochrane Neonatal Group searched the following databases in August 2011 using the Group's standard methods: Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library,* Issue 8, 2011), MEDLINE (search terms vitamin A or retinol; and infant, premature or infant, low birth weight); Oxford Database of Perinatal Trials; and the Science Citation Index.

### Searching other resources

We searched the reference lists of relevant articles and hand-searched recent issues of paediatric and nutritional journals. We also handsearched abstracts from the Pediatric Academic Societies' Annual Meeting from 2002 to 2010.

The Cochrane Neonatal Group searched the following clinical trial registries for ongoing or recently completed trials: ClinicalTrials.gov; Current Controlled Trials (www.controlled-trials.com); and the WHO International Clinical Trials Registry Platform (www.who.int/ictrp).

## Data collection and analysis

### Selection of studies

We included all trials fulfilling the review's selection criteria. We cited all identified articles and made the decision regarding inclusion/exclusion of the studies by consensus. In the event of disagreements, we sought the opinion of a third party.

### Data extraction and management

For each included study, we collected information regarding the method of randomisation, blinding, drug intervention, stratification, trial location, and whether the trial was conducted at a single centre or multiple centres. We also collected information regarding inclusion criteria, including gestational age and postnatal age at the time of treatment. The list of data extraction fields for the trial interventions and outcomes are shown in Appendix 1.

We completed data collection sheets before comparing them and resolving any discrepancies resolved by referring to the original sources. For each study, one author entered the final and agreed data into Review Manager 5, and the second review author checked the data. We referred to a third party to resolve any disagreements.

### Assessment of risk of bias in included studies

For the 2010 update, one person assessed the risk of bias in the included studies according to the methods in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). This built on the previous version's assessment of the methodological quality of the included studies. Any uncertainties were resolved through discussion with a second person. The following components of the risk of bias tool were assessed and judged as having a high, low, or unclear risk of bias using the criteria in Higgins 2008: sequence generation (checking for possible selection bias); allocation concealment (checking for possible selection bias); blinding (checking for possible performance bias); incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations); selective outcome reporting (whether all of the study's pre-specified outcomes were reported (by checking the trial

protocol if available) or whether the study fails to include results of a key outcome that would have been expected to have been reported); and other biases (including source of funding and sample size calculation). For each item and where possible, we have provided a supporting quotation from the trial article.

### Measures of treatment effect

We conducted separate analyses for each of the following outcomes: death; neonatal chronic lung disease; retinopathy of prematurity; sepsis (one or more defined episodes); and neurodevelopmental disability. Since there were only a small numbers of deaths, we conducted analyses using the composite endpoint of neonatal chronic lung disease or death, and neurodevelopmental disability or death. All analyses were conducted on an intention-to-treat basis. The data did not allow a quantitative analysis of vitamin A concentrations among survivors. We stratified the analyses by route of vitamin A administration.

For dichotomous outcomes, we analysed the effect of vitamin A supplementation via both the risk ratio (RR) and the risk difference (RD) with 95% confidence intervals (CI). From 1/RD, we calculated the number need to treat to benefit (NNTB). For vitamin A concentrations the intention was to focus the analysis on the mean difference between the supplemented and control groups. We combined continuous data using the standard mean difference (SMD) and 95% CI.

### Assessment of heterogeneity

We assessed between-study heterogeneity using standard $Chi^2$ test and the $I^2$ statistic.

### Data synthesis

We performed the meta-analysis using Review Manager 5. For estimates of the pooled RR and RD, we used the Mantel-Haenszel method. For measured quantities, we used the inverse variance method. We used the fixed-effect model for all meta-analyses.

We used GRADE methodology (GRADE 2010) and the GRADEprofiler software (GRADEpro) to generate Summary of Findings tables with the following outcome measures: death before one month, oxygen use at one month in survivors, death before 36 weeks PMA, oxygen use at 36 weeks PMA in survivors, death before 18 to 22 months, neurodevelopmental impairment at 18 to 22 months, failure of ductal closure or treatment by day 14, one or more episodes of sepsis, necrotizing enterocolitis, intraventricular haemorrhage (IVH) - any IVH, retinopathy of prematurity (any grade).

### Subgroup analysis and investigation of heterogeneity

If data were available, we planned subgroup analyses to address the effect of the route, dose, and timing of supplementation.

### Sensitivity analysis

Where appropriate, we planned sensitivity analyses to explore the impact of the risk of bias assessments.

## RESULTS

### Description of studies

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

### Results of the search

We identified 15 potentially relevant trials of which nine met the eligibility criteria (Ambalavanan 2003; Bental 1994; Papagaroufalis 1988; Pearson 1992; Ravishankar 2003; Shenai 1987; Tyson 1999; Wardle 2001; Werkman 1994). Eight trials compared vitamin A with a control, while one trial, Ambalavanan 2003, compared three different vitamin A dosing regimens and had a primary outcome of serum retinol concentrations at 28 days; see trial details in the 'Characteristics of included studies'.

We excluded seven trials from the review (see 'Characteristics of excluded studies'). Robbins 1993 was not a randomised controlled trial. Coutsoudis 2000 enrolled low birthweight infants up to 35 weeks' gestation, and the primary outcome was incidence of respiratory infections in the first year of life. Aurvag 2007 compared vitamin A supplementation of human milk fortifier to historical controls and did not report clinical outcomes. Four studies reported vitamin A concentrations but not clinical outcomes (Aranda 1992; Koo 1993; Landman 1992; Rush 1994). The unpublished study by Aranda 1992 did not state the route of vitamin A supplementation, and reported vitamin A levels appear to contain a decimal point error. Landman 1992 and Rush 1994 both compared equivalent doses of vitamin A administered either enterally or intramuscularly, and data in Rush 1994 were only reported graphically. Koo 1993 compared three doses of vitamin A added to preterm formula and given for an unstated period of time.

### Trial location and size

Most trials were conducted in the USA (Ambalavanan 2003; Pearson 1992; Ravishankar 2003; Shenai 1987; Tyson 1999; Werkman 1994). Two trials were conducted in Europe - in Greece (Papagaroufalis 1988) and the UK (Wardle 2001), and one trial was conducted in South Africa (Bental 1994).

Most trials included less than 100 infants (Bental 1994; Papagaroufalis 1988; Pearson 1992; Ravishankar 2003; Shenai 1987; Werkman 1994), two included between 100 and 200 participants (Ambalavanan 2003; Wardle 2001), and one trial included 807 infants (Tyson 1999).

## Participants

### Vitamin A versus control

The eight trials comparing vitamin A with a control reported outcomes for 1291 infants, 653 treated with vitamin A and 638 control infants. One trial, Ravishankar 2003, studied infants of gestational age < 32 weeks with a birthweight 500 to 1500 g who had an indwelling umbilical catheter and were less than 24 hours of age. The remaining seven trials studied infants with a birthweight ≤ 1500 g and "at risk for bronchopulmonary dysplasia".

The specific entry criteria for birthweight and gestation varied between the trials: birthweight of 1000 to 1500 g and ≤ 34 weeks' gestation (Bental 1994); birthweight ≤ 1300 g and < 29 weeks' gestation (Papagaroufalis 1988); birthweight 700 to 1100 g (Pearson 1992); birthweight 700 to 1300 g and 26 to 30 weeks' gestation (Shenai 1987); birthweight of 401 to 1000 g (Tyson 1999); birthweight < 1000 g (Wardle 2001); and birthweight 725 to 1300 g (Werkman 1994).

Some trials had other specific entry requirements. Tyson 1999 enrolled infants who required supplemental oxygen or mechanical ventilation at 24 hours of age. Wardle 2001 required consent before 24 hours of age and absence of life-threatening congenital abnormalities. Werkman 1994 required infants to be less than 96 hours of age without contraindications to study; whereas all other studies required infants to be receiving supplemental oxygen and to have been treated with mechanical ventilation for at least 72 hours in the first week. Pearson 1992 and Shenai 1987 excluded growth-retarded infants.

Bental 1994 included only black South African infants, and Shenai 1987 included only Caucasian infants.

### Vitamin A dosing regimens

Ambalavanan 2003, which addressed the secondary question of vitamin A dosage, had the same entry criteria as Tyson 1999 and included 120 infants.

## Interventions

### Vitamin A versus control

Eight trials compared vitamin A with a control. All but two trials (Wardle 2001; Werkman 1994) gave supplemental vitamin A (water soluble retinyl palmitate) by intramuscular injection soon after birth, usually day four, and over the next 28 days. The trials varied in the vitamin A dose (where 1 IU is equivalent to 0.3 mg) and regimen: injections of 4000 IU three times a week in Bental 1994 and on alternate days in Papagaroufalis 1988; injections of 2000 IU were given on alternate days in Pearson 1992 and Shenai 1987; injections of 5000 IU on three days a week for four weeks in Tyson 1999; 1500 IU to 3000 IU, based on birthweight, but only on three occasions (days one, three, and seven) in Ravishankar 2003. Papagaroufalis 1988, Pearson 1992, and Shenai 1987 compared supplementation with normal saline placebo injections; Ravishankar 2003 and Tyson 1999 versus sham injections; and Bental 1994 versus no supplementation.

In Wardle 2001, supplemental vitamin A was given orally as a bolus through an orogastric tube in a dose of 5000 IU/kg daily from postnatal day one until day 28, with control infants receiving an equivalent volume of a look-alike inert placebo solution. In Werkman 1994, supplemental vitamin A was given as retinyl palmitate in lipid emulsion at a concentration of 80,000 RE/L (1 IU is equivalent to 0.3 RE) over 16 hours, and study infants received approximately an additional 1300 to 3300 IU/kg/d vitamin A in the first two weeks and additional amounts depending on whether they remained on parenteral nutrition.

Study and control infants were also administered standard vitamin A. However, the amount of vitamin A in standard therapy, and hence received by control groups, varied between studies. When on parenteral nutrition, infants in Shenai 1987 received vitamin A 400 IU/100 mL protein-dextrose infusion and usually < 700 IU/kg/d from all sources. Infants in Pearson 1992 received 1200 to 1500 IU/d of vitamin A in the protein-dextrose solution. In Bental 1994, infants on parenteral nutrition received no vitamin A but some received 1500 to 3000 IU/ d after one week when fed orally. In Papagaroufalis 1988, the amount of standard vitamin A is not stated. In Werkman 1994, standard vitamin A was added to the protein dextrose solution with infants < 1000 g receiving 700 IU/d and infants > 1000 g receiving 1580 IU/d. In Tyson 1999, infants received approximately 700 IU/kg/d in the first week, principally in protein-dextrose solution, and closer to 1000 IU/kg/d in weeks two to four from all sources (data estimated from graph). Infants in Wardle 2001 were stated to receive 23 IU/kg/d added to intralipid when on parenteral nutrition (however, the standard United Kingdom dose was at that time 233 IU/kg/d, and it is probable infants in this study received this dose) and 5000 IU/kg/day orally when on full enteral feeds from the fourteenth postnatal day. In Ravishankar 2003, most infants on parenteral nutrition received 466 IU vitamin A added to 100 mL of the protein dextrose solution, and 1500 IU/d orally when fully enterally fed.

### Vitamin A dosing regimens

In Ambalavanan 2003, infants were randomised to receive a standard vitamin A supplement by intramuscular injection of 5000 IU on three days per week for four weeks (considered as the control group), a higher dose of 10,000 IU on three days per week for four weeks, or a once-per-week dose of 15,000 IU for four weeks.

## Outcomes

We contacted several trial authors for further details about the trial outcomes and data. Bental 1994 gives complete data published in

an earlier abstract from 1990, and we sought and obtained further clarification from the trial authors concerning two outcomes: oxygen use at one month in survivors; and death or oxygen use at one month. We were able to update data of Papagaroufalis 1988 with information provided by the trial author to Dr K Kennedy at the time of an earlier review (Kennedy 1997). We obtained information on the age at death for infants from the corresponding author of Ravishankar 2003. Further information on the numbers examined for retinopathy of prematurity and numbers with any retinopathy in Wardle 2001 were provided by the trial author. We also received further information on the timing of death, numbers of infants having serum retinol estimations at 28 days, and any retinopathy of prematurity was obtained from the author of Ambalavanan 2003.

#### Vitamin A versus control

The primary outcome measure for the studies by Bental 1994, Papagaroufalis 1988, Pearson 1992, and Shenai 1987 was the presence of an oxygen requirement and characteristic chest x-ray at 31 days (28 days after enrolment). (Unpublished data of Papagaroufalis 1988 are available for 28, 29, 30, and 31 days, and in the Kennedy 1997 review day 28 outcomes rather than day 31 were used.) Data on this outcome for Bental 1994 were not clear and have been obtained from the authors. Werkman 1994 reported this outcome at 28 days of age.

All trials with the exception of Werkman 1994 reported deaths before 31 days of age (with clarification of data for Bental 1994 obtained from the authors). Wardle 2001 and Tyson 1999 reported on supplemental oxygen requirement at or death before 28 days of age; and oxygen requirement at or death before 36 weeks' postmenstrual age. Pearson 1992 additionally reported on oxygen requirement at or death before 34 weeks' postmenstrual age, but because the incidence of oxygen requirement may decrease rapidly with each week increasing age, these data have not been included.

The primary outcome measure for Ravishankar 2003 was "failure of ductal closure", defined as the presence of a moderate or large patent ductus arteriosus on day 14, receipt of indomethacin therapy, or having undergone a surgical ligation. Only Wardle 2001 also reported on a patent ductus arteriosus requiring treatment with indomethacin or surgical closure, but the timing of this is uncertain as to whether some infants had died before this outcome; hence we have not included these data. Ravishankar 2003 also reported deaths (and further information on the timing of these has been obtained from the trial authors) and oxygen requirement at 36 weeks' postmenstrual age.

Shenai 1987 and Pearson 1992 reported on retinopathy of prematurity. Pearson 1992 states 61% of each group had retinopathy of prematurity and knowing the number of infants alive at 34 weeks' postmenstrual age and assuming all were examined for retinopathy, we computed the data. Wardle 2001 reported on treatment for retinopathy of prematurity, but not overall incidence, and we obtained further data from the author.

Bental 1994 and Tyson 1999 reported on one or more episodes of sepsis, defined as culture-proven (Bental 1994) and a positive blood culture plus at least five days of antibiotics (Tyson 1999). Papagaroufalis 1988 reported on sepsis episodes, but these were undefined and may have included early onset sepsis. Shenai 1987 reported on suspected rather than culture-proven episodes of sepsis, and Wardle 2001 reported on the median number of sepsis episodes in each group; hence we have excluded these data.

