Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age (Review)

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[Intervention Review]

Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

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ABSTRACT

Background

Vitamin and mineral deficiencies, particularly those of iron, vitamin A and zinc, affect more than two billion people worldwide. Young children are highly vulnerable because of rapid growth and inadequate dietary practices. Micronutrient powders (MNP) are single-dose packets containing multiple vitamins and minerals in powder form that can be sprinkled onto any semi-solid food.The use of MNP for home or point-of-use fortification of complementary foods has been proposed as an intervention for improving micronutrient intake in children under two years of age.

Objectives

To assess the effects and safety of home (point-of-use) fortification of foods with multiple micronutrient powders on nutritional, health and developmental outcomes in children under two years of age.

Search methods

We searched the following databases in February 2011: Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE (1948 to week 2 February 2011), EMBASE (1980 to Week 6 2011), CINAHL (1937 to current), CPCI-S (1990 to 19 February 2011), Science Citation Index (1970 to 19 February 2011), African Index Medicus (searched 23 February 2011), POPLINE (searched 21 February 2011), ClinicalTrials.gov (searched 23 February 2011), mRCT (searched 23 February 2011), and World Health Organization International Clinical Trials Registry Platform (ICTRP) (searched 23 February 2011). We also contacted relevant organisations (25 January 2011) for the identification of ongoing and unpublished studies.

Selection criteria

We included randomised and quasi-randomised trials with either individual or cluster randomisation. Participants were children under the age of two years at the time of intervention, with no specific health problems. The intervention was consumption of food fortified at the point of use with multiple micronutrient powders formulated with at least iron, zinc and vitamin A compared with placebo, no intervention or the use of iron containing supplements, which is the standard practice.

Data collection and analysis

Two review authors independently assessed the eligibility of studies against the inclusion criteria, extracted data from included studies and assessed the risk of bias of the included studies.

Main results

We included eight trials (3748 participants) conducted in low income countries in Asia, Africa and the Caribbean, where anaemia is a public health problem. The interventions lasted between two and 12 months and the powder formulations contained between five and 15 nutrients. Six trials compared the use of MNP versus no intervention or a placebo and the other two compared the use of MNP versus daily iron drops. Most of the included trials were assessed as at low risk of bias.

Home fortification with MNP reduced anaemia by 31% (six trials, RR 0.69; 95% CI 0.60 to 0.78) and iron deficiency by 51% (four trials, RR 0.49; 95% CI 0.35 to 0.67) in infants and young children when compared with no intervention or placebo, but we did not find an effect on growth.

In comparison with daily iron supplementation, the use of MNP produced similar results on anaemia (one trial, RR 0.89; 95% CI 0.58 to 1.39) and haemoglobin concentrations (two trials, MD -2.36 g/L; 95% CI -10.30 to 5.58); however, given the limited amount of data these results should be interpreted cautiously.

No deaths were reported in the trials and information on side effects and morbidity, including malaria, was scarce.

It seems that the use of MNP is efficacious among infants and young children six to 23 months of age living in settings with different prevalences of anaemia and malaria endemicity, regardless of whether the intervention lasts two, six or 12 months or whether recipients are male or female.

Authors' conclusions

Home fortification of foods with multiple micronutrient powders is an effective intervention to reduce anaemia and iron deficiency in children six months to 23 months of age. The provision of MNP is better than no intervention or placebo and possibly comparable to commonly used daily iron supplementation. The benefits of this intervention as a child survival strategy or on developmental outcomes are unclear. Data on effects on malaria outcomes are lacking and further investigation of morbidity outcomes is needed. The micronutrient powders containing multiple nutrients are well accepted but adherence is variable and in some cases comparable to that achieved in infants and young children receiving standard iron supplements as drops or syrups.

PLAIN LANGUAGE SUMMARY

Use of a powder mix of vitamins and minerals to fortify complementary foods immediately before consumption and improve health and nutrition in children under two years of age

Deficiencies of vitamins and minerals, particularly of iron, vitamin A and zinc, affect approximately half of the infants and young children under two years of age worldwide. Exclusive breastfeeding until six months of age and continued breastfeeding for at least two years are recommended to maintain children's adequate health and nutrition. After six months of age, infants start receiving semi-solid foods but the amount of vitamins and minerals can be insufficient to fulfil all the requirements of the growing baby. Micronutrient powders (MNP) are single-dose packets of powder containing iron, vitamin A, zinc and other vitamins and minerals that can be sprinkled onto any semi-solid food at home or at any other point of use to increase the content of essential nutrients in the infant's diet during this period. This is done without changing the usual baby diet.

This review includes eight good quality trials that involved 3748 infants and young children from low income countries in Asia, Africa and the Caribbean. We found that a variety of MNP formulations containing between five and 15 vitamins and minerals have been given for between two and 12 months to infants and young children aged six to 23 months of age.

The use of MNP containing at least iron, zinc and vitamin A for home fortification of foods was associated with a reduced risk of anaemia and iron deficiency in children under two. The studies did not find any effects on growth. Although the acceptability of this innovative intervention was high, there is no additional benefit to usually recommended iron drops or syrups, however few studies compared these different interventions. No deaths were reported in the trials and information on side effects and morbidity, including malaria, was scarce. The use of MNP was beneficial for male and female infants and young children six to 23 months of age, independent of whether they lived in settings with different anaemia and malaria backgrounds or whether the intervention was provided for two, six

or 12 months. The most appropriate arrangements for use (daily or intermittently), the appropriate vitamin and mineral composition of the mix of powders and the way to deliver this intervention effectively in public health programmes to address multiple micronutrient deficiencies remain unclear.

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

Patient or population: children 6 to 23 months
Settings: community settings
Intervention: home fortification with multiple micronutrient powders
Comparison: placebo/no intervention

Outcomes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
Anaemia	**RR 0.69** (0.60 to 0.78)	1447 (6 studies)	**moderate**[1]
Iron deficiency	**RR 0.49** (0.35 to 0.67)	586 (4 studies)	**high**[2]
Haemoglobin (g/L)	**MD 5.87** (3.25 to 8.49)	1447 (6 studies)	**moderate**[1,3]
Iron status (ferritin concentrations in ng/mL)	**MD 20.38** (6.27 to 34.49)	264 (2 studies)	**low**[1,4]
Weight-for-age Z-score	**MD 0** (-0.37 to 0.37)	304 (2 studies)	**moderate**[1,5]
All-cause mortality	**0**	0 (0 studies)	None of the trials reported on this outcome.

CI: Confidence interval; **RR:** Risk ratio;
GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] One study (Adu-Afarwuah 2007) has serious risk of bias.
[2] Because of the consistent and large effect of the intervention RR 0.49 (95 % CI 0.36 to 0.67), we have refrained from downgrading because of the high risk of bias in one of the four studies.
[3] There was considerable statistical heterogeneity attributable to one study (Lundeen 2010). However, because of the clear conclusion and consistency in the results, assessors chose to not downgrade.
[4] There was imprecision in the results.
[5] There was considerable unexplained statistical heterogeneity, but given the lack of clinical significance of the different results reported in the trials (i.e. all children are within the desirable Z scores), assessors chose to not downgrade

BACKGROUND

Description of the condition

Vitamin and mineral deficiencies affect more than two billion people worldwide (The Micronutrient Initiative 2009). Iron deficiency, which affects over half the world's population, is the most common preventable nutritional deficiency. Together with vitamin A and zinc deficiencies, iron deficiency has the largest documented disease burden among micronutrients (WHO 2001; Black 2008; WHO 2009). There is a disproportionate burden of vitamin and mineral deficiencies in developing countries. Infants and children are the most vulnerable groups to micronutrient malnutrition given the high vitamin and mineral intake they need for rapid growth relative to the amount of food they consume (Dewey 2003). The diets of infants and young children aged six months to 23 months generally provide insufficient amounts of key micronutrients (particularly iron, vitamin A, zinc and calcium) to meet their nutritional needs, and the inclusion of animal-source foods to fill the nutrient gap may be not practical for low-income countries (PAHO 2001; WHO 2005). There are no global estimates of vitamin and mineral deficiencies specifically for children under two years, however it is calculated that 190 million preschool children are affected by vitamin A deficiency (WHO 2009) and 293 million by anaemia (WHO/CDC 2008).

Vitamin A deficiency is the leading cause of childhood blindness (WHO 2009). Iron is essential to red blood cells and is involved in several metabolic reactions; there is compelling evidence that infants aged six months to 23 months with iron-deficiency anaemia are at risk of poor cognitive, motor, social-emotional, and neurophysiologic development (Lozoff 2007). Zinc is important during periods of accelerated growth and for tissues with rapid cellular differentiation and turnover, such as the immune system and the gastrointestinal tract. Critical functions that are affected by zinc nutrition include physical growth, susceptibility to infection and neurobehavioral development (Brown 2001).

Multiple vitamin and mineral deficiencies frequently occur simultaneously, and their joint effects during the critical period from conception to two years of age can be associated with irreversible physical and cognitive consequences, increased perinatal mortality, and reduced physical work capacity and productivity (WHO 2001; Lozoff 2007; Sanghvi 2007), leading to lifelong detrimental consequences on health, productivity and economic growth. In fact, it has been estimated that nutritional risk factors, including underweight status, suboptimal breastfeeding, and vitamin and mineral deficiencies, particularly vitamin A, iron and zinc, are responsible for 3.9 million deaths (35% of total deaths) and 144 million disability-adjusted life years (DALYs) (33% of total DALYs) in children less than five years of age worldwide (WHO 2009).

Description of the intervention

Interventions to prevent and treat micronutrient malnutrition typically include exclusive breastfeeding during the first six months of life, dietary diversification to include foods with highly absorbable vitamins and minerals, fortification of staple and complementary foods, and provision of supplements (Bhutta 2008), with the latter being the most widespread intervention.

It has been reported that vitamin A supplementation of children between six months and five years of age significantly reduces total mortality by about 23% to 30% (Beaton 1993; Fawzi 1993; Glasizou 1993; Imdad 2010) and reduces childhood blindness by 70%. The reduction in mortality is believed to be mediated through improved vitamin A status, which may affect susceptibility to infection by an effect on the immune system (Stephensen 2001). Zinc supplementation leads to a 9% reduction in child mortality and a 23% reduction in incidence of childhood diarrhoea (WHO 2006; Brown 2009). Since adequate iron status early in life is critical for motor and cognitive development, the World Health Organization (WHO) has recommended blanket iron supplementation to all infants and children six to 24 months of age in areas where the prevalence of anaemia is 20% to 30%, or higher (INACG 1998; WHO 2001). Micronutrient interventions, particularly vitamin A and zinc supplementation of children and fortification of foods with iron and iodine, have been shown to be among the most cost-effective global development efforts (Horton 2008).

