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Vitamin A for non-measles pneumonia in children (Review)

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[Intervention Review]

Vitamin A for non-measles pneumonia in children

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ABSTRACT

Background

Acute respiratory infections, mostly in the form of pneumonia, are the leading causes of death in children under five years of age in low-income countries. Some clinical trials have demonstrated that vitamin A supplementation reduces the severity of respiratory infections and mortality in children with measles.

Objectives

To determine whether adjunctive vitamin A is effective in children diagnosed with non-measles pneumonia.

Search methods

We searched *The Cochrane Library*, Cochrane Central Register of Controlled Trials (CENTRAL 2010, issue 3) which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1996 to July week 3, 2010), EMBASE (1990 to August 2010), LILACS (1985 to August 2010), CINAHL (1990 to August 2010), Biological Abstracts (1990 to August 2010), Current Contents (1990 to August 2010) and the Chinese Biomedicine Database (CBM) (1994 to June 2010).

Selection criteria

Only parallel-arm, randomized controlled trials (RCTs) and quasi-RCTs, in which children (younger than 15 years of age) with non-measles pneumonia were treated with adjunctive vitamin A, were included.

Data collection and analysis

Two review authors independently extracted data and assessed trial quality. Study authors were contacted for additional information.

Main results

Six trials involving 1740 children were included. There was no significant reduction in mortality associated with pneumonia in children treated with vitamin A compared to those who were not (pooled odds ratio (OR) 1.29; 95% confidence interval (CI) 0.63 to 2.66). Also, there was no statistically significant difference in duration of hospital stay (mean difference (MD) 0.08; 95% CI -0.43 to 0.59). Disease severity after supplementary high-dose vitamin A was significantly worse compared with placebo. However, low-dose vitamin A significantly reduced the recurrence rate of bronchopneumonia (OR 0.12; 95% CI 0.03 to 0.46). Moderate vitamin A significantly reduced the time to remission of signs in children with normal serum retinol (> 200 µg/L).

Authors' conclusions

The evidence does not suggest a significant reduction in mortality, measures of morbidity, nor an effect on the clinical course of pneumonia with vitamin A adjunctive treatment in children with non-measles pneumonia. However, not all studies measured all outcomes, which limited the number of studies that could be incorporated into the meta-analyses, so that there may have been a lack of statistical power to detect statistically significant differences.

PLAIN LANGUAGE SUMMARY

Vitamin A for non-measles pneumonia in children

Acute respiratory infections, mostly in the form of pneumonia, are the leading cause of death in children under five years of age living in low-income countries. Vitamin A supplementation has been found to reduce mortality and the severity of respiratory infections in children with measles. This updated review was undertaken to assess the effectiveness of vitamin A adjunctive therapy in children with non-measles respiratory infections, particularly pneumonia.

We found six trials (1740 participants) that used vitamin A adjunctive therapy in children with non-measles pneumonia. There was no significant reduction in mortality or duration of hospital stay. Supplementary high-dose vitamin A may result in a worsening of the disease, and low-dose vitamin A significantly reduces the recurrence of bronchopneumonia. Moderate-dose vitamin A significantly reduces the time to remission of signs in children with normal serum retinol. The possible reason of the lack of benefit of vitamin A in non-measles pneumonia is that the effects of vitamin A may be disease-specific, with vitamin A only being effective when pneumonia is complicated with measles. Further high-quality research is required.

BACKGROUND

Description of the condition

Acute respiratory tract infections (ARTIs) and vitamin A deficiency are important public health problems in many low-income countries. Vitamin A deficiency is associated with impaired humoral and cellular immune function, keratinisation of the respiratory epithelium and decreased mucus secretion, which weaken barriers to infection (Ross 1996). In low-income countries, ARTIs, mostly in the form of pneumonia, are the leading cause of death in children under five years of age. The incidence of clinical pneumonia in low-income countries is estimated at 0.29 episodes per child per year. This equates to an annual incidence of 150.7 million new cases, 11 to 20 million (7% to 13%) of which are severe enough to require hospital admission. No comparable data are available for high-income countries. However, from large population-based studies, the incidence of community-acquired pneumonia among children less than five years of age is approximately 0.026 episodes per child per year (Rundan 2004). Pneumonia is associated with and causes about 3.8 million childhood deaths annually; 30.3% of these are in children under the age of five (Kirkwood 1995).

Description of the intervention

Vitamin A functions in a very different way in human metabolism. It is needed by the retina of the eye's specific metabolite, the light-absorbing molecule retinal; and as an irreversibly oxidized form retinoic acid, which is an important hormone-like growth factor for epithelial and other cells. Lack of vitamin A will cause some severe problems such as night blindness, xerophthalmia and complete blindness. Vitamin A deficiency also contributes to maternal mortality and other poor outcomes in pregnancy and lactation (WHO 2010).

How the intervention might work

Community-based clinical trials have been conducted in order to determine whether periodic high-dose vitamin A supplementation reduces the incidence, severity or both of ARTIs in children. The association between vitamin A deficiency and child mortality was first observed in the 1930s when vitamin A supplementation significantly reduced mortality among measles patients (Ellison 1932). Two meta-analyses (Fawzi 1993; Glasziou 1993) examined the relationship between vitamin A supplementation and infectious diseases. Glasziou (Glasziou 1993) reported that vitamin A reduced all-cause mortality by one third in children in low-income countries. However, the reduction in deaths from respiratory disease was seen only in the measles studies. Fawzi (Fawzi 1993) also reported that supplementation was protective against overall mortality in community-based studies (odds ratio (OR) 0.70) and highly protective against mortality in hospitalised patients with measles (OR 0.39).

From the current evidence it appears that vitamin A supplementation reduces the severity of respiratory infection and other systemic complications of measles. However, the association between vitamin A and non-measles ARTIs is unclear. The World Health Organization (WHO) Programme for the Control of Acute Respiratory Infections published a meta-analysis to assess the impact of supplementation on pneumonia morbidity and mortality (VAPWG 1995). They reported no consistent overall protective or detrimental effect on pneumonia-specific mortality and no effect on the incidence or the prevalence of pneumonia.

Why it is important to do this review

Hospital-based clinical trials examining the effectiveness of high-dose vitamin A, administered during an acute episode of non-measles ARTI, in reducing morbidity or mortality, have been performed. However, no meta-analyses have been carried out. Given the apparent effectiveness of vitamin A in reducing mortality in hospitalised patients with measles, and the inexpensiveness of the intervention, clarification of the association between vitamin A and non-measles ARTIs is of some importance.

OBJECTIVES

The objective of this review was to assess the effectiveness and safety of vitamin A in children with diagnosed non-measles pneumonia.

METHODS

Criteria for considering studies for this review

Types of studies

We considered only parallel-arm, randomized controlled trials (RCTs) and quasi-RCTs in which children with diagnosed non-measles pneumonia were treated with vitamin A (at the time of confirmed disease) for inclusion in this review. We did not consider studies that examined the effectiveness of vitamin A in preventing episodes of non-measles pneumonia or studies including patients with measles.

Types of participants

We included children of either gender and under 15 years of age with non-specific pneumonia that was uncomplicated by measles. The definition of pneumonia was a clinical case definition, radiological confirmation or both.

Types of interventions

Vitamin A plus standard medical treatment versus standard medical treatment with or without placebo.

Types of outcome measures

Primary outcomes

1. Mortality.

Secondary outcomes

1. Signs of pneumonia (for example, fever, tachypnoea, dyspnoea, chest X-ray findings).
2. Clinical severity (for example, oxygen saturation, requirement for mechanical ventilation or need for supplemental oxygen, crepitations, bronchial breathing, duration of hospitalization, failure of first line treatment or change of antibiotic required).
3. Adverse events associated with the intake of vitamin A such as diarrhea and signs of toxicity, including vomiting and desquamation.