All trials analysed plasma vitamin A concentrations at various times; however, no data were reported by Papagaroufalis 1988, Bental 1994, and Pearson 1992. Shenai 1987 only reported data as points on a graph, and Tyson 1999 reported on mean levels in the first 300 enrolled infants and grouped according to receipt of postnatal steroids two weeks before sampling. Wardle 2001 reported on median vitamin A concentrations for the first 84 infants in the study, and Werkman 1994 has reported data grouped according to pulmonary status. Hence, we have not analysed these outcomes in this version of the review.

Ambalavanan 2005 reported on neurodevelopmental impairment as any one of the following occurring at 18 to 22 months for infants enrolled in the study by Tyson 1999: bilaterally blind; deaf in both ears requiring aids; a Bayley II Mental Developmental Index < 70; or a Bayley II Psychomotor Developmental Index < 70.

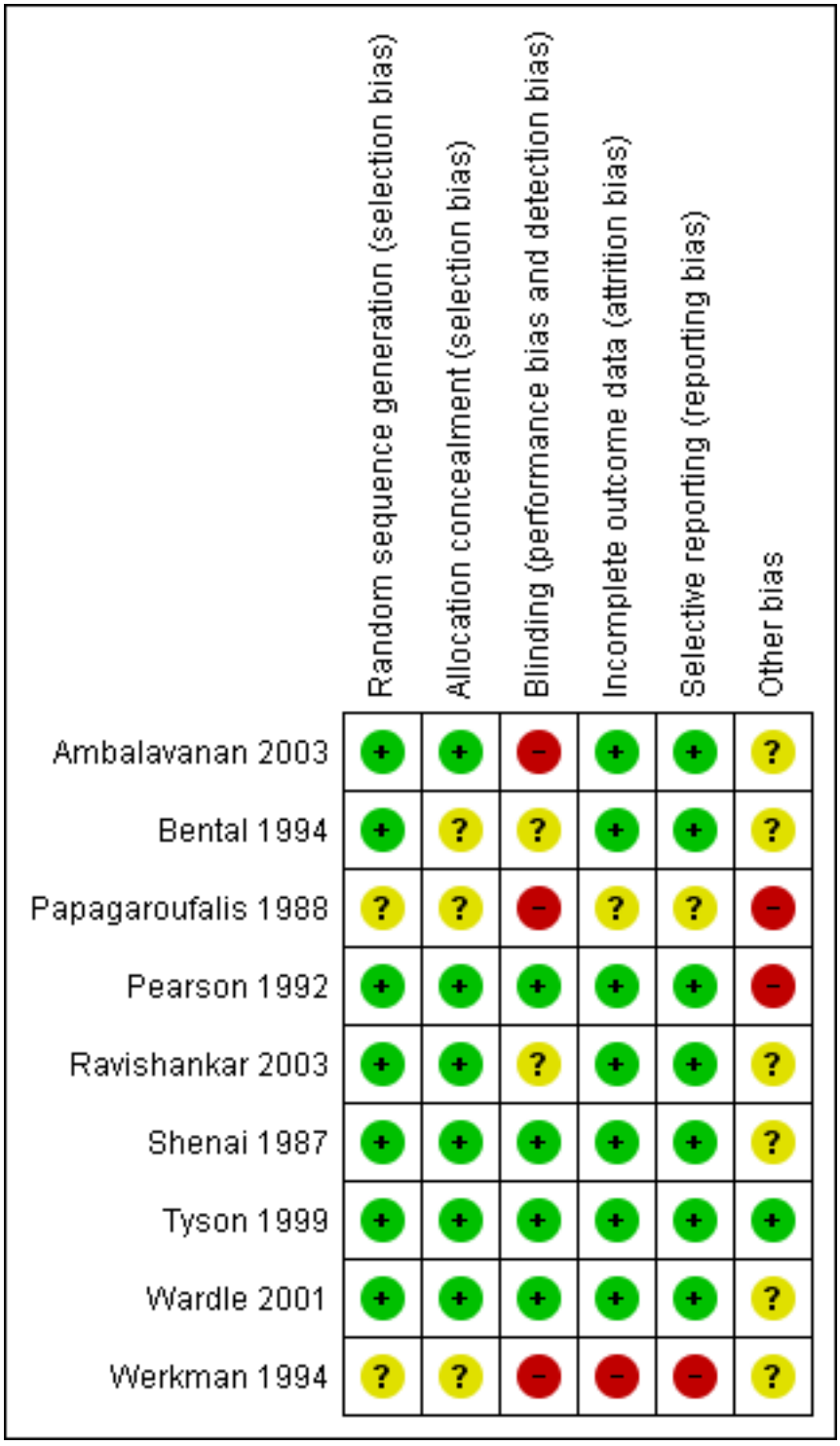
The primary outcome measure for the trial by Ambalavanan 2003 was serum retinol concentrations in $\mu$g/L at 28 days. Ambalavanan 2003 also reported on death before 36 weeks' postmenstrual age, oxygen requirement at or death before 36 weeks' postmenstrual age, and threshold retinopathy of prematurity. We obtained further information on timing of death, numbers of infants having serum retinol estimations, and any retinopathy of prematurity from the trial authors.

Bental 1994 and Papagaroufalis 1988 made no comment on monitoring for adverse effects of vitamin A supplementation. Shenai 1987 noted that monitoring for toxicity included periodic anterior fontanelle pressure assessment to detect raised intracranial pressure. Infants in Tyson 1999 were independently examined weekly for four weeks for signs of toxicity, including fontanelle tension, head circumference, liver size, presence of oedema, cutaneous abnormalities, bony tenderness, and lethargy or irritability. In Ambalavanan 2003, these examinations were carried out by one of the investigators. Wardle 2001 recorded three potential adverse effects - persistent vomiting, pulmonary haemorrhage and seizures requiring anticonvulsants.

### Risk of bias in included studies

Full details of the risk of bias assessment are available by trial in the risk of bias tables in the 'Characteristics of included studies' and are summarized in Figure 1.

**Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study**



### Allocation

Of the nine included trials, seven used adequate methods to generate the allocation sequence, and six used adequate methods to conceal allocation (low risk of bias). Papagaroufalis 1988 and Werkman 1994 did not provide details to allow this risk of bias component to be assessed, and Bental 1994 provided details only for the sequence generation method (computer-generated random numbers).

Ambalavanan 2003 used shuffled blocks of sealed opaque envelopes for randomisation and stratified randomisation by birthweight. The randomisation and allocation for Pearson 1992, Ravishankar 2003, Shenai 1987, and Wardle 2001 were conducted by someone outside of the trial team and used sealed envelopes.

### Blinding

Four trials used blinded participants to the intervention and outcome assessors (Shenai 1987; Pearson 1992; Tyson 1999; Wardle 2001). Pearson 1992, for example, used opaque tape to conceal the contents of the syringes and reported that the "staff responsible for patient care had no knowledge of group designation".

### Incomplete outcome data

All but Werkman 1994 and Papagaroufalis 1988 had complete follow-up of participants. Werkman 1994 did not report outcomes on all infants entered into the study, excluding 10 who transferred to another centre for surgery and two who died and for whom group assignment was not stated. For Papagaroufalis 1988, no information was available in the study abstract.

### Selective reporting

Most trials were free of selective reporting, in that it was clear that all of the trial's pre-specified outcome measures and all expected outcome measures of interest to the review were reported. This was unclear for Papagaroufalis 1988 because only a study abstract (from a conference proceedings) was available, while Werkman 1994 did not report all outcome measures of interest.

### Other potential sources of bias

This item was evaluated in relation to information about trial funding (such as industry funding) and sample size calculation. Tyson 1999 appeared to be free of these sources of bias because the study protocol was described in detail, including the sample size calculation, and the trial was free of industry funding. Papagaroufalis 1988 and Pearson 1992 were assessed as having a high risk of bias for this component; Papagaroufalis 1988 because little information was available in the abstract, and Pearson 1992 because few of the eligible infants were enrolled in the trial. Information about this item for the risk of bias assessment was unclear in the other studies.

## Effects of interventions

### 1. Supplemental vitamin A versus no supplementation

#### 1.1. Death (before one month)

Six trials reported death by one month of age (Bental 1994; Papagaroufalis 1988; Pearson 1992; Shenai 1987; Tyson 1999; Wardle 2001), and none showed a significant difference between the vitamin A and control groups (RR 0.86, 95% CI 0.66 to 1.11; RD -0.02, 95% CI -0.06 to 0.02; 1165 infants, Analysis 1.1).

#### 1.2. Chronic lung disease (oxygen use at one month in survivors)

Seven trials (the six above plus Werkman 1994) reported on this outcome. One trial, Shenai 1987, reported a significant reduction in vitamin A-treated infants (RR 0.50, 95% CI 0.28 to 0.87; 39 infants), but overall the pooled data does not reach statistical significance (RR 0.93, 95% CI 0.86 to 1.01; RD -0.05, 95% CI -0.10 to 0.00; 1070 infants, Analysis 1.2).

#### 1.3. Death or chronic lung disease (oxygen use at one month)

Data for this combined outcome were available in six trials (Bental 1994; Papagaroufalis 1988; Pearson 1992; Shenai 1987; Tyson 1999; Wardle 2001). One of these, Shenai 1987, reported a significant reduction in this outcome in the vitamin A group (RR 0.53, 95% CI 0.32 to 0.89; 40 infants). When the meta-analysis was confined to the five trials reporting on supplementation via intramuscular injection (excluding Wardle 2001), there was a trend towards a reduction in death or oxygen use at one month that was of borderline statistical significance (RR 0.93, 95% CI 0.86 to 1.00; RD -0.06, 95% CI -0.11 to -0.00; NNTB 17, 95% CI 9 to 1000+; 1011 infants, Analysis 1.3). When Wardle 2001, in which oral vitamin A supplementation was given to treated infants, is included in the meta-analysis, the pooled data showed a significant reduction in this outcome (RR 0.93, 95% CI 0.88 to 0.99; RD -0.05, 95% CI -0.10 to -0.01; NNTB 20, 95% CI 10 to 100; 1165 infants, Analysis 1.3).

#### 1.4. Death (before 36 weeks' postmenstrual age)

Three trials reported on this outcome (Ravishankar 2003; Tyson 1999; Wardle 2001), and together there was no significant difference between the vitamin A and control groups (RR 1.00, 95% CI 0.77 to 1.30; 1001 infants, Analysis 1.4).

#### 1.5. Chronic lung disease (oxygen use at 36 weeks' postmenstrual age)

Three trials reported on this outcome (Ravishankar 2003; Tyson 1999; Wardle 2001). Tyson 1999 reported a significant reduction in oxygen use at this time in the vitamin A group, and pooling the trials' data did not alter this finding (RR 0.87, 95% CI 0.77 to 0.98; RD -0.08, 95% CI -0.14 to -0.01; NNTB 13, 95% CI 7 to 100; 824 infants, Analysis 1.5).

#### 1.6. Death or chronic lung disease (oxygen use at 36 weeks' postmenstrual age)

Three trials reported on this outcome (Ravishankar 2003; Tyson 1999; Wardle 2001). Tyson 1999 showed a trend towards reduction in death or chronic lung disease in the vitamin A group that is of borderline statistical significance; pooling the data from the three trials did not alter this finding (RR 0.91, 95% CI 0.82 to 1.00; RD -0.06, 95% CI -0.12 to 0.00; NNTB 17, 95% CI 8 to 1000+; 1001 infants, Analysis 1.6). When we included the outcome data at 34 weeks' postmenstrual age from Pearson 1992 in this analysis, there was essentially no difference to these results.

#### 1.7. Death (at 18 to 24 months)

Tyson 1999 reported on this outcome and found no significant difference between the vitamin A and control groups (RR 0.95, 95% CI 0.71 to 1.27; RD -0.01, 95% CI -0.06 to 0.04; 807 infants, Analysis 1.7).

#### 1.8. Neurodevelopmental impairment at 18 to 24 months

Ambalavanan 2005 followed up 88% of surviving infants who participated in the Tyson 1999 trial at 18 to 22 months corrected age. Forty-one infants could not be assessed leaving 290 infants in the intervention group and 289 in the control group (15% lost to follow-up in both groups). There was no difference between the groups in either neurodevelopment impairment, defined as one or more of Bayley II Mental Index < 70, Psychomotor Index < 70, any cerebral palsy, blind in both eyes, or bilateral hearing aids (RR 0.89, 95% CI 0.74 to 1.08; RD -0.05, 95% CI -0.04 to 0.03; 1538 infants, Analysis 1.8).

#### 1.9. Death or neurodevelopmental impairment at 18 to 24 months

Tyson 1999 reported on this outcome and found no significant differences the between the vitamin A and control groups (RR 0.92, 95% CI 0.81 to 1.05; RD -0.05, 95% CI -0.12 to 0.03; 687 infants, Analysis 1.9).

#### 1.10. Patent ductus arteriosus

Ravishankar 2003 found no significant difference in the failure of ductal closure or treatment by day 14 between the vitamin A and control groups (RR 0.98, 95% CI 0.56 to 1.72; RD -0.01, 95% CI -0.32 to 0.30; 40 infants, Analysis 1.10).

#### 1.11. Sepsis

Two trials reported on one or more episodes of culture-proven nosocomial sepsis (Bental 1994; Tyson 1999). The pooled data showed a non-significant trend towards a reduction in sepsis in the vitamin A group (RR 0.89, 95% CI 0.76 to 1.05; RD -0.05, 95% CI -0.11 to 0.02; 867 infants, Analysis 1.11).

#### 1.12. Necrotizing enterocolitis

Three trials reported on necrotizing enterocolitis (Bental 1994; Tyson 1999; Wardle 2001), and the pooled data showed no significant difference between the vitamin A and control groups (RR 0.93, 95% CI 0.66 to 1.30; RD -0.01, 95% CI -0.05 to 0.03; 1021 infants, Analysis 1.12).

#### 1.13. Intraventricular haemorrhage

Three trials reported on any intraventricular haemorrhage (Bental 1994; Tyson 1999; Ravishankar 2003). The pooled data found no significant difference between the vitamin A and control groups (RR 0.95, 95% CI 0.82 to 1.10; RD -0.02, 95% CI -0.09 to 0.04; 907 infants, Analysis 1.13).

Two of the trials also reported on severe intraventricular haemorrhage (Bental 1994; Tyson 1999). There was no significant difference between the vitamin A and control groups (RR 0.94, 95% CI 0.71 to 1.25; RD -0.01, 95% CI -0.06 to 0.04; 867 infants, Analysis 1.13).

