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RESEARCH

Vitamin A supplements for preventing mortality, illness, and blindness in children aged under 5: systematic review and meta-analysis

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Abstract

Objective To determine if vitamin A supplementation is associated with reductions in mortality and morbidity in children aged 6 months to 5 years.

Design Systematic review and meta-analysis. Two reviewers independently assessed studies for inclusion. Data were double extracted; discrepancies were resolved by discussion. Meta-analyses were performed for mortality, illness, vision, and side effects.

Data sources Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, Medline, Embase, Global Health, Latin American and Caribbean Health Sciences, metaRegister of Controlled Trials, and African Index Medicus. Databases were searched to April 2010 without restriction by language or publication status.

Eligibility criteria for selecting studies Randomised trials of synthetic oral vitamin A supplements in children aged 6 months to 5 years. Studies of children with current illness (such as diarrhoea, measles, and HIV), studies of children in hospital, and studies of food fortification or β carotene were excluded.

Results 43 trials with about 215 633 children were included. Seventeen trials including 194 483 participants reported a 24% reduction in all cause mortality (rate ratio=0.76, 95% confidence interval 0.69 to 0.83). Seven trials reported a 28% reduction in mortality associated with diarrhoea (0.72, 0.57 to 0.91). Vitamin A supplementation was associated with a reduced incidence of diarrhoea (0.85, 0.82 to 0.87) and measles (0.50, 0.37 to 0.67) and a reduced prevalence of vision problems, including night blindness (0.32, 0.21 to 0.50) and xerophthalmia (0.31, 0.22 to 0.45). Three trials reported an increased risk of vomiting within the first 48 hours of supplementation (2.75, 1.81 to 4.19).

Conclusions Vitamin A supplementation is associated with large reductions in mortality, morbidity, and vision problems in a range of settings, and these results cannot be explained by bias. Further placebo controlled trials of vitamin A supplementation in children between 6 and 59 months of age are not required. However, there is a need for further studies comparing different doses and delivery mechanisms (for example, fortification). Until other sources are available, vitamin A supplements should be given to all children at risk of deficiency, particularly in low and middle income countries.

Introduction

Vitamin A refers to a subclass of retinoic acids[1] long understood to help regulate immune function and to reduce morbidity of infectious diseases.[2] Vitamin A is required for normal functioning of the visual system, maintenance of cell function for growth, epithelial integrity, production of red blood cells, immunity, and reproduction.[3] Different forms of vitamin A include β carotene, which is found in plants, and preformed vitamin A, which is found in animal sources. Vitamin A is an essential nutrient that cannot be synthesised so it must be obtained through diet.[1]

Vitamin A deficiency increases vulnerability to a range of illnesses including diarrhoea, measles, and respiratory infections.[3 4] These are leading causes of mortality among children in low and middle income countries,[5] where risk of infection and risk of mortality can be compounded by coexisting undernutrition.[6] The bioavailability of provitamin A carotenoids in fruit and vegetables is lower than once believed,[7 8] and it is difficult for children to fulfil their daily requirements through plant foods alone. Consequently, vitamin A deficiency is

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Appendix 1: Search strategy for other databases

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common among children whose families cannot afford eggs and dairy products.

Preformed vitamin A (retinol, retinal, retinoic acid, and retinyl esters) is the most active in humans; it is usually used in supplements in the form of retinyl esters.[1 3] High intake of synthetic vitamin A over a prolonged period can lead to toxicity,[9] but toxicity from food sources is rare. Periodic supplementation should not cause serious adverse effects.[10]

Previous meta-analyses suggested that vitamin A supplementation for children in developing countries is associated with up to 30% reductions in mortality,[11-13] especially deaths from diarrhoea and measles. The World Health Organization has long recommended vitamin A supplementation for children aged under 5 and for pregnant and breastfeeding mothers.[14] The Countdown to 2015 identified 68 "priority countries" in which over 90% of the world's maternal and childhood deaths occur[15]; the programme aims to hold governments accountable for their commitments to Millennium Development Goals. Vitamin A is now being provided in many low and middle income countries with coverage rates of 86%.[15] Nonetheless, some critics have questioned the value and effectiveness of vitamin A supplementation programmes, and several studies have been conducted since initial recommendations were made.[16 17]

We undertook a review to synthesise all available evidence for vitamin A supplementation in children aged 6 months to 5 years, adding to previous reviews by investigating effects on mortality and the illnesses that lead to death. By investigating all effects in the same review, we provided current estimates of treatment effects and identified potential pathways through which vitamin A supplementation might reduce mortality. A complete protocol was peer reviewed and published by the Cochrane Collaboration, and the review is available in the Cochrane Library.[18]

Methods

We evaluated the effect of prophylactic synthetic oral vitamin A supplementation compared with no treatment or placebo. We planned to conduct five subgroup analyses:

- Dose: WHO recommended dose (up to 100 000 IU for children aged 6-11 months and 200 000 IU for children aged 1-5 years) *v* lower and higher doses
- Frequency: high (doses within 6 months) *v* low (1 dose or ≥6 month interval)
- Location: by continent
- Age: 6-12 months *v* 1-5 years
- Sex: boys *v* girls.

Eligibility criteria

Types of trials—Randomised controlled trials including cluster trials and factorial trials were included irrespective of publication status or language.

Types of participants—At the time of recruitment, children had to be aged 6 months to 5 years and apparently healthy. Children in hospital at the time of recruitment were excluded.

Types of interventions—Included studies examined synthetic oral vitamin A supplementation compared with no treatment or placebo, irrespective of dose or frequency. Studies of food fortification and β carotene supplementation were excluded as their effects can differ.

Types of outcome measures

Primary—We examined all cause mortality at the longest follow-up. We also analysed outcomes within the first year and more than one year after supplementation.

Secondary—We analysed cause specific mortality from diarrhoea, lower respiratory tract infection, measles, and meningitis. We compared the incidence and prevalence of diarrhoea, lower respiratory tract infection, measles, malaria, meningitis, Bitot's spots, night blindness, and xerophthalmia. Adverse events were noted and analysed when possible (vomiting and bulging fontanelle). Finally, we examined vitamin A status (serum retinol) as a continuous and dichotomous outcome.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2010, issue 2), Medline (see box), Embase, Global Health, Latin American Database (LILACS), metaRegister of Controlled Trials, and African Index Medicus (see appendix 1 on bmj.com). All searches were conducted on 27 April 2010. To identify ongoing and unpublished trials, we used the WHO international clinical trials registry, which searches multiple trial registries. Reference lists of reviews, included studies, and excluded studies were searched for additional citations. We contacted organisations and researchers by email and by phone. Two authors (from AI, KH, and MYY) independently screened abstracts and resolved differences with a third author (EMW).

Assessment of bias

Studies were assessed with the Cochrane Collaboration's risk of bias tool.[19] Two authors rated each study for risk of bias from sequence generation (was the method truly random?), allocation concealment (before enrolment, were participants' group assignments disguised?), blinding of participants, assessors, and providers (was assignment adequately disguised after randomisation?), selective outcome reporting (were all outcome measures reported?), and incomplete data (do the results account for all participants randomised?). Risk of bias for each domain was rated as high (seriously weakens confidence in the results), low (unlikely to seriously alter the results), or unclear. Discrepancies were resolved through discussion. The primary analysis was repeated without studies at high risk of bias for sequence generation.

Data management

Two independent people, at least one of whom was an author, completed data extraction and assessments of risk of bias online with Distiller software.[20] We collected data on the time points and measures (both collected and reported) and recruitment, inclusion/exclusion criteria, co-interventions, dose, frequency, duration, age, sex, setting, and location.