Despite the well-recognized benefits of supplementation with one, two or multiple micronutrients, implementation has been hindered by poor adherence to dosing regimens, inadequate supply, low coverage, and potential dose-related side effects and safety concerns (Sazawal 2006; Stoltzfus 2011; UNICEF 2011). In response to these operational constraints, 'home' or 'point-of-use' food fortification with micronutrient powders (MNP) was developed as a novel alternative to daily supplementation for delivering iron and other micronutrients with foods. MNP are single-dose packets of dry powder containing lipid-encapsulated iron and other micronutrients that can be sprinkled onto any semi-solid food (Zlotkin 2005). The lipid-encapsulation coating prevents iron from dissolving into the food and therefore prevents any change in colour, flavour or taste. Home fortification with MNP is being proposed for complementary feeding based on the rationale that 1) various vitamins and minerals can be added to the formulation in the MNP sachet; 2) the MNP sachets are lightweight and simple to store, transport and distribute; 3) MNP are easy to produce, with a relatively low production cost; 4) MNP does not affect the maintenance of usual dietary practices that facilitate the transition from exclusive breastfeeding to complementary feeding; 5) MNP are easy to use even without literacy; and 6) the potential for overdose is low (Zlotkin 2004). A drawback mentioned has been the waste disposal challenge with single-dose sachets. Because MNP products usually have higher acceptability and fewer side effects than iron drops, the approach of home fortification of foods

with MNP for treating anaemia is being used in some developing countries (World Vision 2005; De Pee 2008; Dewey 2009).

The cost of increasing the number of micronutrients in the powder is minimal (the primary cost of the product is in the packaging) (De Pee 2008). Many programmes use a formulation containing 14 vitamins and minerals (Sprinkles Global Health Initiative 2010), although the formulation and the compound specifications may vary in other programmes. The efficacy of the standard 'multi-micronutrient' formulation for anaemia has been evaluated in some studies, but the potential for negative interaction among multiple micronutrients, possibly limiting their absorption and utilization, as well as the effects on other outcomes warrant further investigation.

Provision of iron in malaria-endemic areas has been a long-standing controversy due to concerns that iron therapy may exacerbate infections, in particular malaria given that the parasite requires iron for growth (Oppenheimer 2001). On the one hand, a large clinical trial of iron and folic acid supplementation in Zanzibar, an area with high rates of malaria transmission and poor malaria control at the time of the study, found that those who received iron and folic acid with or without zinc were more likely to die or need treatment in hospital for an adverse event (Sazawal 2006). On the other hand, a recent Cochrane review found that providing iron supplementation to children does not increase the risk of clinical malaria in the presence of regular surveillance of malaria and appropriate treatment (Ojukwu 2009). Because of this situation, policy makers and experts in nutrition, worldwide, have forthrightly discussed the safety of iron interventions in malaria-endemic areas in order to promote the use of safe and effective interventions (Suchdev 2009). Due to the way in which iron is absorbed and metabolized, not all forms of iron will necessarily have the same effect on susceptibility to infection. MNP may be less likely to increase the risk of infection because they are mixed with food and thus are absorbed more slowly, yielding lower peak concentrations of unbound iron in the circulation (Liyanage 2002; Dewey 2007).

From the implementation perspective, MNP programmes are currently on a national scale in several countries, such as Bangladesh, Mongolia and Haiti, and numerous countries are planning large-scale distribution for children (Hyder 2007; Menon 2007). Based on a 2009 UNICEF regional workshop in Asia, 32 programmes of home fortification with MNP have been implemented or are being planned (UNICEF 2009). However, few studies have reported operational and cost considerations, including effective distribution mechanisms (Dewey 2009; Loechl 2009). In addition, there is great variability in the formulation of MNP (for example, the number and doses of the micronutrients), producers that are manufacturing MNP, target age group of children receiving MNP, and settings in which MNP are distributed (De Pee 2008).

Why it is important to do this review

The WHO recommends exclusive breastfeeding until six months of age and continued breastfeeding for at least two years (PAHO 2001; WHO 2005). Intake of several vitamins and minerals after six months, including iron, zinc, calcium, selected B vitamins and (in some settings) vitamin A, remain problematic because commonly available, low-cost foods contain inadequate amounts of these nutrients.

Various Cochrane reviews or protocols have evaluated the effects of supplementation with different vitamins and minerals in children. The effects of iron supplementation with tablets or elixirs, alone or in combination with folic acid or other micronutrients, in children less than 18 years of age living in malaria-endemic areas is evaluated by Ojukwu 2009. Published reviews have also evaluated the effects of 1) iron supplementation for improving clinical, immunologic and virologic outcomes in children infected with HIV (Adetifa 2009); 2) micronutrient supplementation in children and adults with HIV infection (Irlam 2011); 3) oral or intramuscular iron therapy for improving psychomotor development and cognitive function in children under the age of three years with iron deficiency anaemia (Martins 2001); 4) iodine supplementation for preventing iodine deficiency disorders in children (Angermayr 2004); and 5) vitamin A supplementation for preventing mortality and morbidity in children aged six months to five years (Imdad 2010). A Cochrane protocol for a review to assess the effects of any form of iron supplementation for treating iron deficiency anaemia in children (Zeng 2007) is available.

Several countries are at the stage of implementing large-scale projects with home (point-of-use) fortification of foods with MNP, so a systematic review on the effectiveness and safety of this intervention is urgently needed to help guide programmes on the effectiveness and safety, as well as on the appropriate dose, frequency and duration, of this intervention. This review is focused on nutrition, health and developmental outcomes in infants and young children whose food is fortified with multiple micronutrients, particularly iron, zinc and vitamin A, before consumption. We include the effects of this intervention on morbidity outcomes in malaria-endemic areas.

OBJECTIVES

To assess the effects and safety of home (point-of-use) fortification of foods with multiple micronutrient powders on nutritional, health and developmental outcomes in children under two years of age.

For the purpose of this review, home fortification with multiple micronutrient powders refers to the addition of these powders containing vitamins and minerals to semi-solid foods immediately before consumption. This can be done at home or in any other place where meals are to be consumed (for example, schools or refugee camps) and thus is also referred to as point-of-use fortification.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials and quasi-randomised trials with either individual or cluster randomisation.

Types of participants

Infants and young children aged six to 23 months at the start of the intervention. Infants under six months are not included as exclusive breastfeeding is recommended from birth to six months. We intended to include apparently healthy children from the general population, although some may be at risk of having highly prevalent diseases such as malaria, diarrhoea or even undernutrition.

Types of interventions

Micronutrient powders (MNP) including at least the three micronutrients iron, zinc and vitamin A. We considered trials where the MNP were given to whole families (added to the family meal) provided that the results are presented separately for our population. We included MNP given at point of care for any dose, frequency and duration.

The comparison groups included no intervention, placebo or usual supplementation as follows.

1. Home (point-of-use) fortification of foods with MNP versus no intervention or placebo.
2. Home (point-of-use) fortification of foods with MNP versus iron only supplement.
3. Home (point-of-use) fortification of foods with MNP versus iron and folic acid supplements.
4. Home (point-of-use) fortification of foods with MNP versus the same multiple micronutrients as supplements.

Interventions that combined home provision of MNP for home (point-of-use) fortification with co-interventions such as education or other approaches were included only if the other co-interventions were the same in both the intervention and comparison groups. We excluded studies examining supplementary food-based interventions with lipid-based supplements, micronutrient crushable tablets, fortified complementary foods and other fortified foods.

Types of outcome measures

Primary outcomes

1. Anaemia (defined as haemoglobin values lower than 110 g/L)
2. Iron deficiency (as defined by trialists)
3. Haemoglobin concentration (g/L)
4. Iron status (as defined by trialists)
5. Weight-for-age (Z-scores)
6. All-cause mortality

Secondary outcomes

1. Length-for-age (Z-scores)
2. Weight-for-height (Z-scores)
3. All-cause morbidity
4. Side effects (such as staining of teeth, vomiting, stool discolouration, constipation, coughing)
5. Diarrhoea
6. Upper respiratory tract infections
7. Ear infections
8. Iron overload
9. Serum retinol concentration (µmol/L)
10. Serum zinc concentration (g/dL)
11. Mental development and motor skill development (as defined by trialists, for example it might include the Bayley Mental Development Index, Bayley Psychomotor Development Index, Stanford-Binet Test, DENVER II Developmental Screening Test)

For populations in malaria-endemic areas we will report two additional outcomes:

- malaria incidence;
- malaria severity.

We presented adverse effects were presented separately for each outcome. We planned to group the outcome time points as follows: immediately after the end of the intervention, one to six months after the end of the intervention, and seven to 12 months after the end of the intervention. However, we limited our analyses to the end of the intervention as only one trial reported on continued follow-up after the end of the intervention, and only for the intervention arm. We have described this in the Characteristics of included studies and plan to extract this information in future updates, if available.

We recorded other relevant outcomes reported by trial authors and labelled these as 'not prespecified'.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases.

Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*). Searched 18 February 2011.

MEDLINE (1948 to week 2 February 2011). Searched 18 February 2011.

EMBASE (1980 to Week 6 2011). Searched 18 February 2011.

African Index Medicus. Searched 23 February 2011.
CINAHL (1937 to current). Searched 20 February 2011.
Conference Proceedings Citation Index - Science (1990 to 19 February 2011). Searched 21 February 2011.
LILACS. Searched 21 February 2011.
POPLINE. Searched 21 February 2011.
Science Citation Index (1970 to 19 February 2011). Searched 21 February 2011.
WHO International Clinical Trials Registry Platform (ICTRP). Searched 23 February 2011.
metaRegister of Clinical Trials. Searched 23 February 2011.
ClinicalTrials.gov. Searched 23 February 2011.
The search strategies for each database are in Appendix 1.
We did not apply any date or language restrictions, and no translation of relevant data was necessary.

Searching other resources

We searched through the bibliographies of included studies and asked authors of included studies for lists of other studies that should be considered for inclusion. For assistance in identifying ongoing or unpublished studies, on 25 January 2011 we contacted the Sprinkles Global Health Initiative, the Home Fortification Technical Advisory Group, the nutrition section of the United Nations Children's Fund (UNICEF), the World Food Programme (WFP), the Micronutrient Initiative (MI), the Global Alliance for Improved Nutrition (GAIN), Helen Keller International (HKI), Sight and Life Foundation, the Departments of Nutrition for Health and Development from the World Health Organization (WHO) and the U.S. Centers for Disease Control and Prevention (CDC).
The International Clinical Trials Registry Platform (ICTRP) was also searched for any ongoing or planned trials (24 January 2011). We did not apply any language restrictions.

Data collection and analysis

Selection of studies

LMD screened all the titles and GEV assessed all of the selected abstracts, while SW, PSS and JPR each assessed a third. LMD and GEV both independently assessed the potentially relevant references in full text for inclusion according to the above inclusion criteria. We resolved any disagreement through discussion or, if required, we consulted one of the other review authors. Two review authors (LMD and JPR) assessed the eligibility of trials identified through other sources.
If studies were published only as abstracts, or study reports contained little information on methods, we attempted to contact the authors to obtain further details on the study design, population and intervention to properly assess the eligibility.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors independently extracted the data using the agreed form. Each study was extracted in duplicate. We resolved discrepancies through discussion. We attempted to extract the data for children aged six to 23 months from those studies targeted at broader age groups. We entered data into Review Manager 5 (RevMan) software (RevMan 2011) and carried out checks for accuracy.
When information regarding the methods and results was unclear, we contacted the authors of the original reports for further details. If there was insufficient information for us to be able to assess risk of bias, we placed studies under 'awaiting assessment' until further information is published or made available to us.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

1. Sequence generation (checking for possible selection bias).
2. Allocation concealment (checking for possible selection bias).
3. Blinding (checking for possible performance bias and detection bias).
4. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations).
5. Selective reporting bias (checking if expected outcomes were reported).
6. Other sources of bias (such as stopping the trial early or changing methods during the trial).