#### 1.14. Periventricular leukomalacia

Tyson 1999 reported on this outcome and found no significant differences in periventricular leukomalacia between the vitamin A and control groups (RR 0.74, 95% CI 0.44 to 1.25; RD -0.01, 95% CI -0.05 to 0.03; 646 infants, Analysis 1.14).

### 1.15. Retinopathy of prematurity

Two trials reported on this outcome (Shenai 1987; Pearson 1992), and we obtained additional data from the trial author of Wardle 2001. Shenai 1987 noted a trend to reduced incidence of retinopathy of prematurity in the vitamin A group; this was reflected in the pooled trial data (RR 0.85, 95% CI 0.68 to 1.06; RD -0.10, 95% CI -0.24 to 0.03; 175 infants, Analysis 1.15).

### 1.16. Adverse effects

No adverse effects of vitamin A supplementation were reported. The studies by Bental 1994, Papagaroufalis 1988, and Ravishankar 2003 make no comment on monitoring for adverse effects. Shenai 1987 noted that clinical monitoring for toxicity included periodic anterior fontanelle pressure assessment to detect raised intracranial pressure and reported no clinical or biochemical evidence of toxicity. Pearson 1992 reported that intramuscular injections of vitamin A were painful, and both this trial and Werkman 1994 found no evidence of biochemical toxicity. Wardle 2001 noted that the incidence of potential adverse effects, seizures, and persistent vomiting did not differ between the groups. Infants in Tyson 1999 were independently assessed for signs of toxicity on a weekly basis; a suspected or definite increase in fontanelle tension was slightly more frequent in control than supplemented infants (18% versus 15%, P value = 0.26), and potential toxicity unexplained by other factors occurred in 0.8% controls and 1.0% supplemented infants.

## 2. Vitamin A dosing regimens

Ambalavanan 2003 compared a "standard" intramuscular regimen of supplemental vitamin A (5000 IU 3 x per week for four weeks), as used in Tyson 1999, with a higher dose (10,000 IU 3 x per week for four weeks) and with a once-per-week dose (15,000 IU weekly for four weeks). The vitamin A was given intramuscularly, and the trial's primary outcome was serum retinol concentrations at 28 days.

### 2.1. Death before 36 weeks' postmenstrual age

There was no significant difference for this outcome between the higher and standard dose groups (80 infants, Analysis 2.1), or between the once-a-week and standard regimens (80 infants, Analysis 3.1).

### 2.2. Oxygen use at 36 weeks' postmenstrual age in survivors

There was no significant difference for this outcome between the higher and standard dose groups (61 infants, Analysis 2.2), or between the once-a-week and standard regimens (61 infants, Analysis 3.2).

### 2.3. Death or oxygen use at 36 weeks' postmenstrual age

There was no significant difference for this outcome between the higher and standard dose groups (80 infants, Analysis 2.3), or between the once-a-week and standard regimens (80 infants, Analysis 3.3).

### 2.4. Vitamin A concentration (retinol)

There was no significant difference between the standard dose and higher dose for this outcome when measured as retinol ($\mu$g/L) on study day 28 (55 infants, Analysis 2.4) or as retinol (< 200 $\mu$g/L) on day 28 (%) (55 infants, Analysis 2.5).

The once-per-week regimen resulted in significantly lower concentrations than the standard regimen on study day 28 (SMD -0.97, 95% CI -1.56 to -0.38; 50 infants, Analysis 3.4). The once-per-week dose regimen also resulted in a higher proportion of infants with 28-day retinol concentrations below 200 $\mu$g/L (RR 2.52, 95% CI 1.24 to 5.09; 50 infants, Analysis 3.5).

### 2.5. Necrotizing enterocolitis

There were no significant differences for this outcome between the higher and standard dose groups (80 infants, Analysis 2.6), or between the once-a-week and standard regimens (80 infants, Analysis 3.6).

### 2.6. Retinopathy of prematurity

There was a trend to fewer infants with retinopathy of prematurity in the higher dose group compared to the standard dose group, for both any grade (63 infants, Analysis 2.7) and threshold disease (63 infants, Analysis 2.8).

When we compared the once-a-week regimen with the standard regimen there was a trend to fewer infants with retinopathy of prematurity for any grade (64 infants, Analysis 3.7), but there was no significant difference between the groups when measured as threshold disease (64 infants, Analysis 3.8).

For both analyses, only small numbers of infants were involved and the trial lacked power to assess this outcome.

### 2.7. Sepsis

There were no significant differences in the number of episodes of sepsis between the higher and standard dose groups (80 infants, Analysis 2.9), or between the once-a-week and standard regimens (80 infants, Analysis 3.9).

### 2.8. Adverse effects

Ambalavanan 2003 monitored for potential adverse effects. One infant in the higher dose group was noted to have transient fullness of the anterior fontanelle without other causes and which resolved in 48 hours.

## DISCUSSION

This Cochrane Review includes nine randomised controlled trials, eight comparing vitamin A with placebo and one comparing different vitamin A regimens. Tyson 1999 is the largest trial included in the review with a sample size (807 infants) more than twice that of the next largest trial (154 infants, Wardle 2001).

The first version of this review (Darlow 1998) reported a significant reduction in death or oxygen use at one month of age in vitamin A-treated infants (RR 0.75, 95% CI 0.62 to 0.91), but the addition of Tyson 1999, which found no difference in outcome at one month, to the pooled data resulted in the meta-analysis showing only a trend of borderline significance towards reduction in death or oxygen use at this time (RR 0.93, 95% CI 0.86 to 1.00) (Darlow 2000). Wardle 2001, the only trial to give supplemental vitamin A via the enteral route, had a moderate sample size (154) and found no significant benefit for supplementation; however, the further addition of data from this trial resulted in the meta-analysis showing a small but significant reduction in this outcome (RR 0.93, 95% CI 0.88 to 0.99; RD -0.05, 95% CI -0.10 to -0.01; NNTB 20, 95% CI 10 to 100).

Three trials reported outcomes at 36 weeks' postmenstrual age ( Ravishankar 2003; Tyson 1999; Wardle 2001). Tyson 1999, which gave intramuscular vitamin A to supplemented infants, reported a significant reduction in oxygen use in vitamin A-treated infants (RR 0.85, 95% CI 0.73 to 0.98), and a trend towards reduction in death or oxygen use of borderline significance (RR 0.89, 95% 0.79 to 1.00). Pooling the data from the three trials did not alter these conclusions. From the meta-analysis of the combined data, the NNTB in one infant with regard to oxygen requirement at 36 weeks is 13, and with regard to death or oxygen requirement at 36 weeks is 17. It is important to note that the 95% confidence intervals are wide, being 7 to 100 and 8 to 1000 respectively. It is also noteworthy that there was no difference in other outcomes, including days of ventilation and length of stay, between vitamin A supplemented and control infants in Tyson 1999.

Some differences between the trials may be explained by the differences in patient populations (birthweight and ethnicity), by the differences in both the route of vitamin A supplementation (intramuscular, intravenous in lipid emulsion, or enteral), and the dose given. Tyson 1999 and Wardle 2001 included somewhat lower birthweight infants (401 to 1000 g and < 1000 g respectively) than most other trials, whereas other trials used various lower weight limits (500 g for Ravishankar 2003; 700 g for Pearson 1992 and Shenai 1987; 725 g for Werkman 1994; and 1000 g for Bental 1994). The incidence of supplemental oxygen requirement at one month of age in vitamin A-supplemented infants was higher at 73% in Tyson 1999 and 83% in Wardle 2001; this is consistent with their lower birthweight and gestational age compared with a range of 34% to 67% in the other trials. For the smallest infants, the outcome at 36 weeks' postmenstrual age may be more clinically relevant.

In all the included trials there were higher vitamin A or retinol concentrations at most time periods studied in the infants in the vitamin A group compared with the control group. Kennedy 1997 reported that an intramuscular dose of 5000 IU vitamin A three times per week was required to achieve serum concentrations > 250 $\mu$g/L in most very low birthweight infants. This was the dose used by Tyson 1999 and was generally greater than the dose used in earlier studies; for example, Bental 1994 used 4000 IU three times weekly, Papagaroufalis 1988 used 4000 IU on alternate days while the infant was ventilated, Pearson 1992 and Shenai 1987 used 2000 IU on alternate days, and Ravishankar 2003 used between 1500 IU and 3000 IU for only three doses. Nevertheless, in Tyson 1999, 25% of infants who received supplemental vitamin A and 54% of controls (data from the first 300 enrolled infants) had vitamin A concentrations below 200 $\mu$g/L on day 28. Similar percentages, 22% of those who received supplemental vitamin A and 45% of controls, had a relative dose response (change in the serum retinol concentration divided by the preinjection concentration) of more than 10% following an intramuscular dose of 2000 IU. Taken together, these data suggested that an even higher dose of vitamin A given intramuscularly may be required to achieve vitamin A sufficiency in very premature infants.

In Wardle 2001, infants received a much higher cumulative dose of supplemental vitamin A than in other studies (140,000 IU in 28 days compared with 60,000 IU in Tyson 1999), but by the enteral route. Vitamin A concentrations were only measured in the first 84 infants enrolled, and the median concentration 24 hours after the first dose was significantly higher in supplemented infants (230 $\mu$g/L versus 150 $\mu$g/L). At seven and 28 days of age, however, there were no significant differences in vitamin A concentrations between the groups, and the median concentration in both groups was less than 200 $\mu$g/L at these times. Vitamin A absorption is less efficient using the enteral route. Rush 1994 compared the same dose of vitamin A (2000 IU/kg on alternate days) given by intramuscular injection or orally and reported the former route gave higher plasma vitamin A concentrations after one week. Landman 1992 reported that enteral supplementation with 5000 IU vitamin A daily resulted in similar plasma concentrations at 32 days of age to those resulting from 2000 IU vitamin A on alternate days by the intramuscular route.

There were also quite marked differences in the vitamin A dose received by the control groups. This has previously been suggested to account for differences in outcome between the early studies (Lorch 1994). Infants in the control group in Pearson 1992 received higher doses of vitamin A and had mean vitamin A concentrations in weeks three and four of greater than 200 $\mu$g/L. This is higher than in infants in the control group in Shenai 1987 in which mean vitamin A concentrations were less than 150 $\mu$g/L at these times. One interpretation is that Shenai 1987 demonstrated a benefit of supplemental vitamin A in a population with vita-

min deficiency, while Pearson 1992 showed a minimal benefit of additional supplementation in a population with more adequate vitamin status. However, Georgieff 1989 reported that postnatal steroids led to a near doubling of plasma vitamin A concentrations, and this finding was confirmed in Tyson 1999. Certainly variability in exposure to postnatal steroids complicates interpretation of these data. Two trials included in this review reported the incidence of treatment with postnatal steroids (Pearson 1992, 46% in vitamin A group and 44% in controls; Wardle 2001, 39% and 34% respectively), while two others noted that steroids were used in some infants (Bental 1994; Tyson 1999) .

Further information on the optimal dosage of intramuscular vitamin A for infants with birthweight 401 to 1000 g is available from the Ambalavanan 2003 trial. Ambalavanan 2003 compared the dose regimen used by Tyson 1999 (5000 IU 3 x weekly for four weeks) with both a higher dose (10,000 IU 3 x weekly for four weeks) and a once-a-week dose (15,000 IU weekly for four weeks) in 120 infants. Only two infants received postnatal steroids between study day 21 and 28. Compared with the standard regimen, the higher dose regimen was not associated with a significantly higher mean retinol concentration at 28 days and there were no differences between the groups in the proportion of infants having concentrations < 200 $\mu$g/L at this time (26% versus 21%). The once-a-day regimen, however, was associated with significantly lower mean concentrations at 28 days and increased the risk of infants having concentrations < 200 $\mu$g/L at this time by a factor of 2.5 (26% versus 65%).

Many other variables will also affect the rate of chronic lung disease, which is known to vary considerably between centres. These factors include use of antenatal steroids (stated in four trials; Pearson 1992 where they were received by 26% study infants and 41% controls, Tyson 1999 where the rates were 76% and 74%, Wardle 2001 where the rates were 77% and 82%, and Ravishankar 2003 where the rates were 86% and 72%), exogenous surfactant (stated in three trials; Pearson 1992 where > 90% received an artificial surfactant, Tyson 1999 where > 80% received a natural surfactant, and Wardle 2001 where all but one infant in the control group received an artificial surfactant), mode of ventilation including early nasal continuous positive airway pressure, postnatal steroids, and criteria for prescribing supplemental oxygen.

Important information on follow-up at 18 to 24 months of infants who participated in the Tyson 1999 trial is now available in Ambalavanan 2005. Eighty-five percent of surviving infants were assessed. There was no difference between the groups in either neurodevelopment impairment (RR 0.89, 95% CI 0.74 to 1.08), or the combined outcome of death or neurodevelopmental impairment (RR 0.92, 95% CI 0.81 to 1.05). More infants who received supplemental vitamin A than controls were prescribed home oxygen (36% versus 32%) and were on home oxygen for more than 6 months (20% versus 26%), although these differences were not significant. Although this trial was not powered appropriately to assess long-term outcomes, there was no evidence of either benefit or harm from repeat intramuscular vitamin A following birth.

The data do suggest that, in the dosages employed, supplemental vitamin A is safe and free from adverse effects, although Pearson 1992 noted repeat intramuscular injections may have been painful.

# AUTHORS' CONCLUSIONS

## Implications for practice

Supplementing very low birthweight infants with vitamin A is associated with a benefit in terms of reducing death or oxygen use at one month of age and oxygen use at 36 weeks' postmenstrual age. Supplementation with vitamin A may also reduce the incidence of retinopathy of prematurity and of nosocomial sepsis. Trials do not allow judgement as to the best route of supplementation, although the one trial that gave enteral vitamin A found no significant benefit for supplementation. One trial compared different intramuscular dosing regimens, and the results suggest that, at least for infants with birthweight 401 to 1000 g, the optimal dose appears to be 5000 IU 3 x weekly for four weeks, although on this regimen 26% of infants still had plasma vitamin A concentrations below 200 $\mu$g/L (0.70 $\mu$mol/L), which may indicate deficiency (Ambalavanan 2003).

