Vitamin A for treating measles in children (Review)

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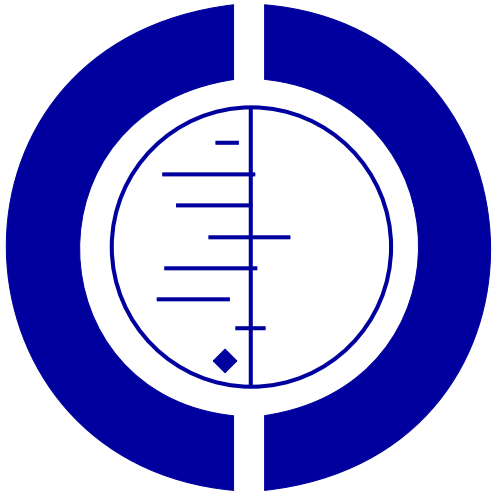

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ABSTRACT

Background
Measles is a major cause of childhood morbidity and mortality. Vitamin A deficiency is a recognized risk factor for severe measles infections. The World Health Organization (WHO) recommends administration of an oral dose of vitamin A (200,000 international units (IU), or 100,000 IU in infants) each day for two days to children with measles when they live in areas where vitamin A deficiency may be present.

Objectives
To determine whether vitamin A therapy, commenced after measles has been diagnosed, is beneficial in preventing mortality, pneumonia and other secondary complications in children.

Search strategy
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2005), MEDLINE (1966 to March 2005), EMBASE (1980 to December 2004) and looked for unpublished studies.

Selection criteria
Only randomized controlled trials in which children with measles were given vitamin A or placebo along with standard treatment were considered.

Data collection and analysis
Studies were assessed independently by two authors. The analysis of dichotomous outcomes was done using the StatXact software and results expressed as relative risk (RR) with 95% confidence interval (CI). Subgroup analyses were carried out for dose, formulation, age, hospitalization and pneumonia-specific mortality. Weighted mean differences (WMD) with 95% CI were calculated for continuous outcomes.

Main results
There was no significant reduction in the risk of mortality in the vitamin A group when all the studies were pooled using the random-effects model (RR 0.70; 95% CI 0.42 to 1.15). Using two doses of vitamin A (200,000 IU) on consecutive days was associated with a reduction in the risk of mortality in children under the age of two years (RR 0.18; 95% CI 0.03 to 0.61) and a reduction in the risk of pneumonia-specific mortality (RR 0.33; 95% CI 0.08 to 0.92). There was no evidence that vitamin A in a single dose was associated with a reduced risk of mortality among children with measles. There was a reduction in the incidence of croup (RR 0.53; 95% CI 0.29 to 0.89) but no significant reduction in the incidence of pneumonia (RR 0.92; 95% CI 0.69 to 1.22) or diarrhoea (RR 0.80; 95% CI 0.27 to 2.34) with two doses.

Authors' conclusions
Although we found no overall significant reduction in mortality with vitamin A therapy for children with measles there was evidence that two doses were associated with a reduced risk of mortality and pneumonia-specific mortality in children under the age of two years. There were no trials that directly compared a single dose with two doses.

SYNOPSIS

Two megadoses of vitamin A lowers the risk of death from measles in hospitalized children under the age of two years, but not in all children with measles

Measles is caused by a virus and results in a high fever and rash. Possible complications include pneumonia. Measles is a major cause of death in children in developing countries and is particularly dangerous for children with a vitamin A deficiency. This review found that there was no significant reduction in mortality in children receiving vitamin when all the studies were pooled together. However, vitamin A megadoses (200,000 international units on each of two days) lowered the number of deaths from measles in hospitalized children who were under the age of two years. A single dose did not lower death rates.

BACKGROUND

Measles is still a major cause of childhood morbidity and mortality in some developing countries. The fatality rates in hospitalized children often exceeds 10% (Morley 1969a) and case fatality ratios of up to 20% have been found in community studies in West Africa (Aaby 1984). An estimated 36.5 million cases and 1 million deaths caused by measles still occur each year. About half of these deaths occur in Africa (MMWR 1998). Measles is by no means limited to developing countries. There were 1750 cases reported in the Netherlands in 1999 despite a 96% immunization rate in children over 14 months of age (Sheldon 2000).

Ellison (Ellison 1932) first documented the protective effect of vitamin A on measles mortality almost 70 years ago. Barclay's study (Barclay 1987) drew attention to the importance of vitamin A therapy in reducing measles mortality and led to the 1987 World Health Organization (WHO) recommendation. In 1987, WHO and the United Nations International Children's Fund (UNICEF) jointly recommended administration of a single oral dose of vitamin A (200,000 IU, or 100,000 IU in infants) at the time of initial measles diagnosis in non-xerophthalmic children who lived in areas where measles case fatality rates were greater than 1% (WHO 1988). In 1993, WHO expanded its recommendation to vitamin A being given to all cases of severe measles; the dose remained the same (WHO 1993). There was sufficient evidence at that time to demonstrate that vitamin A supplementation reduced childhood mortality and morbidity (Sommer 1996) but there were only two studies demonstrating the effect of vitamin A in the treatment of children with measles. Hussey's work (Hussey 1990) confirmed that treatment with vitamin A reduced measles morbidity and mortality. In 1997, WHO and UNICEF recommended that 200,000 IU of vitamin A be given twice to children with measles who were over the age of one year and lived in populations where vitamin A deficiency may be present (WHO 1997).

Vitamin A deficiency is a recognized risk factor for severe measles (Frieden 1992). It is also biologically possible for vitamin A to be of benefit in measles (Anonymous 1987). Vitamin A can, therefore, be used for the treatment of measles and may be beneficial either by reducing the effects of measles infection (therapeutic effect) or preventing the subsequent development of secondary infection (protective effect), or both (Coutsoudis 1991).

Measles can decrease serum concentrations of vitamin A in well-nourished children to levels less than those observed in malnourished children without measles (Inua 1983). There could be two mechanisms of how this hyporetinemia occurs in measles. One explanation that has been postulated is through depletion of hepatic stores. Another possible explanation could be that vitamin A is not mobilized fast enough, even in the presence of adequate hepatic stores (Hussey 1990). This could be the reason for the hyporetinemia in children with severe measles living where vitamin A deficiency is uncommon, as in Zaire (Markowitz 1989), Cape Town (Hussey 1990) and Nairobi (Ogaro 1993). Retinol concentrations have been found to be depressed in children with measles even in industrialized countries like the US. The degree of retinol depression was associated with the severity of illness (Butler 1993).

Vitamin A is essential for the maintenance of normal epithelial tissues throughout the body (Wolbach 1925). Measles is a viral disease that infects and damages these tissues (Morley 1969a). Vitamin A deficiency is known to depress the immune function and destroy epithelial tissue; and measles produces similar effects (Coutsoudis 1991). The combined effect of vitamin A deficiency and measles infection could be serious. Therefore, when a child who has marginal vitamin A stores gets measles the already depleted vitamin A stores are exhausted thereby reducing the ability to resist secondary infection or their consequences (Bhaskaram 1975). This would also further accentuate the reduction of immunocompetence that is associated with measles infection (Whittle 1979).

In Asia, measles was found to be an important risk in severe vitamin A deficiency (Tielsch 1984). In a number of community studies in Asia, vitamin A deficiency has been linked to an increased risk of childhood morbidity (Bloem 1990; Milton 1987; Sommer 1984) and mortality (Sommer 1983). Reductions in mortality of 6% to 54% were reported in children who were given vitamin A (Daulaire 1992; Muhilal 1988a; Rahmathullah 1990; Sommer 1986; Vijayaraghavan 1990; West 1991). In four studies that reported large reductions in mortality, measles mortality fell but the acute respiratory infection (ARI) mortality did not change

(Daulaire 1992; Rahmathullah 1990; VAST Study 1993; West 1991).

Some studies have found vitamin A to have little effect on morbidity, while causing a significant reduction in mortality (Rahmathullah 1990; Rahmathullah 1991; Sommer 1986). Other studies reported no significant effect on morbidity or mortality (Dollimore 1997; Vijayaraghavan 1990) even though they were sufficiently large to do so. In some clinical trials vitamin A reduced the severity of illness and mortality in children with measles (Barclay 1987; Coutsoudis 1991; Hussey 1990) even in areas where eye signs of vitamin A deficiency were rare (VAST Study 1993).

A meta-analysis (Glasziou 1993) on the role of vitamin A supplementation for infectious diseases found that vitamin A reduced all-causes mortality in children in developing countries by around one third. A similar but apparently stronger (reduction of 66%) effect was seen in children hospitalized with measles, although this was not significantly different from the 30% seen in developing country community settings. The reduction in deaths from respiratory diseases was seen only in the measles studies. The results of this meta-analysis supports the 1987 WHO recommendation to give vitamin A to children in countries where vitamin A deficiency is a recognized problem (WHO 1987). Since then new trials have been published.