We made explicit judgements about whether studies were at high, low or unclear risk of bias according to the criteria given in the Handbook (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact the findings. We resolved any disagreement by discussion or by involving a third assessor.
The main findings of the review are set out in summary of findings (SoF) tables prepared using GRADE profiler software (GRADEpro 2008). The primary outcomes for each comparison have been listed with estimates of relative effects along with the number of participants and studies contributing data for those outcomes. For each individual outcome the quality of the evidence has been assessed independently by two review authors using the GRADE approach (Balshem 2010), which involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias. The results are expressed as one of four levels of quality (high, moderate, low or very low). This assessment was limited only to the randomised trials included in this review.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as average risk ratio (RR) with 95% confidence interval (CI).

Continuous data

For continuous data, we used mean difference (MD) with standard deviation if outcomes were measured in the same way between trials. There was no need to use the standardized mean difference (SMD) to combine trials that measured the same outcome but used different units of measurement.

Unit of analysis issues

Cluster-randomised trials

We combined cluster and individually-randomised trial results. All the cluster trials reported that the sample size was calculated taking into account the effect of clustering in data. We obtained the intra-cluster correlation co-efficient (ICC) for primary outcomes from two trials (Menon 2007; Suchdev 2011). We imputed the ICCs from Suchdev 2011 to other trials that did not provide this information (Hirve 2007; Lundeen 2010), as appropriate, and calculated their effective sample size. The results of one trial (Christofides 2006) were not adjusted as the average cluster size was 1.1. Some trials reported that the sample size calculation considered a design effect of 2.0 to account for clustering and we have used this value, along with the average cluster size in each trial, to obtain a plausible range of intra-cluster correlation coefficients. We then conducted sensitivity analyses to examine the potential effect of clustering on the confidence intervals of the summary estimates. As the confidence intervals did not change significantly (5%), we do not report the results of the sensitivity analysis.

Studies with more than two treatment groups

For studies with more than two intervention groups (multi-arm studies), we included the directly relevant arm only (Higgins 2011). Each group was only included in the analysis once. If we came across a study that compared home (point-of-use) fortification of foods with MNP with two of our comparison possibilities, then we combined groups, where possible, to create a single pairwise comparison (Higgins 2011).

Dealing with missing data

We noted levels of attrition in all the included studies. None of the included studies had high levels of attrition (all < 20%) so we did not use sensitivity analysis to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect.

For all outcomes we carried out analyses, as far as possible, on an intention-to-treat basis. We conducted analysis using available cases and we conducted sensitivity tests (assuming worst-case scenario and assuming best-case scenario) for the four primary outcomes.

For continuous measures, where necessary, we used actual measures (no imputations).

Assessment of heterogeneity

We examined the forest plots from the meta-analyses to look for heterogeneity among studies. We considered the size and direction of effect and used the I^2 and Chi^2 statistics to quantify the level of heterogeneity among the trials in each analysis. If we identified substantial heterogeneity (I^2 between 30% and 100%), we noted this in the text and explored it by prespecified subgroup analyses. We advise caution in the interpretation of those results where there were high levels of unexplained heterogeneity.

Assessment of reporting biases

Where we suspected reporting bias (see 'Selective reporting bias' above), we contacted study authors asking them to provide missing outcome data or clarifications about the study design. We advise caution in the interpretation of those results where we suspected outcome reporting bias.

We planned to use funnel plots to investigate the relationship between effect size and standard error but this was not possible as we did not have enough studies to have a powered test.

Data synthesis

We carried out statistical analysis using RevMan (RevMan 2011). We expected there would be differences between trials in both the population and the intervention, so we used random-effects meta-analysis for combining data.

Subgroup analysis and investigation of heterogeneity

We planned to conduct several subgroup analyses irrespective of heterogeneity. We interpreted all subgroup analyses cautiously. The planned subgroups arose from current clinical dilemmas and uncertainties (see Background). We explored subgroup analyses on the primary outcomes based on the following criteria.

1. By anaemic status of participants at start of intervention: anaemia defined as haemoglobin values < 110 g/L, anaemic, non-anaemic or unknown anaemic status.
2. By iron status of participants at start of intervention: iron deficient, not iron deficient or unknown, as defined by trialists.
3. By age of participants at the start of the intervention: six to 11 months, 12 to 17 months, 18 to 23 months.
4. By refugee status: yes, no.
5. By malaria status of the area at the time of the trial: yes, no, as reported by trialists.
6. By frequency: daily versus weekly versus flexible.

7. By duration of intervention: less than six months versus six months or more.

8. By elemental iron content of product: less than 12.5 mg versus 12.5 mg or more.

9. By zinc content of product: less than 5 mg versus 5 mg or more.

For the comparisons related to malaria-endemic areas, we planned to conduct a subgroup analysis by treatment and prevention of malaria but no information was available.

Sensitivity analysis

We carried out sensitivity analysis to examine the effects of removing studies at high risk of bias (studies with poor or unclear allocation concealment and either blinding or loss to follow-up) from the analysis and of including studies with children six to 59 months of age from which it was not possible to extract information only for children aged six to 23 months.

RESULTS

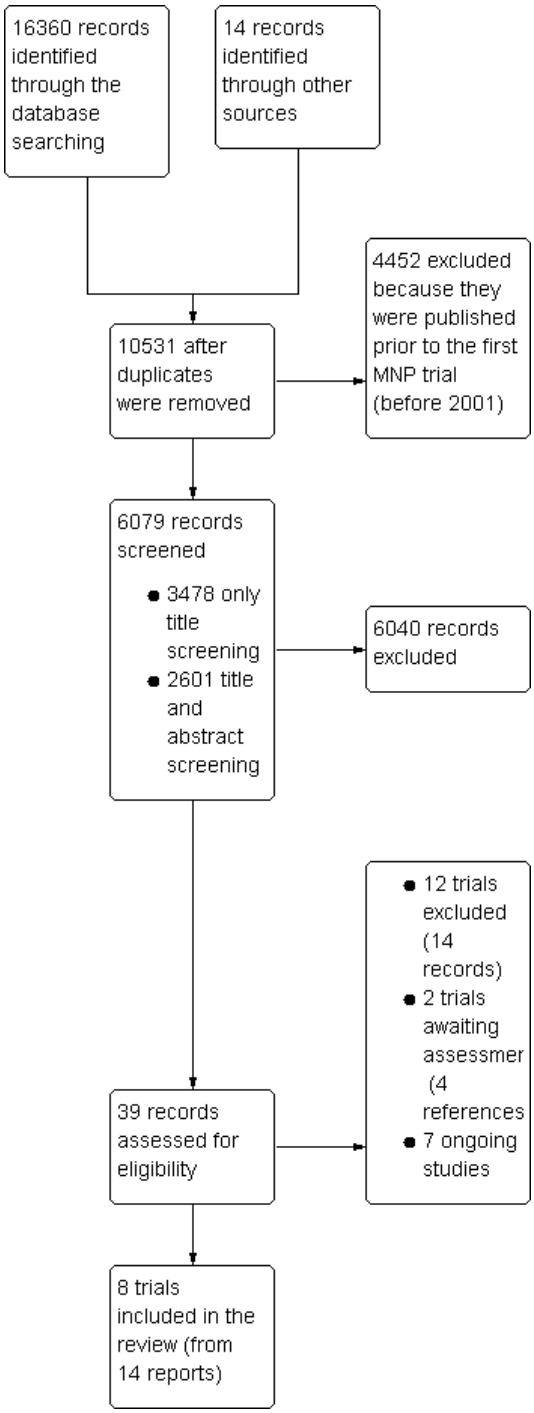
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

The search strategy identified 16,374 references for possible inclusion; 5843 of which were duplicated references. Figure 1 depicts the process for assessing and selecting the studies. We included eight trials (Christofides 2006; Giovannini 2006; Sharieff 2006a; Adu-Afarwuah 2007; Hirve 2007; Menon 2007; Lundeen 2010; Suchdev 2011) and excluded 12. Two are awaiting assessment (Neufeld 2008; Bilenko 2010) and seven studies are still ongoing (Fitzsimons 2009; Jack 2008; Ribeiro Da Costa 2009; van der Kam 2010; Zavaleta 2010; Zimmermann 2010; Zlotkin 2010). All the included studies contributed data in this review.

Figure 1. Study flow diagram



Included studies

Intervention

We included eight trials; six of them (Giovannini 2006; Sharieff 2006a; Adu-Afarwuah 2007; Menon 2007; Lundeen 2010; Suchdev 2011) evaluated the effects of the provision of MNP versus no intervention or placebo (comparison 1). Two trials (Christofides 2006; Hirve 2007) compared the effects of the provision of MNP versus iron drops or syrup (comparison 2). No studies compared provision of MNP versus iron and folic acid supplements (comparison 3) or versus multiple vitamin and mineral supplements (comparison 4). The interventions lasted between two and 12 months; and one study reported a follow-up period of seven months post-end of the intervention, albeit it did not provide data for the comparison group (Menon 2007).

Settings

The studies included in the review were carried out over the last five years in low income countries in Asia, Africa and the Caribbean where anaemia is a public health problem (that is more than 40% of the population are affected): Cambodia (Giovannini 2006), Ghana (Christofides 2006; Adu-Afarwuah 2007), Haiti (Menon 2007), India (Hirve 2007), Kenya (Suchdev 2011), Kyrzgyz Republic (Lundeen 2010), and Pakistan (Sharieff 2006a). None of the included trials enrolled only non-anaemic children. Five of the studies were described as having been performed in malaria-endemic areas (Christofides 2006; Giovannini 2006; Adu-Afarwuah 2007; Menon 2007; Suchdev 2011). It was unclear from the reports whether malaria prevention and control programmes were in place in the study sites or whether concomitant malaria interventions were made available for study participants.

Participants

The participant age range was from six to 36 months. When possible, we included data only for children less than 24 months of age. All the studies included children of both sexes. The sample sizes ranged from 133 to 1869 children, however the analyses only include the estimated effective sample size after adjusting the data to account for the clustering effect.

Vitamin and minerals composition

In one study, MNP were formulated with 15 micronutrients (Suchdev 2011); in three trials the MNP formulation contained six micronutrients (Giovannini 2006; Sharieff 2006a; Adu-Afarwuah 2007) and in four trials the MNP provided five micronutrients (Hirve 2007; Menon 2007; Lundeen 2010). All of them provided 12.5 mg of elemental iron (as ferrous fumarate) in one of the study arms, although two trials (Christofides 2006; Hirve 2007) also tested micronized ferrous pyrophosphate as the iron compound and three dosages of elemental iron (as ferrous fumarate): 12.5 mg, 20 mg or 30 mg. The 5 mg amount of elemental zinc (as gluconate) was a constant across trials. The content of vitamin A in the MNP was 300 μg vitamin A in five trials (Christofides 2006; Giovannini 2006; Sharieff 2006a; Adu-Afarwuah 2007; Hirve 2007; Lundeen 2010) and 400 μg vitamin A in two trials (Menon 2007; Suchdev 2011). All the trials also provided folic acid as part of the MNP formulations.

See the table Characteristics of included studies for a detailed description of all the studies.