Statistical analysis

For continuous outcomes, we calculated the standardised mean difference, Hedges' g.[21] For dichotomous outcomes, we calculated an overall risk ratio. For incidence data, risk ratio (events per child) and rate ratio (events per child year) were combined because these ratios use the same scale and can be interpreted in the same way for these studies (the duration of studies was short and there was no interaction between the intervention and time at risk). All outcomes are reported with 95% confidence intervals, and overall effects are weighted by the inverse of variance with a fixed effect model. In the case of

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Search strategy for Medline

Medline (1950 to April (week 2) 2010)

1. exp infant/ or exp child/ or exp child, preschool/
2. (baby or babies or infant$ or toddler$ or child$ or girl$ or boy$ or pre school$ or pre-school$ or preschool$).tw.
3. 1 or 2
4. exp Vitamin A/
5. (retinol$ or retinal$ or aquasol a or vitamin a).ab,ti.
6. 4 or 5
7. randomised controlled trial.pt.
8. controlled clinical trial.pt.
9. randomized.ab.
10. placebo.ab.
11. drug therapy.fs.
12. randomly.ab.
13. trial.ab.
14. groups.ab.
15. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp animals/ not humans.sh.
17. 15 not 16
18. 3 and 6 and 17

cluster randomised controlled trials, we used adjusted estimates reported by the authors. Where results did not control for clustering, we contacted authors to request the intracluster correlation coefficient. If authors were unable to provide this, we used design effects calculated previously[11] to calculate it using Cochrane methods.[19] For estimated values, we conducted sensitivity analyses using larger and smaller design effects to determine if the results were robust.

Missing data were noted for each outcome. When the numbers of dropouts were not reported, we contacted the authors. When analyses were reported for completers as well as controlled for dropouts (for example, imputed with regression methods), we used the latter.

Statistical heterogeneity was assessed by visual inspection of forest plots, by performing χ^2 tests (assessing the P value), and by calculating the I^2 statistic,[22 23] which describes the percentage of observed heterogeneity that would not be expected by chance. If the P value was less than 0.10 and I^2 exceeded 50%, we considered heterogeneity to be substantial. In subgroup analyses, we tested differences between groups with χ^2. To assess the possibility of small study bias, we compared random effects estimates with fixed effects estimates, drew funnel plots for outcomes with 10 or more studies, and conducted a trim and fill analysis,[24] which yields an effect adjusted for funnel plot asymmetry. Meta-analysis was conducted with RevMan[25] and Biostat CMA (comprehensive meta-analysis)[26] and a summary of results was prepared with the GRADE system.[27]

Results

Trial flow

We included 43 trials[28-69] reported in 90 papers; 39 (90%) reported data that could be included in a meta-analysis (fig 1⇓). The others reported outcomes that were not relevant to the review[35] and data that were not available by group[43] or were incomplete.[62 66] Post hoc, we included two studies in which participants were assigned using quasi-random methods (alternating assignment) as described below.[41 65]

Eight trials nearly met the inclusion criteria but were excluded because they were not randomised controlled trials,[70-73] were designed to treat diarrhoea[74] or Bitot's spots,[75] focused on children with HIV, [76] or did not include an eligible comparison.[77]

Two trials could not be assessed at this time. One including 36 children could not be located and is unlikely to affect the results.[78] One completed trial, the deworming and vitamin A (DEVTA) trial, seems likely to meet the eligibility criteria and could be included in further updates of this review.[79] To assess how the results of that trial could affect the conclusions of our review, we conducted a sensitivity analysis for the primary outcome.

Study characteristics

Trials included 215 633 participants with a median sample size of 480, ranging from 35[66] to over 29 000.[63] The 39 trials that were analysed included 215 043 participants (99.8% of children included in the review).

Of the 43 included trials, 37 compared vitamin A supplementation with placebo. Four used factorial designs, combining vitamin A supplementation with other treatments such as zinc[46 51 62] or deworming.[55] In one trial,[51] raw data were not available and we could not identify outcome data for an eligible comparison. Different doses were combined for the main analysis in one trial.[40]

The median of the mean ages was 30.5 months. Most trials assigned equal numbers of boys and girls; three studies favoured boys by more than 10%.[45 54 57] When trials reported outcomes at multiple time points, we analysed the longest follow-up; most studies lasted about one year. Table 1⇓ describes characteristics for individual studies, and table 2⇓ shows counts for subgroup characteristics.

Risk of bias

Figure 2 shows the risk of bias ratings[19] for each trial.⇓ Three trials were at high risk of bias for sequence generation (not truly random), and these included 41 139 participants.[29 41 65] In two

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quasi-random studies (included post hoc), the authors and the Cochrane editors agreed that the methods of assignment had the desirable characteristics of randomisation and were at no greater risk of bias than other included studies. Only one study was at high risk of bias because of inadequate allocation concealment, but concealment of the allocation sequence was not sufficiently described in 27 trials.

Lack of blinding of assessors created a high risk of bias in only two studies, but it was unclear if assessors were blind in 14 trials. Two studies were at high risk of bias for failing to blind project staff, and 13 trials were unclear on this issue. At the trial level, nine were at high risk of bias for missing data and 12 were unclear, though missing data for the primary outcome was not a concern.

Only four studies seemed to be completely free from selective outcome reporting. It was unclear if 24 trials reported all outcomes, but the primary outcome (mortality) was known for almost all participants in the review. To test for bias, the primary analysis was repeated without studies at high risk of bias for sequence generation.

Quantitative data synthesis

All cause mortality

Mortality (fig 3⇓) was reported in 17 trials including 194 483 children (90% of the children in the review); one reported no events and was not analysed.[45] Thus, 16 trials were included in the primary meta-analysis. Two studies[41 65] randomised households, and we treated them as if they had randomised individuals. Previously reported design effects[11] were used to calculate intracluster correlation coefficients for six cluster randomised studies.[37 52 56 63 68 69] The coefficients were consistent, and we imputed an intracluster correlation coefficient of 0.002 for all studies in which clustering was not considered in the original analysis. A sensitivity analysis was conducted for all cause mortality with coefficients of 0 and 0.01 for those studies in which the mean design effect was estimated.

Vitamin A was associated with a 24% reduction in all cause mortality (0.76, 95% confidence interval 0.69 to 0.83; fig 3), though there was moderate heterogeneity (χ^2=29.10, df=15, P=0.02; I^2=48%). Only five trials[36 38 48 56 68] (7% of trials) measured mortality after 13 months, and the effect was similar (0.75, 0.64 to 0.88) with substantial and significant heterogeneity (χ^2=9.29, df=4, P=0.05; I^2=57%).

We then added a study awaiting assessment to the analysis.[79] In an analysis of 17 trials, this study (the deworming and vitamin A trial) accounted for 65.2% of the combined effect (fig 4⇓), which remained significant (0.88, 0.84 to 0.94) with substantial and significant heterogeneity (χ^2=44.31, df=16, P<0.001; I^2=64%). Though the benefit of vitamin A decreased by half (24% to 12%), the result remained clinically important. As we were unable to assess the trial, we cannot explain this substantially different result; its impacts on the conclusions of this review are considered below.

Of those in the main analysis, 10 trials were conducted in Asia, five in Africa, and one in Latin America. There was no clear difference (P=0.12) between the Asia subgroup (0.69, 0.61 to 0.79) and the Africa subgroup (0.85, 0.73 to 0.98), though the Latin American trial reported no effect (1.00, 0.14 to 7.08). We planned to compare trials in urban and rural areas, but only two urban trials reported the primary outcome; an analysis comparing 1982 and 192 501 participants would be difficult to interpret.