In another meta-analysis of 12 controlled trials, including community preventative studies (Fawzi 1993), vitamin A supplementation for hospitalized measles patients (children) was found to be highly protective against mortality. The most recent review (Beaton 1993) concludes that " ... in the specific case of measles, there is evidence that improvement of vitamin A status even after the onset of infection can improve both the course of the episode and the case fatality rate".

The World Bank (World Bank 1993) has declared vitamin A supplementation to be one of the most cost effective of all health interventions. Programs to control vitamin A deficiencies are now in place or in planning in more than 60 countries (Sommer 1997).

Despite, all this the situation is far from satisfactory. According to Ogaro, "the WHO recommendation of vitamin A supplementation has not been implemented in developing countries because vitamin A deficiency is usually identified because of high rates of xerophthalmia, a problem that exists in only selected places in the developing world. More commonly, developing country populations have inadequate or marginal vitamin A body stores without a high incidence of eye disease. Secondly, not all settings even in Africa have high measles case fatality rates and the usefulness of vitamin A supplementation where mortality and severe complications are much less frequent, has had limited study" (Ogaro 1993).

OBJECTIVES

To determine whether vitamin A is beneficial in preventing mortality, pneumonia and other secondary infections in children with measles.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomized controlled trials in which children with measles were given vitamin A or placebo along with standard treatment.

Types of participants

Children under the age of 15 years and of either gender with measles

Types of intervention

Vitamin A or placebo, given orally.

Types of outcome measures

As stated a priori (D'Souza 1999), outcomes were mortality; pneumonia-specific mortality; development of pneumonia, diarrhoea, croup and otitis media; and duration of hospitalization, fever, pneumonia and diarrhoea. The definition of pneumonia was a clinical case definition or by radiological confirmation.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: Acute Respiratory Infections Group search strategy

For the primary version of the review published in *The Cochrane Library* (Issue 1, 2001) the authors used the search strategy developed for the Acute Respiratory Infections Group (Cochrane 1999). A MEDLINE (PubMed) search was conducted in July 1999 (1994 to 1998). *The Cochrane Library* at that time (Issue 4, 1999) included search results of MEDLINE (1966 to 1997) and EMBASE (1974 to 1997). Keywords used were measles, vitamin A, randomized, controlled trial, respiratory disease, pneumonia, random allocation and clinical trial. Sixty-six references were found using this search strategy.

In this updated review we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2005) MEDLINE (1966 to March 2005) and EMBASE (1980 to December 2004). We also searched references of the available primary studies, review articles, and editorials to identify trials not found in the database searches. Two additional trials (Chowdhury 2002; Dollimore 1997) were found.

The following terms were used in MEDLINE and CENTRAL and the terms were adapted for EMBASE. The highly sensitive search strategy was combined with the MEDLINE search strategy (Dickersin 1994).

MEDLINE (OVID)
1 exp MEASLES/
2 exp MEASLES VIRUS/
3 measles.mp.
4 exp PNEUMONIA/
5 pneumonia.mp.
6 or/1-5
7 exp Vitamin A/
8 Vitamin A.mp.
9 retinol.mp.
10 or/7-9
11 6 and 10

Experts in the field were also contacted and one additional unpublished trial was found, but the data were unavailable (Lucero 1993). Trialists were contacted for missing data. Finally, a permanent search has been registered with Current Contents to notify the authors by e-mail of any new trials published in journals indexed by Current Contents. There were no language restrictions.

METHODS OF THE REVIEW

The authors independently selected the trials to be included in the review. Each author assessed the methodological quality of identified trials. In particular, authors examined details of the randomization method, concealment of the treatment-allocation schedule, whether the trial was blinded and whether intention-to-treat analyses were possible from the available data. Each author using standard data acquisition forms to independently extract data. When disagreement arose on the suitability of a trial for inclusion in the review, or on its quality, we tried to reach a consensus by discussion.

One hundred and eighteen references were found using the updated search strategy. From the abstracts 69 of these appeared to meet the inclusion criteria. Two authors rated the reports blinded, using the Jadad method (Jadad 1996) for assessing the quality of trials. The study by Chowdhury (Chowdhury 2002) found in the updating search was excluded and the study by Dollimore (Dollimore 1997) was included.

Only eight trials met the inclusion criteria. See the 'Characteristics of included studies' table for scores.

This method assigns points as follows.
1. Was the study described as randomized? (0 = no; 1 = yes)
2. Was the study described as double-blind? (0 = no; 1 = yes)
3. Was there a description of withdrawals and drop-outs? (0 = no; 1 = yes)
4. Was the method of randomization well described and appropriate? (0 = no; 1 = yes)
5. Was the method of double blinding well described and appropriate? (0 = no; 1 = yes)
6. Deduct 1 point if methods for randomization or blinding were inappropriate.

From this assessment eight trials, each with a score of three or more (out of a possible maximum of five), were included.

Although Ellison (Ellison 1932) is a large study (600 children) it received a low quality score because it was not randomized. Secondly, the quality of health care, availability of antibiotics and immunization have affected the incidence and case fatalities of measles quite substantially in the last 30 years; however, the case fatality rate is quite similar to that in studies done in Africa 60 years later. The other 21 studies were excluded not for their scores but because vitamin A was given to all children in communities and not just children with measles.

The scores from this assessment were used to do a sensitivity analysis (that is, including and excluding studies of low quality to determine how robust the summary effect measures were). Only one study (Ellison 1932) received a score of less than three and was included in the sensitivity analysis.

To assess the strength of the evidence for giving vitamin A to all children with measles, a meta-analysis was done of selected studies in which administration of vitamin A was compared with placebo. As the outcomes had small numbers the analysis for dichotomous outcomes was done using the StatXact software package (StatXact; Cytel Software Corporation Version 3.1, 1997). Odds ratios and their 95% confidence intervals (CI) were used to calculate the relative risks (RR) and 95% CI. The data used for calculating the odds ratios and 95% CI are given in the Review Manager graphs. Weighted mean differences (WMD) with 95% CI were calculated for continuous outcomes using the random-effects model in the Review Manager 4.2 software with MetaView 3.1.

A test for heterogeneity using a standard chi square statistic was performed. If a test for heterogeneity was negative then a weighted estimate of the typical treatment effect across trials was calculated. If, however, there was evidence of heterogeneity of the treatment effect between trials then either only homogeneous results were pooled or a random-effects model was used (in which case the confidence intervals would be broader than those of a fixed-effect model).

Subgroup analyses, determined a priori (D'Souza 1999), were carried out for: age, dosage, formulation (oil or water based), setting (hospital or community) and geographic area (varying measles case-fatality rates).

DESCRIPTION OF STUDIES

All included studies were published and included 2574 participants. There was considerable variation in the outcomes measured and reported in the studies. The only outcome reported by all

seven studies was death. Six of the studies (Barclay 1987; Coutsoudis 1991; Dollimore 1997; Hussey 1990; Ogaro 1993; Rosales 1996) were done in Africa, one in Japan (Kawasaki 1999) and one in England (Ellison 1932). Except for the community studies by Rosales and Dollimore, the studies were in hospitalized patients. One of the side effects of high doses of vitamin A is bulging fontanelles, evident in some very young infants (WHO 1998). However, no side effects were reported in any of the studies.

METHODOLOGICAL QUALITY

The quality of studies was generally high except for Ellison (Ellison 1932), which was not randomized and hence was only included in a sensitivity analysis. Five studies (Coutsoudis 1991; Dollimore 1997; Hussey 1990; Ogaro 1993; Rosales 1996) were double blinded. In Barclay's study (Barclay 1987) the staff and patients were blinded but not the treating physician who also assessed the outcomes.

RESULTS

As mentioned in the description of studies mortality was the only outcome reported by all trials. Nonetheless, all results have been reported, even those measured and reported by a single study.

It is clear that the studies were heterogeneous in several ways. They were of different durations, in slightly different age groups, using different doses of Vitamin A in different formulations (oil- or water-based), different settings (hospital or community), and different geographical areas with varying measles case-fatality rates. We attempted to take this into account by using subgroup analyses. This heterogeneity should make one cautious in interpreting the results.