Excluded studies

We excluded 12 trials. Three studies assessed interventions with micronutrient powders but provided only one or two of the relevant micronutrients (Zlotkin 2003a; Zlotkin 2003b; Zlotkin 2001); two trials evaluated food-like tablets (Smuts 2005; Wijaya-Erhardt 2007); one trial assessed fortification of rice for use in childcare centre meals (Bagni 2009); another compared MNP versus multivitamin supplements (drops) but the drops did not include all three micronutrients we used as inclusion criteria: vitamin A, iron and zinc (Geltman 2009). Another trial (Ip 2009) was excluded because it did not include any of the comparisons of interest (for example, it did not compare MNP versus placebo or supplements). Other trials were excluded because the participants were in other age groups, such as two to six years of age (Chen 2008) or children three to six years of age (Sharieff 2006b), school age children five to 11 years of age (Troesch 2011) or young women (Troesch 2009).

See the Characteristics of excluded studies table for a detailed description of the studies and the reasons for exclusion.

Risk of bias in included studies

See the risk of bias tables included in Characteristics of included studies for an assessment of the risk of bias for each included trial and Figure 2 and Figure 3 for an overall summary of the risk of bias of all included trials. With the single exception of Adu-Afarwuah 2007, all trials were of high quality according to our pre-established criteria. We considered studies to be of high quality if they were assessed as having low risk of bias for random sequence generation, low risk of bias for allocation concealment (selection bias) and were also rated as low risk of bias for either blinding (performance or detection bias) or incomplete outcome data (attrition bias).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

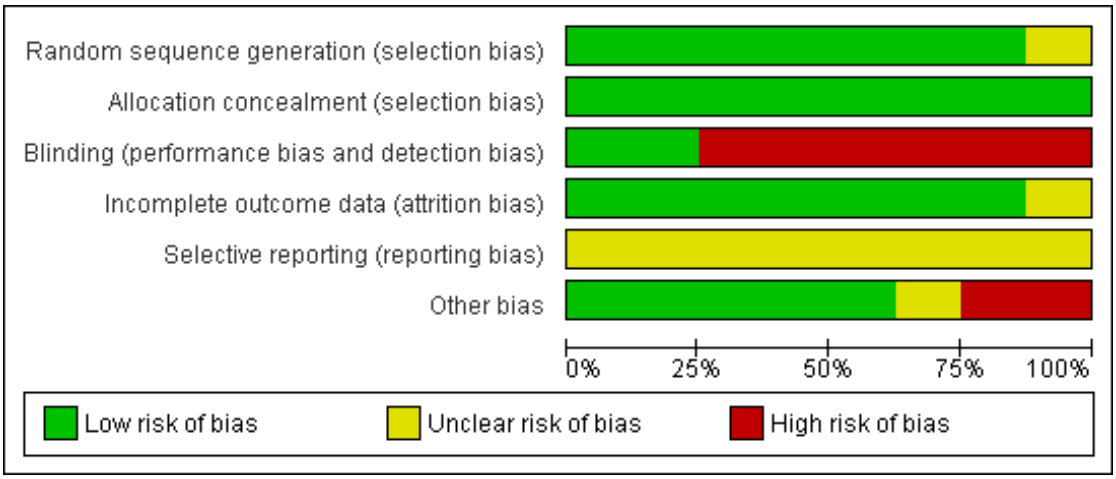
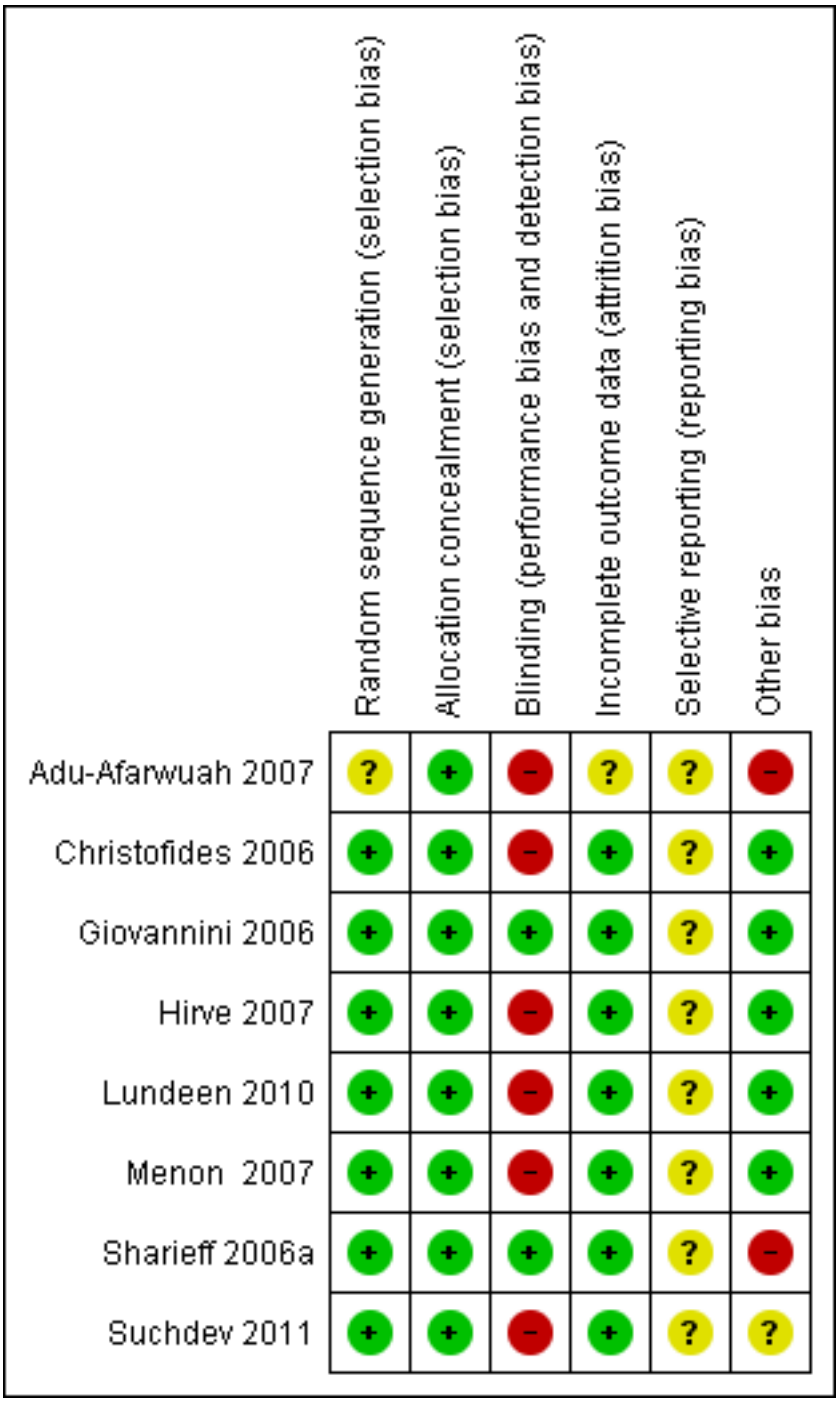


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



In the 'Summary of findings' tables, we present the overall quality of the evidence for each primary outcome, by comparison (Summary of findings for the main comparison; Summary of findings 2).

Allocation

We assessed seven trials as having adequate methods for generating the randomisation sequence (Christofides 2006; Giovannini 2006; Sharieff 2006a; Hirve 2007; Menon 2007; Bagni 2009; Lundeen 2010). One trial allocated the interventions randomly but not the group receiving no intervention, although it was randomly selected from the original population (Adu-Afarwuah 2007).
Five trials were randomised at cluster level (Christofides 2006; Hirve 2007; Menon 2007; Lundeen 2010; Suchdev 2011).

Blinding

Investigators in two trials attempted to blind participants, caregivers and staff by using placebos of similar appearance to the active treatment or coded or opaque bottles (Giovannini 2006; Sharieff 2006a).

Incomplete outcome data

We judged that trials with more than 20% loss to follow-up, or with imbalanced loss to follow-up in different arms of trials, were inadequate in terms of completeness of outcome data. Seven trials were judged to be at low risk of bias as the highest rate of loss to follow-up was 19% (Suchdev 2011). Adu-Afarwuah 2007 had an unclear risk of bias.

Selective reporting

We did not formally assess outcome reporting bias; for most of the included trials we did not have access to study protocols and assessing outcome reporting bias from published reports alone can be difficult. Additionaly, given the small number of trials, we were not able to generate funnel plots to investigate the relationship between effect size and standard error.

Other potential sources of bias

We have noted other concerns about studies in the notes and other risk of bias sections of the Characteristics of included studies tables.

Effects of interventions

See: **Summary of findings for the main comparison** Provision of multiple micronutrient powders versus placebo or no intervention in children less than 2 years; **Summary of findings 2** Provision of multiple micronutrient powders versus iron supplements in children less than 2 years

In this review we have included eight trials, involving 3748 children; however in trials that had more than two treatment arms we may not have included all arms in our analyses. We have organised the summary results by the different comparisons and by primary and secondary outcomes. Most of the included studies focused on anaemia and haematological indices, and few reported on any of the other prespecified outcomes in the protocol. Because all the results showed significant heterogeneity that could not be explained by standard sensitivity analyses, including quality assessment, we used a random-effects model to analyse the results.
See the Data and analyses section for detailed results on the primary and secondary outcomes.

1. Home (point-of-use) fortification of foods with MNP versus no intervention or placebo

Six trials including 3182 children under two years of age examined this comparison (Giovannini 2006; Sharieff 2006a; Adu-Afarwuah 2007; Menon 2007; Lundeen 2010; Suchdev 2011).

Primary outcomes

Anaemia (defined as haemoglobin values < 110 g/L)

All included trials evaluated this outcome. Children receiving multiple micronutrient powders were significantly less likely to have anaemia at follow-up than those children receiving no treatment or a placebo (average risk ratio (RR) 0.69; 95% confidence interval (CI) 0.60 to 0.78) (Analysis 1.1). The risk remained almost the same after removing the one low quality trial (Adu-Afarwuah 2007) from the analysis (RR 0.69; 95% CI 0.59 to 0.80).
The visual examination of the subgroup analyses indicated that the intervention appeared equally effective in populations with different anaemia prevalence; among all infants six months to 23 months of age whether the intervention lasted two months or six or more months; and in settings described as malaria-endemic when compared with settings where malaria cases were sporadic.

Iron deficiency (as defined by trialists)

Four trials with 586 children (Giovannini 2006; Sharieff 2006a; Adu-Afarwuah 2007; Suchdev 2011) indicated that those children receiving MNP were significantly less likely to have iron deficiency at follow-up than those children receiving no treatment or a placebo (RR 0.49; 95% CI 0.35 to 0.67). There were no apparent differences among subgroups. The RR after removing

Adu-Afarwuah 2007 from the analysis was 0.46 (95% CI 0.26 to 0.82).

Haemoglobin concentration (g/L)

All the six included trials evaluated this outcome. Compared to children receiving no treatment or placebo, children receiving MNP had a 5.87 g/L higher haemoglobin concentration at follow-up (mean difference (MD) 5.87 g/L; 95% CI 3.25 to 8.49). There were no obvious differences among subgroups. The mean haemoglobin difference after removing Adu-Afarwuah 2007 from the analysis was 6.14 g/L (95% CI 3.13 to 9.15).