Four trials reported separate effects for children aged 6-12 months (0.59, 0.43 to 0.82) and children aged 1-5 years (0.68, 0.57 to 0.82); the subgroups did not differ significantly (P=0.46). Five trials reported separate effects for boys (0.80, 0.66 to 0.97) and girls (0.79, 0.65 to 0.95), which were not significantly different (P=0.89). Notably, effects for sex and age subgroups are all larger than the overall result, and these results should be interpreted with caution.

Only one trial providing small frequent doses reported mortality data, and the effects were larger (0.46, 0.30 to 0.71) than the effects for the WHO recommended dose delivered every four to six months (0.81, 0.72 to 0.90) or the recommended dose delivered once (0.66, 0.52 to 0.83). Differences between subgroups were significant (P=0.02), but only the greater effect for small frequent doses seems clinically plausible (fig 5⇓).

Of the trials at high risk of bias from sequence generation, only one contributed to primary analysis, and it reported no effect (1.06, 0.82 to 1.37), indicating that these trials were not likely to inflate the combined effect.

The primary analysis was repeated with a random effects model, and the overall estimate was slightly larger; thus, heterogeneity is partially explained by small studies reporting larger effects (0.71, 0.61 to 0.84), which could be related to bias or to clinical differences (such as better implementation in small trials). We drew a funnel plot and conducted a trim and fill analysis (fig 6⇓). There was some evidence of asymmetry (five studies trimmed), but the overall effect was strongly influenced by five studies that accounted for over 80% of the weighted mean, and there was no effect of replacing missing studies (adjusted value rate ratio=0.80, 0.73 to 0.87).

We also conducted a sensitivity analysis to determine if the intracluster correlation coefficients used to adjust for clustering influenced the overall effect. The size of the effect was slightly smaller when these trials were treated as if they had randomised individuals (0.81, 0.75 to 0.89) and was unchanged when we increased the coefficient to 0.01 (0.75, 0.68 to 0.83). Adjusting three studies for which the intracluster correlation coefficients was unknown did not affect our conclusions; further inflating their standard errors would increase the size of the overall effect.

Cause specific mortality

Vitamin A supplementation was associated with a 27% reduction in deaths from diarrhoea. Differences in deaths from measles and meningitis were not significant (table 3⇓).

Morbidities

Morbidity was measured in different ways, and we combined all available data whenever possible. For example, for diarrhoea we included all types of diarrhoea (mild, moderate, and severe). Pneumonia and lower respiratory tract infection outcomes were combined post hoc because pneumonia is a type of lower respiratory tract infection and many studies did not have complete diagnostic information.

Overall, there was a 15% decrease in diarrhoea incidence (fig 7⇓) and a 50% decrease in incidence of measles (fig 8⇓); heterogeneity in the former analysis was substantial, but heterogeneity in the second was not important. Only one trial reported incidence of malaria, which showed a reduction, and effects on lower respiratory infections were not significant (table 3⇓). Few studies reported prevalence data; results for diarrhoea and malaria were not significant, and there were no data for measles.

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Vision

Evidence for vision outcomes was based on a small number of small studies. The available studies suggest a large reduction in the incidence and prevalence of night blindness and a large reduction in the prevalence of xerophthalmia, but effects on Bitot's spots and the incidence of xerophthalmia were not significant (table 4⇓).

Vitamin A deficiency

Serum concentrations were measured in a small number of small studies. These suggest that vitamin A supplementation reduces the proportion of children who are deficient and increases vitamin A serum concentrations (table 4⇓), but heterogeneity was substantial. These results could be influenced by bias, and serum concentrations might be a poor indicator of vitamin A status.

Adverse events

Three trials reported that high doses of vitamin A triple the risk of vomiting within 48 hours. Results for fontanelle side effects were not significant in one study (table 4), and two studies that measured the outcome could not be analysed.

Discussion

Comparable with previous reviews, this review shows that vitamin A supplementation is associated with large and important reductions in mortality for children in low and middle income countries. This adds substantively to previous reviews[11-13] in providing a plausible pathway and indicating that vitamin A supplementation reduces the incidence of and mortality from diarrhoea and measles. Vitamin A also reduces precursors to blindness. While there was a slight increase in the risk of vomiting within 48 hours, there was no evidence of serious adverse events as a result of periodic supplementation. Most trials did not measure vitamin A serum concentrations at baseline as children are unlikely to experience serious harm under these conditions; continuous supplementation, however, might lead to toxicity and cause more severe side effects. It is unclear if smaller more frequent doses would lead to the same minor side effects observed in this review.[9]

Vitamin A deficiency is common during childhood in many low and middle income countries, even among populations whose diets rely heavily on vegetables and fruits.[80] The reasons are multiple and include widespread maternal undernutrition, poor dietary quality, and losses during diarrhoea.[81 82] WHO estimates that 122 countries have a moderate to severe public health problem.[83]

Strengths and limitations

For the primary outcome, the evidence in this review is strong. Sixteen studies were analysed, which included a large number of children. Subgroup and sensitivity analyses show that the result is robust and the effects of bias were not important.

For the primary outcome, the quality of the evidence was "high" on the GRADE scale[27]—that is, further trials are unlikely to change the conclusion that vitamin A supplementation has a large and significant effect (table 3). It seems unlikely that the primary outcome is significantly overestimated because of bias from any source. Almost all studies were randomised with appropriate methods for sequence generation, and allocation was well concealed. It was easy to blind participants and providers, and most trials reported that people were unaware of the treatments being provided. Furthermore, lack of blinding might underestimate rather than overestimate effects—for example, a teacher might give extra food to a child receiving a placebo. Failure to blind assessors is unlikely to influence mortality data. Risks of selective outcome reporting and publication bias are low; the primary analysis included nearly all participants who had been randomised, and all studies large enough to make a difference in this analysis are probably known.

Two trials at high risk of bias for sequence generation were included post hoc, but steps to maintain allocation concealment and blinding minimised the possibility that participants were treated differently between groups. In the first, participants were assigned alternately by household.[41] The second used a random starting point and alternating distribution of red or green pills; the manufacturer held the code until the study was completed.[65] The decision to include these studies was made before data were extracted, and the one study that contributed to the primary outcome[41] reported no effect (1.06, 0.82 to 1.37). The decision to include these studies did not result in an overestimation of the primary outcome.

This review makes an important contribution by identifying several pathways though which vitamin A could reduce mortality. Much of the reduction in all cause mortality is probably explained by reductions in death from diarrhoea and measles, which are leading contributors to child mortality in low and middle income countries.[5] This hypothesis is strengthened by a review indicating that vitamin A supplementation prevents acute diarrhoea from becoming chronic.[84] Though the overall effect for mortality from measles was not significant, the trend was consistent with the overall results, and the therapeutic effects of vitamin A supplementation for measles are well established.[78]

For the secondary outcomes, the quality of the evidence was variable on the GRADE scale (tables 3 and 4), though evidence for measles incidence was high quality. We downgraded ratings for diarrhoea and measles mortality to "moderate" because of uncertainty about the size of the effects; these results are consistent with other findings and consistent with biological mechanisms through which vitamin A supplementation could cause an overall reduction in mortality.

In general, large studies examined effects on mortality while small studies measured illness, vision, and vitamin A serum concentrations. A few studies measured growth, though we did not include this as an outcome. Different outcomes are appropriate for studies with different purposes, but many secondary analyses include only a small proportion of the participants in the review. Recent evidence suggests that the prevalence of selective reporting of outcomes is high and that this might substantially bias systematic reviews.[85 86] If outcomes were reported selectively, addition of unreported data might influence the observed effects in some secondary analyses; we have more confidence in the internal validity of the primary outcome than the secondary outcomes.