Search methods for identification of studies

Electronic searches

We searched *The Cochrane Library*, Cochrane Central Register of Controlled Trials (CENTRAL 2010, issue 3) which contains the Acute

Respiratory Infections Group's Specialised Regsiter, MEDLINE (1996 to July week 3, 2010), EMBASE (1990 to August 2010), LILACS (1985 to August 2010), CINAHL (1990 to August 2010), Biological Abstracts (1990 to August 2010), Current Contents (1990 to August 2010) and the Chinese Biomedicine Database (CBM) (1994 to June 2010).

We used the following search strategy to search CENTRAL and MEDLINE. We combined the MEDLINE search with the Cochrane

Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE:sensitivity- and precision- maximizing version (2008 revision); Ovid format ([Lefebvre 2009](#)). The search strategy was modified to search Embase (see [Appendix 1](#)), LILACS (see [Appendix 2](#)), CINAHL (see [Appendix 3](#)), Biological Abstracts (see [Appendix 4](#)) and Current Contents (see [Appendix 5](#)). The search strategy for the Chinese databases is presented in [Figure 1](#). See [Appendix 6](#) for details of original search.

Figure 1. Search strategy in the Chinese databases.

肺炎ti.	AND	维生素A ti.
肺炎ti.	AND	维生素A ab.
肺炎ti.	AND	维生素A tx.
肺炎ab.	AND	维生素A ti.
肺炎ab.	AND	维生素A ab.
肺炎ab.	AND	维生素A tx.
肺炎tx.	AND	维生素A ti.
肺炎tx.	AND	维生素A ab.
肺炎tx.	AND	维生素A tx.

MEDLINE (OVID)

- 1 exp Vitamin A/
- 2 (vitamin a or retinol).tw,nm.
- 3 Dietary Supplements/
- 4 or/1-3
- 5 exp Pneumonia/
- 6 pneumon*.tw.
- 7 Respiratory Tract Infections/
- 8 (respiratory adj2 (infection* or disease* or acute)).tw.

In addition to electronic databases, we searched reference lists. There were no language or publication restrictions.

Searching other resources

We searched the WHO ICTRP for ongoing studies. This site contains records provided by nine primary registries (<http://apps.who.int/trialsearch/>).

Data collection and analysis

Selection of studies

One review author (JN) collated study citations into a single library, excluded duplicates and articles unlikely to be relevant by scanning the abstracts. We retrieved citations without abstracts in full text.

Two review authors (JN, TW) independently reviewed a sample of the selection process. Two review authors (JN, WT) independently retrieved relevant articles in full text and applied the inclusion criteria.

Data extraction and management

Two review authors (JN, WJ) independently extracted data from included studies using standardized forms. They obtained a copy of the original article from Dr. Quinlan and telephoned the original authors of Chinese articles. All data were extracted from published papers and differences were resolved by discussion among the review authors.

Assessment of risk of bias in included studies

We assessed study quality using an adaptation of the method specified in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Julian 2009](#)). The following characteristics were assessed.

Adequacy of the randomisation process

Adequate sequence generation was reported using one of following approaches: random number tables, computer-generated random numbers, coin tossing, or shuffling.

Yes: with low risk of selection bias.

Unclear: did not specify one of the adequate methods outlined above but only mentioned 'random' in which situation moderate risk of selection bias existed.

No: other methods of allocation that appeared to be biased with high risk.

Adequacy of the allocation concealment process

Adequate measures to conceal allocations such as central randomisation; serially numbered, opaque, sealed envelopes; or another description that contained convincing elements of concealment.

Yes: with low risk of selection bias.

Unclear: did not report an allocation concealment approach at all in which situation moderate risk of selection bias existed.

No: inadequately concealed allocation that reported an approach that did not fall into one of the categories described above, and did not conceal allocation. In which situation a high risk of selection bias existed.

Level of masking

Low risk of both performance and detection bias: the healthcare providers and outcome assessors were masked to know what interventions were received in each participants.

Moderate risk of both performance and detection bias: single blinding used only.

High risk of both performance and detection bias: blinding not been used.

Free of other bias

Yes: it was specified that without any potential bias, for example, conflict of interest.

No: there was conflict of interest or other risk of bias.

Measures of treatment effect

Dichotomous data were expressed as an odds ratio (OR) with 95% confidence intervals (CI). We converted continuous data to mean differences (MD). All meta-analyses were based on a fixed-effect model.

Unit of analysis issues

Only individual participants data were included and assessed.

Dealing with missing data

Original investigators of Chinese studies were contacted by telephone to request missing data include randomisation method and allocation concealment.

Incomplete outcome data bias were assessed depending on the percentage of missing data:

Low risk: only few withdraw or losses to follow up occurred.

Moderate risk: exclusions were about 10%.

High risk: exclusions of at least 10%, or wide differences in exclusions between groups.

Assessment of heterogeneity

We were able to perform only limited pooled analyses. We presented a statistical summary of treatment effects only in the absence of significant clinical or statistical heterogeneity. We tested

heterogeneity using the Cochran Q statistic (Cochran 1954) with significance at $P = < 0.10$ (Boissel 1989; Fleiss 1986).

Assessment of reporting biases

We planned to assess publication bias by using funnel plots. However, due to the small number of included studies we did not perform this assessment. Free of selective reporting was assessed depends on whether all the outcomes were reported or not:

Yes: all outcomes were addressed and reported.

No: some of outcomes appeared in protocol but not reported in the article.

Data synthesis

We statistically combined data when it appropriate. Some data were analyzed separately using Review Manager 5 software (RevMan 2008). We expressed the effects as OR with 95% confidence intervals (CI) for dichotomous data. However, as mortality was an unlikely event, we used Peto OR with 95% CI. For continuous outcomes mean differences (MD) with 95% CI were calculated.

Subgroup analysis and investigation of heterogeneity

We intend to explore the following potential sources of heterogeneity using subgroup analyses or meta-regression. However there was insufficient data.

1. Different doses (low, medium, high).
2. Duration of treatment.

Sensitivity analysis

We tested the robust of evidence by sensitivity analysis when pooling analysis takes place.

1. Repeating the analysis excluding unpublished studies (if any).
2. Repeating the analysis excluding poor quality studies, as specified above.
3. Comparing the results of fixed-effect models to random-effects models. Robust evidence should not be reversed by changing these models.

RESULTS

Description of studies

Results of the search

After full-text examination of the search results, we identified 72 papers. No new trials were identified for inclusion or exclusion in our updated searches.

Included studies

Although we failed to contact the authors of two Chinese studies, we identified their trials as a randomized controlled trial (RCT) (Liu 1997) and a quasi-RCT (Zhang 1999) based on the information provided in the studies. One study (Fawzi 1998) conducted in Africa, and three studies conducted in South America (Nacul 1997; Rodriguez 2005; Stephensen 1998) were identified as RCTs. Finally, a total of six studies were included in the review (Fawzi 1998; Liu 1997; Nacul 1997; Rodriguez 2005; Stephensen 1998; Zhang 1999).

Participants

A total of 1740 infants and children participated in the six studies. One study (Fawzi 1998) included 687 participants; three studies (Nacul 1997; Rodriguez 2005; Stephensen 1998) included 854 participants; and two studies (Liu 1997; Zhang 1999) conducted in China included 119 participants, of which 80 children had recurrent bronchopneumonia. All participants were hospitalised children with ages ranging from one month to 14 years.