1. Overall Mortality

Deaths were reported in all studies except Kawasaki. When the seven studies reporting on mortality (Barclay 1987; Coutsoudis 1991; Dollimore 1997; Hussey 1990; Kawasaki 1999; Ogaro 1993; Rosales 1996) were pooled together the summary estimate of the effect of vitamin A on the risk of mortality associated with measles was not significant (RR 0.83; 95% CI 0.51 to 1.34) (StatXact estimate). The study carried out by Barclay showed a 48% reduction (RR 0.52; 95% CI 0.16 to 1.40) and Hussey showed a statistically significant 79% reduction in the risk of mortality (RR 0.21; 95% CI 0.02 to 0.95). The study carried out by Dollimore showed there was no significant difference in risk of mortality (RR 1.22; 95% CI 0.65 to 2.30). The studies by Rosales and Ogaro were associated with no effect on the risk of mortality in the supplemented group.

Five of the studies were hospital-based and only the studies by Rosales and Dollimore were carried out in a community setting, in a group of patients with mild disease (i.e. outpatients). Barclay, Hussey and Coutsoudis used 200,000 IU of vitamin A on the first and second days. Coutsoudis gave two additional doses on days 8 and 42. These three studies in hospitalized patients (Barclay 1987; Coutsoudis 1991; Hussey 1990) used at least two doses of vitamin A and were associated with a statistically significant 64% reduction in risk of mortality (RR 0.36; 95% CI 0.13 to 0.82). These three studies were also done in areas where the hospital case-fatality rate was more than 10%. The Coutsoudis study had only one death but dropping this study did not change the summary estimate.

Two studies used water-based vitamin A formulations (Coutsoudis 1991; Hussey 1990) while the others used an oil-based formulation. When the studies that used the two-dose regimen were stratified by formulation (whether water- or oil-based) an 81% reduction in the risk of mortality (RR 0.19, 95% CI 0.02 to 0.85) was seen in studies that used water-based preparations. Dollimore used at least two doses of vitamin A and showed there was no significant difference in risk of mortality in the community between vitamin A-supplemented and placebo groups (RR 1.22; 95% CI 0.65 to 2.30).

The two studies (Ogaro 1993; Rosales 1996) that used an oil-based single dose of vitamin A (200,000 IU) were carried out in areas where the case fatality was less than 6% and were not associated with any reduction in the risk of mortality (RR 1.25; 95% CI 0.48 to 3.12). Vitamin A status appeared to be satisfactory and at least 30% of Ogaro's patients had vitamin A levels greater than 20 ?g/dl. These factors, in addition to the fact that a single dose of vitamin A was used in both studies, are probably the major reasons for perceived lack of efficacy of vitamin A treatment.

As part of a sensitivity analysis, when the study of poor methodological quality score (Ellison 1932) was included, vitamin A was associated with a 47% reduction in overall mortality (RR 0.53; 95% CI 0.33 to 0.83). The argument for including this study as part of the sensitivity analysis is that the mortality rates of 8.66 and 3.66 in the placebo and vitamin A groups, respectively, were less than what was observed in studies done almost 60 years later in Africa. This suggests that basic health care then was not dissimilar to that available in Africa in the 1980s and 1990s. The magnitude of mortality reduction in the Ellison study was remarkably similar to that of the other included studies.

Four of the eight studies reported the age distribution of the participants and the ages of those who died. There was an 83% reduction in risk of mortality (RR 0.17; 95% CI 0.03 to 0.61) in the vitamin A supplemented group in children under two years of age, in studies that used two doses of 200,000 IU of vitamin A (Barclay 1987; Coutsoudis 1991; Hussey 1990). The two-dose, oil-based vitamin A was associated with a statistically significant reduction in risk of mortality in the study by Barclay (RR 0.13; 95% CI 0.002 to 0.95) while the water-based preparations almost reached statistical significance (RR 0.23; 95% CI 0.02 to 1.01). There was no evidence of reduction in the risk of mortality in children older than two years (RR 0.94; 95% CI 0.23 to 3.1). Even

when the study by Ellison was included as part of the sensitivity analysis there was no reduction in the risk of mortality in children older than two years (RR 0.64; 95% CI 0.20 to 1.76).

Although the subgroup analyses were determined a priori these factors are highly correlated, which means that their effects cannot be separately identified; and sample sizes were also small. Three significant studies (Barclay 1987; Coutsoudis 1991; Hussey 1990) present most frequently in all the five subgroup analyses: dose, formulation, hospitalization, age and case fatality in the study area. They used two doses, hospitalized patients, children under the age of two and were carried out in areas where the case fatality is high. Only Barclay's study slightly deviates from the other two studies as he used an oil-based preparation rather than a water-based formulation. Therefore, the presence of correlated characteristics between these factors cannot be ruled out as the data cannot be stratified because the raw data was not available and, secondly, there were too few studies to stratify across the five subgroups. There were no trials comparing mortality reductions in children with measles who were given a single dose compared to two doses of vitamin A. However, the precision of the estimates from trials that used a single dose were similar to the trials that used two doses.

Pneumonia-specific mortality

Four studies specified the cause of death. Most of the deaths were due to pneumonia. In Ogaro's study (Ogaro 1993) all children who died had pneumonia as did 10 out of 18 in the Barclay study (Barclay 1987) and 10 of 12 in Hussey's study (Hussey 1990). The pooled estimate of the three studies which used two doses of vitamin A (oil- or water-based) (Barclay 1987; Coutsoudis 1991; Hussey 1990) suggests a 67% reduction in the risk of pneumonia-specific mortality (RR 0.33; 95% CI 0.08 to 0.92); none of these studies showed statistically significant reductions on their own. Water-based preparations showed no statistically significant reduction in the risk of pneumonia-specific mortality (RR 0.23; 95% CI 0.02 to 1.05). Ogaro's study used a single dose of vitamin D and did not show any benefit either.

2. Morbidity

2.1 Respiratory outcomes:

2.1.1 Post-measles croup

Four studies (Barclay 1987; Coutsoudis 1991; Hussey 1990; Ogaro 1993) reported on post-measles croup. From Tte summary estimate of the four studies, vitamin A was associated with a statistically significant 41% reduction in the risk of croup (RR 0.59; 95% CI 0.36 to 0.94). When these studies were stratified by dose, the reduction in the incidence of croup was greater for the three studies (Barclay 1987; Coutsoudis 1991; Hussey 1990) that used two doses of vitamin A (200,000 IU) (RR 0.53; 95% CI 0.29 to 0.89).

2.1.2 Development of pneumonia

Development of pneumonia was reported in only two studies (Kawasaki 1999; Ogaro 1993). These two studies individually did not show any statistical reduction in the incidence of pneumonia. The estimate in Ogaro's study was RR 0.68 (95% CI 0.28 to 1.36) and for Kawasaki's it was RR 0.97 (95% CI 0.66 to 1.18). These studies were not combined as they were carried out in completely different settings and used different doses.

2.1.3 Duration of pneumonia

Duration of pneumonia was reported in only two studies (Coutsoudis 1991; Hussey 1990). The summary estimate from these studies showed a reduction in the duration of pneumonia by more than three days in the vitamin A treated group but this was not statistically significant (WMD -3.69; 95% CI -7.53 to 0.16). Both studies were individually statistically significant. In Hussey's study there was almost six days reduction in duration of pneumonia in the vitamin A treated group (WMD -5.8; 95% CI -8.2 to -3.5) and two days reduction in the Coutsoudis study (WMD -1.9; 95% CI -2.2 to -1.6).

2.2 Other outcomes:

2.2.1 Development of diarrhoea

Only Barclay and Ogaro (Barclay 1987; Ogaro 1993) reported on the development of diarrhoea. The summary estimate from these studies showed a slight reduction in diarrhoea in the vitamin A treated group but this was not statistically significant (RR 0.96; 95% CI 0.53 to 1.63). In Barclay's study, which used two doses, there was a 65% reduction in risk of developing diarrhoea (RR 0.35; 95% CI 0.33 to 1.83) while there was no evidence of reduction in Ogaro's study, which used a single dose (RR 1.13; 95% CI 0.69 to 1.62).

2.2.2 Duration of diarrhoea

Two studies (Coutsoudis 1991; Hussey 1990) reported the duration of diarrhoea in days. The summary estimate of these studies shows a statistically significant reduction in duration of diarrhoea by almost two days in the vitamin A treated group (WMD -1.92; 95% CI -3.40 to -0.44).

2.2.3 Duration of fever

Two studies (Coutsoudis 1991; Kawasaki 1999) reported on the duration of fever, in days. Kawasaki showed a one and a half day statistically significant reduction in the duration of fever (WMD -1.5; 95% CI -2.04 to -0.96) while Coutsoudis showed a little over half a day (WMD -0.60; 95% CI - 0.81 to -0.39). These studies were not combined because they were carried out in completely different settings and used different doses of vitamin A.