Secondary outcomes also have less external validity than the primary analysis, and differences in the size of included studies could mask differences in the size of the analyses. For example, the primary analysis includes 16 trials while analyses for incidence of diarrhoea and serum concentration include 12 and 13 trials. Only five trials appear in both the primary analysis and the diarrhoea analysis, and only three appear in both the primary and serum analyses. While the primary outcome includes 194 483 participants (90% of those randomised), the analysis of incidence of diarrhoea includes only 37 710 (17%) and the serum analysis includes 6623 (that is, less than 3% of participants in the review). To draw attention to these differences

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in external validity and risk of bias, tables 3 and 4 include the number of participants in each analysis as a percentage of those randomised.[87]

Comparison with earlier reviews

Landmark reviews of vitamin A for children appeared in 1993.[11 13] Since then, nine studies contributing 30% of the children in this review have improved the quality of the evidence for vitamin A supplementation in children aged under 5 years.

For the primary outcome, we conducted a cumulative meta-analysis (fig 9⇓) to show how the effect has shifted with the addition of studies over time. That is, each point on the plot shows the combined effect of the new study and all studies reported before it, and the weight is the combined weight of all studies up to that time. Eight trials were included in a 1993 review,[11] which reported a 23% reduction in all cause mortality (0.77, 0.70 to 0.86). Eight trials were added to this analysis (one additional trial reported no events), and the overall estimate has changed by 1%. The overall effect is not meaningfully different from the result of the first trial published in 1986. Therefore, this review confirms that previous estimates remain valid, finding little evidence of secular trends.

Supplementation in other populations is more controversial. A recent review of vitamin A supplementation for children aged under 6 months found no overall effect, but differences between regional subgroups might have been important.[88]

Comparison with the deworming and vitamin A (DEVTA) trial

The most important qualification of these findings is that a large study, awaiting assessment, found no benefit of vitamin A supplementation. Some reviews have found only fair agreement between the results of meta-analyses and the results of large trials[89]; in extreme cases, large trials might indicate that the combined results of smaller trials are incorrect in magnitude or direction.[90] When the results of large trials differ from the results of small trials, commonly used methods for meta-analysis could be inappropriate.[91] All things being equal (such as risk of bias and implementation), researchers and clinicians have been advised to trust large simple trials rather than meta-analyses of small trials.[92 93]

The deworming and vitamin (DEVTA) trial is the largest randomised controlled trial ever conducted, including about a million children in 72 clusters, more than four times the number of children in this review. The trial registration describes a factorial study comparing deworming and vitamin A, which was delivered every six months for two years.[79] The study began in 1999 and recruitment closed in 2004. The authors were contacted several times before our review was completed, but they did not provide information about the conduct of the study. We are unaware of any published results. We were therefore unable to assess eligibility, potential risk of bias, implementation of the intervention, or the generalisability of results. The authors did provide an early analysis of the primary outcome (rate ratio=0.96, 0.89 to 1.03), as well as analyses of cause specific mortality and vitamin A serum concentration.

Details that might explain differences between DEVTA and our review were not available, but we find it unlikely that the results of our review can be explained by small study bias. Small studies could differ from mega-trials, but five trials in this review included more than 20 000 participants and nine included more than 10 000 participants. Furthermore, when the mortality data for DEVTA are included, results of the primary analysis remain significant with a fixed effect model, and that effect remains clinically meaningful.

Heterogeneity

Statistical heterogeneity suggests there might be differences in the effects of vitamin A supplementation across settings and populations, and we conducted prespecified subgroup analyses for all analyses with 10 or more studies.

Trials were conducted in 18 countries. As described above, vitamin A supplementation was associated with significant reductions in mortality in both Asia and Africa. While the difference between subgroups for the primary outcome was not significant, biochemical concentrations of vitamin A seem lower in Asia than in Africa,[83] and our results are consistent with the hypothesis that the benefits of supplementation in Asia might be greater.[94]

For ethical reasons, some trials provided supplements to all children with symptoms of vitamin A deficiency (such as Bitot's spots). Exclusion of such children limits the magnitude of effects on vision outcomes, and such restrictions could contribute to observed heterogeneity across other outcomes in this review. Universal supplementation could result in larger benefits than those reported here.

A non-representative subset of studies reported data by age and sex, but these comparisons cannot be interpreted meaningfully except insofar as vitamin A supplementation was associated with significant reductions in mortality for all subgroups. All studies reporting the primary outcome used the standard dose recommended by WHO (table 2), except for one.[52] While differences between these subgroups were significant, the results might be a statistical artefact; it is possible that small frequent doses will lead to large reductions in mortality, but it seems unlikely that a single supplement is more effective than multiple supplements of the same dose.

Though we did not find evidence of specific contributors to heterogeneity in this review, effects might differ according to baseline vitamin A status, the availability of other nutrients, or the prevalence of disease—for example, concomitant nutrient deficiencies could impair the bioavailability of vitamin A supplementation[95] and differences in the prevalence of pathogens, sanitation, immunisation, and access to healthcare could affect the relative impact of vitamin A supplementation. Heterogeneity might be related to differences in the implementation of interventions, details of which are routinely under-reported in trials.[96] For example, it is essential that providers distribute capsules effectively, that capsules have been stored properly and remain active, and that children ingest the supplements.

Subgroup analyses in this review were limited by the available data, and meta-analyses of group level data to explore individual level moderators should be interpreted with caution. Further analyses with individual patient data from randomised controlled trials and observational studies would be more informative.

Implications for policy

Vitamin A deficiency is a common condition that contributes to illness, blindness, and death; supplements can reduce these problems for children aged under 5 in low and middle income countries. National and regional supplementation programmes could be among the world's most cost effective public health interventions.[97] If the risk of death for 190 million children deficient in vitamin A were reduced by 24%, estimates from

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2008 suggest that over 600 000 lives could be saved each year[98] and 20 million disability adjusted life years would be gained.[99]

Although vitamin A supplementation has been available in many countries for over a decade, direct evidence for its contribution to reducing child mortality is not available. Many countries have experienced significant reductions in child mortality,[5 100] and vitamin A supplementation programmes might have contributed to these declines.

Supplementation responds to an immediate need, but, in the long term, good nutrition requires reliable access to various fresh foods. Fortification, food distribution programmes, and horticultural developments might provide more permanent solutions. For example, growers could increase access to agricultural products like the orange fleshed sweet potato.[101] Vitamin A could be added to rice, though fortification programmes must minimise risk of toxicity. Until such long term solutions are in place, supplementation should continue. As access to vitamin A increases, it will be important to continue to identify at risk groups and to deliver supplements to them.

Our review suggests potential pathways through which vitamin A supplementation reduces mortality. Increased vaccination against measles and other diseases will reduce the effect of vitamin A supplementation if its primary effect is to prevent infection; widespread supplementation, however, will remain important because vitamin A affects other systems—for example, supplementation can prevent blindness.

Based on these results, we strongly recommend vitamin A supplementation for children aged under 5 in areas at risk of vitamin A deficiency. Despite widespread efforts, vitamin A programmes do not reach all children who could benefit.[15] Universal distribution could be achieved in several ways. Vitamin A supplementation can be provided when children receive other services like vaccinations,[102] and it can be provided on a large scale. Child health days or other strategies might be used to increase awareness,[103] and vitamin A uptake could be increased through national food programmes[104] or through delivery by community health workers.[105]

Implications for future research

The effectiveness of vitamin A supplementation is so well established that further placebo controlled studies are not required. Nevertheless, this review does not identify the most effective dose or frequency of delivery. Large doses in the included studies were effective. Smaller, more frequent doses might produce larger reductions in mortality; more complex and burdensome programmes, however, could result in lower coverage. We suggest that policymakers consider including trials of dose and frequency in vitamin A distribution programmes. Other studies might investigate different delivery channels, including food supplementation, horticultural innovations, improved access to food, or psychosocial programmes to increase uptake of foods rich in vitamin A.