Iron status (as defined by trialists)

Two trials (n = 264) (Giovannini 2006; Adu-Afarwuah 2007) provided information on ferritin concentrations. On average, children receiving multiple micronutrient powders had 20.73 ng of ferritin more per mL at follow-up than those children receiving no treatment or a placebo (mean difference (MD) 20.38 ng/mL; 95% CI 6.27 to 34.49). Both trials were included in the same subgroups. The ferritin difference after removing Adu-Afarwuah 2007 from the analysis was 13.10 ng/mL (95% CI 4.38 to 21.82).

Weight-for-age (Z-scores)

Two trials with 304 children (Giovannini 2006; Adu-Afarwuah 2007) in which the intervention was given for six and 12 months did not find a significant effect on weight-for-age (MD 0.00; 95% CI -0.37 to 0.37). We did not perform a subgroup analysis as both trials were very similar and were included in the same subgroup category. The Z-score difference after removing Adu-Afarwuah 2007 from the analysis was -0.17 (95% CI -0.41 to 0.07).

All-cause mortality

One trial (Giovannini 2006) stated that no deaths occurred over the 12 month intervention period. In one of the trials, two deaths were reported after the intervention was finalized but were judged not to be related to the study (Hirve 2007).

Secondary outcomes

Length-for-age and weight-for-height (Z-scores)

Two trials with 304 children (Giovannini 2006; Adu-Afarwuah 2007) in which the intervention was given for six and 12 months, respectively, did not find a significant effect on length-for-age Z-scores (MD 0.04; 95% CI -0.15 to 0.23) or weight-for-height Z-scores (MD 0.44; 95% CI -0.44 to 0.52). We did not perform a subgroup analysis as both trials were very similar and were included in the same subgroup category.

Diarrhoea

It was not possible to pool the results due to the differences in the definitions of this indicator. In one trial (Menon 2007) children receiving MNP were on the borderline of having more diarrhoea that those who received placebo during the first month of intervention; thereafter both groups showed a similar prevalence (Analysis 1.13). In 8.9% of the participants, recurrent diarrhoeal diseases were accompanied by recurrent respiratory infections and were more prevalent in children who received MNP than those receiving placebo but this was not statistically significant (Analysis 1.11).

Recurrent diarrhoea (we did not prespecify this outcome)

One trial (Giovannini 2006) reported that seven children receiving MNP had recurrent diarrhoea (10%) versus four of the placebo group (6.4%) (Analysis 1.14).

Upper respiratory tract infections

Giovannini 2006 found that upper respiratory infections were equally prevalent among those children receiving MNP (7.6%) as in those allocated to the placebo group (6.5%) (Analysis 1.15).

Serum zinc concentration (g/dL)

One trial that reported this outcome (Adu-Afarwuah 2007) did not find an effect of daily provision of MNP with 5 mg of zinc for six months on children's serum zinc concentrations (Analysis 1.16).

Mental development and motor skill development (as defined by trialists)

One trial (Adu-Afarwuah 2007) reported that children receiving MNP were more likely to walk independently at 12 months of age than those receiving no intervention (RR 1.58; 95% CI 1.02 to 2.46).

Malaria outcomes

Although four studies were conducted in settings considered as malaria-endemic, only Adu-Afarwuah 2007 reported results on the presence of positive malaria smears and found that there were no differences between the study groups (Analysis 1.12).

Other outcomes

No studies reported on the outcomes we defined as all-cause morbidity, side effects, ear infections, iron overload, serum retinol concentrations or malaria incidence.

2. Home (point-of-use) fortification of foods with MNP versus iron supplements

Two studies including 565 children under two years of age examined this comparison (Christofides 2006; Hirve 2007).

Primary outcomes

Anaemia (defined as haemoglobin values < 110 g/L)

Hirve 2007 found that after two months of follow-up there were no statistical differences in anaemia (RR 0.89; 95% CI 0.58 to 1.39) between the children who received MNP with five nutrients and those supplemented with iron drops (Analysis 2.1).

Haemoglobin concentration (g/L)

Data from the two trials showed that there was no evidence that haemoglobin concentrations were different between the groups receiving the multiple micronutrient powders or the iron supplements (RR -2.36; CI -10.30, 5.58) (Analysis 2.2).

Secondary outcomes

Side effects

Data from the two trials showed that children receiving MNP were less likely to have stained teeth than those receiving iron syrup daily (Analysis 2.6).

Diarrhoea (and vomiting)

Hirve 2007 reported that children receiving MNP were less likely to have vomiting, diarrhoea and recurrent diarrhoea than those receiving daily iron supplements (RR 0.52; 95% CI 0.38 to 0.72). Christofides 2006 and Hirve 2007 found that differences in the mean number of episodes of diarrhoea per child between interventions were not significant (Analysis 2.4).

Other outcomes

No studies reported on the outcomes we defined as iron deficiency, iron status, weight-for-age, all-cause mortality, length-for-age, weight-for-age, all-cause morbidity, upper respiratory tract infections, ear infections, iron overload, serum retinol concentration, serum zinc concentration, mental development and motor skill development, malaria incidence and malaria severity.

3. Home (point-of-use) fortification of foods with MNP versus iron and folic acid supplements

No studies were included in this comparison.

4. Home (point-of-use) fortification of foods with MNP versus same multiple micronutrients as supplements

No studies were included in this comparison.

Subgroup analysis

We planned to conduct a subgroup analysis for all primary outcomes in all comparisons to look for possible differences between studies by anaemia and iron status at the beginning of the intervention, age of the children, refugee and malaria-endemic settings, frequency of the provision of MNP, duration of the intervention, and iron and zinc content in the MNP formulations. As not all the trials contributed data to all the outcomes examined, and only two trials were included in comparison 2, we pragmatically decided not to conduct a subgroup analyses for those outcomes with three trials or fewer.

For several subgroup comparisons all the trials were in the same subgroup category. In the subgroup analysis we provided subtotals for each subgroup and visual examination of the forest plots suggested that there were no clear differences between groups; for most outcomes there was considerable overlap in the confidence intervals for the effects of intervention in different subgroups.

As more data become available with updates of the review, we hope to explore possible subgroup differences by carrying out formal statistical tests. In the results below, we have drawn attention to any findings in subgroups that may assist in the interpretation of results.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Patient or population: children 6 to 23 months
Settings: community settings
Intervention: home fortification with multiple micronutrient powders
Comparison: iron supplements

Outcomes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
Anaemia	**RR 0.89** (0.58 to 1.39)	145 (1 study)	**low** [1]
Iron deficiency	Not estimable	0 (0)	None of the trials reported on this outcome.
Haemoglobin (g/L)	**MD -2.36** (-10.30 to 5.59)	278 (2 studies)	**low** [2,3]
Iron status (ferritin concentrations in ng/mL)	**0**	0 (0)	None of the trials reported on this outcome.
Weight-for-age Z-score	**0**	0 (0)	None of the trials reported on this outcome.
All-cause mortality	**0**	0 (0)	None of the trials reported on this outcome.

CI: Confidence interval; **RR:** Risk ratio;
GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Only one study reported on this outcome; it is a relatively small study and assessors downgraded for this.
[2] There was considerable statistical heterogeneity and inconsistency in the results between trials.
[3] There was imprecision in the results

DISCUSSION

Summary of main results

We have included eight trials in this review, six of which compared groups of children receiving MNP to groups receiving no treatment or placebo. Results show that provision of MNP to infants and children under two years of age reduced anaemia by 31% at

the end of the intervention, and those who received the intervention had significantly higher haemoglobin and ferritin concentrations in comparison with infants and children who did not receive the intervention or received a placebo. There were no effects on any of the growth measurements or on zinc status. The haematological effects of MNP seemed comparable to those observed with daily oral iron supplementation with drops; however, given the small number of trials evaluating the equivalence between both interventions, the results should be cautiously interpreted.

Although the real effect of an intervention is context-specific, the provision of MNP was effective in various settings including in populations with a high prevalence of anaemia (25% to 100%) and when provided for two months or for six months, or more, and to all infants and young children six to 23 months of age.

Data on side effects and morbidity are scarce and definitions for each of the outcomes were variable among trials, making it difficult to assess the overall safety of this intervention (for example, diarrhoea was reported as the average number of episodes of diarrhoea per child, longitudinal diarrhoea or number of children with at least one episode of diarrhoea). Nonetheless, none of the trials reported deaths attributable to the intervention and the pattern of disease seemed similar to that of children receiving placebo or no intervention. It is clear that a standardized approach to reporting side effects and morbidity is needed as well as improved malaria surveillance and reporting in trials conducted in malaria settings.

Overall completeness and applicability of evidence

The use of micronutrient powders that contain iron, zinc and vitamin A in children less than two years of age significantly reduces the prevalence of anaemia and iron deficiency in populations with high prevalence of anaemia, but there is not sufficient information to assess the effect on other health and nutrition outcomes.

Home fortification with MNP is a novel approach to increase vitamin and mineral intake that has rapidly expanded worldwide. Although doses as high as 80 mg of elemental iron per day were initially used to test the efficacy of this intervention and its equivalence to 40 mg of iron given as drops (Zlotkin 2001; Zlotkin 2003a), the widely used dose of 12.5 mg of elemental iron per sachet is based on the recommended daily dose to supplement children aged six to 23 months for iron deficiency anaemia prevention (INACG 1998; WHO 2001). Its effectiveness was confirmed by a dose response trial in which 12.5 mg of elemental iron (as encapsulated ferrous fumarate) was as effective as 20 mg and 30 mg of iron in the same form and 20 mg of elemental iron (as ferrous sulphate drops) to improve haemoglobin and ferritin concentrations of anaemic children aged six to 18 months (Hirve 2007).

Most of the evidence included in this review examines a dose of 12.5 mg of iron given on a daily basis. However, other studies suggest that providing this intervention in a flexible or intermittent regimen for two to four months, and hence a lower overall monthly dose, produces the same haematological response as daily use of MNP (Sharieff 2006b; Hyder 2007; Ip 2009). For example, it has been reported that the weekly provision of MNP containing 30 mg of elemental iron was as effective as the daily provision of MNP with 12.5 mg of elemental iron in anaemic infants six to 23 months old (Hyder 2007) and non-anaemic school-aged children (Sharieff 2006b). The intermittent provision of iron was proposed more than 25 years ago as a feasible public health strategy to supplement children's and women's diet and to reduce anaemia as it is supposed to maximize absorption by provision of iron in synchrony with the turnover of the mucosal cells (Berger 1997; Viteri 1997; Beaton 1999).

The lasting effect of the benefits of using MNP on haematological outcomes is still unclear. However, evidence from two studies suggests that, independently of the dosing regimen, the positive effects of MNP on anaemia prevalence may be maintained for a period of approximately six months after the end of the intervention (Menon 2007; Ip 2009).

MNP can be prepared in various formulations, but for inclusion in this review they had to contain zinc, vitamin A and iron. In the included studies these three nutrients were always accompanied by folic acid and vitamin C; in two studies also by vitamin D; and in only one case were they part of a 15 micronutrient formulation (WHO/WFP/UNICEF 2007). Leaving aside iron, only one trial evaluated the effect of this intervention on vitamin A deficiency (Suchdev 2011) and another on zinc status (Sharieff 2006a). The addition of 5 mg of elemental zinc, which is a lower dose than that recommended to treat diarrhoea (WHO/UNICEF 2004) but is sufficient to avoid competition with iron for sites of absorption, was efficacious in reducing the incidence of longitudinal diarrhoea among Pakistani infants (Sharieff 2006a). This finding was not confirmed with certainty by other trials because the incidence (and recurrence) of morbidity and side effects were not reported in a standardized way, and frequently they were under-reported.