2.2.4 Days in hospital

Hussey (Hussey 1990) showed a statistically significant reduction in hospital stay by almost five days in the vitamin A treated group (WMD -4.72; 95% CI -7.22 to 2.21) while Kawasaki (Kawasaki 1999) showed a reduction by almost half a day but this was not statistically significant (WMD -0.40; 95% CI -1.08 to 0.28). These studies were not combined because they were carried out in completely different settings and used different doses of vitamin A.

2.2.5 Herpes stomatitis

Hussey (Hussey 1990) and Coutsoudis (Coutsoudis 1991) reported on herpes stomatitis. Neither study showed any statistically significant reduction in the risk of developing herpes stomatitis. The estimate by Hussey showed a reduction (RR 0.23; 95% CI 0.05 to 1.06) while Coutsoudis showed an increased risk of developing herpes stomatitis (RR 1.60; 95% CI 0.29 to 8.92) with vitamin A.

The outcomes below were reported in single studies.

2.3 Respiratory outcomes

2.3.1 Recovery from pneumonia in less than eight days

Ogaro (Ogaro 1993) reported the number of patients that recovered from pneumonia in less than eight days. His study used a single dose of vitamin A and did not show any benefit (RR 0.99; 95% CI 0.78 to 1.15).

2.3.2 Pneumonia for more than 10 days

Hussey (Hussey 1990) reported the number of patients who had pneumonia for more than 10 days. This study used two doses and showed a 57% statistically significant reduction in the number of children in the vitamin A group who had pneumonia for more than 10 days (RR 0.43; 95% CI 0.20 to 0.83).

2.3.3 Pneumonia for 14 days

The study by Rosales (Rosales 1996) used a single dose of vitamin A and did not show any benefit on pneumonia continuing for two weeks (RR 1.24; 95% CI 0.76 to 1.82).

2.3.4 Days of cough

Kawasaki (Kawasaki 1999) alone reported the duration of cough, in days. The study showed a statistically significant reduction by two days in the vitamin A treated group (WMD -2.00; 95% CI -2.71 to -1.29).

2.3.5 Cough after two weeks

Rosales (Rosales 1996) reported on this outcome and there was an increased risk that the vitamin A group still had cough at the end of two weeks but this was not statistically significant (RR 1.54; 95% CI 0.75 to 2.81).

2.3.6 Development of acute laryngitis

Kawasaki (Kawasaki 1999) reported on this outcome and there was an increased risk in the vitamin A group of developing acute laryngitis but this was not statistically significant (RR 1.86; 95% CI 0.79 to 3.4).

2.3.7 Development of otitis media

Ogaro (Ogaro 1993) reported on the development of otitis media with a 74% reduction in the incidence of otitis media in vitamin A treated patients, which was statistically significant (RR 0.26; 95% CI 0.05 to 0.92).

2.4 Other outcomes

2.4.1 Recovery from diarrhoea in less than five days

Ogaro reported on this outcome and showed increased chances of recovery in the vitamin A supplemented group, which were statistically significant (RR 2.05; 95% CI 1.06 to 3.99).

2.4.2 Diarrhoea for more than ten days

Hussey (Hussey 1990) showed a statistically significant reduction of diarrhoea at 10 days in the vitamin A treated group (RR 0.41; 95% CI 0.14 to 0.89).

2.4.3 Diarrhoea for 14 days

Rosales (Rosales 1996) did not find any benefit in the vitamin A treated group (RR 0.00; 95% CI 0.0 to 2.54).

2.4.4 Complete clinical recovery

Coutsoudis (Coutsoudis 1991) found that the vitamin A group had a 1.5 times better chance of complete clinical recovery than the placebo group, which was statistically significant (RR 1.54; 95% CI 1.04 to 1.88).

2.4.5 Asymptomatic in week two

Rosales (Rosales 1996) found that at two weeks the vitamin A group did not show any benefit in terms of complete clinical recovery compared with the placebo group (RR 1.01; 95% CI 0.74 to 1.24).

2.4.6 Transferred to an intensive care unit

Hussey (Hussey 1990) reported that the vitamin A supplemented group had a lesser chance of being transferred to the intensive care unit but this was not statistically significant (RR 0.39; 95% CI 0.80 to 1.23).

DISCUSSION

The quality of the trials included in this review is high. The factors included in the subgroup analysis, of dose, formulation, setting and age, were highly correlated and three studies (Barclay 1987; Coutsoudis 1991; Hussey 1990) were strongly represented in these analyses.

Dose and formulation

This review demonstrates that vitamin A administered to children with measles and receiving standard treatment was associated with a reduction in mortality when children were under the age of two, hospitalized and the dose (200,000 IU) was repeated on the second day. The evidence partly supports the WHO recommendation of two 200,000 IU doses.

Although the data do not allow us to examine the individual effects of dose and formulation, these are issues that need to be considered. Vitamin A preparations in oil and in water are different in terms of their action in the body over a period of time because of differences in the processes of absorption, distribution, localization in tissues, bio-transformation and excretion. Water-based vitamin A preparations lead to greater absorption, which results in higher serum retinol levels. The oil-based preparation is more stable, readily available and costs less. For these reasons it is the latter that is recommended by WHO.

The Coutsoudis study and others (Inua 1983; Markowitz 1989; Reddy 1986b) support the finding that serum retinol concentra-

tions are lowered during measles. In Coutsoudis' study (Coutsoudis 1991) the supplemented group had significantly higher concentrations than the placebo group, which indicates that the liver stores were not depleted but that there was temporary impairment of mobilization and increased utilization of vitamin A.

The children in the Rosales (Rosales 1996) and Ogaro (Ogaro 1993) studies may not have benefited from receiving vitamin A oil-based preparations in a single dose (200,000 IU) as this might not have been sufficient to reverse the hyporetinemia occurring during measles; the dose may have been stored, mostly in the liver. Rosales reported a 70% increase in serum retinol after a single dose of oil-based vitamin A as compared to the 215% increase observed by Coutsoudis (Coutsoudis 1991) using two doses of water miscible vitamin A. The Rosales study was a community-based study and, therefore, the protective effect of vitamin A may not have been as great as seen in the more severe hospital-based cases.

The results in this review confirmed that two doses of vitamin A (200,000 IU) were associated with reductions in the risk of overall mortality and of pneumonia-specific mortality. In 1991, Rosales (Rosales 1996) came to the same conclusion as did Sommer, who suggested that it was prudent to follow the double-dose schedule already proven in the Barclay, Hussey and Coutsoudis trials rather than the single dose recommended by WHO at that time. Doubling the WHO dose was also advocated by Chan (Chan 1990) and Hussey (Hussey 1997). Although use of two doses and the water-based product was associated with a greater reduction in risk of mortality, no recommendation can be made as to whether a single dose of water-based preparation would have a similar benefit as no studies have been conducted looking at the effect of a single dose of water-based vitamin A as compared to two doses. Therefore, single-dose, water-based and oil-based preparations need to be compared to two-dose schedules. The trade off of using high-dose, oil-based vitamin A versus a water-based formula has to be viewed in terms of the advantages of each product. Although the water-based product may be associated with greater mortality reductions the advantage may be offset by its lower stability, higher cost, and non-availability.

One study (Barclay 1987) used two doses of oil-based vitamin A and the effect on overall mortality was not significant on its own, except for children under the age of two years. The evidence for oil-based vitamin A having a protective effect on mortality was demonstrated when an old study by Ellison with a lower quality score was included as part of the sensitivity analysis. Although this study used very small doses of vitamin A (3000 IU for 7 days) the supplemented group had statistically significant reductions in risks of mortality, even in the absence of antibiotics and immunization. This study was not randomized and two separate wards were allocated to receive the placebo or vitamin A supplementation. The study participants in this study could be comparable to the African children enrolled in the other five studies almost 60 years later as the case-fatality rates in the Ellison study were very similar, and in some cases, lower than the case fatality in the placebo and supplemented groups in some more recent studies.

The effect of vitamin A was more pronounced in children under the age of two years as a greater reduction in the risk of mortality was observed in this age group. This was seen across all studies but more so in the studies that used the two-dose regimen (Barclay 1987; Coutsoudis 1991; Hussey 1990). In children under the age of two years formulation did not make any difference as the oil-based product was associated with a statistically significant reduction in the risk of mortality and the water-based vitamin A effect almost reached statistical significance. The study by Markowitz et al (Markowitz 1989) highlighted the fact that children aged less than two years of age with low vitamin A levels had a higher risk of dying than those with higher levels; the number of children in the age group older than two years were too few to detect any statistically significant difference.