The major conclusion of a benefit at 36 weeks' postmenstrual age is derived from the results of three trials in which most infants had a birthweight less than 1000 g. An earlier version of this Cochrane Review, Darlow 2002, stated that whether clinicians decide to utilise repeat intramuscular doses of vitamin A may well depend upon the incidence of supplemental oxygen requirement at 36 weeks' postmenstrual age in extremely low birthweight infants in their unit and their own assessment in conjunction with the review's findings of the benefits of a modest reduction in this outcome balanced against lack of other proven benefits and the acceptability of treatment. Long-term follow-up data at 18 to 22 months corrected age of the largest included trial (Tyson 1999) has shown no evidence of either benefit or harm at this time. If a decision has been made not to treat for the early benefits, the follow-up study is unlikely to change that decision. On the other hand, if a decision has been made to treat for early benefits, the follow-up study is reassuring in that long-term harmful effects are unlikely.

## Implications for research

Further investigations are warranted as to the relationship between biochemical and functional vitamin A status in very low birthweight infants. Also, the benefits, in terms of vitamin A status, clinical outcomes, safety, and acceptability to caretakers and parents, of delivering vitamin A in an intravenous lipid emulsion from the first days of life compared with delivery by intramuscular injections should be investigated in a randomised controlled trial.

There is an epidemic of retinopathy of prematurity in middle-income and low-income countries that affects many infants who are more mature at birth and have a greater birthweight than the most infants who acquire severe retinopathy in more developed countries. In many of these countries, the vitamin A status of both mothers and infants is particularly poor. The trends towards less retinopathy of prematurity associated with supplemental vitamin A and higher dose regimens seen in this review suggest that further trials should be undertaken in these countries to assess the possible contribution of poor perinatal vitamin A status to retinopathy of prematurity and the need for intervention studies in these populations.

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**Shenai 1985**

Shenai JP, Chytil F, Stahlman MT. Vitamin A status of neonates with bronchopulmonary dysplasia. *Pediatric Research* 1985;**19**(2):185–8.

**Shenai 1990**

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**Zachman 1996**

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**Darlow 1998**

Darlow BA, Graham PJ. Vitamin A supplementation in very low birthweight infants. *Cochrane Database of Systematic Reviews* 1998, Issue 4. [DOI: 10.1002/14651858.CD000501]

**Darlow 2000**

Darlow BA, Graham PJ. Vitamin A supplementation for preventing morbidity and mortality in very low birthweight infants. *Cochrane Database of Systematic Reviews* 2000, Issue 2. [DOI: 10.1002/14651858.CD000501]

**Darlow 2002**

Darlow BA, Graham PJ. Vitamin A supplementation for preventing morbidity and mortality in very low birthweight infants. *Cochrane Database of Systematic Reviews* 2002, Issue 4. [DOI: 10.1002/14651858.CD000501]

**Darlow 2007**

Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: 10.1002/14651858.CD000501.pub2]

* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

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

**Ambalavanan 2003**

| | |
|---|---|
| Methods | Single centre randomised controlled trial |
| Participants | Number: 120<br>Description: birthweight between 401 and 1000 g; requiring mechanical ventilation or supplemental oxygen at 24 hours of age; and no major congenital anomalies, non-bacterial infection, or terminal illness |
| Interventions | Comparison of vitamin A (water soluble retinyl palmitate) regimens<br>1. Standard vitamin A regimen: 5000 IU vitamin A intramuscular injection 3 times a week for 4 weeks) (n=40)<br>2. High dose vitamin A regimen: 10,000 IU vitamin A intramuscular injection 3 times a week for 4 weeks) (n=40)<br>3. Once-per-week vitamin A regimen: 15,000 IU vitamin A intramuscular injection weekly for 4 weeks) (n=40)<br>Other: 2 infants received postnatal steroids between study day 21 and 28 |
| Outcomes | • Median retinol concentrations on day 28<br>• Percentage of each group with retinol concentrations < 200 $\mu$g/L<br>• Death before 36 weeks' postmenstrual age<br>• Oxygen requirement at, or death before, 36 weeks' postmenstrual age<br>• Threshold retinopathy of prematurity<br>• Examination for potential toxicity at least 3 times weekly |
| Notes | Location: University of Alabama at Birmingham (UAB), USA<br>Trial author provided further information on the timing of death, numbers of infants having serum retinol estimations at 28 days, and any retinopathy of prematurity |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "random assignment stratified by birth weight (401-750 g, 751-1000 g)" (pg 657) |
| Allocation concealment (selection bias) | Low risk | Used "shuffled blocks (of sizes 3, 6, or 9) of sealed opaque envelopes" (pg 657) |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Blinding of intervention: interventions were not provided in the same way for the three groups<br>Blinding of outcome measurements: yes ("Outcome evaluations were performed by one of the investigators, masked to treat- |

**Ambalavanan 2003** (*Continued*)

| | | |
|---|---|---|
| | | ment group assignment", pg 657) |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Detailed outcome information is provided for all randomised participants; intention-to-treat analysis was conducted |
| Selective reporting (reporting bias) | Low risk | Authors reported all pre-specified outcomes |
| Other bias | Unclear risk | Source of funding not reported |

**Bental 1994**

| | |
|---|---|
| Methods | Single centre randomised controlled trial |
| Participants | Number: 60<br>Description: birthweight between 1000 and 1500 g; gestational age of $\leq$ 34 weeks; infants were receiving supplemental oxygen and mechanical ventilation for at least 72 h during the first week; no congenital anomalies or infection; black South African infants |
| Interventions | Vitamin A (water soluble retinyl palmitate) vs control<br>1. Supplemental 4000 IU vitamin A intramuscular injection 3 times a week from day 4 for a total of 12 injections (n=31)<br>2. No supplementation (n=29)<br>Other: Some control and study infants received vitamin A 1500 to 3000 IU after 1 week of age when fed orally |
| Outcomes | • Death before 31 days<br>• Bronchopulmonary dysplasia (oxygen or ventilation on day 31 and characteristic chest x-ray; full data obtained from trial authors)<br>• Culture-proven sepsis<br>• Vitamin A levels at various times |
| Notes | Location: Baragwanath Hospital, Soweto, South Africa<br>Complete data published in an earlier abstract from 1990; we sought and obtained further clarification from the trial authors concerning 2 outcomes: oxygen use at 1 month in survivors; and death or oxygen use at 1 month |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random numbers were computer generated in blocks of 10 (pg 142) |
| Allocation concealment (selection bias) | Unclear risk | No information provided |

**Bental 1994** (*Continued*)

| | | |
|---|---|---|
| Blinding (performance bias and detection bias)<br>All outcomes | Unclear risk | Blinding of intervention: unclear because no information about the control group intervention<br>Blinding of outcome measurement: 2 investigators administered the vitamin A and were not involved in the treatment of study infants; and the intensive care unit staff were unaware of the group allocation of infants (pg 142) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Detailed outcome information is provided for all randomised participants |
| Selective reporting (reporting bias) | Low risk | All expected outcomes were reported |
| Other bias | Unclear risk | Poor reporting of study design; supported by a grant from the South African Medical Research Council |

**Papagaroufalis 1988**

| | |
|---|---|
| Methods | Single centre randomised controlled trial |
| Participants | Number: 55<br>Description: birthweight ≤ 1300 g; gestation < 29 weeks; requirement for > 40% oxygen and mechanical ventilation for > 72 h in first week |
| Interventions | Vitamin A (water soluble retinyl palmitate) vs control<br>1. Supplemental 4000 IU vitamin A intramuscular injection from day 4 to 6 on alternate days until extubated (n=27)<br>2. Normal saline placebo (n=28) |
| Outcomes | • Death before 31 days<br>• Bronchopulmonary dysplasia (oxygen requirement and characteristic chest x-ray on day 31)<br>Vitamin A levels at various times |
| Notes | Location: not stated; possibly Aghia Sophia Children's Hospital and Institute of Child Health, Athens, Greece (authors' affiliation)<br>Amount of vitamin A in unsupplemented infants not stated<br>Trial author provided Dr K Kennedy with additional data at the time of an earlier review (Kennedy 1997), and these data are included in this review |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|

**Papagaroufalis 1988** (*Continued*)

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomised, blind controlled study |
| Allocation concealment (selection bias) | Unclear risk | No information |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Blinding of intervention: no information provided<br>Blinding of outcome measurement: no |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | No information provided in the conference proceeding |
| Selective reporting (reporting bias) | Unclear risk | Based on the conference proceeding, no relevant information is provided to make a judgement |
| Other bias | High risk | Report of the study is poor and only based on a abstract |

**Pearson 1992**

| | |
|---|---|
| Methods | Multicentre randomised controlled trial |
| Participants | Number: 49<br>Description: birthweight 700 to 1100 g; requiring supplemental oxygen and mechanical ventilation between 72 and 96 h of age with previous cumulative duration of ventilation and oxygen > 48 h; no growth retardation (undefined), congenital, or chromosomal abnormalities, hydrops fetalis, congenital infection, neonatal hepatitis or "do not resuscitate" order |
| Interventions | Vitamin A (water soluble retinyl palmitate) vs control<br>1. Supplemental 2000 IU vitamin A by intramuscular injection alternate days from day 4 for 14 doses (n=27)<br>2. Normal saline placebo or mock injection (n=22)<br>Other: both control and study infants received 1200 to 1500 IU/d vitamin A in protein-dextrose solution when on parenteral nutrition; when fed orally all infants received vitamin A 250 to 1030 IU/100 mL milk; antenatal steroids received by 26% infants in the vitamin A group and 41% in the control group; > 90% received an artificial surfactant |
| Outcomes | • Death before 31 days<br>• Bronchopulmonary dysplasia (oxygen requirement at 31 days and characteristic chest x-ray)<br>• Oxygen requirement at 34 weeks post-conceptual age<br>• Retinopathy of prematurity<br>• Plasma vitamin A levels and retinyl binding protein at various times |
| Notes | Location: hospitals in North Carolina, USA |

**Pearson 1992** (*Continued*)

| *Risk of bias* | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | Multicentre randomised controlled trial; infants were stratified according to hospital, gender, and weight (pg 421) |
| Allocation concealment (selection bias) | Low risk | Randomisation was performed using sequential sealed envelopes; randomisation and drug preparation performed by someone not involved with patients (pg 421) |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Blinding of intervention: "Opaque tape concealed the contents of syringes to ensure blinding" (pg 421)<br>Blinding of outcome: "At all sites, staff responsible for patient care had no knowledge of group designation" (pg 421) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Detailed outcome information is provided for all randomised participants |
| Selective reporting (reporting bias) | Low risk | All clinically relevant outcomes reported |
| Other bias | High risk | Small study; sample size calculation performed based on high incidence rate of bronchopulmonary dysplasia; blinded interim analysis performed of the 49 patients enrolled (pg 423)<br>161 infants eligible, 74 of them met the inclusion criteria and 49 were enrolled |

**Ravishankar 2003**

| | |
|---|---|
| Methods | Single centre randomised controlled trial |
| Participants | Number: 40<br>Description: birthweight 500 to 1500 g; gestation < 32 wk; having indwelling umbilical line; no major congenital malformations or chromosomal anomalies; and < 24 h of age |
| Interventions | Vitamin A (water-miscible preparation of vitamin A (Aquasol A)) vs control<br>1. Supplemental 1500 to 3000 IU vitamin A (based on weight) by intramuscular injection on days 1, 3, and 7 (n=22)<br>2. Sham injection (n=18)<br>Other: most infants received parenteral nutrition including 466 IU/dL vitamin A and an additional 1000 IU supplement when fed orally; antenatal steroids received by 86% |

**Ravishankar 2003** (*Continued*)

| | |
|---|---|
| | of infants in the vitamin A group and 72% in the control group |
| Outcomes | • Failure of patent ductus arteriosus closure, defined as patent ductus arteriosus larger than trivial on day 14, indomethacin treatment, or surgical ligation<br>• Death<br>• Bronchopulmonary dysplasia (oxygen requirement at 36 weeks' postmenstrual age) |
| Notes | Location: Mount Sinai Medical Center, New York, New York, USA<br>Patent ductus arteriosus closure primary outcome<br>Corresponding author provided information on the age at death for infants |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Block randomisation was performed with stratification by weight; the categories were 500 to 750 g, 750 to 1000 g, 1000 to 1250 g, and 1250 to 1500 g (pg 645) |
| Allocation concealment (selection bias) | Low risk | "Sealed envelopes containing cards with the group designation were maintained in the pharmacy department" (pg 645) |
| Blinding (performance bias and detection bias)<br>All outcomes | Unclear risk | Blinding of intervention: none - infants in the intervention group received intramuscular injections and the placebo group did not receive these<br>Blinding of outcome measurement: yes - "The staff responsible for the care of these infants had no knowledge of group assignment or outcome of study echocardiograms" (pg 645) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Detailed outcome information is provided for all randomised participants |
| Selective reporting (reporting bias) | Low risk | Authors reported all pre-specified outcomes |
| Other bias | Unclear risk | Small sample size; source of funding not reported |

**Shenai 1987**

| | |
|---|---|
| Methods | Single centre randomised controlled trial |
| Participants | Number: 40<br>Description: birthweight 700 to 1300 g; gestation 26 to 30 wk; requiring supplemental oxygen and mechanical ventilation for at least 72 h in the first week; Caucasian infants only; birthweight appropriate for gestational age; no congenital abnormalities |
| Interventions | Vitamin A (water soluble retinyl palmitate) vs control<br>1. Supplemental 2000 IU vitamin A by intramuscular injection alternate days from day 4 for a total of 14 injections (n=20)<br>2. Normal saline placebo (n=20)<br>Other: both control and study infants received vitamin A 400 IU/dL in parenteral nutrition and 240 to 550 IU/dL from milk plus 1500 IU supplements when fed orally |
| Outcomes | • Death before 31 days<br>• Bronchopulmonary dysplasia (oxygen requirement or ventilation at 31 days plus characteristic chest x-ray)<br>• Total days oxygen<br>• Episodes of sepsis<br>• Retinopathy of prematurity<br>• Vitamin A levels at various times |
| Notes | Location: Vanderbilt Medical Centre, Nashville, Tennessee, USA |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Single centre randomised controlled trial; sealed envelopes containing cards indicating group designation were used for randomisation (pg 270) |
| Allocation concealment (selection bias) | Low risk | Randomisation was carried out by pharmacists who had no knowledge of the clinical status of the infants (pg 270) |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Blinding of intervention: control group received intramuscular saline solution exactly in the same manner of the intervention (pg 270-1)<br>Blinding of outcome measurement: neonatal intensive care unit staff responsible for patient management had no knowledge of the group designation (pg 270) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Detailed outcome information is provided for all randomised participants; all but one infant enrolled in the study completed the |

**Shenai 1987** (*Continued*)

| | | |
|---|---|---|
| | | trial |
| Selective reporting (reporting bias) | Low risk | All clinically relevant outcomes reported |
| Other bias | Unclear risk | Sample size calculation performed based on high incidence rate of bronchopulmonary dysplasia |