Interventions

Two studies (Fawzi 1998; Nacul 1997) administered 200,000 IU of vitamin A to children aged one year and older, and 100,000 IU to infants under the age of one year, daily for two days. One study (Rodriguez 2005) administered 100,000 IU of vitamin A to children aged one year and older, and 50,000 IU to infants under the age of one year. One study (Liu 1997) administered 150,000 IU of vitamin A. One study (Stephensen 1998) used a different dosing scheme: children younger than one year old received 100,000 IU of vitamin A on admission to the study and 50,000 IU on the second day of hospitalization; children one year of age or more received 200,000 IU on the first day and 100,000 IU on the second day. The final study (Zhang 1999) administered 10,000 IU twice daily for the first six days; following this, 1500 IU/day was administered for the next 20 days. All of the studies used a placebo control.

Outcomes

Three studies (Fawzi 1998; Nacul 1997; Rodriguez 2005) reported mortality, two studies (Fawzi 1998; Stephensen 1998) reported the duration of hospitalization, and one study (Nacul 1997) reported a change in antibiotic use. One study (Stephensen 1998)

reported clinical severity scores with eight individual components that included, for example, oxygen saturation, requirement of supplemental oxygen and signs of pneumonia from chest X-ray results. Three studies (Fawzi 1998; Nacul 1997; Stephensen 1998) reported the frequency of children requiring supplemental oxygen. We contacted the trial authors for further information but as yet no response has been forthcoming. One study (Nacul 1997) reported on adverse outcomes including vomiting, diarrhea, irritability and bulging fontanelle. Two studies (Liu 1997; Rodriguez 2005) reported variable outcomes and we only extracted data for outcomes which matched the inclusion criteria of this review: time to resolution of fever and cough, time until positive auscultation and positive chest X-ray results. The study by Zhang (Zhang 1999) reported on a lack of improvement of bronchopneumonia at short-term follow up and the recurrence rate of bronchopneumonia at long-term follow up.

Excluded studies

One trial author (Quinlan 1996) kindly sent us her paper. After careful consideration it was excluded. Ten Chinese studies seemed to meet the inclusion criteria and we contacted eight authors by telephone. We discovered that the allocation methods they had used were not actually randomized, thus these studies were excluded.

Risk of bias in included studies

One study (Rodriguez 2005) was identified as low risk of bias and four studies (Fawzi 1998; Liu 1997; Nacul 1997; Stephensen 1998) as moderate risk. One study (Zhang 1999) was identified as high risk of bias. An overview of the study quality can be found in the [Characteristics of included studies](#) table and [Figure 2](#) and [Figure 3](#).

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Fawzi 1998	?	?	+	+		
Liu 1997	?	-	+	-		
Nacul 1997	?	?	+	+		
Rodriguez 2005	+	+	+	+		
Stephensen 1998	?	?	+	+		
Zhang 1999	-	-				

Allocation

Four studies (Fawzi 1998; Nacul 1997; Rodriguez 2005; Stephensen 1998) used block randomisation design and two studies (Liu 1997; Zhang 1999) use individual randomisation. All studies except for Rodriguez 2005 did not mention the randomisation method and allocation concealment in detail. Four studies (Fawzi 1998; Liu 1997; Nacul 1997; Stephensen 1998) were judged to have a moderate risk of selection bias and one study (Zhang 1999) had a high risk of selection bias.

Rodriguez 2005 used block randomisation to allocate the participants and the sequence was generated by using tables of random numbers and was converted into a sequence of envelopes that contained the regimen assignments for all children in the trial. The Ethical Committee of the Corporacion Ecuatoriana de Biotecnología held the blinded randomisation codes in a secure place. The study code was not broken until all the data were entered and the initial analyses performed. It was judged to have a low risk of selection bias.

Blinding

Five studies (Fawzi 1998; Liu 1997; Nacul 1997; Rodriguez 2005; Stephensen 1998) performed double-blinding by masking the containers, they were judged to have a low risk of both performance and detection bias. One study (Zhang 1999) did not perform blinding and was thus judged to have a high risk of performance and detection bias.

Incomplete outcome data

Four studies (Fawzi 1998; Nacul 1997; Rodriguez 2005; Stephensen 1998) addressed the number of withdrawals or loss of follow-up. In the study by Rodriguez 2005, 48 children (16.7%) were lost to follow-up during the course of the study. There was a moderate risk of incomplete outcome data bias. Two studies (Liu 1997; Zhang 1999) did not address the incomplete outcome data.

Selective reporting

All studies were judged as unclear for selective reporting.

Other potential sources of bias

All studies were judged as unclear for other potential sources of bias.

Effects of interventions

The outcome measures included in the meta-analysis were 1. mortality; 2. time period with signs of pneumonia, indicators of disease severity including duration of hospitalization, time with fever, time with rapid respiratory rate, time with hypoxia, time with positive findings on auscultation, time with cough, time with positive at X-ray findings, requirement for mechanical ventilation, failure of first line antibiotic treatment, slight improvement at short-term follow up, and recurrent rate of bronchopneumonia (no improvement) at long-term follow up; 3. adverse events including vomiting, diarrhea and bulging fontanelles.

We did not perform a sensitivity analysis as there were no low quality studies included in a pooled analysis.

Primary outcomes

Mortality

Pooled analysis across three studies (Fawzi 1998; Nacul 1997; Rodriguez 2005) showed no statistically significant difference in deaths during hospitalization (OR 1.29; 95% CI 0.63 to 2.66) between the vitamin A and placebo groups. Two studies used the same high dose of vitamin A (Fawzi 1998; Nacul 1997); the other study (Rodriguez 2005) used a moderate dose of vitamin A. There was no statistically significant heterogeneity ($P = 0.64$, I^2 statistic = 0%). (Figure 4).

Figure 4. Forest plot of comparison: 1 Vitamin A versus control, outcome: 1.1 Mortality during hospitalisation.

Secondary outcomes

Time with fever

Pooled analysis across three studies (Fawzi 1998; Liu 1997; Rodriguez 2005) showed no statistical significance (MD -1.11, 95%

CI -5.66 to 3.44) and no heterogeneity was detected ($P = 0.58$, I^2 statistic = 0%) (Figure 5)

Figure 5. Forest plot of comparison: 1 Vitamin A versus control, outcome: 1.2 Time with signs of pneumonia and treatment issues (continuous).

Time with respiratory rate greater than 40 breaths/minute/day

Two studies (Fawzi 1998; Rodriguez 2005) reported this outcome; no differences were found (MD 0.03; 95% CI -0.32 to 0.38) and no heterogeneity was detected ($P = 0.19$, I^2 statistic = 42.5%) (Figure 5).

Time with positive finding on auscultation

Two studies (Liu 1997; Rodriguez 2005) reported the time with positive findings on auscultation; there was no difference between the two groups (MD -0.54; 95% CI -1.14 to 0.05) and no heterogeneity was detected ($P = 0.10$, I^2 statistic = 62.8%) (Figure 5).

Time with positive finding on chest X-ray

Two studies (Liu 1997; Stephensen 1998) reported the signs of pneumonia in chest X-ray examinations after giving high doses of vitamin A. There was no statistically significant difference between the vitamin A and placebo groups (MD 0.90; 95% CI -1.10 to 2.90) (Liu 1997). There were also no positive findings on hyperinflation (in two of 41 children receiving vitamin A versus one of 31 receiving placebo), perihilar infiltrate (three of 41 versus six of 31), interstitial

infiltrate (three of 41 versus none of 31), consolidation (seven of 41 versus three of 31), atelectasis (three of 41 versus none of 31), or effusions (three of 41 versus one of 31) (Stephensen 1998) (Figure 5).

Time with cough

One study (Liu 1997) reported that the time with cough was shortened by vitamin A (MD -2.00; 95% CI -3.51 to -0.49) (Figure 5).