Case fatality rate in country of study

As the studies using two doses (Barclay 1987; Coutsoudis 1991; Hussey 1990) were from areas where case fatality was more than 10% it is important to be careful in generalizing the results. It raises the issue of whether the decrease in mortality was a result of the higher dose, or whether the vitamin A supplementation in higher case fatality areas had a greater effect, as there was a greater potential for mortality decline in those populations. It may be possible that there would be a decline in mortality even with a single dose of vitamin A in high case fatality areas and this needs to be further explored. Although in South Africa the measles case fatality was greater than 10% in hospitals Coutsoudis had low case-fatality rates in both the vitamin A and control groups. She remarked that this could be attributed to the absence of emergency and malnourished cases.

Hospital versus community studies

The protective effect of vitamin A supplementation was seen only in hospitalized children. Hospitalization may be a measure of severity of illness. There is the possibility that more severe clinical cases of measles are more likely to benefit from vitamin A treatment. Three of the four hospital-based studies (Barclay 1987; Coutsoudis 1991; Hussey 1990) which used the two dose regimen demonstrated a protective effect on mortality. These studies were done under controlled conditions and their follow up was relatively brief. Only the Coutsoudis study indicated some long-term benefit of vitamin A as children were followed for six months; the outcomes used for this review were at the time of discharge from hospital. These factors affect the generalizability of the results to the general population of patients with measles.

An absence of vitamin A effect, or a smaller effect, in the community studies (Dollimore 1997; Rosales 1996) may be due to the study populations being healthier than the studies in hospitals. The community studies did not include children who were very sick as they were referred for hospitalization. The Rosales and Dol-

limore studies differed from the other studies in patient setting, follow up, disease severity, patient age, vitamin A preparation used and analytical approach. They looked at ambulatory patients who were followed up closely for one month with daily and weekly visits to urban health centres. This reflects the patient-care conditions under which the majority of measles cases are diagnosed and treated in developing countries (Dollimore 1997; Rosales 1996).

Baseline differences and the presence of complications on admission

The demographic, nutritional, immunological and clinical status at baseline all affect the comparability between the vitamin A treated and control groups (Coutsoudis 1991). Although all the studies reported the baseline nutritional status of the vitamin A supplemented and placebo groups only Barclay specified the nutritional status of the children who died; vitamin A recipients suffered lower mortality at every nutritional level.

In the Ogaro study (Ogaro 1993) 10 children were severely malnourished in the vitamin A supplemented group and five children in the placebo group. This raises an issue about whether randomization balanced this important confounder. This could have been an important difference, possibly resulting in an inability to demonstrate a protective effect of vitamin A in the supplemented group. All the deaths in this study were due to pneumonia (five in the vitamin A group and three in the placebo group).

Five of the studies were carried out in Africa. The baseline prevalence of vitamin A deficiency and other baseline characteristics vary across countries and even within the same country, as in South Africa. The health services in the five areas of the included studies could be different and this could be one of the reasons, in addition to dose, that the studies showed different results.

Rosales suggested that as the population in his study was a healthier population than in previous studies this may explain an absence of, or smaller, vitamin A effect compared with that found in other studies (Rosales 1996).

Morbidity

In Hussey's study 64% of children had diarrhoea and pneumonia on admission; while in Barclay's study pneumonia was the most frequent complication, affecting 85 children: 43% in the vitamin A group and 51% in the control group.

Most of the morbidity outcomes are either based on single or two studies, except for croup. As all studies did not report on all possible morbidity outcomes the conclusions we were able to draw about the effect of vitamin A on measles-related morbidity are limited.

There was a significant decrease in the incidence of croup with vitamin A supplementation while there was no significant reduction in the incidence of pneumonia, although a reduction was observed in the duration of diarrhoea, pneumonia, fever, hospital stay and cough. Treatment of measles cases with vitamin A also have relevance to developed countries as reduction is seen in morbidity outcomes in Kawasaki's study. The Kawasaki (Kawasaki 1999) study reported no mortality and the morbidity outcomes were not pooled with those of the other studies as this study was from a developed country, that is Japan; it used only a single dose of 100,000 IU of vitamin A.

Limitations of this review

Nutritional status is an important predictor of vitamin A deficiency and mortality. The small number of studies and sample sizes have made it difficult to stratify or do a meta-regression. The subgroup analyses are very restricted as the same studies are represented in all of them. The apparent differences between trials may be related to the subgroup but could equally be confounded by some other aspect of trial design.

In these trials it was not always apparent as to which day after the onset of measles vitamin A was administered. Another limitation is that the follow-up period is not the same in all studies. It is assumed that all have been followed up until they were discharged from hospital. For the purposes of this review, the outcomes were taken at the time of discharge hence it is not possible to make comparisons for delayed mortality across these studies.

It would have been useful to have the baseline incidence of measles in the study populations reported and if there were epidemics during the study period. The cases enrolled during a measles epidemic could vary in severity from measles cases at other times.

There was also a lack of reporting on the immunization status of children in the general population and in the study population, which was reported in only two studies (Dollimore 1997; Hussey 1990). The level of immunization would have had an impact on the severity of measles as it could reduce the intensity of exposure and hence the dose of the infecting virus (Hussey 1997). This would have had an impact on the severity of the disease as well as the severity of any epidemic. The severity of measles would be less in already vaccinated children (showing vaccine failure) and in areas where the immunization coverage was high.

Not every study collected information on recovery from morbidity. We have some concern about whether some trialists collected data but later chose not to report these findings. As there were many outcomes reported by single studies there is the possibility that some effects would appear to be significant by chance alone.

Cost

Vitamin A is not only effective but also cost saving. Hussey (Hussey 1990) demonstrated that the duration of hospital stay for children given vitamin A was decreased by an average of 4.7 days; by half a day in another study (Kawasaki 1999). The cost of a dose of vitamin A is around US$ 0.02 (WHO 1998). At this cost ... "to achieve significant reductions in hospitalization and costs in terms of mortality and long-term morbidity, vitamin A therapy for the management of measles is highly cost-effective" (Cervinskas 1996).

Side effects

Until 1993, there were no reports of acute vitamin A toxicity in children with measles who took the WHO recommended dose as reported by the Committee on Infectious Diseases of the American Academy of Pediatrics (Pediatrics 1993). Even doses up to 400,000 IU have been reported to be relatively safe (Frieden 1992). None of the studies included in this review reported any adverse effects.

Headaches, loss of appetite, vomiting and bulging fontanelles (in infants) are some of the known adverse effects occasionally occurring with the administration of high doses of vitamin A. However, these symptoms are minor and transitory, with no known long-term effects and requiring no special treatment (WHO 1998). Under these circumstances it would appear that two doses of vitamin A are not too expensive, not likely to produce adverse effects and still have the capacity to reduce morbidity and mortality.

Comparison with other reviews

The conclusions of this review are in keeping with the previous three reviews (Beaton 1993; Fawzi 1993; Glasziou 1993), which were carried out at a time when only three trials (Barclay 1987; Coutsoudis 1991; Hussey 1990) were available. These are also the studies using two doses and showing a protective effect on measles mortality in the children treated with vitamin A. Later studies (Dollimore 1997; Kawasaki 1999; Ogaro 1993; Rosales 1996) used a single dose or more doses of oil-based vitamin A and did not show reduced measles mortality. Hence, authors of earlier reviews were not able to compare dosages in subgroup analyses. In addition, Fawzi's meta-analysis (Fawzi 1993) included Ellison's study of 1932 (Ellison 1932). Although it is a large study it has been included in this review only as part of the sensitivity analysis as it received a low quality score. It may also be worth mentioning that the objectives of those reviews were different from the objective of this review.

The findings of this review are consistent with one of the largest observational studies that reported on mortality as an outcome (Hussey 1997). A retrospective hospital record review of 1720 cases of measles, during 1985 to 1986, and 1989 to 1990, was carried out. There were 651 children in the latter time period who received two doses of vitamin A (200,000 IU) and had a shorter hospital stay, lower requirement for intensive care, and lower death rate as compared to 1069 children during 1985 to 1986 who received a single dose of 3000 IU.

This review confirms that two doses of vitamin A were associated with a statistically significant reduction in the risk of overall mortality. The only conclusion that can be drawn with any degree of certainty is that high doses of oil- or water-based vitamin A were associated with greater reductions in mortality in children under the age of two years. It is possible that, in high doses, oil-based and water-based vitamin A have similar effects in children under the age of two years. Therefore, in this age group formulation did not make any difference. On the other hand, as studies that used two doses were also done in high case-fatality areas, there was no evidence to show that a single dose would not be effective as there were no studies using a single dose of oil-based vitamin A in these areas. Similarly, subgroup analyses by causes of morbidity and mortality by age group and formulation could not be done as the information was not available.