Conclusions

Our review reaffirms compelling evidence that vitamin A supplements can prevent death and illness in children aged 6 months to 5 years. Supplements are inexpensive and have few side effects. Further trials are needed to determine the most effective dose and frequency of supplementation, but placebo controlled trials would be unethical. Policymakers should continue working to provide supplements for all children at risk of deficiency, particularly those in low and middle income countries.

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What is already known on this topic

Vitamin A is an essential nutrient; it must be obtained through diet

In low and middle income countries, many people (especially children) do not eat enough vitamin A

Vitamin A deficiency is related to vision problems and increased susceptibility to infectious disease and death

WHO recommends vitamin A supplements for children, pregnant women, and breastfeeding mothers

What this study adds

There have been 43 trials of vitamin A for children aged 6 months to 5 years old, including about 215 633 children

In low and middle income countries, vitamin A supplementation is associated with a 24% reduction in mortality

Vitamin A supplementation might reduce mortality by preventing measles and diarrhoea; it also prevents blindness

The evidence for vitamin A is compelling and clear; further trials comparing vitamin A with placebo would be unethical

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Tables

Table 1| Characteristics of included studies in review of effect of vitamin A supplementation on mortality, illness, and blindness in children aged under 5

Study	Country	Age (months)	No of participants	Follow-up (months)	Dose (1000 IU)	Frequency*
Agarwal 1995[28]	India	0-72	17 778†	15, 27	50 at 1-6 m; 100 at >6 m	0, 4, 8, 12 m
Arya 2000[29]	India	9-12	256	24 hour	100	1 dose
Bahl 1999[30]	India	6-9	618	4	100	1 dose
Barreto 1994[31]	Brazil	6-48	1240	12	100 at <12 m; 200 ≥12 m	0, 4, 8, 12 m
Benn 1997[32]	Guinea Bissau	6-9	462	12	100	1 dose
Biswas 1994[33]	India	12-71	180	6	200	1 dose
Cheng 1993[34]	China	6-36	198	12	100 at <12 m; 200 ≥12 m	4, 10 m
Cherian 2003[35]	India	6-9	395	6	100	1 dose
Chowdhury 2002[8,36]	India	<120	1520	15	50 at <6 m; 100 at 6-12 m; 200 at >12m	0, 5, 10 m
Daulaire 1992‡[37]	Nepal	1-59	7197†	5	50 at <6 m; 100 at 6-12 m; 200 at ≥12 m	1 dose
Dibley 1996[38]	Indonesia	6-47	1405	24	103 at <12 m; 206 at ≥12 m	0, 4, 8, 12, 16, 20, 24 m
Donnen 1998‡[39]	Congo (Zaire)	0-72	235	12	100 at <12 m; 200 at ≥12 m	0, 6, 12 m
Florentino 1990[40]	Philippines	12-72	2471	1 week	100, 200§	1 dose
Herrera 1992[41]	Sudan	9-72	28 753	18	200	0, 6, 12, 18 m
Kartasamita 1995[42]	Indonesia	12-54	267	12	200	0, 6, 12 m
Lima 2010‡[43]	Brazil	2-108	79	36	100 at <12 m; 200 at ≥12 m	0, 4, 8m
Lin 2008[45]	China	24-84	70	3	100	0, 0.5, 1, 1.5, 2, 2,5, 3 m
Lin 2009[44]	China	6-84	86	3	100	0, 1, 2, 3 m
Long 2006[46]	Mexico	6-15	786	12	20 at <12 m; 45 at ≥12 m	0, 2, 4, 6, 8, 10, 12 m
Long 2007[47]	Mexico	6-15	195	12	20 at <12 m; 45 at ≥12 m	0, 2, 4, 6, 8, 10, 12 m
Pant 1996‡[48]	Nepal	6-120	25 301†	24	100 at 6-12 m; 200 at ≥12 m	1 dose
Pinnock 1986[49]	Australia	1-48	147	20 weeks	3.9	3/week for 20 weeks
Pinnock 1988[50]	Australia	0-24	206	12	14	Weekly for 1 year
Rahman 2001[51]	Bangladesh	12-35	800	6	200	1 dose
Rahmathullah 1990[52]	India	6-60	15 419†	12	8.333	Weekly for 1 year
Ramakrishnan 1995[53]	India	6-36	583	12	100 at <12 m; 200 at ≥12 m	0, 4, 8, 12 m
Ranjini 2001[54]	India	12-60	61	6	200	1 dose
Reddy 1986[55]	India	12-60	487	12	200	1 dose
Ross 1993 health[56]	Ghana	6-59	1455	12	100 at 6-12 m; 200 at ≥12 m	0, 4, 8, 12 m
Ross 1993 survival[56]	Ghana	6-90	21 906†	12	100 at 6-12 m; 200 at ≥12 m	0, 4, 8, 12, 16, 20, 24 m
Semba 1992[57]	Indonesia	36-72	236	1	200	1 dose
Semba 1995[58]	Indonesia	6	336	6	100	1 dose
Sempertegui 1999[59]	Ecuador	6-36	400	9	10	Weekly for 40 w
Shankar 1999[60]	Papa New Guinea	6-60	480	13	100 at <12 m; 200 at ≥12 m	0, 4, 8, 12 m
Sinha 1976[61]	India	2-54	306	12	200	0, 4, 8, 12 m
Smith 1999[62]	Belize	26-66	51	6	10	Weekly for 26 w
Sommer 1986‡[63]	Indonesia	0-71	29 236†	9-13	200	0, 6 m
Stabell 1995[64]	Guinea Bissau	6	68	30	100	0, 3 m
Stansfield 1993[65]	Haiti	6-83	13 651	12	100 at 6-11 m; 200 at ≥12 m	0, 4, 8 m
van Agtmaal 1988[66]‡	Thailand	37	30	4	200	1 dose
Venkatarao 1996[67]	India	6	612	6	200	1 dose
Vijyagharvan 1990[68]	India	12-60	15 775†	12	200	0, 6, 12 m
West 1991[69]	Nepal	6-72	28 630†	16	100 at 6-11 m; 200 at ≥12 m	0, 4, 8, 12 m

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Table 1 (continued)

Study	Country	Age (months)	No of participants	Follow-up (months)	Dose (1000 IU)	Frequency*

*Several studies did not explicitly state number of doses received. We assumed that children received doses at baseline and end point—for example, "every 4 months for 1 year" appears as 0, 4, 8, and 12 months.
†Cluster randomised.
‡Compared vitamin A with treatment as usual (control group did not receive placebo).
§Two eligible intervention groups combined for analysis.
¶Mean.