**Tyson 1999**

| | |
|---|---|
| Methods | Multicentre randomised controlled trial |
| Participants | Number: 807<br>Description: birthweight 401 to 1000 g; requiring supplemental oxygen or mechanical ventilation at 24 h of age; and no major congenital anomalies, non-bacterial infection, or terminal illness |
| Interventions | Vitamin A (water soluble retinyl palmitate) vs control<br>1. Supplemental 5000 IU vitamin A intramuscular injection 3 times a week for 4 weeks (n=405)<br>2. Sham injection (n=402)<br>Other: control and study infants received similar intakes of vitamin A from non-study enteral and parenteral sources but amounts not stated; antenatal steroids received by 76% of infants in the vitamin A group and 74% in the control group; > 80% received a natural surfactant |
| Outcomes | • Oxygen requirement at, or death before, 36 weeks' postmenstrual age<br>• Oxygen requirement at, or death before, 28 days of age<br>• Culture-proven sepsis Grade 3 or 4 intracranial haemorrhage<br>• Periventricular leukomalacia<br>• Vitamin A on study day 28 in subset of infants and relative dose-response to 2000 IU vitamin A intramuscular<br>• Examination for potential toxicity weekly<br>• Assessment of neurodevelopmental status at 18 to 22 months corrected age is available in Ambalavanan 2005 (companion paper for Tyson 1999) |
| Notes | Location: hospitals in the USA |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "The infants were stratified according to center and birth weight (401 to 750 g or 751 to 1000 g) and assigned to the vitamin A or control group by a hospital pharmacist using a randomization list." (pg 1962) |

**Tyson 1999** (*Continued*)

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | Sealed envelopes containing the treatment assignments were used (pg 1963) |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Blinding of intervention: yes<br>Blinding of outcome: outcome were assessed by research nurses that transmitted the data electronically to a biostatistical coordinating centre (pg 1963) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Detailed outcome information is provided for all randomised participants; intention-to-treat analysis was conducted |
| Selective reporting (reporting bias) | Low risk | Authors reported all pre-specified outcomes |
| Other bias | Low risk | Study protocol described in detail, including sample size calculation<br>Supported by cooperative agreements with the National Institute of Child Health and Human Development, and by General Clinical Research Center grants |

**Wardle 2001**

| | |
|---|---|
| Methods | Multicentre randomised controlled trial |
| Participants | Number: 154<br>Description: birthweight < 1000 g; no life-threatening congenital abnormalities; consent before 24 h of age |
| Interventions | Vitamin A (form not stated) vs control<br>1. Supplemental 5000 IU vitamin A orally daily until day 28 (n=77)<br>2. Same volume look-a-like placebo liquid (n=77)<br>Other: control and study infants received 23 IU/kg/d vitamin A (stated amount but probably 233 IU) in intralipid when on parenteral nutrition; when on full enteral feeds and more than 14 days of age all infants received 5000 IU/kg/d vitamin A orally; antenatal steroids received by 77% in the vitamin A group and 82% in the control group; all but 1 infant in the control group received an artificial surfactant |
| Outcomes | • Oxygen requirement at 28 days<br>• Death pre-discharge<br>• Oxygen requirement at 36 weeks' postmenstrual age<br>• Retinopathy of prematurity requiring treatment |
| Notes | Location: Liverpool Women's Hospital, Liverpool, UK<br>Trial author provided further information on the numbers examined for retinopathy of prematurity and numbers with any retinopathy |

**Wardle 2001** (*Continued*)

| *Risk of bias* | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | Randomization assigned using a computerised random number generator (pg F10) |
| Allocation concealment (selection bias) | Low risk | Sealed opaque numbered envelopes containing the treatment allocation (pg F10) |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Blinding of intervention: "The control group received an equivalent volume of an inert placebo solution (which had been prepared in the hospital pharmacy to look identical with the vitamin A solution) given in the same way" (pg F10)<br>Blinding of outcome: "Both the medical and nursing staff caring for the infants and administering the vitamin A and placebo solutions were unaware of the treatment allocation" (pg F10) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Detailed outcome information is provided for all randomised participants; intention-to-treat analysis was conducted |
| Selective reporting (reporting bias) | Low risk | Authors reported all pre-specified outcomes |
| Other bias | Unclear risk | Study protocol described in detail, including sample size calculation; source of funding not reported |

**Werkman 1994**

| | |
|---|---|
| Methods | Single centre randomised controlled trial |
| Participants | Number: 86<br>Description: birthweight 725 to 1300 g; < 96 h of age; no intraventricular or periventricular haemorrhage, history of maternal substance abuse, or sexually transmitted disease; no congenital anomalies |
| Interventions | Vitamin A (retinyl palmitate) vs control<br>1. Supplemental vitamin A 80,000 RE/L (giving c. 1300 to 3300 IU/kg/d) in intravenous lipid infused over 16 h from randomisation (48 to 96 h) and while receiving parenteral nutrition (n=44)<br>2. No supplementation (n=42)<br>Other: both control and study infants received vitamin A as multivitamin preparation |

**Werkman 1994** (*Continued*)

| | |
|---|---|
| | added to protein-dextrose solution (birthweight < 1000 g 1.5 mL/d, 210 RE/d; > 1000 g 3.4 mL/d, 476 RE/d) and oral supplements when fed orally |
| Outcomes | • Bronchopulmonary dysplasia (oxygen beyond 28 days and characteristic chest x-ray)<br>• Total days oxygen requirement<br>• Vitamin A and retinyl binding protein levels at various times |
| Notes | Location: Newborn Centre, University of Tennessee, Tennessee, USA |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Eligible infants were randomly assigned; method of sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment not reported |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Blinding of intervention: details not reported<br>Blinding of outcome: no |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 12/98 randomised participants left the study early (10 transferred to another hospital, 2 died from sepsis) and their data were not included in the analysis |
| Selective reporting (reporting bias) | High risk | Not all outcomes of interest were reported |
| Other bias | Unclear risk | Supported by a grant of the National Eye Institute and a gift from Ross Laboratories (pg 586)<br>Not enough detail of protocol is provided |

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

| Study | Reason for exclusion |
|---|---|
| Aranda 1992 | Route of supplementation not stated and reported vitamin A levels appear to contain a decimal point error; no clinical outcomes |
| Aurvag 2007 | Compared vitamin A supplementation of human milk fortifier to historical controls; no clinical outcomes reported |

(*Continued*)

| | |
|---|---|
| Coutsoudis 2000 | Compared 3 doses of oral vitamin A versus placebo in infants of < 36 weeks' gestation with primary outcome incidence of respiratory infections during the first year of life |
| Koo 1993 | Compared 3 doses of vitamin A added to preterm formula for an unstated period of time; no clinical outcomes |
| Landman 1992 | Compared enteral with intramuscular administration of vitamin A; no clinical outcomes |
| Robbins 1993 | Groups not randomised |
| Rush 1994 | Compared enteral with intramuscular administration of vitamin A; vitamin A concentrations only reported graphically; no clinical outcomes |

## DATA AND ANALYSES

### Comparison 1. Supplemental vitamin A vs no supplementation

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death (before 1 month) | 6 | 1165 | Risk Ratio (M-H, Fixed, 95% CI) | 0.86 [0.66, 1.11] |
| 1.1 Supplementation via intramuscular injection | 5 | 1011 | Risk Ratio (M-H, Fixed, 95% CI) | 0.86 [0.62, 1.18] |
| 1.2 Supplementation via oral route | 1 | 154 | Risk Ratio (M-H, Fixed, 95% CI) | 0.86 [0.56, 1.33] |
| 2 Chronic lung disease (oxygen use at 1 month in survivors) | 7 | 1070 | Risk Ratio (M-H, Fixed, 95% CI) | 0.93 [0.86, 1.01] |
| 2.1 Supplementation via intramuscular injection | 5 | 884 | Risk Ratio (M-H, Fixed, 95% CI) | 0.93 [0.86, 1.01] |
| 2.2 Supplementation via intravenous route | 1 | 86 | Risk Ratio (M-H, Fixed, 95% CI) | 0.95 [0.54, 1.70] |
| 2.3 Supplementation via oral route | 1 | 100 | Risk Ratio (M-H, Fixed, 95% CI) | 0.95 [0.80, 1.11] |
| 3 Death or chronic lung disease (oxygen use at 1 month) | 6 | 1165 | Risk Ratio (M-H, Fixed, 95% CI) | 0.93 [0.88, 0.99] |
| 3.1 Supplementation via intramuscular injection | 5 | 1011 | Risk Ratio (M-H, Fixed, 95% CI) | 0.93 [0.86, 1.00] |
| 3.2 Supplementation via oral route | 1 | 154 | Risk Ratio (M-H, Fixed, 95% CI) | 0.96 [0.86, 1.06] |
| 4 Death before 36 weeks' postmenstrual age | 3 | 1001 | Risk Ratio (M-H, Fixed, 95% CI) | 1.00 [0.77, 1.30] |
| 4.1 Supplementation via intramuscular injection | 2 | 847 | Risk Ratio (M-H, Fixed, 95% CI) | 1.06 [0.77, 1.47] |
| 4.2 Supplementation via oral route | 1 | 154 | Risk Ratio (M-H, Fixed, 95% CI) | 0.86 [0.56, 1.33] |
| 5 Chronic lung disease (oxygen use at 36 weeks' postmenstrual age in survivors) | 3 | 824 | Risk Ratio (M-H, Fixed, 95% CI) | 0.87 [0.77, 0.98] |
| 5.1 Supplementation via intramuscular injection | 2 | 724 | Risk Ratio (M-H, Fixed, 95% CI) | 0.84 [0.73, 0.97] |
| 5.2 Supplementation via oral route | 1 | 100 | Risk Ratio (M-H, Fixed, 95% CI) | 1.00 [0.81, 1.24] |
| 6 Death or chronic lung disease (oxygen use at 36 weeks' postmenstrual age) | 3 | 1001 | Risk Ratio (M-H, Fixed, 95% CI) | 0.91 [0.82, 1.00] |
| 6.1 Supplementation via intramuscular injection | 2 | 847 | Risk Ratio (M-H, Fixed, 95% CI) | 0.89 [0.79, 0.99] |
| 6.2 Supplementation via oral route | 1 | 154 | Risk Ratio (M-H, Fixed, 95% CI) | 0.98 [0.86, 1.12] |
| 7 Death before 18 to 22 months | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 7.1 Supplementation via intramuscular injection | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |

| | | | | |
|---|---|---|---|---|
| 8 Neurodevelopmental impairment at 18 to 22 months | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 8.1 Supplementation via intramuscular injection | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 9 Death or neurodevelopmental impairment at 18 to 22 months | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 9.1 Supplementation via intramuscular injection | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 10 Failure of ductal closure or treatment by day 14 | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 10.1 Supplementation via intramuscular injection | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 11 Sepsis (≥ 1 episodes) | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 11.1 Supplementation via intramuscular injection | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 12 Necrotizing enterocolitis | 3 | 1021 | Risk Ratio (M-H, Fixed, 95% CI) | 0.93 [0.66, 1.30] |
| 13 Intraventricular haemorrhage | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 13.1 Any intraventricular haemorrhage | 3 | 907 | Risk Ratio (M-H, Fixed, 95% CI) | 0.95 [0.82, 1.10] |
| 13.2 Severe intraventricular haemorrhage (Grade 3 or 4) | 2 | 867 | Risk Ratio (M-H, Fixed, 95% CI) | 0.94 [0.71, 1.25] |
| 14 Periventricular leukomalacia | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 15 Retinopathy of prematurity (any grade) | 3 | 175 | Risk Ratio (M-H, Fixed, 95% CI) | 0.85 [0.68, 1.06] |
| 15.1 Supplementation via intramuscular injection | 2 | 79 | Risk Ratio (M-H, Fixed, 95% CI) | 0.71 [0.45, 1.10] |
| 15.2 Supplementation via oral route | 1 | 96 | Risk Ratio (M-H, Fixed, 95% CI) | 0.95 [0.75, 1.20] |

**Comparison 2. Vitamin A regimens: higher dose (10,000 IU) vs standard dose (5000 IU); both intramuscular and 3 x week for 4 weeks**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death before 36 weeks' postmenstrual age | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2 Oxygen use at 36 weeks' postmenstrual age in survivors | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 3 Death or oxygen use at 36 weeks' postmenstrual age | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 4 Retinol concentration on study day 28 ($\mu$g/L) | 1 | | Std. Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 5 Retinol < 200 $\mu$g/L on day 28 (%) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 6 Necrotizing enterocolitis | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 7 Retinopathy of prematurity (any grade) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |

| | | | |
|---|---|---|---|
| 8 Retinopathy of prematurity (threshold disease) | 1 | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 9 Sepsis (≥ 1 episodes) | 1 | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |

**Comparison 3. Vitamin A regimens: once-a-week (15,000 IU) vs standard dose (5000 IU 3 x week); both intramuscular and for 4 weeks**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death before 36 weeks' postmenstrual age | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2 Oxygen use at 36 weeks' postmenstrual age in survivors | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 3 Death or oxygen use at 36 weeks' postmenstrual age | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 4 Retinol concentration on study day 28 ($\mu$g/L) | 1 | | Std. Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 5 Retinol < 200 $\mu$g/L on day 28 (%) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 6 Necrotizing enterocolitis | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 7 Retinopathy of prematurity (any grade) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 8 Retinopathy of prematurity (threshold disease) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 9 One or more episodes of sepsis | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |

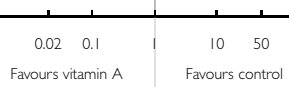
## Analysis 1.1. Comparison 1 Supplemental vitamin A vs no supplementation, Outcome 1 Death (before 1 month).