AUTHORS' CONCLUSIONS

Implications for practice

We support the WHO recommendation that two doses of vitamin A (200,000 IU) be given to all cases of measles, especially to children under the age of two with severe measles, in addition to the standard treatment. The evidence from these studies can only be generalized in relation to developing countries. There is limited information to permit a generalization in relation to developed countries. The only study carried out in a developed country (Japan) used one-fourth of the recommended dose (100,000 IU), showed a reduced morbidity and did not report any toxicity.

Implications for research

This review has shown that mortality reductions were observed in hospitalized children under the age of two years who were given two doses of vitamin A, and in areas where the case fatality was greater than 10%. This review was unable to separate out which of these factors contributed a greater benefit of vitamin A in preventing mortality. Therefore, randomized controlled trials need to be conducted that would compare single doses (200,000 IU) of oil- or water-based vitamin A with two doses, and have sufficiently large sample sizes that the results could be stratified across subgroups for age, geographical areas with low and high case fatality and hospitalized and non-hospitalized children.

To study the benefits in children older than two years of age, more children in this age group need to be enrolled. If trials are conducted, trialists should report on all outcomes and baseline data including age, nutritional status, immunization status, immunization coverage of the general population, complications on enrolment and vitamin A levels. In addition, the number of deaths and morbidity conditions should be reported in each of these subgroups.

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POTENTIAL CONFLICT OF INTEREST

None known

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** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Barclay 1987
Methods	Randomized clinical trial using a random number table
Participants	180 children with measles in hospital

Characteristics of included studies (*Continued*)

Interventions	200,000 IU vitamin A orally for two days, or routine treatment without vitamin A
Outcomes	Death
Notes	Quality score = 3
Allocation concealment	A

Study	**Coutsoudis 1991**
Methods	Randomized, placebo controlled, double blind trial
Participants	60 children aged 4 to 24 months hospitalized with complicated measles
Interventions	WHO recommended dose (54.5 mg < 12 months or 109 mg > 12 months) of retinyl palmitate drops or a placebo syrup
Outcomes	Death Recovery in < 8 days Duration of pneumonia in days Duration of diarrhea in days Duration of fever in days Herpes stomatitis, laryngo-tracheobronchitis, integrated morbidity score
Notes	Quality score 5
Allocation concealment	A

Study	**Dollimore 1997**
Methods	Randomized, placebo controlled, double blind trial
Participants	946 children aged 6 to 90 months, in the community
Interventions	100,000 IU of vitamin A for children aged 6 to 11 months or 200,000 IU of vitamin A for older children every 4 months for 2 years
Outcomes	Death
Notes	Quality score 5
Allocation concealment	A

Study	**Ellison 1932**
Methods	A controlled trial
Participants	600 children in two hospital wards
Interventions	300 Carr and Price units for 7 to 12 days
Outcomes	Death
Notes	Quality score 1
Allocation concealment	C

Study	**Hussey 1990**
Methods	Randomised double-blind trial
Participants	189 children < 13 years of age, hospatialized with measles complicated with pneumonia, diarrhea or croup
Interventions	Either 200,000 IU retinyl palmitate given orally for two days or a placebo, within 5 days of the onset of the rash
Outcomes	> 10 days with pneumonia > 10 days of diarrhea Croup, duration of diarrhoea and pneumonia, herpes stomatitis Transferred to intensive care

Characteristics of included studies (*Continued*)

	Hospital stay in days Death
Notes	Quality score 4
Allocation concealment	A

Study	**Kawasaki 1999**
Methods	A randomized controlled trial
Participants	105 children with measles age 5 months to 4 years in hospital
Interventions	Oral vitamin A (100,000 IU) supplementation
Outcomes	Pneumonia, laryngitis, duration of cough, fever and hospitalization.
Notes	Quality score 3
Allocation concealment	A

Study	**Ogaro 1993**
Methods	Randomized, double blind trial
Participants	294 children under five years admitted to hospital with measles in Kenya
Interventions	50,000 IU of vitamin A (retinyl palmitate) to children < 6 months, 100,000 IU to children between 6 to 12 months, and 200,000 IU to children > 12 months in a single dose on admission.
Outcomes	Croup, pneumonia, diarrhea, otitis media, death
Notes	Quality score 3
Allocation concealment	A

Study	**Rosales 1996**
Methods	Randomized, double masked, placebo controlled clinical trial
Participants	200 children with acute measles not requring hospitalization
Interventions	Single dose of 200,000 IU vitamin A in oil (100,000 IU for infants) or placebo
Outcomes	Measles-associate cough or pneumonia, croup fever, diarrhoea, Failure to improve from pneumonia
Notes	Quality score 5
Allocation concealment	A

mo = months

Characteristics of excluded studies

Chowdhury 2002	The trial studied the effect of vitamin A supplementation on childhood morbidity but not for treating measles in children.

GRAPHS

Comparison 01. Vitamin A versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mortality			Relative Risk (Random) 95% CI	Subtotals only
02 Morbidity (dichotomous data)			Relative Risk (Random) 95% CI	Totals not selected
03 Morbidity (continuous data)			Weighted Mean Difference (Random) 95% CI	Subtotals only
04 Morbidity (single-study outcomes)			Relative Risk (Fixed) 95% CI	Totals not selected

INDEX TERMS

Medical Subject Headings (MeSH)

Adolescent; Child; Child, Preschool; Infant; Infant, Newborn; Measles [drug therapy]; Randomized Controlled Trials; Vitamin A [therapeutic use]; Vitamin A Deficiency [complications]

Medical MeSH check words

Female; Humans; Male

COVER SHEET

Title	Vitamin A for treating measles in children
Authors	Huiming Y, Chaomin W, Meng M
Contribution of author(s)	Yang Huiming was responsible for contacting the Acute Respiratory Infections Review Group. Yang Huiming and Wan Chaomin were responsible for the data extraction and rewriting the updated review. Professor Mao Meng gave instructions during the review update and was involved in the data analysis along with Yang Huiming.
Issue protocol first published	1999/1
Review first published	2001/2
Date of most recent amendment	01 July 2005
Date of most recent SUBSTANTIVE amendment	01 July 2005
What's New	Yang Huiming, Wan Chaomin and Mao Meng took this review over from D'Souza RM and D'Souza R and updated it during the period 2004 to 2005. In the updated review two new trials were found, of which one (Dollimore 1997) was included and another (Chowdhury 2002) was excluded.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	18 March 2005

Date authors' conclusions section amended	16 February 2001
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Editorial group	Cochrane Acute Respiratory Infections Group
Editorial group code	HM-ARI

GRAPHS AND OTHER TABLES

Fig. 1. Comparison 01. Vitamin A versus placebo

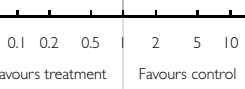
01.01 Mortality

Review: Vitamin A for treating measles in children

Comparison: 01 Vitamin A versus placebo

Outcome: 01 Mortality

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 All patients (seven studies)					
Barclay 1987	6/88	12/92		18.0	0.52 [0.21, 1.33]
Coutsoudis 1991	0/29	1/31		2.2	0.36 [0.02, 8.39]
Dollimore 1997	65/421	76/525		46.3	1.07 [0.79, 1.45]
Hussey 1990	2/92	10/97		8.8	0.21 [0.05, 0.94]
× Kawasaki 1999	0/47	0/58		0.0	Not estimable
Ogaro 1993	5/146	3/148		9.6	1.69 [0.41, 6.94]
Rosales 1996	6/90	7/110		15.2	1.05 [0.37, 3.01]
Subtotal (95% CI)	913	1061		100.0	0.83 [0.51, 1.34]