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Table 2| Subgroup analyses for all cause mortality at longest follow-up in studies of effect of vitamin A supplementation in children aged under 5

Subgroup (test for difference)	All trials	No (%) in primary analysis		Fixed effect rate ratio (95% CI)	Heterogeneity: I^2 (%); Q
		Trials	Participants		
All studies[28-69]	43	16 (37)	194 483 (90)	0.76 (0.69 to 0.83)	48%; 29.10 (P=0.02)
Location (P=0.12):					
All	—	16 (37)	194 483 (90)	—	—
Africa[33 39 41 56 64]	6	5 (12)	52 811 (25)	0.85 (0.73 to 0.98)	59%; 9.81 (P=0.04)
Australia[49 50]	2	0	0	—	—
Asia[28-30 33-38 40 42 44 45 48 51-55 57 58 60 61 63 66-69]	28	10 (23)	140 432 (65)	0.69 (0.61 to 0.79)	40%; 15.00 (P=0.09)
Latin America[31 43 46 47 59 62 65]	7	1 (2)	1240 (<1)	1.00 (0.14 to 7.08)	—
Setting (NA):					
All	—	16 (37)	194 483 (90)	—	—
(Peri)urban [29 30 32 33 35 36 42 43 45-47 49-51 54 59]	16	2 (5)	1982 (<1)	NA	NA
Rural[28 31 34 37-41 44 48 52 53 55-58 60-69]	27	14 (33)	192 501 (89)	NA	NA
Dose (P=0.02):					
All	—	16 (37)	194 483 (90)	0.76 (0.69 to 0.83)	48%; 29.10 (P=0.02)
WHO (single)[29 30 32 33 36 37 40 48 51 54 55 57 58 66 67]	15	4 (9)	33 572 (16)	0.66 (0.52 to 0.83)	0%; 2.15 (P=0.54)
WHO (4-6m)[28 31 34 36 38 39 41-47 53 56 60 61 63-65 68 69]	18	11 (26)	147 933 (69)	0.81 (0.72 to 0.90)	48%; 19.17 (P=0.04)
More frequent[44-47 49 50 52 59 62 64]	10	1 (2)	15 419 (7)	0.46 (0.30 to 0.71)	—
Age* (P=0.46):					
All	—	5 (12)	61 544 (29)	0.66 (0.56 to 0.77)	0.0%; 6.77 (P=0.45)
6-12 months[28-32 34-39 41 44 44 46-50 52 53 56 58-61 64-65 67 69]	32	4 (9)	4739 (2)	0.59 (0.43 to 0.82)	15%; 3.51 (P=0.32)
12-60 months[28 31 33 34 36-57 59-66 68 69]	37	4 (9)	56 805 (26)	0.68 (0.57 to 0.81)	0.0%; 2.72 (P=0.44)
Sex† (P=0.89):					
All	—	5 (12)	85 568 (40)	0.80 (0.70 to 0.91)	34%; 10.69 (P=0.15)
Males[28-69]	43	5 (12)	43 567 (20)	0.80 (0.66 to 0.97)	62%; 7.79 (P=0.05)
Females[28-69]	43	5 (12)	42 001 (20)	0.79 (0.65 to 0.95)	0.0%; 2.87 (P=0.41)
With DEVTA[28-69 79]	44	17 (39)	1 194 483 (98)	0.88 (0.84 to 0.94)	64%; 44.31 (P<0.001)

NA=not available; planned analysis not conducted; DEVTA=deworming and vitamin A trial.

*For primary outcome, trials reported mortality for children <12 months,[33] children >12 months,[64] or both.[38 53 70]

†One trial reporting data by sex reported no events,[46] and four trials appear in both analysis.[38 42 64 70]

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Table 3| Summary of pooled analyses for mortality and illness in studies of effect of vitamin A supplementation in children aged under 5

Outcome	No (%) of trials (n=43)	No (%) of participants (n=215 633)	Rate ratio (95% CI), fixed effect	Heterogeneity: I^2; χ^2	Follow-up (weeks)	Quality of evidence (GRADE)
Primary outcome						
All cause mortality[31 32 36-39 41 45 48 52 56 63 68 69 107]	16 (37)	194 483 (90)	0.76 (0.69 to 0.83)	48%; 29.10 (P=0.02)	12-96	High
Cause specific mortality						
Diarrhoea[28 36 37 41 52 56 67]	7 (16)	90 951 (42)	0.72 (0.57 to 0.91)	2%; 6.12 (P=0.41)	48-104	Moderate
Measles[28 37 41 52 56]	5 (12)	88 261 (41)	0.80 (0.51 to 1.24)	0%; 0.40 (P=0.98)	52-104	Moderate
Meningitis[28 36 56]	3 (7)	41 204 (19)	0.57 (0.17 to 1.88)	0%; 0.75 (P=0.69)	48-108	Low
LRTI[28 36 37 41 52 56 67]	7 (16)	90 951 (42)	0.78 (0.54 to 1.14)	14%; 7.00 (P=0.32)	48-104	Low
Illness						
Diarrhoea:						
Incidence[29 31 33 34 36 38 40 41 47 53 59 60 67]	13 (30)	37 710(17)	0.85 (0.82 to 0.87)	95%; 217.99 (P<0.01)	24-60	Low
Prevalence[35 47 65]	2 (5)	14 437 (7)	1.08 (1.05 to 1.12)	87%; 15.76 (P<0.01)	48	Very low
Malaria:						
Incidence[60]	1 (2)	480 (<1)	0.73 (0.60 to 0.88)	NA	52	Very low
Prevalence[56]	2 (5)	23 361 (11)	0.72 (0.41 to 1.28)	0%; 0.02 (P=0.88)	48	Moderate
Measles:						
Incidence[30-32 36 41 58]	6 (14)	19 566 (9)	0.50 (0.37 to 0.67)	0%; 0.55 (0.99);	16-78	High
Prevalence	0 (0)	0 (0)	NA	NA	NA	NA
LRTI:						
Incidence[31 34 36 42 47 59 67]	7 (16)	18 179 (8)	1.14 (0.95 to 1.37)	22%; 7.66 (0.26)	24-60	Very low
Prevalence[46]	1 (2)	786 (0.4)	0.46 (0.21 to 1.03)	NA	48	Very low

LRTI=lower respiratory tract infection.

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Table 4| Summary of pooled analyses for admission to hospital, vision, vitamin A deficiency, and adverse events in studies of effect of vitamin A supplementation in children aged under 5

Outcome	No (%) of trials (n=43)	No (%) of participants (n=215 633)	Rate ratio (95% CI), fixed effect	Heterogeneity: I^2; χ^2	Follow-up (weeks)	Quality of evidence (GRADE)
Admission to hospital						
All cause[56]	1 (2)	1185 (0.5)	0.64 (0.40 to 1.02)	NA	48	Very low
Diarrhoea[34]	1 (2)	198 (<1)	0.25 (0.01 to 6.11)	NA	48	Very low
LRTI[34]	1 (2)	198 (<1)	0.11 (0.01 to 2.06)	NA	48	Very low
Vision						
Bitot's spots:						
Incidence[41]	1 (2)	28 753 (13)	0.93 (0.76 to 1.14)	NA	72	Very low
Prevalence[48 61 63 69]	4 (9)	63 278 (29)	0.45 (0.33 to 0.61)	64%; 8.25 (P=0.04)	36-96	Moderate
Night blindness:						
Incidence[41]	1 (2)	28 753 (13)	0.53 (0.28 to 0.99)	NA	72	Low
Prevalence[63 69]	2 (5)	22 972 (11)	0.32 (0.21 to 0.50)	0%; 0.19 (P=0.66)	52-68	Moderate
Xerophthalmia:						
Incidence[31 41 69]	3 (7)	58 623 (27)	0.85 (0.70 to 1.03)	63%; 2.69 (P=0.10)	48-72	Low
Prevalence[31 63 69]	2 (5)	57 866 (27)	0.31 (0.22 to 0.45)	0%; 0.22 (P=0.64)	36-64	Moderate
Vitamin A deficiency						
Number deficient[38 54 56 60]	4 (9)	2262 (1)	0.71 (0.65 to 0.78)	78%; 13.58 (P<0.01)	24-96	High
Serum concentration[34 38 42 44 49 50 54-57 59 60]	13 (30)	6623 (3)	g=0.31 (0.26 to 0.36)	95%; 270.23 (P<0.01)	4-96	Moderate
Adverse events						
Vomiting[29 40 61]	3 (7)	2994 (1)	2.75 (1.81 to 4.19)	21%; 2.53 (P=0.28)	48 hours	Very low
Bulging fontanelle[29 30 64]	3 (7)	885 (<1)	5.00 (0.24 to 103.72)	NA	48 hours	Low

NA=not available; LRTI=lower respiratory tract infection.