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 1 Supplemental vitamin A vs no supplementation

Outcome: 1 Death (before 1 month)

| Study or subgroup | Vitamin A n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Supplementation via intramuscular injection | | | | | |
| Bental 1994 | 5/31 | 10/29 | | 10.5 % | 0.47 [ 0.18, 1.21 ] |
| Papagaroufalis 1988 | 9/27 | 8/28 | | 8.0 % | 1.17 [ 0.53, 2.58 ] |
| Pearson 1992 | 1/27 | 4/22 | | 4.5 % | 0.20 [ 0.02, 1.69 ] |
| Shenai 1987 | 1/20 | 0/20 | | 0.5 % | 3.00 [ 0.13, 69.52 ] |
| Tyson 1999 | 43/405 | 46/402 | | 47.0 % | 0.93 [ 0.63, 1.37 ] |
| **Subtotal (95% CI)** | **510** | **501** | | **70.5 %** | **0.86 [ 0.62, 1.18 ]** |
| Total events: 59 (Vitamin A), 68 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 4.69, df = 4 (P = 0.32); $I^2$ =15% | | | | | |
| Test for overall effect: Z = 0.96 (P = 0.34) | | | | | |
| 2 Supplementation via oral route | | | | | |
| Wardle 2001 | 25/77 | 29/77 | | 29.5 % | 0.86 [ 0.56, 1.33 ] |
| **Subtotal (95% CI)** | **77** | **77** | | **29.5 %** | **0.86 [ 0.56, 1.33 ]** |
| Total events: 25 (Vitamin A), 29 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.67 (P = 0.50) | | | | | |
| **Total (95% CI)** | **587** | **578** | | **100.0 %** | **0.86 [ 0.66, 1.11 ]** |
| Total events: 84 (Vitamin A), 97 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 4.69, df = 5 (P = 0.45); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 1.17 (P = 0.24) | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.00, df = 1 (P = 0.98), $I^2$ =0.0% | | | | | |



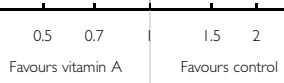
## Analysis 1.2. Comparison 1 Supplemental vitamin A vs no supplementation, Outcome 2 Chronic lung disease (oxygen use at 1 month in survivors).

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 1 Supplemental vitamin A vs no supplementation

Outcome: 2 Chronic lung disease (oxygen use at 1 month in survivors)

| Study or subgroup | Vitamin A n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Supplementation via intramuscular injection | | | | | |
| Bental 1994 | 11/26 | 10/19 | | 3.0 % | 0.80 [ 0.43, 1.49 ] |
| Papagaroufalis 1988 | 12/18 | 18/20 | | 4.4 % | 0.74 [ 0.52, 1.06 ] |
| Pearson 1992 | 12/26 | 8/18 | | 2.5 % | 1.04 [ 0.54, 2.01 ] |
| Shenai 1987 | 8/19 | 17/20 | | 4.3 % | 0.50 [ 0.28, 0.87 ] |
| Tyson 1999 | 265/362 | 269/356 | | 70.5 % | 0.97 [ 0.89, 1.06 ] |
| **Subtotal (95% CI)** | **451** | **433** | | **84.7 %** | **0.93 [ 0.86, 1.01 ]** |
| Total events: 308 (Vitamin A), 322 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 7.64, df = 4 (P = 0.11); $I^2$ =48% | | | | | |
| Test for overall effect: Z = 1.74 (P = 0.081) | | | | | |
| 2 Supplementation via intravenous route | | | | | |
| Werkman 1994 | 15/44 | 15/42 | | 4.0 % | 0.95 [ 0.54, 1.70 ] |
| **Subtotal (95% CI)** | **44** | **42** | | **4.0 %** | **0.95 [ 0.54, 1.70 ]** |
| Total events: 15 (Vitamin A), 15 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.16 (P = 0.87) | | | | | |
| 3 Supplementation via oral route | | | | | |
| Wardle 2001 | 43/52 | 42/48 | | 11.3 % | 0.95 [ 0.80, 1.11 ] |
| **Subtotal (95% CI)** | **52** | **48** | | **11.3 %** | **0.95 [ 0.80, 1.11 ]** |
| Total events: 43 (Vitamin A), 42 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.68 (P = 0.50) | | | | | |
| **Total (95% CI)** | **547** | **523** | | **100.0 %** | **0.93 [ 0.86, 1.01 ]** |
| Total events: 366 (Vitamin A), 379 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 7.64, df = 6 (P = 0.27); $I^2$ =21% | | | | | |
| Test for overall effect: Z = 1.82 (P = 0.069) | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.04, df = 2 (P = 0.98), $I^2$ =0.0% | | | | | |



## Analysis 1.3. Comparison 1 Supplemental vitamin A vs no supplementation, Outcome 3 Death or chronic lung disease (oxygen use at 1 month).

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 1 Supplemental vitamin A vs no supplementation

Outcome: 3 Death or chronic lung disease (oxygen use at 1 month)

| Study or subgroup | Vitamin A n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Supplementation via intramuscular injection | | | | | |
| Bental 1994 | 16/31 | 20/29 | | 4.5 % | 0.75 [ 0.49, 1.14 ] |
| Papagaroufalis 1988 | 21/27 | 26/28 | | 5.5 % | 0.84 [ 0.67, 1.05 ] |
| Pearson 1992 | 13/27 | 12/22 | | 2.9 % | 0.88 [ 0.51, 1.52 ] |
| Shenai 1987 | 9/20 | 17/20 | | 3.7 % | 0.53 [ 0.32, 0.89 ] |
| Tyson 1999 | 308/405 | 315/402 | | 68.2 % | 0.97 [ 0.90, 1.05 ] |
| **Subtotal (95% CI)** | **510** | **501** | | **84.7 %** | **0.93 [ 0.86, 1.00 ]** |
| Total events: 367 (Vitamin A), 390 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 7.70, df = 4 (P = 0.10); $I^2$ =48% | | | | | |
| Test for overall effect: Z = 2.06 (P = 0.039) | | | | | |
| 2 Supplementation via oral route | | | | | |
| Wardle 2001 | 68/77 | 71/77 | | 15.3 % | 0.96 [ 0.86, 1.06 ] |
| **Subtotal (95% CI)** | **77** | **77** | | **15.3 %** | **0.96 [ 0.86, 1.06 ]** |
| Total events: 68 (Vitamin A), 71 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.81 (P = 0.42) | | | | | |
| **Total (95% CI)** | **587** | **578** | | **100.0 %** | **0.93 [ 0.88, 0.99 ]** |
| Total events: 435 (Vitamin A), 461 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 7.88, df = 5 (P = 0.16); $I^2$ =37% | | | | | |
| Test for overall effect: Z = 2.20 (P = 0.027) | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.24, df = 1 (P = 0.62), $I^2$ =0.0% | | | | | |

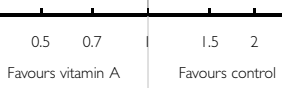
## Analysis 1.4. Comparison 1 Supplemental vitamin A vs no supplementation, Outcome 4 Death before 36 weeks' postmenstrual age.

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 1 Supplemental vitamin A vs no supplementation

Outcome: 4 Death before 36 weeks' postmenstrual age

| Study or subgroup | Vitamin A n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Supplementation via intramuscular injection | | | | | |
| Ravishankar 2003 | 5/22 | 4/18 | | 5.0 % | 1.02 [ 0.32, 3.26 ] |
| Tyson 1999 | 59/405 | 55/402 | | 62.3 % | 1.06 [ 0.76, 1.50 ] |
| **Subtotal (95% CI)** | **427** | **420** | | **67.3 %** | **1.06 [ 0.77, 1.47 ]** |
| Total events: 64 (Vitamin A), 59 (Control) | | | | | |
| Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² =0.0% | | | | | |
| Test for overall effect: Z = 0.36 (P = 0.72) | | | | | |
| 2 Supplementation via oral route | | | | | |
| Wardle 2001 | 25/77 | 29/77 | | 32.7 % | 0.86 [ 0.56, 1.33 ] |
| **Subtotal (95% CI)** | **77** | **77** | | **32.7 %** | **0.86 [ 0.56, 1.33 ]** |
| Total events: 25 (Vitamin A), 29 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.67 (P = 0.50) | | | | | |
| **Total (95% CI)** | **504** | **497** | | **100.0 %** | **1.00 [ 0.77, 1.30 ]** |
| Total events: 89 (Vitamin A), 88 (Control) | | | | | |
| Heterogeneity: Chi² = 0.58, df = 2 (P = 0.75); I² =0.0% | | | | | |
| Test for overall effect: Z = 0.03 (P = 0.98) | | | | | |
| Test for subgroup differences: Chi² = 0.57, df = 1 (P = 0.45), I² =0.0% | | | | | |



## Analysis 1.5. Comparison 1 Supplemental vitamin A vs no supplementation, Outcome 5 Chronic lung disease (oxygen use at 36 weeks' postmenstrual age in survivors).

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 1 Supplemental vitamin A vs no supplementation

Outcome: 5 Chronic lung disease (oxygen use at 36 weeks' postmenstrual age in survivors)

| Study or subgroup | Vitamin A n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Supplementation via intramuscular injection | | | | | |
| Ravishankar 2003 | 4/17 | 5/14 | | 2.3 % | 0.66 [ 0.22, 2.00 ] |
| Tyson 1999 | 163/346 | 193/347 | | 81.4 % | 0.85 [ 0.73, 0.98 ] |
| **Subtotal (95% CI)** | **363** | **361** | | **83.7 %** | **0.84 [ 0.73, 0.97 ]** |
| Total events: 167 (Vitamin A), 198 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 0.19, df = 1 (P = 0.66); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 2.33 (P = 0.020) | | | | | |
| 2 Supplementation via oral route | | | | | |
| Wardle 2001 | 40/52 | 37/48 | | 16.3 % | 1.00 [ 0.81, 1.24 ] |
| **Subtotal (95% CI)** | **52** | **48** | | **16.3 %** | **1.00 [ 0.81, 1.24 ]** |
| Total events: 40 (Vitamin A), 37 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.02 (P = 0.98) | | | | | |
| **Total (95% CI)** | **415** | **409** | | **100.0 %** | **0.87 [ 0.77, 0.98 ]** |
| Total events: 207 (Vitamin A), 235 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 1.98, df = 2 (P = 0.37); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 2.23 (P = 0.026) | | | | | |
| Test for subgroup differences: $Chi^2$ = 1.66, df = 1 (P = 0.20), $I^2$ =40% | | | | | |

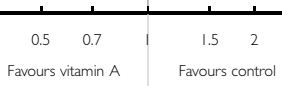
## Analysis 1.6. Comparison 1 Supplemental vitamin A vs no supplementation, Outcome 6 Death or chronic lung disease (oxygen use at 36 weeks' postmenstrual age).

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 1 Supplemental vitamin A vs no supplementation

Outcome: 6 Death or chronic lung disease (oxygen use at 36 weeks' postmenstrual age)

| Study or subgroup | Vitamin A n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Supplementation via intramuscular injection | | | | | |
| Ravishankar 2003 | 9/22 | 9/18 | | 3.0 % | 0.82 [ 0.41, 1.62 ] |
| Tyson 1999 | 222/405 | 248/402 | | 76.6 % | 0.89 [ 0.79, 1.00 ] |
| **Subtotal (95% CI)** | **427** | **420** | | **79.7 %** | **0.89 [ 0.79, 0.99 ]** |
| Total events: 231 (Vitamin A), 257 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 0.05, df = 1 (P = 0.82); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 2.05 (P = 0.040) | | | | | |
| 2 Supplementation via oral route | | | | | |
| Wardle 2001 | 65/77 | 66/77 | | 20.3 % | 0.98 [ 0.86, 1.12 ] |
| **Subtotal (95% CI)** | **77** | **77** | | **20.3 %** | **0.98 [ 0.86, 1.12 ]** |
| Total events: 65 (Vitamin A), 66 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.23 (P = 0.82) | | | | | |
| **Total (95% CI)** | **504** | **497** | | **100.0 %** | **0.91 [ 0.82, 1.00 ]** |
| Total events: 296 (Vitamin A), 323 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 1.72, df = 2 (P = 0.42); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 2.03 (P = 0.042) | | | | | |
| Test for subgroup differences: $Chi^2$ = 1.39, df = 1 (P = 0.24), $I^2$ =28% | | | | | |



### Analysis 1.7. Comparison 1 Supplemental vitamin A vs no supplementation, Outcome 7 Death before 18 to 22 months.

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 1 Supplemental vitamin A vs no supplementation

Outcome: 7 Death before 18 to 22 months

| Study or subgroup | Vitamin A n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| 1 Supplementation via intramuscular injection | | | | |
| Tyson 1999 | 73/405 | 76/402 | | 0.95 [ 0.71, 1.27 ] |

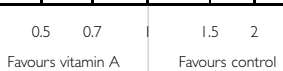

### Analysis 1.8. Comparison 1 Supplemental vitamin A vs no supplementation, Outcome 8 Neurodevelopmental impairment at 18 to 22 months.

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 1 Supplemental vitamin A vs no supplementation

Outcome: 8 Neurodevelopmental impairment at 18 to 22 months

| Study or subgroup | Vitamin A n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| 1 Supplementation via intramuscular injection | | | | |
| Tyson 1999 | 117/272 | 128/266 | | 0.89 [ 0.74, 1.08 ] |

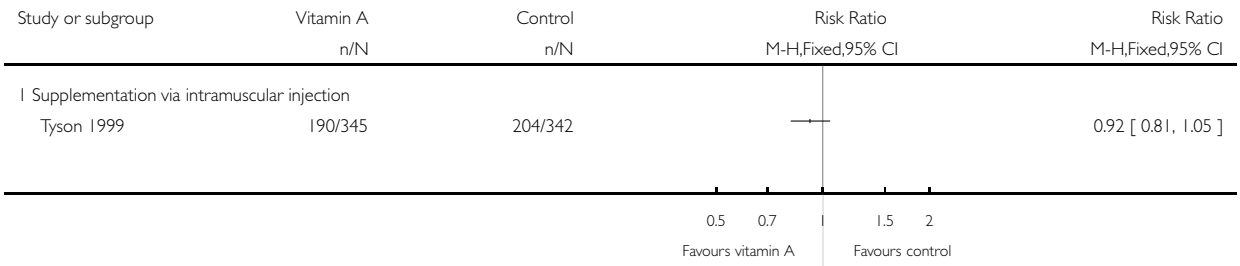


### Analysis 1.9. Comparison 1 Supplemental vitamin A vs no supplementation, Outcome 9 Death or neurodevelopmental impairment at 18 to 22 months.

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 1 Supplemental vitamin A vs no supplementation

Outcome: 9 Death or neurodevelopmental impairment at 18 to 22 months

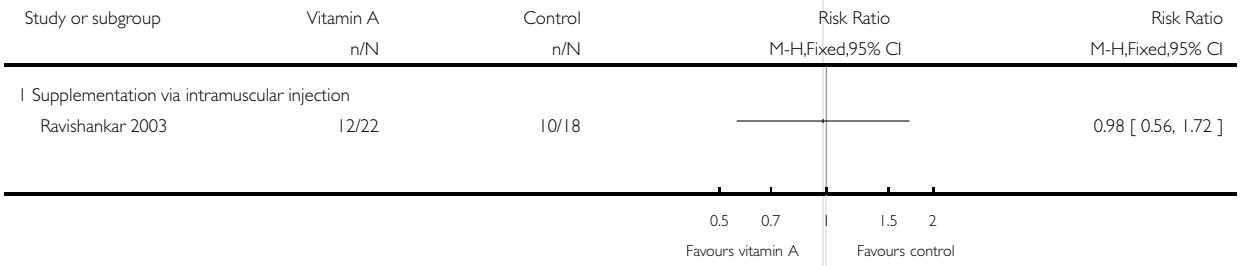



### Analysis 1.10. Comparison 1 Supplemental vitamin A vs no supplementation, Outcome 10 Failure of ductal closure or treatment by day 14.