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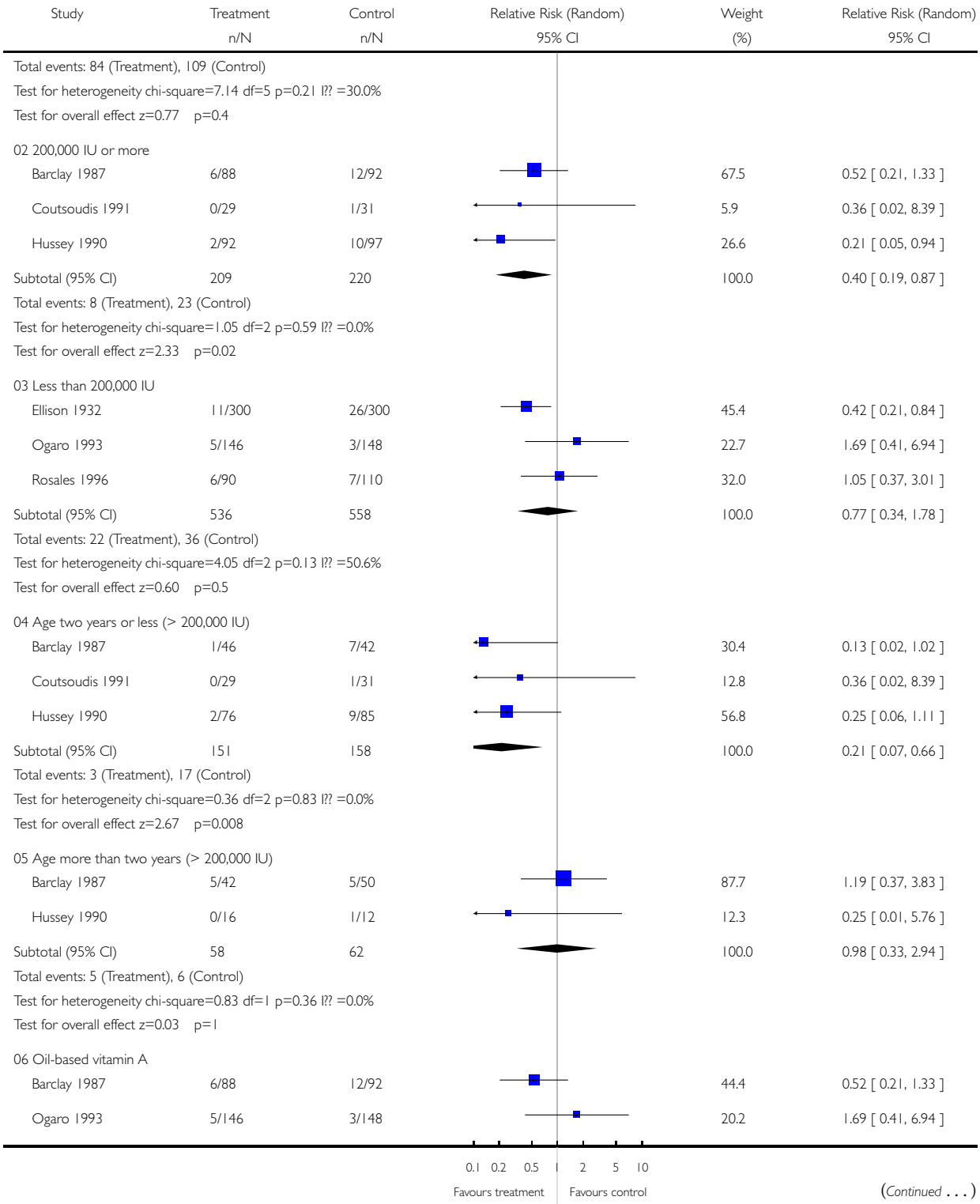

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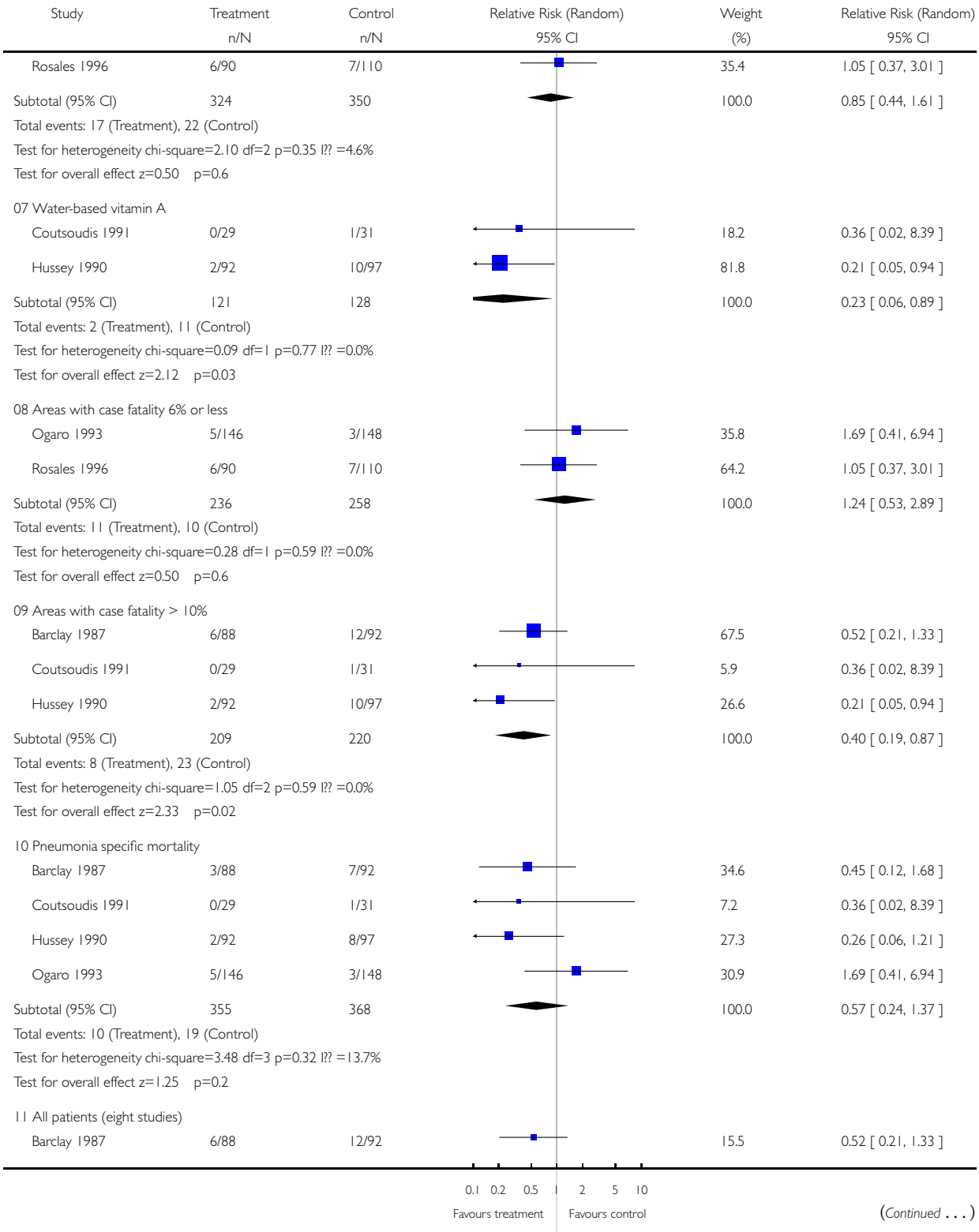

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Rosales 1996	6/90	7/110		35.4	1.05 [0.37, 3.01]
Subtotal (95% CI)	324	350		100.0	0.85 [0.44, 1.61]
Total events: 17 (Treatment), 22 (Control)					
Test for heterogeneity chi-square=2.10 df=2 p=0.35 I?? =4.6%					
Test for overall effect z=0.50 p=0.6					
07 Water-based vitamin A					
Coutsoudis 1991	0/29	1/31		18.2	0.36 [0.02, 8.39]
Hussey 1990	2/92	10/97		81.8	0.21 [0.05, 0.94]
Subtotal (95% CI)	121	128		100.0	0.23 [0.06, 0.89]
Total events: 2 (Treatment), 11 (Control)					
Test for heterogeneity chi-square=0.09 df=1 p=0.77 I?? =0.0%					
Test for overall effect z=2.12 p=0.03					
08 Areas with case fatality 6% or less					
Ogaro 1993	5/146	3/148		35.8	1.69 [0.41, 6.94]
Rosales 1996	6/90	7/110		64.2	1.05 [0.37, 3.01]
Subtotal (95% CI)	236	258		100.0	1.24 [0.53, 2.89]
Total events: 11 (Treatment), 10 (Control)					
Test for heterogeneity chi-square=0.28 df=1 p=0.59 I?? =0.0%					
Test for overall effect z=0.50 p=0.6					
09 Areas with case fatality > 10%					
Barclay 1987	6/88	12/92		67.5	0.52 [0.21, 1.33]
Coutsoudis 1991	0/29	1/31		5.9	0.36 [0.02, 8.39]
Hussey 1990	2/92	10/97		26.6	0.21 [0.05, 0.94]
Subtotal (95% CI)	209	220		100.0	0.40 [0.19, 0.87]
Total events: 8 (Treatment), 23 (Control)					
Test for heterogeneity chi-square=1.05 df=2 p=0.59 I?? =0.0%					
Test for overall effect z=2.33 p=0.02					
10 Pneumonia specific mortality					
Barclay 1987	3/88	7/92		34.6	0.45 [0.12, 1.68]
Coutsoudis 1991	0/29	1/31		7.2	0.36 [0.02, 8.39]
Hussey 1990	2/92	8/97		27.3	0.26 [0.06, 1.21]
Ogaro 1993	5/146	3/148		30.9	1.69 [0.41, 6.94]
Subtotal (95% CI)	355	368		100.0	0.57 [0.24, 1.37]
Total events: 10 (Treatment), 19 (Control)					
Test for heterogeneity chi-square=3.48 df=3 p=0.32 I?? =13.7%					
Test for overall effect z=1.25 p=0.2					
11 All patients (eight studies)					
Barclay 1987	6/88	12/92		15.5	0.52 [0.21, 1.33]