No improvement at short-term follow up and recurrence rate at long-term follow up

One study (Zhang 1999) reported lower rates of no improvement at both short-term follow up and of recurrence rate at long-term follow up in the low-dose vitamin A supplement group than in the control group. There were statistically significant differences (OR 0.06, 95% CI 0.01 to 0.30 and OR 0.12, 95% CI 0.03 to 0.46, respectively). These results suggest that vitamin A can promote the recovery rate at short-term follow up and decrease the recurrence rate of recurrent bronchopneumonia at long-term follow up (Figure 6).

Figure 6. Forest plot of comparison: 1 Vitamin A versus control, outcome: 1.3 Time with signs of pneumonia and treatment issues (dichotomous).

Time with fever, tachypnoea and hypoxaemia in children with basal serum retinol concentration > 200 ug/L

One study (Rodriguez 2005) reported the time with fever, tachypnoea and hypoxaemia in children with basal serum retinol

concentration > 200 ug/L. There was a significant difference between the two groups (MD -61.40; 95% CI -119.10 to -3.7). This result suggests that vitamin A can shorten the time to remission of signs in children whose basal serum retinol was > 200 ug/L (Figure 7).

Figure 7. Forest plot of comparison: 1 Vitamin A versus control, outcome: 1.5 Time with fever, tachypnoea and hypoxaemia of pneumonia (serum retinol > 200 ug/L).

Indicators of disease severity

Duration of hospitalization

Duration of hospitalization was reported in two studies (Fawzi 1998; Stephensen 1998). There was no statistically significant heterogeneity ($P = 0.83$ and I^2 statistic = 0%) between the studies. The summary OR indicated that vitamin A treatment did not have a significant effect on hospital stay duration (MD 0.08; 95% CI -0.43 to 0.59) (Figure 5).

Time with hypoxia, less than 95% oxygen saturation per day

One study (Fawzi 1998) analyzed time with hypoxia; there was no difference (MD 0.07; 95% CI -0.21 to 0.34) to be found between the vitamin A and placebo groups (Figure 5).

Requirement for mechanical ventilation

None of the studies reported on requirements for mechanical ventilation.

Failure of first line antibiotic treatment

Children that required a change of antibiotic due to failure of first line treatment were reported in only one paper (Nacul 1997). This study reported no statistically significant reduction in the odds of first line antibiotic failure (OR 0.65; 95% CI 0.42 to 1.01) in children receiving vitamin A compared to those receiving placebo (Figure 6).

Disease severity

One study (Stephensen 1998) assessed disease severity during hospitalization by using a clinical severity score that consisted of 12 variables. Commencing measurement at 24 hours post-treatment, the mean blood oxygen saturation levels of the placebo group

increased to a higher level than the mean levels for the vitamin A group, and this difference persisted throughout hospitalization ($P = 0.003$ for treatment period). Significantly more children in the vitamin A group than in the placebo group eventually required supplementary oxygen ($P < 0.0005$ for the treatment period). The mean respiratory rate ($P < 0.0005$ for the treatment period) and heart rate ($P = 0.001$ for the treatment period) were significantly higher in the vitamin A group than in the placebo group when compared over time. The prevalence of auscultatory evidence of consolidation was initially the same in both groups but the prevalence decreased steadily in the placebo group while staying nearly constant in the vitamin A group, resulting in a significant difference between the groups ($P = 0.0014$ for the treatment period).

Adverse events

Three studies reported adverse effects of vitamin A intake. Four children (four out of 99) were observed with bulging fontanelle in Nacul 1997; none in the placebo group. The difference was not statistically significant (OR 8.25; 95% CI 0.44 to 155.37). The incidence of vomiting was 27 of 171 in the vitamin A group and 34 of 167 in the placebo group of one study (Nacul 1997); and one of 47 in the vitamin A group and none of 45 in the placebo group in a second study (Stephensen 1998). There was no statistical significance in the pooled analysis across these two studies (OR 0.77; 95% CI 0.45 to 1.33). The incidence of diarrhea was 19 of 206 in the vitamin A group and 30 of 199 in the placebo group (Nacul 1997); there was no statistical significance (OR 0.57; 95% CI 0.31 to 1.05). The incidence of irritability (Nacul 1997) was 38 of 157 in the vitamin A group and 38 of 149 in the placebo group. No statistical significance was apparent (OR 0.93; 95% CI 0.56 to 1.57). Nausea was observed in one child from each group (Stephensen 1998) (Figure 8).

Figure 8. Forest plot of comparison: 1 Vitamin A versus control, outcome: 1.4 Adverse events.

DISCUSSION

Vitamin A supplementation appears to have had little effect on the clinical course of non-measles pneumonia in children. The lack of a clear beneficial effect after vitamin A treatment is a little surprising given the protective effects of vitamin A in pneumonia associated with measles.

Summary of main results

Headaches, loss of appetite, vomiting and bulging fontanelles in infants are some of the adverse effects known to occasionally occur with the administration of high doses of vitamin A. These symptoms are minor and transitory, with no known long-term effects, and require no special treatment (Yang 2009). From three included studies in this review (Fawzi 1998; Nacul 1997; Stephensen 1998), the incidence of toxicity as an adverse event was not statistically different between the vitamin A and placebo-treated groups.

There was a borderline relative increase in the placebo group of children who failed to respond satisfactorily to first line antibiotic treatment. However, only one study reported on this and whether it represents a consistent effect of vitamin A, or is the result of chance, needs further investigation.

Rodriguez (Rodriguez 2005) conducted a subgroup analysis according to the serum retinol concentration, and found vitamin A can shorten the duration of signs in children with normal serum retinol (> 200 ug/L) but no benefit in children with vitamin A deficiency. However, this trial did not report on the nutritional status and severity of illness, which may be confounding factors. This study also found the time to remission of respiratory signs did not differ significantly between the groups of normal weight children and underweight children. However, data regarding this issue were unavailable to review.

Supplemental vitamin A in a lower dose seems to result in a beneficial effect on recurrent bronchopneumonia. This finding was from one study of poor methodological quality and lacking nutritional information about the vitamin A status of included children (Zhang 1999). More well-designed, large RCTs are needed to support this positive finding.

Fawzi (Fawzi 1998) observed a trend towards a higher incidence of death in the vitamin A group (13 of 346 participants versus eight of 341 in the placebo group) although this was not statistically significant (OR 1.63; 95% CI 0.66 to 3.97). Stephensen (Stephensen 1998) reported more severe clinical scores in children receiving

vitamin A than those who received a placebo. We expect that studies in the future will provide more conclusive evidence.

The possible explanation for the lack of benefit of vitamin A in non-measles pneumonia is that the effects of vitamin A may be disease-specific, with vitamin A only being effective when pneumonia is complicated with measles.

Overall completeness and applicability of evidence

The benefit of vitamin A as an adjunct to the treatment of non-measles pneumonia was not clarified, but vitamin A might be

beneficial to children with high basal serum retinol. Further RCTs, possibly with measured vitamin A levels and varying vitamin A doses, may provide sufficient evidence to clarify the role of vitamin A in non-measles pneumonia.

Quality of the evidence

The quality of the evidence of outcomes, which include mortality and adverse events (rates of diarrhea, bulging fontanelles and irritability), have a higher quality (moderate); the quality of other evidence ranks from very low to low (see [Figure 9](#); [Figure 10](#); [Figure 11](#)).

Figure 9. Primary outcomes

Author(s): Wu TX

Date: 2010-07-10

Question: Should vitamin A be used for non-measle pneumonia in children?