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 1 Supplemental vitamin A vs no supplementation

Outcome: 10 Failure of ductal closure or treatment by day 14

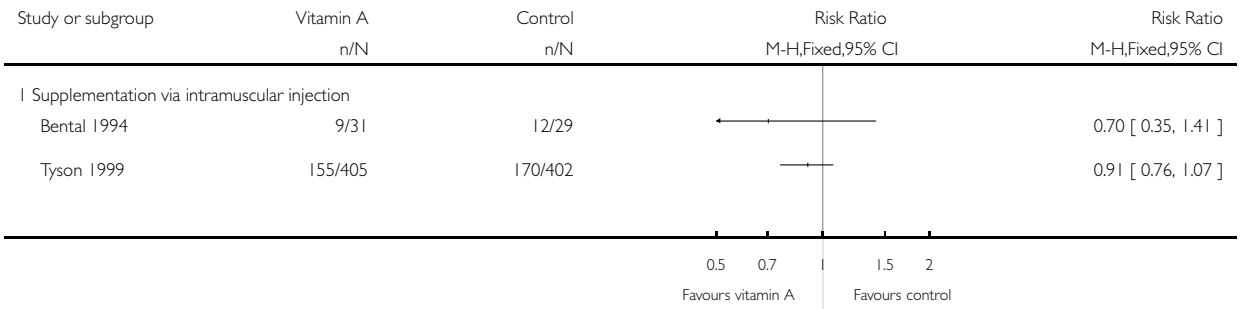


### Analysis 1.11. Comparison 1 Supplemental vitamin A vs no supplementation, Outcome 11 Sepsis (≥ 1 episodes).

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 1 Supplemental vitamin A vs no supplementation

Outcome: 11 Sepsis (≥ 1 episodes)

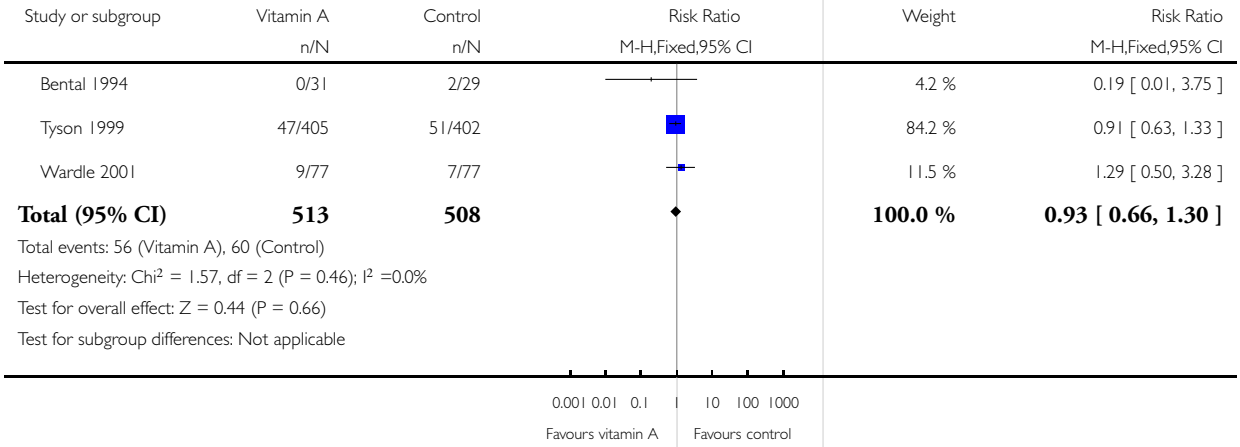



### Analysis 1.12. Comparison 1 Supplemental vitamin A vs no supplementation, Outcome 12 Necrotizing enterocolitis.

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 1 Supplemental vitamin A vs no supplementation

Outcome: 12 Necrotizing enterocolitis

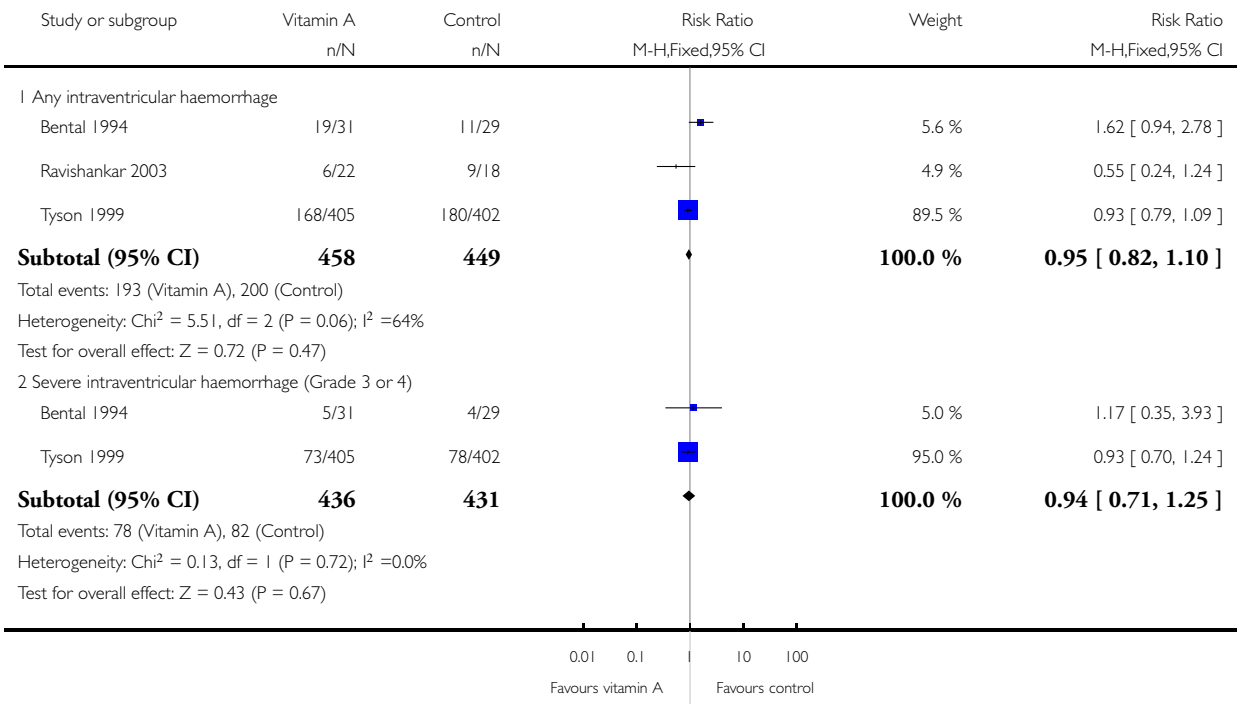


## Analysis 1.13. Comparison 1 Supplemental vitamin A vs no supplementation, Outcome 13 Intraventricular haemorrhage.

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 1 Supplemental vitamin A vs no supplementation

Outcome: 13 Intraventricular haemorrhage

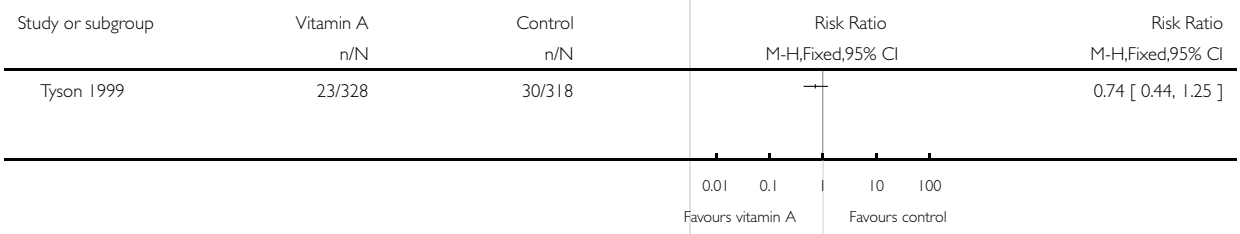



## Analysis 1.14. Comparison 1 Supplemental vitamin A vs no supplementation, Outcome 14 Periventricular leukomalacia.

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 1 Supplemental vitamin A vs no supplementation

Outcome: 14 Periventricular leukomalacia

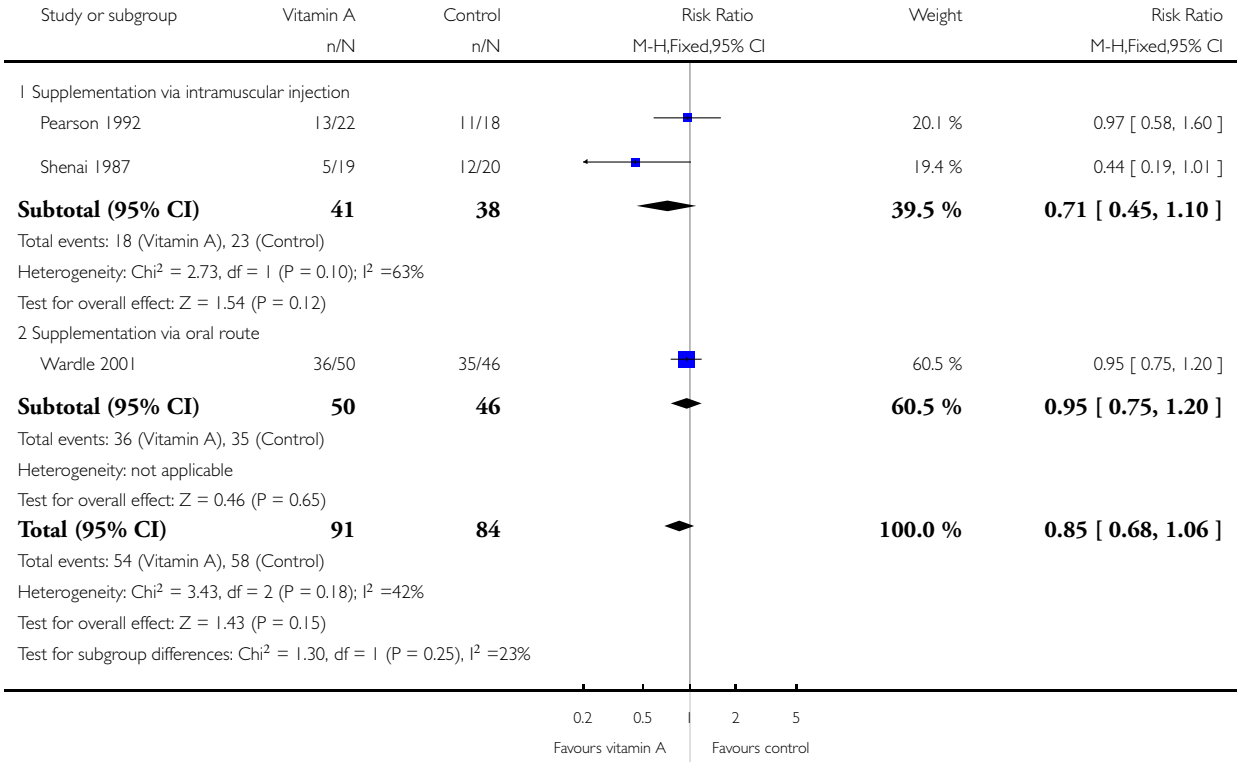


### Analysis 1.15. Comparison 1 Supplemental vitamin A vs no supplementation, Outcome 15 Retinopathy of prematurity (any grade).

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 1 Supplemental vitamin A vs no supplementation

Outcome: 15 Retinopathy of prematurity (any grade)



## Analysis 2.1. Comparison 2 Vitamin A regimens: higher dose (10,000 IU) vs standard dose (5000 IU); both intramuscular and 3 x week for 4 weeks, Outcome 1 Death before 36 weeks' postmenstrual age.

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 2 Vitamin A regimens: higher dose (10,000 IU) vs standard dose (5000 IU); both intramuscular and 3 x week for 4 weeks

Outcome: 1 Death before 36 weeks' postmenstrual age

| Study or subgroup | Higher dose n/N | Standard dose n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Ambalavanan 2003 | 8/40 | 11/40 | | 0.73 [ 0.33, 1.62 ] |


## Analysis 2.2. Comparison 2 Vitamin A regimens: higher dose (10,000 IU) vs standard dose (5000 IU); both intramuscular and 3 x week for 4 weeks, Outcome 2 Oxygen use at 36 weeks' postmenstrual age in survivors.

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 2 Vitamin A regimens: higher dose (10,000 IU) vs standard dose (5000 IU); both intramuscular and 3 x week for 4 weeks

Outcome: 2 Oxygen use at 36 weeks' postmenstrual age in survivors

| Study or subgroup | Higher dose n/N | Standard dose n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Ambalavanan 2003 | 9/32 | 3/29 | | 2.72 [ 0.81, 9.08 ] |

### Analysis 2.3. Comparison 2 Vitamin A regimens: higher dose (10,000 IU) vs standard dose (5000 IU); both intramuscular and 3 x week for 4 weeks, Outcome 3 Death or oxygen use at 36 weeks' postmenstrual age.

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 2 Vitamin A regimens: higher dose (10,000 IU) vs standard dose (5000 IU); both intramuscular and 3 x week for 4 weeks

Outcome: 3 Death or oxygen use at 36 weeks' postmenstrual age

| Study or subgroup | Higher dose n/N | Standard dose n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Ambalavanan 2003 | 17/40 | 14/40 | | 1.21 [ 0.70, 2.12 ] |

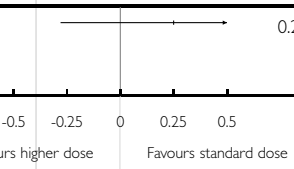

### Analysis 2.4. Comparison 2 Vitamin A regimens: higher dose (10,000 IU) vs standard dose (5000 IU); both intramuscular and 3 x week for 4 weeks, Outcome 4 Retinol concentration on study day 28 ($\mu$g/L).