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Figures

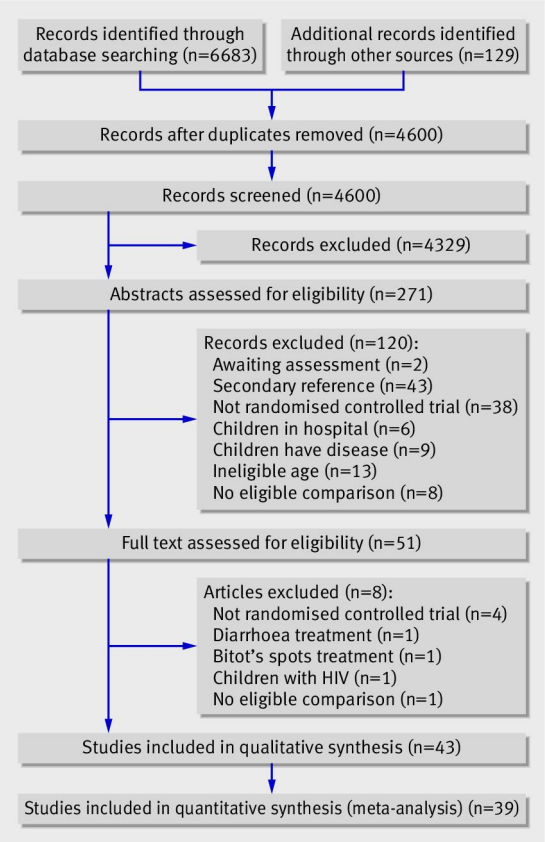

Fig 1 Identification of studies to include in review of effect of vitamin A supplementation on mortality, illness, and blindness in children aged under 5

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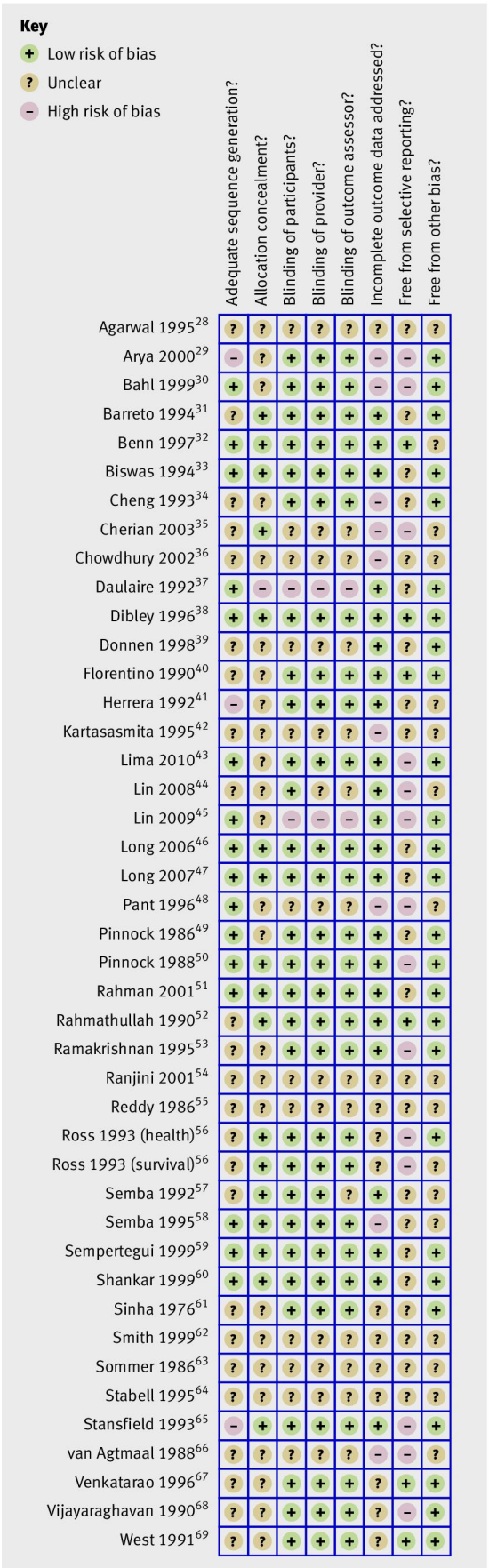

Fig 2 Assessment of risk of bias in studies on effect of vitamin A supplementation on mortality, illness, and blindness in children aged under 5

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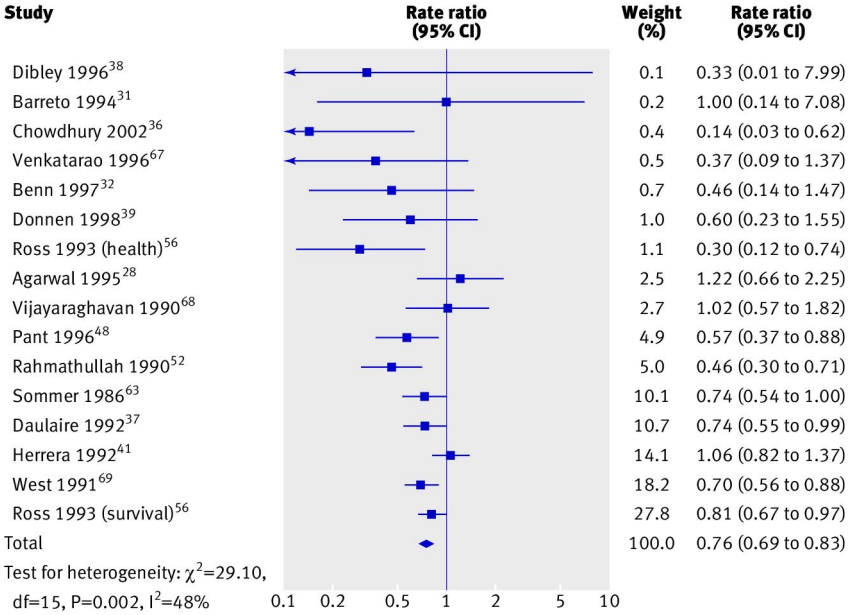

Fig 3 All cause mortality in studies on effect of vitamin A supplementation in children aged under 5

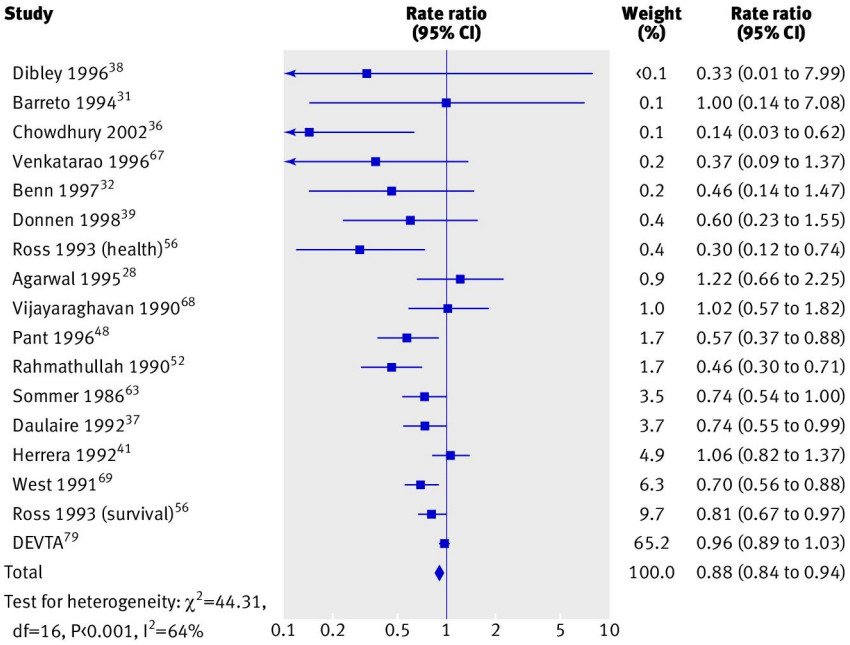

Fig 4 All cause mortality sensitivity analysis in studies on effect of vitamin A supplementation in children aged under 5, including deworming and vitamin A (DEVTA) trial