Settings:

Bibliography: Wu TX, 10 July, 2010

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	vitamin A	control	Relative (95% CI)	Absolute		
Mortality												
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/730 (2.3%)	13/716 (1.8%)	OR 1.29 (0.63 to 2.66)	5 more per 1000 (from 7 fewer to 29 more)	⊕⊕⊕⊕ MODERATE	CRITICAL
						0.01%		0 more per 1000 (from 0 fewer to 0 more)				
						2.1%		6 more per 1000 (from 8 fewer to 33 more)				
Time with fever (measured with: hours of the fever to be cleared; Better indicated by lower values)												
3	randomised trials	serious ²	serious ³	no serious indirectness	serious ⁴	none	484	474	-	MD 1.11 lower (5.66 lower to 3.44 higher)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
Time with rapid respiratory rate, >40 breaths/min./day (Better indicated by lower values)												
2	randomised trials	no serious limitations	very serious ⁵	no serious indirectness	no serious imprecision	none	467	459	-	MD 0.03 higher (0.32 lower to 0.38 higher)	⊕⊕⊕⊕ LOW	IMPORTANT
Time with hypoxia, PO<95% per day (Better indicated by lower values)												
2	randomised trials	serious ⁶	serious ⁷	no serious indirectness	no serious imprecision	none	467	459	-	MD 0.07 higher (0.21 lower to 0.34 higher)	⊕⊕⊕⊕ LOW	IMPORTANT
Length of hospitalisation (days) (Better indicated by lower values)												
2	randomised trials	serious ⁸	no serious inconsistency	no serious indirectness	no serious imprecision	none	393	386	-	MD 0.08 higher (0.43 lower to 0.59 higher)	⊕⊕⊕⊕ MODERATE	
Time with positive findings on auscultation (Better indicated by lower values)												
2	randomised trials	serious ⁹	serious ¹⁰	no serious indirectness	no serious imprecision	none	139	139	-	MD 0.54 lower (1.14 lower to 0.05 higher)	⊕⊕⊕⊕ LOW	IMPORTANT
Time with cough (Better indicated by lower values)												
1	randomised trials	very serious ¹¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ¹²	20	18	-	not pooled	⊕⊕⊕⊕ VERY LOW	IMPORTANT

¹ Two trials with moderate risk and one trial with low risk of selection bias.

² A high quality trial shown different result with other two lower quality studies.

³ The confidence intervals were rather wide.

⁴ The results of two studies shown different trends.

⁵ One trial with moderate risk of selection bias and one with low risk.

⁶ The results between two studies shown a difference.

⁷ Two studies with moderate risk of selection bias.

⁸ One trial with high risk of selection bias and one with low risk.

⁹ The scores had a big difference between two studies.

¹⁰ The study with high risk of selection bias.

¹¹ Only one study reported this outcome.

¹² The study with high risk of selection bias.

Figure 10. Secondary outcomes

Author(s): Wu TX

Date: 2010-07-28

Question: Should Vitamin A be used for none-measles pneumonia in children?

Settings:

Bibliography: Wu TX

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin A	control	Relative (95% CI)	Absolute		
Time with positive findings at x-ray (Better indicated by lower values)												
1	randomised trials	serious	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	18	21	-	MD 0.9 higher (1.10 lower to 2.90 higher)	⊕⊕⊕⊕ LOW	CRITICAL
Short-term effects: slight improvement												
1	randomised trials	very serious	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	2/40 (5%)	18/40 (45%)	OR 0.06 (0.01 to 0.3)	403 fewer per 1000 (from 253 fewer to 442 fewer)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		
Long-term effects: no improvement (number of recurrences)												
1	randomised trials	very serious	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	3/40 (7.5%)	16/40 (40%)	OR 0.12 (0.03 to 0.46)	326 fewer per 1000 (from 165 fewer to 380 fewer)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
								40%		326 fewer per 1000 (from 165 fewer to 380 fewer)		
Change of antibiotic required												
1	randomised trials	serious	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	43/239 (18%)	59/233 (25.3%)	OR 0.65 (0.42 to 1.01)	73 fewer per 1000 (from 129 fewer to 2 more)	⊕⊕⊕⊕ LOW	IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 more)		

Figure 11. Adverse events and secondary outcome

Author(s): Wu TX
Date: 2010-07-28
Question: Should vitamin A be used for none-measles pneumonia in children?
Settings:
Bibliography: Wu TX

Quality assessment							Summary of findings				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	vitamin A	control	Relative (95% CI)	Absolute		
Vomiting												
2	randomised trials	no serious limitations	very serious	no serious indirectness	no serious imprecision	none	28/218 (12.8%)	34/212 (16%)	OR 0 (0 to 1.33)	160 fewer per 1000 (from 160 fewer to 42 more)	⊕⊕⊕⊕ LOW	IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 more)		
Diarrhoea												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	19/206 (9.2%)	30/199 (15.1%)	OR 0.57 (0.31 to 1.05)	59 fewer per 1000 (from 99 fewer to 6 more)	⊕⊕⊕⊕ MODERATE	IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 more)		
Building fontanelles												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	4/99 (4%)	0/87 (0%)	OR 0 (0 to 155.37)	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕⊕⊕ MODERATE	IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 more)		
Irritability												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	38/157 (24.2%)	38/149 (25.5%)	OR 0.93 (0.56 to 1.57)	14 fewer per 1000 (from 94 fewer to 95 more)	⊕⊕⊕⊕ MODERATE	IMPORTANT
								0%		0 fewer per 1000 (from 0 fewer to 0 more)		
Time of fever (serum retinol>200ug/L) (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious	reporting bias	25	27	-	MD 61.40 lower (119.1 to 3.7 lower)	⊕⊕⊕⊕ VERY LOW	IMPORTANT

Potential biases in the review process

We included English language and Chinese language articles only as we were unable to search articles in other languages. This might result in selection bias.

Agreements and disagreements with other studies or reviews

Similar findings were reported in a meta analysis (Brown 2004) which reviewed vitamin A for children aged from one month to six years with acute respiratory infections in low-income countries. Five studies including a total of 2177 children (1067 intervention, 1110 controls) were included in this meta analysis. There were no significant differences in any of the recovery measures or mortality between the intervention and control groups. Pooled results showed no statistical significant differences between the vitamin A group and placebo group: fever: 0.03 (-0.10 to 0.17);

oxygen requirement: -0.08 (-0.31 to 0.16); raised respiratory rate: -0.09 (-0.38 to 0.19); and hospital stay: -0.06 (-0.52 to 0.40). Mortality was below 2% in both groups, with a non-significant higher risk in the intervention group (odds ratio 1.16, 95% CI: 0.61 to 2.21).

AUTHORS' CONCLUSIONS

Implications for practice

From the evidence available at this time and given the lack of clinical benefit associated with vitamin A treatment in children with non-measles pneumonia, it is difficult to recommend vitamin A as an adjunctive therapy in this patient group, particularly if the risk of vitamin A deficiency is low.