It is difficult to assess the safety of this intervention in malaria settings. Although no deaths were reported, none of the five trials conducted in malarial areas reported malaria incidence. Only one trial (Adu-Afarwuah 2007) included data on positive malaria smears post-intervention, with no differences between children receiving MNP and those receiving no intervention.

Albeit they were not specific outcomes of this review, it is well-known that adherence and acceptability of a product are instrumental for an intervention to be implemented successfully. Overall, multiple micronutrient powders seem to be well accepted by infants, with fewer 'dislike faces', and caregivers. Formative research in Kenya shows that children eat food with MNP without problems and that the key benefits associated with this intervention are prevention of anaemia and avoidance of treatment for anaemia, such as blood transfusions (Jefferds 2010). The results of the randomised controlled trials (RCT) included in this review, along with some RCT that were excluded because of the number

of nutrients, show that the acceptance of the intervention is not always translated into better adherence. High adherence (defined as consumption of four sachets or more per week) to daily provision of MNP has ranged from 32% to around 90% (Zlotkin 2001; Giovannini 2006; Geltman 2009), and the highest adherence has been observed in those trials in which children received the product on an intermittent basis (Ip 2009; Hyder 2007). This may be related to the perception of an intermittent regimen as one that produces less mental pressure and anxiety among caregivers (Ip 2009). Adherence to MNP has not always proven to be higher than daily iron supplementation with drops. Geltman 2009 found that high adherence ranged from 32% to 63% at any assessment in the participants receiving iron drops compared with 30% to 46% in those receiving MNP. This result is consistent with the findings of other trials (Zlotkin 2003a; Zlotkin 2001).

Quality of the evidence

Although not all reports included detailed information on the methods followed in the studies, an effort was made to contact authors in order to obtain more data. Only one study was classified as at high risk of bias and its exclusion from the analyses in a sensitivity analysis did not affect the significance of the results and hence the review's conclusions. Blinding of mothers or caregivers, care providers and outcome assessors was not attempted in 75% of the trials although in some studies technical staff carrying out laboratory investigations were reported to be unaware of group allocation. While for some outcomes the lack of blinding is unlikely to have an impact on results (for example, anaemia), for others (for example, maternal reports on infant's side effects) lack of blinding may represent a potentially serious source of bias. Attrition was not considered a serious problem in the included studies.

When the provision of MNP was compared with a placebo, the overall quality of the evidence for iron deficiency was high whereas it was moderate for anaemia, haemoglobin concentration and growth, and low for iron status.

Potential biases in the review process

We were aware of the possibility of introducing bias at every stage of the review process. In this review we tried to minimize bias in a number of ways as two review authors assessed eligibility for inclusion, carried out data extraction and assessed risk of bias. Each worked independently. Nevertheless, the process of assessing risk of bias, for example, is not an exact science and includes many personal judgements. Further, the process of reviewing research studies is known to be affected by prior beliefs and attitudes. It is difficult to control for this type of bias in the reviewing process.

Since this intervention is very recent and well-known among implementing agencies, and they were contacted as part of the search strategy, we consider there is minimal risk of publication bias.

Agreements and disagreements with other studies or reviews

A systematic review on the efficacy and effectiveness of complementary feeding interventions carried out in developing countries evaluated various interventions that targeted children within the age range of six to 24 months (Dewey 2009). The interventions assessed included fortification of complementary foods with micronutrients (centrally processed fortified foods or home fortification products with or without additional energy). The authors restricted the evaluation of MNP specifically to anaemia prevention and included two other types of micronutrient supplements that were added to home-prepared complementary foods: crushable tablets and fat-based products. They concluded that fortification of complementary foods (either processed complementary foods or home fortification) was a feasible option in most circumstances given the cost of iron-rich foods (such as liver or meat) for complementary feeding. Home fortification requires little change in dietary practices thus allowing families to continue to use home-prepared or purchased complementary foods as the basis for the child's diet.

Our review focuses specifically on home fortification of foods with MNP, with an inclusion criterion that established three micronutrients of critical importance: iron, vitamin A and zinc, and assessed a broader spectrum of outcomes. We excluded other types of home fortification with lipid-based spreads or crushable tablets to isolate the effects of this single intervention.

An area of potential concern relates to iron interventions in areas of high malaria transmission. A technical working group convened by the US National Institutes of Health concluded that there was little evidence regarding the safety of iron-containing home fortification mixtures in malaria-endemic areas, and that there was no evidence that MNP are not safe, but recognized that no published studies have been designed to examine safety in malaria-endemic areas (NIH 2011). Our systematic review concurs with the results of this report and acknowledges the limitations of studies designed specifically to examine the safety of home fortification with multiple micronutrient powders in malaria-endemic areas on malarial outcomes. The limited evidence does not seem to suggest that there is an increased risk of mortality or morbidity associated with malaria, but ongoing trials specifically addressing this issue will help us to understand better any potential risks associated with the provision of iron through home fortification with multiple micronutrient powders.

Home fortification has been mostly targeted at infants and young children. The results of this review are only applicable to this age group. Another systematic review is underway to assess the benefits and safety of this intervention in preschool and school-age children (De-Regil 2011). The wealth of ongoing research in this area highlights the need to update the evidence appraisal when these results are available.

AUTHORS' CONCLUSIONS

Implications for practice

The use of MNP for home fortification of foods is an effective intervention to reduce anaemia and iron deficiency in infants and young children. This intervention can be integrated into strategies to prevent anaemia and reduce the risk of iron deficiency in infants and children aged six to 23 months, but its benefit in reducing the risk of other vitamins and mineral deficiencies has not yet been demonstrated. It can be assumed that improving the dietary intake of vitamins and minerals in the daily diet through this mechanism is beneficial but evidence is lacking as trials have mostly focused on iron deficiency and anaemia outcomes.

In this context, the dose of 12.5 mg of elemental iron (as ferrous fumarate) along with 5 mg of zinc and 300 μg of vitamin A has proven effective and the addition of other vitamins and minerals could be considered within the recommended nutrient intake levels for this age group. Other more bioavailable iron compounds may be used but to date the evidence is limited in this age group. The use of sodium iron-ethylenediamine tetraacetic acid (FeNaEDTA or iron-EDTA) as a more bioavailable source of iron may be feasible but consideration of safe levels of iron and EDTA, a common food additive in some baby foods, is important in order to avoid their excessive intake, particularly among infants.

The provision of the sachets seems to be well accepted by mothers and caregivers. Although the evidence is limited, in comparison to iron supplements (as drops or syrups), home fortification with MNP has similar benefits on haematological outcomes but is associated with less staining of teeth and stools discolouration. If iron supplementation programmes are not in place or are not successfully implemented, the use of multiple micronutrient powders for home fortification of foods can be considered a valid option for anaemia prevention in children six to 23 months of age.

A word of caution is that as this intervention involves the use of ready to eat food as a vehicle, it would be important to assure that basic sanitation is available and food hygiene and handling is done properly with safe water. Since all the trials were performed in low resource settings where sanitation tends to be poor, behavioural and communication campaigns should promote the appropriate use of MNP in addition to the hygienic preparation of complementary foods and hand washing (World Bank 2010).

The benefits of the use of MNP as a child survival strategy or on developmental outcomes are limited. Data on the effects on malaria outcomes are also lacking and further investigation is needed in malarial settings.

Implications for research

The results of this systematic review have highlighted the limited evidence in some areas that merit further research.

1. The side effects associated with home fortification with MNP in settings where infection and malnutrition are common needs to be explored in more depth, with emphasis on the harmonization of outcome definitions that will help better balance harms and benefits of this intervention in various contexts, particularly in areas with high transmission of malaria.

2. The use of other safe and efficacious iron compounds, or their combination, in the formulation of the vitamin and mineral micronutrient powders including the safe amounts of folic acid in areas with high malaria endemicity.

3. The effective regimen for distribution and consumption of MNP in intermittent or flexible schemes as an alternative to daily provision of MNP.

4. The efficacy and effectiveness of home fortification with multiple micronutrient powders in additional nutritional effects (i.e. improvement of iodine status, prevention of vitamin A deficiency) but also on important functional outcomes including growth and motor and cognitive skills

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Adu-Afarwuah 2007

Methods	This is an RCT with a non-randomised control group. Randomisation at individual level
Participants	409 infants of 6 months of age, both sexes, from Koforidua, Ghana. Inclusion criteria:1) 5 months of age, 2) receiving any breast milk, 3) not known to be asthmatic or allergic to peanuts, and 4) planning to stay at the study site during the next 7 months Around 25% of the children who received the interventions were anaemic at the beginning of the study
Interventions	313 infants were randomly allocated to one of the following groups: Group 1 (n=98): infants received daily a micronutrient powder containing 12.5 mg elemental iron (as ferrous fumarate), 5 mg zinc (as gluconate), 300 μg RE as β-carotene and 50 mg vitamin C, 7.5 μg vitamin D_3, 150 μg (0.15 mg) folic acid. Group 2 (n=102): infants received daily multiple micronutrient Nutritabs (crushable tablets) Group 3 (n=98): infants received daily multiple micronutrient Nutributter (lipid based supplement) The control group (n=96) did not receive an intervention. It was not randomised but randomly selected from the original population Length of the intervention: 6 months. For the purposes of this review, only group 1 and the control were included
Outcomes	Haemoglobin, iron status (ferritin (geometric mean), plasma ferritin <5, <12, TfR, TfR >11, IDA) plasma zinc and zinc <9.9, head circumference, positive malaria smear, observed motor milestone acquisition (ability to walk) and Z-scores for weight-for-age, length-for-age, and weight-for-length All the outcomes were measured when the infant were 12 months old, i.e. 6 months after start of the intervention There are no baseline measurements in the control group.
Notes	The percentage of children who had a positive malaria smear (at 12 months of age) ranged from 2 % to 8.3 % There were no significant differences between groups regarding the mothers' responses to most questions about acceptability of the supplements No differences on reported side effects among intervention groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random selection of 75% of the participants, who were randomly allocated to one of the intervention groups by using opaque envelopes. Control group (no-intervention) was not randomised but be-

Adu-Afarwuah 2007 (*Continued*)

		longs to the same sample population as the rest of the participants Even though the infants in the no-intervention group were eligible for the trial at the same place in time, and comparability may be assumed, it is not clear the criteria used by the authors to select the children since the paper states "40 were not randomly selected"
Allocation concealment (selection bias)	Low risk	See above. However, as the intervention to MNP was allocated by using opaque envelopes and the control group was not part of the original study, it may be possible that the concealment was adequate
Blinding (performance bias and detection bias) All outcomes	High risk	Not attempted for participants or caregivers, although outcome assessor were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Few dropouts in the randomised groups (4.7%) with no difference among groups It is impossible the assess the drop outs in the control group since it was not followed up. Overall, only 96 out of 170 of the eligible population were included for the final analysis (56.4%)
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	High risk	The control group does not have baseline values for any of the outcomes, making difficult to assess the comparability of the groups, particularly in indicators such as ferritin that shows large baseline variations among intervention groups, although not significant