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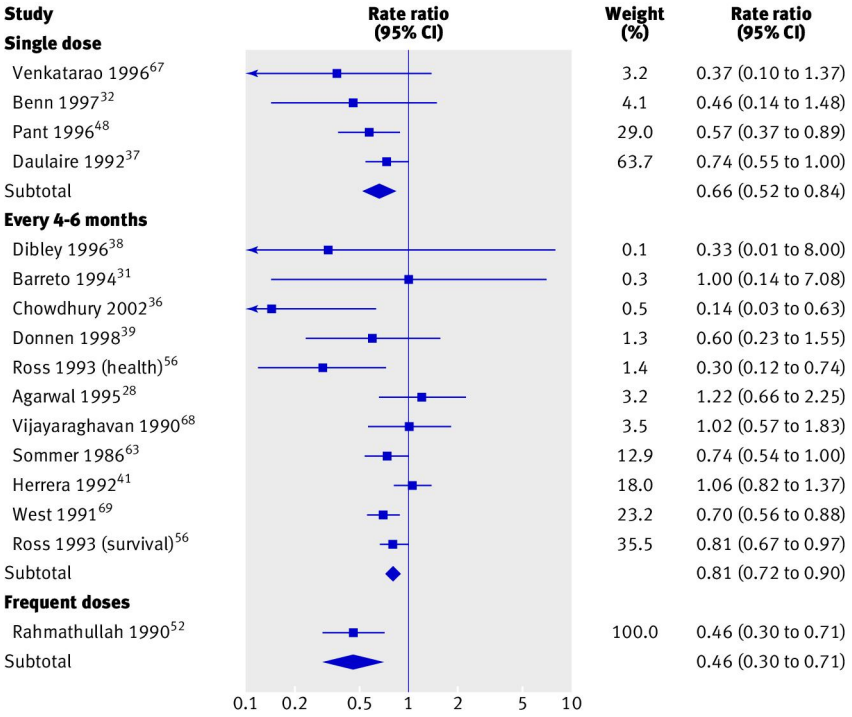

Fig 5 All cause mortality by dose in studies on effect of vitamin A supplementation in children aged under 5

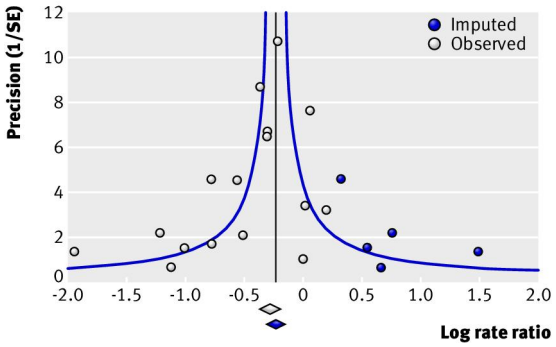

Fig 6 Mortality funnel plot with trim and fill in studies on effect of vitamin A supplementation in children aged under 5. Observed=included studies. Imputed=observed effects trimmed to make funnel plot symmetrical, opposite effects imputed, trimmed studies and imputed effects replaced

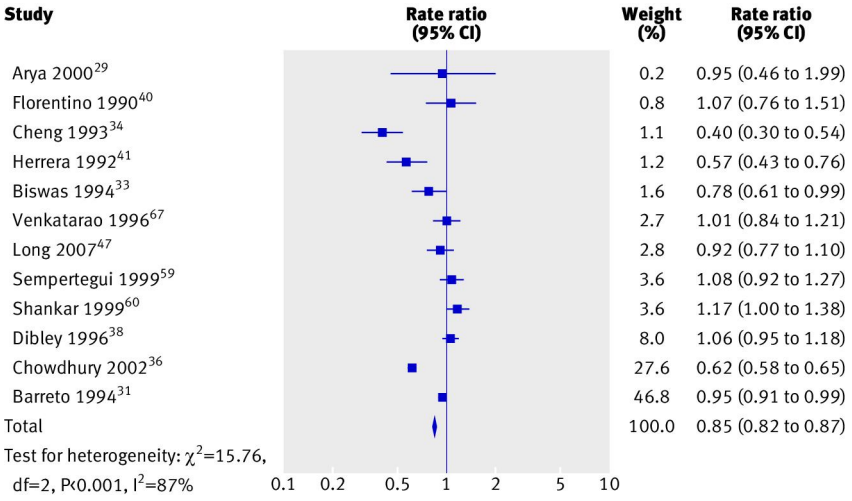

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Fig 7 Incidence of diarrhoea in studies on effect of vitamin A supplementation in children aged under 5

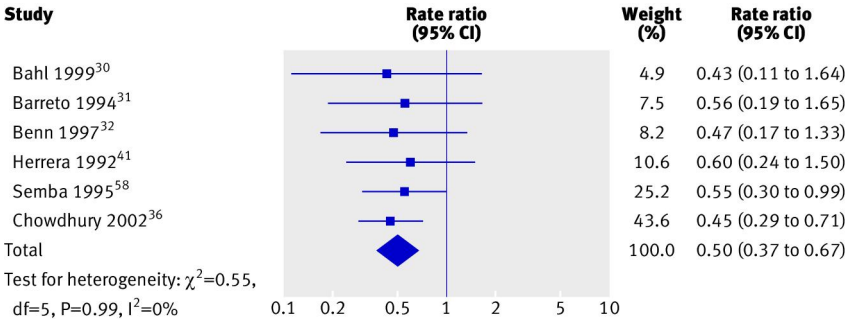

Fig 8 Incidence of measles in studies on effect of vitamin A supplementation in children aged under 5

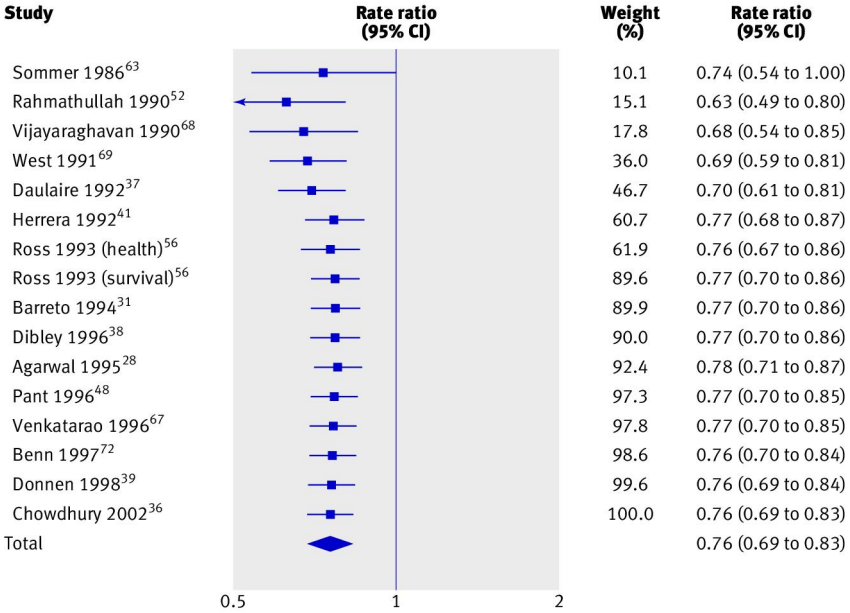

Fig 9 All cause mortality cumulative meta-analysis in studies on effect of vitamin A supplementation in children aged under 5

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