Implications for research

Even though six studies met the inclusion criteria, the variability in the outcomes reported and measured meant that only results from a few studies were eligible for inclusion in the meta-analyses for each of the outcomes. This limited the power of the meta-analyses to detect statistically significant differences. Large RCTs reporting clinically important outcomes are needed to increase the likelihood of obtaining a true and precise estimate of the effect. However, dosage of vitamin A could also be important and RCTs with a risk-stratified population, that is children at high risk and low risk of vitamin A deficiency, and varying administered dosage

may provide evidence of the effectiveness of vitamin A treatment for non-measles pneumonia in children.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Fawzi 1998

Methods	Randomised block design, placebo controlled trial. Double-blind. Baseline was similar
Participants	Children between 6 and 60 months of age admitted to hospital with pneumonia as diagnosed by a paediatrician on the presence of cough and one or more of the following signs: respiratory rates ≥ 40 breaths (50 breaths for infants between the ages of 6 and 11 months) per minute, chest retractions, inability to eat or drink, the presence of decreased air entry, crackling sounds or dullness to percussion
Interventions	Children in vitamin A group received a dose of vitamin A at admission according to the age. Children > 1 year and infants were administered 1 ml (200,000 IU) and 0.5 ml (100,000 IU) of a vitamin A solution, respectively
Outcomes	Clinical outcomes: mortality, duration of hospitalization, time with rapid respiratory rate (> 40 breaths/minute), time with fever (> 37.8 C), time with hypoxia ($PO_2 < 90\%$)
Notes	Setting: Tanzania

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	The randomisation was described as "eligible children were randomly assigned in blocks of 20 to receive a dose of vitamin A or placebo", but how the allocation sequence was generated did not described in detail
Allocation concealment?	Unclear risk	Not mentioned

Fawzi 1998 (Continued)

Blinding? All outcomes except mortality	Low risk	The treatment regimens were prepared especially for the study, and the batch code was retained by the manufacturer until the end of the study
Incomplete outcome data addressed? All outcomes except mortality	Low risk	

Liu 1997

Methods	Both 'completed random method' and double-blind was mentioned	
Participants	4 groups with different interventions (selenium) were selected. Data in vitamin A group and placebo group were extracted. 18 children in vitamin A group and 21 in placebo group. All children were younger than 14 years old	
Interventions	Children in vitamin A group received a dose of vitamin A 150,000 IU orally	
Outcomes	Variate outcomes were used; we only extracted data from those that matched the inclusion criteria for this review: 1. clearance time of fever 2. remission time of cough 3. remission time of positive finding of auscultation 4. remission days of positive finding at chest X-ray	
Notes	Setting: Youyi Hospital, Beijing.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	"Completed random method" was mentioned but lacked a detailed description
Allocation concealment?	High risk	Not concealment mentioned
Blinding? All outcomes except mortality	Low risk	Double-blinding
Incomplete outcome data addressed? All outcomes except mortality	High risk	

Nacul 1997

Methods	Block randomisation, placebo controlled; double-blind. The baseline was broadly similar	
Participants	Children aged 6 to 59 months with a clinical diagnosis either admitted to hospital or treated as outpatients. The diagnosis of pneumonia was made after taking a detailed history and looking for signs of lung infection such as fever, tachypnoea, signs of dyspnoea and consolidation	

Vitamin A for non-measles pneumonia in children (Review)

Nacul 1997 (Continued)

Interventions	Children received a dose of vitamin A on admission to the trial and then again the following day. Children > 1 year and infants were administered 200,000 IU and 100,000 IU of vitamin A respectively. Children who received vitamin A supplements in the preceding month received a capsule (100,000 IU) on admission only
Outcomes	Clinical outcomes: mortality, episode of pneumonia, fever, tachypnoea, lung complications, other complications, hospital admission (for outpatients only), antibiotic change, vomiting, diarrhea, irritability, bulging fontanelle
Notes	Setting: Recife, north east Brazil

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	"Children were individually randomized into one of the two treatment groups. The randomisation was blocked into groups of four". There was no description for how the sequence was generated
Allocation concealment?	Unclear risk	No description about allocation concealment
Blinding? All outcomes except mortality	Low risk	The vitamin A or placebo capsules were put into small brown envelopes labelled with identification numbers
Incomplete outcome data addressed? All outcomes except mortality	Low risk	

Rodriguez 2005

Methods	Randomised block design, placebo controlled trial. Double-blind
Participants	Children between 2 and 59 months of age admitted to hospital with clinical pneumonia (confirmed by X-ray). Clinical pneumonia was defined as the presence of elevated respiratory rate (> 40/minute in children aged > 12 to 59 months; > 50/minute in children aged 2 to 12 months), fever (axial temperature > 37.5 C), cough or chest indrawing or both, and low oxygen saturation (pulse oximetry level < 90%), and at least one clinical sign by auscultation (for example, rales, wheezing, diminished breath sounds, bronchial breath sounds, or pleural rub)
Interventions	Children in vitamin A group received a dose of vitamin A 50,000 IU orally in children aged 2 to 12 months; 100,000 IU orally in children aged > 12 to 59 months
Outcomes	Clinical outcomes: mortality, time to remission of signs, the duration of respiratory sign, resolution of focal infiltrates at 72 hours
Notes	Setting: Baca Ortiz Children's Hospital, Quito, Ecuador

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	The allocation sequence was generated by a random number table

Vitamin A for non-measles pneumonia in children (Review)

Rodriguez 2005 (Continued)

Allocation concealment?	Low risk	The Ethical Committee of the Corporación Ecuatoriana de Biotecnología held the blinded randomisation codes in a secure place. The study code was not broken until all the data were entered and the initial analyses performed
Blinding? All outcomes except mortality	Low risk	Double-blinding
Incomplete outcome data addressed? All outcomes except mortality	Low risk	48 children (16.7%) were lost to follow-up during the course of the study

Stephensen 1998

Methods	Randomised block design, placebo controlled trial. Double-blind	
Participants	Children between 3 months and 10 years of age with a principal diagnosis of pneumonia (confirmed by X-ray) admitted as inpatients to the paediatrics ward. A purified protein derivative (PPD) skin test was applied at the time of admission to the paediatrics ward and was read 48 hours later. 47 in vitamin A group and 48 in placebo group	
Interventions	Children < 1 year received 100,000 IU (2 ml of water-miscible preparation) of vitamin A on admission to the study and 50,000 IU (1 ml) on the second day of hospitalization. Children ≥ 1 year of age received 200,000 IU (4 ml) on the first day and 100,000 (2 ml) on the second day	
Outcomes	Clinical outcomes: temperature, heart rate, respiratory rate, presence or absence of retractions, occurrence of central cyanosis, percent of blood oxygen saturation, use of supplemental oxygen Other: food consumed, mother's impression of child's appetite	
Notes	Setting: Lima, Peru	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Did not mention any means of sequence generation, but block randomisation was mentioned
Allocation concealment?	Unclear risk	Did not mention any means of allocation concealment
Blinding? All outcomes except mortality	Low risk	Double-blinding
Incomplete outcome data addressed? All outcomes except mortality	Low risk	In placebo group 3 participants were excluded after randomisation due to positive PPD tests, 2 participants were withdrawn from additional data collection because of complications of their infection at day 10 (placebo) and day 14 (vitamin A). One participant was withdrawn from the placebo group during the first hospital day because of medical complications

Zhang 1999

Methods	Quasi-randomised parallel design, placebo-controlled trial. Children were allocated into two groups by the order of admission. No blinding
Participants	80 children between 1 and 3 years old with recurrent bronchopneumonia were equally allocated to two groups. Diagnosis of pneumonia was confirmed by X-ray
Interventions	Same routine therapy, including antibiotics, anti-symptoms drugs, given in both groups. Oxygen was given for children with hypoxic and digitalis was given for children with heart failure. In addition to these, vitamin A was added for the vitamin A group with 10,000 IU, b.i.d. orally for 6 days, then 1500 IU/d for 20 days
Outcomes	<p>Short-term effect:</p> <ol style="list-style-type: none"> 1. Marked improvement: all symptoms of pneumonia improved within 6 days, whilst no positive finding at chest X-ray 2. Improvement: 7 to 9 days after treatment, all of symptoms in remission and no positive finding at chest X-ray 3. Slight improvement: symptoms in remission after more than 10 days, but no change at chest X-ray <p>Long-term effects:</p> <ol style="list-style-type: none"> 1. Marked improvement: no recurrence of bronchopneumonia during 1 year post-treatment 2. Improvement: bronchopneumonia recurred 1 to 2 times during 1 year post-treatment 3. No improvement: bronchopneumonia recurred 3 times or more during 1 year post-treatment
Notes	Setting: Sihong County, Jiangsu, China

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	Quasi-randomisation
Allocation concealment?	High risk	D - Not used