Christofides 2006

Methods	Cluster-randomised clinical trial. 5-arm design with randomisation at housing compounds level
Participants	133 anaemic Ghanaian children aged 6 to18 months, both sexes, living in Kintampo district, Ghana during 2003. Inclusion criteria: temperature 37.5 °C or less, no history of iron supplementation within two weeks prior to recruitment, ingesting semi-solid or solid weaning foods. Exclusion criterion: severe anaemia (Hb < 70 g/L)

Interventions	127 clusters of housing compounds (n = 133 children) were randomised into five groups: Group 1 (n = 26, clusters 25): children received daily MNP containing 12.5 mg elemental iron (as microencapsulated ferrous fumarate), 5 mg zinc (as gluconate), 300 μg vitamin A and 30 mg ascorbic acid, 160 μg (0.16 mg) folic acid, 7.5 μg vitamin D (as cholecalciferol) Group 2 (n = 28, clusters 26): children received daily MNP with 20 mg elemental iron (as microencapsulated ferrous fumarate), 5 mg zinc (as gluconate), 300 μg vitamin A (as acetate) and 30 mg ascorbic acid, 160 μg (0.16 mg) folic acid Group 3 (n = 27, clusters 26): children received daily MNP with 30 mg elemental iron (as microencapsulated ferrous fumarate), 5 mg zinc (as gluconate), 300 μg vitamin A (as acetate) and 30 mg ascorbic acid, 160 μg (0.16 mg)folic acid Group 4 (n = 27, clusters 26): children received MNP daily containing 20 mg elemental iron (as micronized ferric pyrophosphate), 30 mg ascorbic acid, 300 μg vitamin A (as acetate), folic acid, and 5 mg zinc (as gluconate) Group 5 (n = 25, clusters 24): children received iron drops containing 15 mg elemental iron per mL (as ferrous glycine sulphate drops) daily, between meals Length of the intervention: 2 months. For the purposes of this review we have considered the four MNP together and compared with drops
Outcomes	Haemoglobin at 3 and 8 weeks post intervention, and serum ferritin, serum transferrin receptors and iron deficiency anaemia at 8 week post interventions Adherence, ease of use, diarrhoeal episodes per child, darkening of stools, and staining of teeth
Notes	The study site a malaria endemic area.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Cluster randomisation by housing compounds, using random digit generator
Allocation concealment (selection bias)	Low risk	Not described. However, since the intervention was allocated at cluster (housing compounds) level, it is unlikely there was a selection bias at the individual level
Blinding (performance bias and detection bias) All outcomes	High risk	Participant: blinding to the multiple micronutrient composition groups. Care provider and field staff blinded to the form and dose of iron in the multiple micronutrient powder. Outcome assessor unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 out of 108 participants lost to follow up in the micronutrient powder groups (groups 1-4) and 4 out of 25 from the iron drops

Christofides 2006 (*Continued*)

		were lost to follow up. There was not imbalance among the groups
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	The study appears to be free of other sources of bias

Giovannini 2006

Methods	Double-blind placebo-controlled trial. Randomisation at individual level
Participants	204 infants, both sexes (109 males, 95 females), aged 6 months living in Tuk Phos district, Kompong Chhanang Province, Cambodia, where prevalence of anaemia in Cambodian infants and young children is 63%. Inclusion criteria included infants being born between January and July 2003 and aged 6 months T 7 days at recruitment. Exclusion criterion was severe anaemia (haemoglobin less than 70 g/L) 100% were anaemic (Hb less than 100 g/L) at start of the intervention
Interventions	Infants were randomly allocated to one of the following groups: Group 1 (n = 68): infants received daily 12.5 mg elemental iron (as ferrous fumarate) , 5 mg zinc (as gluconate), 300 μg vitamin A and 150 μg (0.15 mg) folic acid, 50 mg vitamin C, and 7.5 μg vitamin D as sprinkled powder form Group 2 (n = 68): Infants received daily 12.5 mg elemental iron (as ferrous fumarate) + 150 μg (0.15 mg) folic acid as sprinkled powder form Group 3 (n = 68): infants received daily placebo (potato maltodextrins as sprinkled powder form) Active Sprinkles and placebo, similar in powder form. Length of the intervention: 12 months. Administration of the micronutrient powder started 7 (+/-) 2 days after baseline blood assessment. Content of each sachet was mixed with the infant's meal after it was cooked For the purposes of this review, only groups 1 and 3 were compared
Outcomes	Mortality and malaria parasitaemia. Z-scores for weight-for-age, length-for-age, and weight-for-length. Haemoglobin concentration and serum ferritin Reported adverse events possibly linked to interventions: frequent or loose stool or diarrhoea within 14 days of administration; darkening of stool or mild constipation or mild vomiting
Notes	Treatments were distributed to mothers weekly by three trained health workers and given as micronutrient powder in one-dose sachets. Micronutrient were packaged in a paper, aluminium, polyethylene pouch Immunization, vitamin A capsule, and mebendazole coverage were further provided in all infants according to the Cambodian national (Ministry of Health) guidelines Micronutrient powder's acceptance was evaluated by number of infants refusing the complementary food Blood samples were taken and analysed at the Institute Pasteur du Cambodge to identify

Giovannini 2006 (*Continued*)

	the presence of malaria parasitaemia, at baseline and at the end of the study period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation to group designations were based on allocation lists computer generated at blocks of nine units, and stratified by sex
Allocation concealment (selection bias)	Low risk	Randomisation to treatment was performed with sealed opaque envelopes containing group designations
Blinding (performance bias and detection bias) All outcomes	Low risk	All individuals involved in the trial (including parents, health workers, and research staff) were unaware of group assignment until code was broken after completion of the data analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/68 were (4.4 %) lost to follow up in the MNP group and 6/68 (8.8 %) in the placebo group ITT analysis
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	The study appears to be free of other sources of bias.

Hirve 2007

Methods	Double-blinded cluster-randomised community based trial. Randomisation at village level
Participants	432 anaemic (Hb 70-100 g/L) children aged 6 to18 months, both sexes, living in the state of Maharashtra, India, during 2004 and 2005. Inclusion criteria, children should be taking semi-solid or solid weaning foods, not taking haematinic, likely to remain within study area for 2 months, and absence of any major illness. Exclusion criterion: severe anaemia (Hb less than 70 g/L) 58 % were anaemic at start of two months intervention.
Interventions	21 villages (n = 432) were randomised into five groups: Group 1 (n = 84): children received daily MNP containing 12.5 mg elemental iron (as microencapsulated ferrous fumarate), 5 mg zinc (as gluconate), 300 μg vitamin A, and 30 mg ascorbic acid and 160 μg (0.16 mg) folic acid

	Group 2 (n = 83): children received daily MNP with 20 mg elemental iron (as microencapsulated ferrous fumarate), 5 mg zinc (as gluconate), 300 μg vitamin A (as acetate) and 30 mg ascorbic acid, 160 μg (0.16 mg) folic acid Group 3 (n = 101): children received daily MNP with 30 mg elemental iron (as microencapsulated ferrous fumarate), 5 mg zinc (as gluconate), 300 μg vitamin A and 30 mg ascorbic acid, (as acetate), 160 μg (0.16 mg) folic acid Group 4 (n = 82): children received MNP daily containing 20 mg elemental iron (as micronized ferric pyrophosphate), 5 mg zinc (as gluconate), 300 μg vitamin A (as acetate) and 30 mg ascorbic acid, 160 μg (0.16 mg) folic acid Group 5 (n = 83): children received iron drops containing 20 mg elemental iron (as ferrous glycine sulphate drops) daily Length of the intervention: 2 months. For the purposes of this review we have considered the four MNP together and compared with drops. For subgroups we have extracted the relevant data if it was available
Outcomes	Haemoglobin, serum ferritin, anaemia, side effects like diarrhoea, vomiting and discolouration of stools, cough, cold or fever in the past seven days
Notes	Non malaria endemic area (sporadic cases). There were two deaths after the intervention finalized that were judged not to be related to the study Author calculated the sample size with a design effect of 2.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"We listed all villages on chits of paper and blindly drew lots without replacement from an opaque bag to randomise the 22 villages into 5 groups"
Allocation concealment (selection bias)	Low risk	See above, appears adequate.
Blinding (performance bias and detection bias) All outcomes	High risk	Not attempted. Not possible to blind difference between drops and MNP sachets
Incomplete outcome data (attrition bias) All outcomes	Low risk	51/432 (11.8%) were lost to follow up with no differences between groups
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	The study appears to be free of other sources of bias.

Lundeen 2010

Methods	Cluster-randomised, community-based effectiveness trial. Randomisation at village level
Participants	1869 children aged 6 to 36 months, both sexes, living in three rural districts of the Kyrgyz Republic Approximately 72% were anaemic at start of the intervention.
Interventions	Villages were allocated to one of the following groups: Group 1 (12 clusters, n = 1103): children received daily a micronutrient powder with 12.5 mg elemental iron (as microencapsulated ferrous fumarate), 5 mg zinc (as gluconate), 300 μg vitamin A, 30 mg vitamin C, and 160 μg (0.16 mg) folic acid Group 2 (12 clusters, n = 1090): children did not receive micronutrient powder until after the study period Length of the intervention: two months.
Outcomes	Haemoglobin, morbidity and side effects.
Notes	58.7% of the children consumed more than 80% of the sachets (in average 45 of 60 of the sachets) Cluster-level analyses (conducted for the unit of randomisation) were carried out using a weighted t-test, with weights calculated based on the size of the clusters

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The villages and district centre parts were randomly allocated to the intervention group and control group, using stratified randomisation to balance on the size of the clusters. The sequence was generated by shuffling cards (in envelopes) (information provided by the author)
Allocation concealment (selection bias)	Low risk	Not described. However, since the intervention was allocated at village level, it is unlikely there was a selection bias at the individual level
Blinding (performance bias and detection bias) All outcomes	High risk	Not attempted, both the researchers and caretakers were aware of the intervention and no placebo was used
Incomplete outcome data (attrition bias) All outcomes	Low risk	156/1103 (14%) of the children were lost to follow up in the group that received MNP and 168/1090 (14.4%), mainly because they could not be located
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.

Lundeen 2010 (*Continued*)

Other bias	Low risk	The study appears to be free of other sources of bias.

Menon 2007

Methods	Cluster-randomised design. Randomisation at the level of the Food Distribution Point (FDP)
Participants	415 children aged 12 to 27 months old at the start of the intervention, both sexes, living in rural Haiti. Exclusion criteria: severe anaemia (Hb less than 70 g/L), not receiving wheat-soy-blend, not accompanied by their mother The study was conducted in Haiti, and prevalence of anaemia at start was 46%
Interventions	FDPs were allocated to the following groups: Group 1 (6 FDPs, n = 254): children received daily a micronutrient powder with 12.5 mg elemental iron (as fumarate), 5 mg zinc (as gluconate), 400 μg vitamin A, 160 μg (0.16 mg) folic acid, and 30 mg vitamin C Group 2 (4 FDPs, n = 161): control group. Both groups received 8 kg of wheat-soy-blend, 2,5 kg oil (vitamin A fortified) and indirect ration of 10 kg soy-fortified bulgur, and 2.5 kg brown lentils Length of the intervention: two months. The micronutrient powders were distributed once a month with the fortified wheat-soy-blend, each time 30 sachets with pictorial instructions were given to the intervention group. Control group received the wheat-soy-blend
Outcomes	Haemoglobin concentration, prevalence of anaemia (Hb less than 100 g/L), diarrhoea measured after 1 month
Notes	Individual level data were used and results were adjusted for child age, sex, and baseline Hb The group that received MNP were followed up after 7 months post-end of the intervention

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised by computer generated random numbers (in SPSS).
Allocation concealment (selection bias)	Low risk	Not mentioned. However, since the intervention was allocated at FDP level, it is unlikely there was a selection bias at the individual level
Blinding (performance bias and detection bias) All outcomes	High risk	Not attempted.