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Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Coutsoudis 1991	0/29	1/31		2.3	0.36 [0.02, 8.39]
Dollimore 1997	65/421	76/525		30.4	1.07 [0.79, 1.45]
Ellison 1932	11/300	26/300		20.8	0.42 [0.21, 0.84]
Hussey 1990	2/92	10/97		8.4	0.21 [0.05, 0.94]
× Kawasaki 1999	0/47	0/58		0.0	Not estimable
Ogaro 1993	5/146	3/148		9.1	1.69 [0.41, 6.94]
Rosales 1996	6/90	7/110		13.5	1.05 [0.37, 3.01]
Subtotal (95% CI)	1213	1361		100.0	0.70 [0.42, 1.15]
Total events: 95 (Treatment), 135 (Control)					
Test for heterogeneity chi-square=11.96 df=6 p=0.06 I?? =49.8%					
Test for overall effect z=1.42 p=0.2					

Fig. 2. Comparison 01. Vitamin A versus placebo

01.02 Morbidity (dichotomous data)

Review: Vitamin A for treating measles in children

Comparison: 01 Vitamin A versus placebo

Outcome: 02 Morbidity (dichotomous data)

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Relative Risk (Random) 95% CI
01 Postmeasles croup				
Barclay 1987	8/88	13/92		0.64 [0.28, 1.48]
Coutsoudis 1991	0/29	1/31		0.36 [0.02, 8.39]
Hussey 1990	13/92	27/97		0.51 [0.28, 0.92]
Ogaro 1993	7/30	7/29		0.97 [0.39, 2.41]
02 Development of pneumonia				
Kawasaki 1999	33/47	42/58		0.97 [0.76, 1.24]
Ogaro 1993	10/53	17/61		0.68 [0.34, 1.35]
03 Development of diarrhoea				
Barclay 1987	2/88	6/92		0.35 [0.07, 1.68]
Ogaro 1993	26/63	23/63		1.13 [0.73, 1.75]

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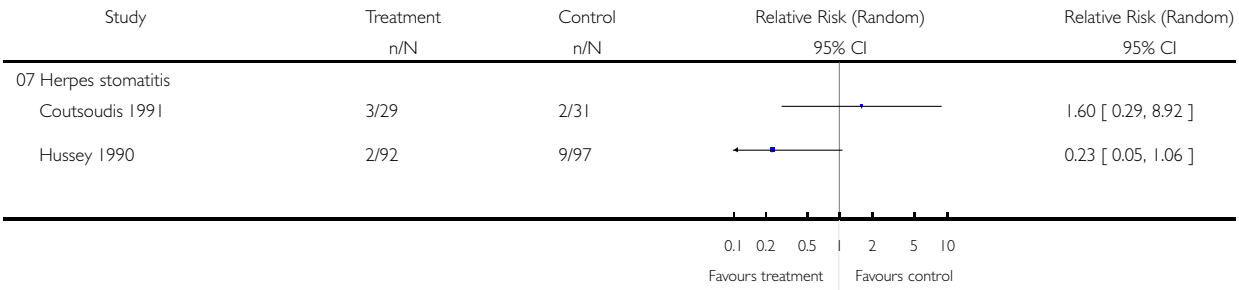

Fig. 3. Comparison 01. Vitamin A versus placebo

01.03 Morbidity (continuous data)

Review: Vitamin A for treating measles in children

Comparison: 01 Vitamin A versus placebo

Outcome: 03 Morbidity (continuous data)

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
01 Duration of pneumonia							
Coutsoudis 1991	29	3.80 (0.40)	31	5.70 (0.79)		54.7	-1.90 [-2.21, -1.59]
Hussey 1990	92	6.53 (4.80)	97	12.37 (10.90)		45.3	-5.84 [-8.22, -3.46]
Subtotal (95% CI)	121		128			100.0	-3.69 [-7.53, 0.16]
Test for heterogeneity chi-square=10.34 df=1 p=0.001 I?? =90.3%							
Test for overall effect z=1.88 p=0.06							
02 Duration of diarrhoea in days							
Coutsoudis 1991	29	3.20 (0.71)	31	4.50 (0.35)		59.6	-1.30 [-1.59, -1.01]
Hussey 1990	92	5.61 (3.90)	97	8.45 (5.50)		40.4	-2.84 [-4.19, -1.49]
Subtotal (95% CI)	121		128			100.0	-1.92 [-3.40, -0.44]
Test for heterogeneity chi-square=4.76 df=1 p=0.03 I?? =79.0%							
Test for overall effect z=2.54 p=0.01							
03 Duration of fever in days							
Coutsoudis 1991	29	3.60 (0.30)	31	4.20 (0.50)		54.0	-0.60 [-0.81, -0.39]
Kawasaki 1999	37	6.80 (1.40)	52	8.30 (1.10)		46.0	-1.50 [-2.04, -0.96]
Subtotal (95% CI)	66		83			100.0	-1.01 [-1.89, -0.13]
Test for heterogeneity chi-square=9.27 df=1 p=0.002 I?? =89.2%							
Test for overall effect z=2.26 p=0.02							
04 Hospital stay in days							
Hussey 1990	92	10.52 (6.60)	97	15.24 (10.60)		46.0	-4.72 [-7.22, -2.22]

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Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Kawasaki 1999	37	5.50 (1.70)	52	5.90 (1.50)		54.0	-0.40 [-1.08, 0.28]
Subtotal (95% CI)	129		149			100.0	-2.39 [-6.60, 1.83]
Test for heterogeneity chi-square=10.64 df=1 p=0.001 I?? =90.6%							
Test for overall effect z=1.11 p=0.3							
05 Days of cough							
Kawasaki 1999	37	7.20 (1.60)	52	9.20 (1.80)		100.0	-2.00 [-2.71, -1.29]
Subtotal (95% CI)	37		52			100.0	-2.00 [-2.71, -1.29]
Test for heterogeneity: not applicable							
Test for overall effect z=5.52 p<0.00001							
06 Integrated morbidity score							
Coutsoudis 1991	29	0.24 (0.15)	31	1.37 (0.40)		100.0	-1.13 [-1.28, -0.98]
Subtotal (95% CI)	29		31			100.0	-1.13 [-1.28, -0.98]
Test for heterogeneity: not applicable							
Test for overall effect z=14.67 p<0.00001							

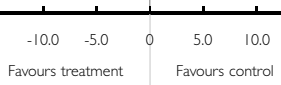


Fig. 4. Comparison 01. Vitamin A versus placebo

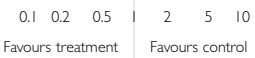
01.04 Morbidity (single-study outcomes)

Review: Vitamin A for treating measles in children

Comparison: 01 Vitamin A versus placebo

Outcome: 04 Morbidity (single-study outcomes)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Relative Risk (Fixed) 95% CI
01 Development of otitis media				
Ogaro 1993	3/79	12/82		0.26 [0.08, 0.88]
02 Recovery from diarrhoea in < five days				
Ogaro 1993	46/83	32/85		1.47 [1.05, 2.06]
03 Development of acute laryngitis				
Kawasaki 1999	14/47	10/58		1.73 [0.85, 3.53]
04 Cough in week two				
Rosales 1996	14/78	11/87		1.42 [0.69, 2.94]
05 Compete clinical recovery in < eight days				
Coutsoudis 1991	28/29	20/31		1.50 [1.14, 1.96]



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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Relative Risk (Fixed) 95% CI
06 Asymptomatic in week two				
Rosales 1996	38/78	47/87		0.90 [0.67, 1.22]
07 Transferred to intensive care				
Hussey 1990	4/92	11/97		0.38 [0.13, 1.16]
08 Diarrhea for more than 10 days				
Hussey 1990	8/92	21/97		0.40 [0.19, 0.86]
09 Diarrhea for 14 days				
Rosales 1996	3/78	5/87		0.67 [0.17, 2.71]
10 Pneumonia for more than 10 days				
Hussey 1990	12/92	29/97		0.44 [0.24, 0.80]
11 Pneumonia for 14 days				
Rosales 1996	26/78	25/87		1.16 [0.74, 1.83]
12 Recovery from pneumonia in < eight days				
Ogaro 1993	68/93	64/87		0.99 [0.83, 1.19]