IU = international units
PO₂ = blood oxygen level
b.i.d. = twice daily
/d = per day

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Anonymous 1991	Patients had pneumonia complicated by measles
Barreto 1994	Vitamin A administered prior to pneumonia diagnosis
Basu 2003	Vitamin A administered prior to pneumonia diagnosis
Bhandari 1997	Vitamin A administered prior to pneumonia diagnosis
Biesalski 2001	Not a RCT
Biswas 1994	Vitamin A administered prior to pneumonia diagnosis

Study	Reason for exclusion
Bresee 1996	Participants included were children with lower respiratory tract diseases not just pneumonia
Buyukgebiz 1990	Clinical outcomes not reported
Chen 2005	The study compared the efficacy of vitamin A administered intravenously and orally
Coles 2001	Vitamin A administered prior to pneumonia diagnosis
Coutsoudis 2000	Vitamin A administered prior to pneumonia diagnosis
Daulaire 1992	Vitamin A administered prior to pneumonia diagnosis
Dibley 1996	Vitamin A administered prior to pneumonia diagnosis
Donnen 1998	Vitamin A administered prior to pneumonia diagnosis
Dowell 1996	Participants included were children with lower respiratory tract diseases not just pneumonia
Dudley 1997	Not a RCT
Fauveau 1992	Not a RCT
Fawzi 1995	Vitamin A administered prior to pneumonia diagnosis
Fawzi 1999	Duplicate patient groups
Fawzi 2000	Duplicate patient groups
Fu 2005	Not a RCT
Ghana VAST team 1993	Vitamin A administered prior to pneumonia diagnosis
Hadi 1999	Vitamin A administered prior to pneumonia diagnosis
Humphrey 1996	Vitamin A administered prior to pneumonia diagnosis
Julien 1999	Participants included were children with lower respiratory tract diseases not just pneumonia
Junhong 1997	Not a RCT
Kao 1996	Although 'randomized allocation' was mentioned, by asking the trial author we understand that the method of randomisation was 'convenience' allocation; not a real RCT
Kartasmita 1995	Vitamin A administered prior to pneumonia diagnosis
Khandait 2000	Not a RCT
Kjolhede 1995	Subjects included were children with lower respiratory tract diseases - not just pneumonia but also bronchiolitis
Li 2004	Not a real RCT, although 'randomisation' was mentioned
Lie 1993	Vitamin A administered prior to pneumonia diagnosis

Study	Reason for exclusion
Lin 1999	'Random' was mentioned, but by asking the trial author we discovered that 'random' meant 'sampling' so this was not a RCT
Liu 2002	Not a RCT
Lloyd 1991	Not a RCT
Long 2006	Vitamin A administered prior to pneumonia diagnosis
Long 2007	Vitamin A administered prior to pneumonia diagnosis
Ma 2000	'Randomised allocation' was mentioned, but by asking the trial author we discovered they performed a convenience allocation
Mahalanabis 2001	Not a RCT
Qin 1999	'Randomised' was mentioned. We asked the trial authors and understood that the method of randomisation was 'convenience' allocation, not a real RCT
Quinlan 1996	Participants included were children with lower respiratory tract disease rather than pneumonia
Rahman 2001	Vitamin A administered prior to pneumonia diagnosis
Rahmathullah 1991	Vitamin A administered prior to pneumonia diagnosis
Ramakrishnan 1998	Not a RCT
Roy 1997	Vitamin A administered prior to pneumonia diagnosis
Ruz 1995	Vitamin A administered prior to pneumonia diagnosis
Semba 1993	Vitamin A administered prior to pneumonia diagnosis
Semba 1995	Not a RCT
Semba 1999	Not a RCT
Sempertegui 1999	Vitamin A administered prior to pneumonia diagnosis
Shah 1994	Not a RCT
Si 1997	Patients had pneumonia complicated by measles
Stansfield 1993	Vitamin A administered prior to pneumonia diagnosis
Stephensen 2002	Clinical outcomes not reported
Tomkins 2000	Not a RCT
Velasquez 1995	Clinical outcomes not reported
Vijayaraghavan 1990	Vitamin A administered prior to pneumonia diagnosis
Villamor 2000a	Not a RCT

Study	Reason for exclusion
Villamor 2000b	Duplicate patient groups
Wang 2003a	Not a real RCT
Wang 2003b	Duplicate publication of Wang 2003a, and not a real RCT
West 1991	Vitamin A administered prior to pneumonia diagnosis
Willumsen 1997	Not a RCT
Winkler 2005	Vitamin A administered prior to pneumonia diagnosis
Wu 2000	'Randomised' was mentioned, but by asking the trial author we understand that the method of randomisation was 'convenience' allocation; not a real RCT
Yang 2002	Non-randomised controlled study
Ying 1998	Although 'randomized' was mentioned, we asked the trial author and understand that the method of randomisation was 'convenience' allocation; not a real RCT
Zhen 2003	'Randomised' was mentioned, we asked the trial author and understand that the method of randomisation was 'convenience' allocation; not a real RCT

DATA AND ANALYSES

Comparison 1. Vitamin A versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality during hospitalisation	3	1446	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.29 [0.63, 2.66]
2 Time with signs of pneumonia and treatment issues (continuous)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Time with fever	3	958	Mean Difference (IV, Fixed, 95% CI)	-1.11 [-5.66, 3.44]
2.2 Time with rapid respiratory rate, > 40 breaths/min/day	2	926	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.32, 0.38]
2.3 Time with hypoxia, PO ₂ < 95% per day	2	926	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.21, 0.34]
2.4 Length of hospitalisation (days)	2	779	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.43, 0.59]
2.5 Time with positive findings on auscultation	2	278	Mean Difference (IV, Fixed, 95% CI)	-0.54 [-1.14, 0.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.6 Time with cough	1	38	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-3.51, -0.49]
2.7 Time with positive findings at x-ray	1	39	Mean Difference (IV, Fixed, 95% CI)	0.90 [-1.10, 2.90]
3 Time with signs of pneumonia and treatment issues (dichotomous)	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Short-term effects: slight improvement	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.06 [0.01, 0.30]
3.2 Long-term effects: no improvement (number of recurrences)	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.12 [0.03, 0.46]
3.3 Change of antibiotic required	1	472	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.42, 1.01]
4 Adverse events	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Vomiting	2	430	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.45, 1.33]
4.2 Diarrhoea	1	405	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.31, 1.05]
4.3 Bulging fontanelles	1	186	Odds Ratio (M-H, Fixed, 95% CI)	8.25 [0.44, 155.37]
4.4 Irritability	1	306	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.56, 1.57]
5 Time with fever, tachypnoea and hypoxaemia of pneumonia (serum retinol > 200 ug/L)	1	52	Mean Difference (IV, Fixed, 95% CI)	-61.40 [-119.10, -3.70]

Analysis 1.1. Comparison 1 Vitamin A versus control, Outcome 1 Mortality during hospitalisation.

Analysis 1.2. Comparison 1 Vitamin A versus control, Outcome 2 Time with signs of pneumonia and treatment issues (continuous).

Analysis 1.3. Comparison 1 Vitamin A versus control, Outcome 3 Time with signs of pneumonia and treatment issues (dichotomous).

Analysis 1.4. Comparison 1 Vitamin A versus control, Outcome 4 Adverse events.

Analysis 1.5. Comparison 1 Vitamin A versus control, Outcome 5 Time with fever, tachypnoea and hypoxaemia of pneumonia (serum retinol > 200 ug/L).