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 2 Vitamin A regimens: higher dose (10,000 IU) vs standard dose (5000 IU); both intramuscular and 3 x week for 4 weeks

Outcome: 4 Retinol concentration on study day 28 (g/L)

| Study or subgroup | Higher dose N | Mean(SD) | Standard dose N | Mean(SD) | Std. Mean Difference IV,Fixed,95% CI | Std. Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Ambalavanan 2003 | 28 | 350 (230) | 27 | 300 (160) | | 0.25 [ -0.28, 0.78 ] |



### Analysis 2.5. Comparison 2 Vitamin A regimens: higher dose (10,000 IU) vs standard dose (5000 IU); both intramuscular and 3 x week for 4 weeks, Outcome 5 Retinol < 200 μg/L on day 28 (%).

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 2 Vitamin A regimens: higher dose (10,000 IU) vs standard dose (5000 IU); both intramuscular and 3 x week for 4 weeks

Outcome: 5 Retinol < 200 g/L on day 28 (%)

| Study or subgroup | Higher dose n/N | Standard dose n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Ambalavanan 2003 | 6/28 | 7/27 | | 0.83 [ 0.32, 2.15 ] |


### Analysis 2.6. Comparison 2 Vitamin A regimens: higher dose (10,000 IU) vs standard dose (5000 IU); both intramuscular and 3 x week for 4 weeks, Outcome 6 Necrotizing enterocolitis.

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 2 Vitamin A regimens: higher dose (10,000 IU) vs standard dose (5000 IU); both intramuscular and 3 x week for 4 weeks

Outcome: 6 Necrotizing enterocolitis

| Study or subgroup | Higher dos n/N | Standard dose n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Ambalavanan 2003 | 2/40 | 2/40 | | 1.00 [ 0.15, 6.76 ] |

### Analysis 2.7. Comparison 2 Vitamin A regimens: higher dose (10,000 IU) vs standard dose (5000 IU); both intramuscular and 3 x week for 4 weeks, Outcome 7 Retinopathy of prematurity (any grade).

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 2 Vitamin A regimens: higher dose (10,000 IU) vs standard dose (5000 IU); both intramuscular and 3 x week for 4 weeks

Outcome: 7 Retinopathy of prematurity (any grade)

| Study or subgroup | Higher dose n/N | Standard dose n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Ambalavanan 2003 | 16/32 | 21/31 | | 0.74 [ 0.48, 1.13 ] |

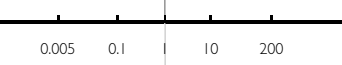

### Analysis 2.8. Comparison 2 Vitamin A regimens: higher dose (10,000 IU) vs standard dose (5000 IU); both intramuscular and 3 x week for 4 weeks, Outcome 8 Retinopathy of prematurity (threshold disease).

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 2 Vitamin A regimens: higher dose (10,000 IU) vs standard dose (5000 IU); both intramuscular and 3 x week for 4 weeks

Outcome: 8 Retinopathy of prematurity (threshold disease)

| Study or subgroup | Higher dose n/N | Standard dose n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Ambalavanan 2003 | 0/32 | 5/31 | | 0.09 [ 0.01, 1.53 ] |



### Analysis 2.9. Comparison 2 Vitamin A regimens: higher dose (10,000 IU) vs standard dose (5000 IU); both intramuscular and 3 x week for 4 weeks, Outcome 9 Sepsis (≥ 1 episodes).

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 2 Vitamin A regimens: higher dose (10,000 IU) vs standard dose (5000 IU); both intramuscular and 3 x week for 4 weeks

Outcome: 9 Sepsis (≥ 1 episodes)

| Study or subgroup | Higher dose n/N | Standard dose n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Ambalavanan 2003 | 20/40 | 26/40 | | 0.77 [ 0.52, 1.13 ] |


### Analysis 3.1. Comparison 3 Vitamin A regimens: once-a-week (15,000 IU) vs standard dose (5000 IU 3 x week); both intramuscular and for 4 weeks, Outcome 1 Death before 36 weeks' postmenstrual age.

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 3 Vitamin A regimens: once-a-week (15,000 IU) vs standard dose (5000 IU 3 x week); both intramuscular and for 4 weeks

Outcome: 1 Death before 36 weeks' postmenstrual age

| Study or subgroup | Once-a-week dose n/N | Standard dose n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Ambalavanan 2003 | 8/40 | 11/40 | | 0.73 [ 0.33, 1.62 ] |

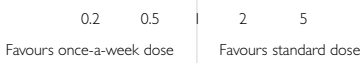
### Analysis 3.2. Comparison 3 Vitamin A regimens: once-a-week (15,000 IU) vs standard dose (5000 IU 3 x week); both intramuscular and for 4 weeks, Outcome 2 Oxygen use at 36 weeks' postmenstrual age in survivors.

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 3 Vitamin A regimens: once-a-week (15,000 IU) vs standard dose (5000 IU 3 x week); both intramuscular and for 4 weeks

Outcome: 2 Oxygen use at 36 weeks' postmenstrual age in survivors

| Study or subgroup | Once-a-week dose n/N | Standard dose n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Ambalavanan 2003 | 6/32 | 3/29 | | 1.81 [ 0.50, 6.59 ] |



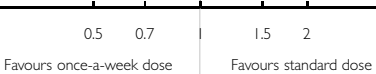

### Analysis 3.3. Comparison 3 Vitamin A regimens: once-a-week (15,000 IU) vs standard dose (5000 IU 3 x week); both intramuscular and for 4 weeks, Outcome 3 Death or oxygen use at 36 weeks' postmenstrual age.

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 3 Vitamin A regimens: once-a-week (15,000 IU) vs standard dose (5000 IU 3 x week); both intramuscular and for 4 weeks

Outcome: 3 Death or oxygen use at 36 weeks' postmenstrual age

| Study or subgroup | Once-a-week dose n/N | Standard dose n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Ambalavanan 2003 | 14/40 | 14/40 | | 1.00 [ 0.55, 1.82 ] |



### Analysis 3.4. Comparison 3 Vitamin A regimens: once-a-week (15,000 IU) vs standard dose (5000 IU 3 x week); both intramuscular and for 4 weeks, Outcome 4 Retinol concentration on study day 28 ($\mu$g/L).

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 3 Vitamin A regimens: once-a-week (15,000 IU) vs standard dose (5000 IU 3 x week); both intramuscular and for 4 weeks

Outcome: 4 Retinol concentration on study day 28 (g/L)

| Study or subgroup | Once-a-week dose | | Standard dose | | Std. Mean Difference | Std. Mean Difference |
|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | IV,Fixed,95% CI |
| Ambalavanan 2003 | 23 | 170 (90) | 27 | 300 (160) | | -0.97 [ -1.56, -0.38 ] |

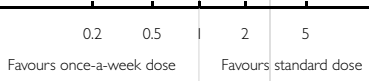

### Analysis 3.5. Comparison 3 Vitamin A regimens: once-a-week (15,000 IU) vs standard dose (5000 IU 3 x week); both intramuscular and for 4 weeks, Outcome 5 Retinol < 200 $\mu$g/L on day 28 (%).

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 3 Vitamin A regimens: once-a-week (15,000 IU) vs standard dose (5000 IU 3 x week); both intramuscular and for 4 weeks

Outcome: 5 Retinol < 200 g/L on day 28 (%)

| Study or subgroup | Once-a-week dose | Standard dose | Risk Ratio | Risk Ratio |
|---|---|---|---|---|
| | n/N | n/N | M-H,Fixed,95% CI | M-H,Fixed,95% CI |
| Ambalavanan 2003 | 15/23 | 7/27 | | 2.52 [ 1.24, 5.09 ] |



### Analysis 3.6. Comparison 3 Vitamin A regimens: once-a-week (15,000 IU) vs standard dose (5000 IU 3 x week); both intramuscular and for 4 weeks, Outcome 6 Necrotizing enterocolitis.

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 3 Vitamin A regimens: once-a-week (15,000 IU) vs standard dose (5000 IU 3 x week); both intramuscular and for 4 weeks

Outcome: 6 Necrotizing enterocolitis

| Study or subgroup | Once-a-week dose n/N | Standard dose n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Ambalavanan 2003 | 3/40 | 2/40 | | 1.50 [ 0.26, 8.50 ] |


### Analysis 3.7. Comparison 3 Vitamin A regimens: once-a-week (15,000 IU) vs standard dose (5000 IU 3 x week); both intramuscular and for 4 weeks, Outcome 7 Retinopathy of prematurity (any grade).

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 3 Vitamin A regimens: once-a-week (15,000 IU) vs standard dose (5000 IU 3 x week); both intramuscular and for 4 weeks

Outcome: 7 Retinopathy of prematurity (any grade)

| Study or subgroup | Once-a-week dose n/N | Standard dose n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Ambalavanan 2003 | 14/33 | 21/31 | | 0.63 [ 0.39, 1.00 ] |

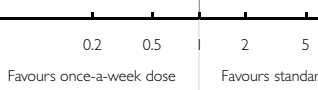
### Analysis 3.8. Comparison 3 Vitamin A regimens: once-a-week (15,000 IU) vs standard dose (5000 IU 3 x week); both intramuscular and for 4 weeks, Outcome 8 Retinopathy of prematurity (threshold disease).

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 3 Vitamin A regimens: once-a-week (15,000 IU) vs standard dose (5000 IU 3 x week); both intramuscular and for 4 weeks

Outcome: 8 Retinopathy of prematurity (threshold disease)

| Study or subgroup | Once-a-week dose n/N | Standard dose n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Ambalavanan 2003 | 3/33 | 5/31 | | 0.56 [ 0.15, 2.16 ] |



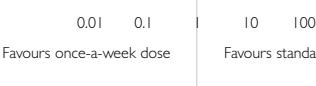

### Analysis 3.9. Comparison 3 Vitamin A regimens: once-a-week (15,000 IU) vs standard dose (5000 IU 3 x week); both intramuscular and for 4 weeks, Outcome 9 One or more episodes of sepsis.

Review: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants

Comparison: 3 Vitamin A regimens: once-a-week (15,000 IU) vs standard dose (5000 IU 3 x week); both intramuscular and for 4 weeks

Outcome: 9 One or more episodes of sepsis

| Study or subgroup | Once-a-week dose n/N | Standard dose n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Ambalavanan 2003 | 26/40 | 18/40 | | 1.44 [ 0.96, 2.18 ] |



# APPENDICES

## Appendix 1. Data extraction fields for interventions and outcomes

The authors collected the following data from each included trial.

- General information:
  - Supplementation dose
  - Supplementation frequency
  - Time of initiation of supplementation
  - Vitamin A intake of control groups
  - Pre-randomisation vitamin A concentrations of supplemented and control groups (if available)
  - Post-randomisation vitamin A concentrations
- Number of the following outcomes in the supplemented and control groups:
  - Deaths
  - Reported as having a significant patent ductus arteriosus at 2 weeks of age
  - Developing neonatal chronic lung disease in the supplemented and control groups
  - Patent ductus arteriosus
  - Necrotizing enterocolitis
  - Intraventricular haemorrhage
  - Periventricular leukomalacia
  - Retinopathy of prematurity
  - $\geq$ 1 episodes of defined sepsis
  - Long-term neurodevelopmental disability
- Mean, standard deviation, and range of the following outcomes in the supplemented and control groups:
  - Gestational age
  - Birthweight

# WHAT'S NEW

Last assessed as up-to-date: 30 August 2011.

| Date | Event | Description |
|---|---|---|
| 31 August 2011 | New search has been performed | This updates the review "Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants" published in the *Cochrane Database of Systematic Reviews* (Darlow 2007). Search updated Augut 2011. No new trials. |
| 31 August 2011 | New citation required but conclusions have not changed | Additional secondary outcomes added. The methods have been updated to include the new risk of bias assessment and 'Summary of findings' tables. The risk of bias assessment has been completed for each trial and 'Summary of findings' tables added to the review |

## HISTORY

Protocol first published: Issue 4, 1998

Review first published: Issue 2, 2000

| Date | Event | Description |
|---|---|---|
| 12 June 2008 | Amended | Converted to new review format. |
| 15 July 2007 | New search has been performed | This review updates the existing review "Vitamin A supplementation for preventing morbidity and mortality in very low birthweight infants", published in the Cochrane Database of Systematic Reviews in 2002, Issue 2 (Darlow 2002).<br>One further small trial has been identified and data from this trial added to the pooled data for the meta-analysis. There are now data on the neurodevelopmental status at 18 to 22 months postmenstrual age for infants included in the largest vitamin A supplementation trial, and this information has been included in this review. In addition, data from one trial that compared three different intramuscular vitamin A dosing regimens have been included<br>The previous version of this review concluded that supplementing very low birthweight infants with vitamin A is associated with a reduction in oxygen requirement among survivors at 36 weeks postmenstrual age, as well as a reduction in death or oxygen requirement at one month of age. With data from the additional study, these conclusions remain the same. The information on follow-up at 18 to 22 months postmenstrual age from the largest included trial showed no evidence or benefit or harm from the intervention<br>Based on biochemical data, the one study that investigated different intramuscular vitamin A dosing regimens suggested that the regimen used in the largest trial (5000 IU 3x weekly for four weeks) was optimal even though some infants still had poor vitamin A status<br>The conclusion remains unchanged: clinicians must decide whether to utilise repeat intramuscular doses of vitamin A based upon the incidence of supplemental oxygen requirement at 36 weeks postmenstrual age in extremely low birthweight infants in their unit and their own assessment, based upon the review, of the benefits of a modest reduction in this outcome balanced against lack of other proven benefits and the acceptability of treatment. The follow-up data would support a decision either to treat or not to treat |
| 15 July 2007 | New citation required but conclusions have not changed | Substantive amendment. |

## CONTRIBUTIONS OF AUTHORS

The original review was conducted and written by Brian A Darlow and PJ Graham. Review update was facilitated by Roger Soll, Coordinating Editor of the Cochrane Neonatal Review Group and approved by the original authors.

## DECLARATIONS OF INTEREST

None.

## SOURCES OF SUPPORT


### Internal sources

- Christchurch School of Medicine, University of Otago, New Zealand.

### External sources

- WHO, Switzerland.

A grant was provided by the WHO for an updated of this Cochrane Review.


## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

## NOTES

None.

## INDEX TERMS

### Medical Subject Headings (MeSH)

*Infant, Very Low Birth Weight; Infant, Newborn; Infant, Premature; Infant, Premature, Diseases [mortality; *prevention & control]; Lung Diseases [mortality; *prevention & control]; Randomized Controlled Trials as Topic; Vitamin A [*therapeutic use]; Vitamins [*therapeutic use]

### MeSH check words

Humans