APPENDICES

Appendix 1. Embase search strategy

14. #10 AND #13
13. #11 OR #12
12. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEAR/2 (blind* OR mask*)):ab,ti
11. 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
10. #4 AND #9
9. #5 OR #6 OR #7 OR #8
8. (respiratory NEAR/2 (acute OR infection OR disease)):ab,ti
7. 'respiratory tract infection'/de OR 'lower respiratory tract infection'/exp
6. pneumon*:ab,ti
5. 'pneumonia'/exp
4. #1 OR #2 OR #3
3. 'diet supplementation'/exp
2. 'vitamin a':ab,ti OR retinol:ab,ti
1. 'retinol'/exp

Appendix 2. LILACS search strategy

Mh vitamin a OR Tw vitamin a OR Tw vitamina a OR Tw retinol OR Mh dietary supplements OR Tw dietary supplement\$ OR Tw suplementos dieteticos [Words] and Mh pneumonia OR Mh aspiration pneumonia or Mh bronchiolitis obliterans organizing pneumonia or Mh cryptogenic organizing pneumonia or Mh eosinophilic pneumonia or Mh lobar pneumonia or Mh mycoplasma pneumonia or Mh pneumocystis pneumonia or Mh staphylococcal pneumonia or Mh ventilator-associated pneumonia or Mh pneumonia aspiration or Mh pneumonia, bacterial or Mh pneumonia, eosinophilic or Mh pneumonia, interstitial or Mh pneumonia, interstitial plasma cell or Mh pneumonia, lipid or Mh pneumonia, lobar or Mh pneumonia, mycoplasma or Mh pneumonia, pneumococcal or Mh pneumonia,

pneumocystis or Mh pneumonia, primary atypical or Mh pneumonia, radiation or Mh pneumonia, staphylococcal or Mh pneumonia, ventilator-associated or Mh pneumonia, viral or Mh chlamydia pneumoniae or Mh chlamydophila pneumoniae or Mh diplococcus pneumoniae or Mh klebsiella pneumoniae or Mh meningitis, streptococcus pneumoniae or Mh mycoplasma pneumoniae or Mh streptococcus pneumoniae or Mh streptococcus pneumoniae infections or Mh idiopathic interstitial pneumonias OR Tw pneumon\$ OR Tw neumon\$ [Words] and ((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535\$ OR (Tw clin\$ AND (Tw trial\$ OR Tw ensa\$ OR Tw estud\$ OR Tw experim\$ OR Tw investiga\$)) OR ((Tw singl\$ OR Tw simple\$ OR Tw doubl\$ OR Tw doble\$ OR Tw duplo\$ OR Tw trebl\$ OR Tw trip\$) AND (Tw blind\$ OR Tw cego\$ OR Tw ciego\$ OR Tw mask\$ OR Tw mascar\$)) OR Mh placebos OR Tw placebo\$ OR (Tw random\$ OR Tw randon\$ OR Tw casual\$ OR Tw acaso\$ OR Tw azar OR w aleator\$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337\$ OR Mh follow-up studies OR Mh prospective studies OR Tw control\$ OR Tw prospectiv\$ OR Tw volunt\$ OR Tw volunteer\$) AND NOT (Ct animal AND NOT (Ct human and Ct animal))) [Words]

Appendix 3. CINAHL search strategy

S22 S11 and S21
S21 S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20
S20 TI (random* or placebo*) or AB (random* or placebo*)
S19 (MH "Quantitative Studies")
S18 (MH "Placebos")
S17 (MH "Random Assignment")
S16 AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)
S15 TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)
S14 TI clinic* W1 trial* or AB clinic* W1 trial*
S13 PT clinical trial
S12 (MH "Clinical Trials+")
S11 S5 and S10
S10 S6 or S7 or S8 or S9
S9 TI (respiratory N2 infection OR respiratory N2 acute OR respiratory N2 disease) or AB (respiratory N2 infection OR respiratory N2 acute OR respiratory N2 disease)
S8 (MH "Respiratory Tract Infections")
S7 TI pneumon* or AB pneumon*
S6 (MH "Pneumonia+")
S5 S1 or S2 or S3 or S4
S4 TI (vitamin a or retinol) or AB (vitamin a or retinol)
S3 (MH "Dietary Supplements")
S2 (MH "Vitamin A Deficiency")
S1 (MH "Vitamin A+")

Appendix 4. Biosis Previews (Thomson ISI) search strategy

Topic=("vitamin a" or retinol or dietary supplement*) AND Topic=(pneumon*)
Refined by: Topic=(random* or placebo* or clinical trial* or singl* blind* or doubl* blind*)
Timespan=2007-2010.

Appendix 5. Current Contents (Thomson ISI) search strategy

Topic=("vitamin a" or retinol or dietary supplement*) AND Topic=(pneumon*)
Refined by: Topic=(random* or placebo* or clinical trial* or singl* blind* or doubl* blind*)
Timespan=2007-2010.

Appendix 6. Original search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 3); MEDLINE (1996 to August Week 2, 2007); EMBASE (1990 to January 2007); LILACS (6 May 2007); CINAHL (1990 to August 2007); Biological Abstracts (1990 to July 2007); Current Contents (1990 to May 2007); and the Chinese Biomedicine Database (CBM) (1994 to June 2007).

We ran the following search strategy in CENTRAL and MEDLINE in combination with the highly sensitive search strategy developed by the Cochrane Collaboration for identifying randomised controlled trials (Dickersin 1994). The search strategy was modified to search the other electronic databases.

MEDLINE (OVID)

1. exp vitamin A/

2. vitamin A.mp
3. retinol.mp
4. exp dietary supplements/
5. or/1-4
6. exp pneumonia/
7. pneumonia\$.mp
8. exp pneumonia, bacterial/
9. exp pneumonia, lipid/
10. exp pneumonia, mycoplasma/
11. exp pneumonia, pneumococcal/
12. exp pneumonia, rickettsial/
13. exp pneumonia, staphylococcal/
14. exp pneumonia, viral/
15. exp respiratory tract infections/
16. acute adj respiratory.mp
17. respiratory adj infection.mp
18. respiratory adj disease.mp
19. or/6-18
20. 5 and 19

In addition to electronic databases, we searched reference lists. There were no language or publication restrictions.

WHAT'S NEW

Date	Event	Description
10 July 2010	New search has been performed	Searches conducted. No new trials were included or excluded in this update.

HISTORY

Protocol first published: Issue 2, 2002

Review first published: Issue 3, 2005

Date	Event	Description
9 January 2008	Amended	Converted to new review format.
9 August 2007	New search has been performed	Searches conducted. Contact details updated. In this updated review, we included one new trial (Rodriguez 2005) and excluded five trials (Chen 2005 ; Fu 2005 ; Long 2006 ; Long 2007 ; Winkler 2005). The included trial reported that moderate vitamin A was associated with a significant reduction in the time to remission of signs in children with normal serum retinol (> 200 ug/L). The conclusions remain unchanged.

CONTRIBUTIONS OF AUTHORS

Taixiang Wu (TW) was responsible for drafting, editing, commenting, making amendments and updating this review.

Juan Ni (JN) was responsible for searching for studies, data extraction and analysis and drafting the review.

Jiafu Wei (JW) was responsible for searching for studies and data extraction.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Chinese Cochrane Center, Chinese Centre of Evidence-Based Medicine, West China Hospital of Sichuan University, China.

External sources

- China Medical Board of New York, USA.

NOTES

1. We used new standards of quality assessment described in new *Cochrane Handbook of Systematic Reviews of Interventions*.
2. We included a summary findings table result using GRADEprofiler to assess the quality of evidence.

INDEX TERMS

Medical Subject Headings (MeSH)

Developing Countries; Measles; Pneumonia, Viral [*drug therapy]; Randomized Controlled Trials as Topic; Vitamin A [*therapeutic use]; Vitamins [*therapeutic use]

MeSH check words

Child; Humans; Infant