Menon 2007 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	10/254 (3.9%) of the children were lost to follow up in the group that received MNP and 7/154 (4.5%), mainly because children moved away from the intervention area
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	The study appears to be free of other sources of bias.

Sharieff 2006a

Methods	Randomised controlled trial conducted from January to March 2003. Randomisation at individual level
Participants	75 infants aged 6 to 12 months, both sexes, living in Bilal Colony, an urban slum neighbourhood in Karachi, Pakistan. Inclusion criteria: intention to reside in the area for two or more months, parental consent was an inclusion criteria, and able to ingest any type of semi-solid weaning food, one or more episode of diarrhoea within the previous two weeks
Interventions	Participants were randomly assigned to one of three groups: Group 1 (n=25): children received daily a micronutrient powder containing 30 mg elemental iron (as encapsulated ferrous fumarate), 5 mg zinc (as gluconate), 300 μg vitamin A, 50 mg vitamin C, 7.5 μg vitamin D_3, and 150 μg (0.15 mg) folic acid. Group 2 (n=25): children received daily a micronutrient powder containing 5 mg zinc (as gluconate), 30 mg elemental iron (as microencapsulated ferrous fumarate), 50 mg vitamin C, 300 μg vitamin A, 7.5 μg vitamin D_3, and 150 μg (0.15 mg) folic acid and heat-inactivated *L acidophilus* at a concentration of 1-2 x10^9 colony forming units (CFU) per dose. Group 3 (n=25): children received daily a placebo (containing ground purple rice with maltodextrin) Length of the intervention: two months. For the purpose of this review only groups 1 and 3 were compared The interventions were provided in small screw-cap plastic containers with the powders that were similar in appearance and taste and mothers and care-givers were instructed to open the containers and mix the entire contents with semi-solid meal provided to the child once each day
Outcomes	Longitudinal prevalence of diarrhoea (defined as three or more liquid or loose stools in the past 24 hours. Longitudinal prevalence was defined as the percentage of days that the child had diarrhoea over the observation period Other outcomes include febrile days per child, compliance, haemoglobin concentrations, serum ferritin concentrations, anaemia, iron deficiency. Stool cultures at baseline (for Salmonella, Shigella, Campylobacter, Yersinia, enteropathic E. coli and Vibrio cholera, and Giardia lamblia

Sharieff 2006a (*Continued*)

Notes	Compliance was measured by counting the used supplements for each child whose supplements were not shared or lost 91% of the children consumed half of MNP (mean number 36).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Children were assigned to the treatment using a computer programme
Allocation concealment (selection bias)	Low risk	Authors provided identical small screw-cap plastic containers filled with micronutrients (with or without LAB) or placebo in powder form which were similar in appearance and taste
Blinding (performance bias and detection bias) All outcomes	Low risk	Authors provided identical small screw-cap plastic containers filled with micronutrients (with or without LAB) or placebo in powder form which were similar in appearance and taste. Study participants, field staff, and the data analyst were blinded to the random allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	One child dropped out from the intervention and other from the control group
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	High risk	Heamoglobin and ferritin were not measured at baseline making difficult to judge the comparability between groups Only 61% of the original population agreed to provide a blood sample at the end-of-study

Suchdev 2011

Methods	Cluster-randomised clinical trial. Randomisation at village level
Participants	703 children 6-23 months at the time of enrolment living in rural western Kenya, Nyando Division. 575 followed for the duration of the intervention and follow-up period. Exclusion criteria: Unavailable for enrolment on 3 separate household visits and parental refusal to give informed consent Children with Hb less than 70 g/L were referred for treatment, but still included in the analysis

Interventions	60 villages were allocated to one of the following groups: Group 1: children received a micronutrient powder with 12.5 mg elemental iron (as ferrous fumarate), 5 mg zinc (as gluconate), 400 μg vitamin A, 150 μg (0.15 mg) folic acid, 35 mg vitamin C, 5 μg vitamin D_3, 6 mg vitamin E, 6 mg niacin, 0.6 mg copper, 50 μg iodine, 0.5 mg vitamins B_1, 0.5 mg vitamin B_2, 0.5 mg vitamin B_6, and 0.9 mg vitamin B_{12} Group 2: no intervention. Length of the intervention: 12 months. Children were instructed to consume maximum one sachet per day but a minimum amount was not specified
Outcomes	Haemoglobin, prevalence of anaemia and iron deficiency and vitamin A deficiency. Product sales and use (coverage)
Notes	The study also included children up to 36 months but were excluded from the analysis for the purpose of this review Follow up continued for another 12 months after the end of the intervention Author provided intra-cluster correlation data and design effect data for haemoglobin, anaemia and serum retinol, for both the control and the comparison groups

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated randomisation sequence.
Allocation concealment (selection bias)	Low risk	Not mentioned. Since interventions were allocated at village level it is unlikely that participants were aware of the group they belonged to
Blinding (performance bias and detection bias) All outcomes	High risk	Not attempted. Survey and laboratory field staff blinded to the intervention groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	1063/1420 children enrolled (74.9% enrolment rate), no difference between intervention and control. Among 357 children excluded from the study, 60.5% were not encountered on three attempted household visits, 32.2% were outside of the age range (due to discrepancies in date of births reported during census), 4.5% had missing data, and 2.8% of parents did not consent. (this is for children 6-35 months) 201/1063 (19%) lost to follow-up. No differences compared to 886 children in-

		cluded For children 6-23 months, 703 were enrolled. 128 were lost to follow up (18.2%). There were no differences in loss to follow up among intervention and control group
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Unclear risk	"Bleeding" or cross-over of Sprinkles use in control group due to community-based market distribution design.

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

Study	Reason for exclusion
Bagni 2009	Randomised controlled trial, children aged between 12 and 60 months attending public childcare centres in Rio de Janeiro, Brasil, in which participants were randomly assigned to receive a daily meal prepared with iron-fortified rice or to receive non-fortified placebo rice. The rice was fortified once a week The type of intervention (fortification) is out of the scope of this review
Chen 2008	Randomised trial including 226 apparently healthy preschool children (2-6 years old) from 15 nurseries or kindergartens in the Banan District of Chongqing, China, and randomly assigned to one of three groups for 6 months: group I received fortified powder containing 500 μg vitamin A (as acetate); group II received a fortified powder containing 500 μg vitamin A (as acetate) and 12 mg elemental iron (as ferric sodium edentate); and group III received a fortified powder containing 500 μg vitamin A (as acetate) and 12 mg elemental iron (as ferric sodium edentate), 12 mg of zinc (as zinc oxide), 0.7 mg thiamin (as thiamin mononitrate), 0.7 mg riboflavin, 200 μg (0.2 mg) folic acid, 7 mg niacinamide, and 800 mg calcium (as calcium carbonate). The powders were to be sprinkled over porridge, soy milk, soup or noodles after cooking and were indistinguishable in taste, colour and packaging. Food prepared with the powders were delivered to each child at lunchtime or afternoon snack time 5 days a week during the study period The study participants are outside of the age range for inclusion in this review
Geltman 2009	Randomised clinical trial with 150 healthy 6-month-old infants. Each infant received either a daily packet of MNP or multiple micronutrient drops. Follow-up included alternating telephone and home visits biweekly for 3 months. Adherence was the primary outcome whereas side effects and caregiver attitude about supplements were secondary outcomes. The use of ferrous fumarate powder rather than traditional ferrous sulphate drops did not improve adherence with daily iron supplementation in low-income infants The study was excluded because the micronutrient powder formulation contained iron and vitamins A, C, D, but not zinc, which was one of three main nutrients evaluated in this review
Ip 2009	Cluster-randomised with 362 Bangladeshi children (haemoglobin (Hb)70 g/L or higher) aged 6-24 months who received 60 sachets of MNP either daily over 2 months; flexibly over 3 months; or flexibly over 4 months. With a flexible regimen, mothers/caregivers decided how frequently to use MNP without exceeding one sachet per day. Outcomes post intervention included adherence, acceptability and haematological status,

(*Continued*)

	which also was evaluated at 6 months post-intervention. The adherence, acceptability and haematological response to flexible administration over 4 months were found preferable to daily The study was excluded because it compares different schemes for providing MNP but did not compare them with a placebo or other type of supplements
Sharieff 2006b	16 classrooms clusters (n=415 children) 3-6 years old attending kindergarten in northern China were randomly assigned to one of 3 groups: (1) daily provision of single-dose Sprinkles sachet containing 30 mg of elemental iron (as encapsulated ferrous fumarate), 5 mg zinc (as gluconate), 300 μg vitamin A, 50 mg vitamin C, 7.5 μg vitamin D_3 and 150 μg (0.15 mg) folic acid for 5 days a week; (2) once a week provision of single-dose Sprinkles sachet containing 30 mg of elemental iron (as encapsulated ferrous fumarate), 5 mg zinc (as gluconate), 300 μg vitamin A, 50 mg vitamin C, 7.5 μg vitamin D_3 and 150 μg (0.15 mg) folic acid.; or (3) no supplements (control group). The intervention lasted for one school term (13 weeks). Consumption of sachets was monitored for each child and SF concentrations were measured at the end of study. The types of participants is outside the scope of this review
Smuts 2005	290 term infants aged 6?12 mo were recruited through the health posts of Valley of a Thousand Hills, Durban in the KwaZulu-Natal Province, South Africa and enrolled in the study and randomly assigned to 1 of 4 groups: group 1 received a daily supplement containing 1 daily allowance of multiple micronutrients for young children; group 2 received a daily placebo supplement containing no micronutrients; group 3 received a weekly supplement containing 2 daily allowances of multiple micronutrients for young children and a placebo supplement on the other days of the week and group 4 was given a daily supplement containing 10 mg of elemental iron The micronutrient supplements provided were large chewable tablets or foodlets. The type of intervention is outside of the scope of this review
Troesch 2009	101 apparently healthy non-pregnant, non-lactating young women studying or working at the Institute of Food Science and Nutrition, Swiss federal Institute of Technology in Zurich and the University of Zurich between January and April 2008 were randomly assigned to 1 of 6 groups receiving a maize porridge fortified with a micronutrient powder containing stable isotope-labelled elemental iron as either ferrous sulphate or NaFeEDTA and different combinations of inhibitors and enhancers (ascorbic acid, calcium, phytase, l-alpha-glycerophosphocholine). They each consumed 2 meals in a crossover design for determination of iron absorption The types of participants and types of interventions are not within the scope of this review.
Troesch 2011	200 apparently healthy South African school children 5 and 11 years of age from two primary schools in low socioeconomic areas of Kimberley, Northern Cape, South Africa with low iron status, haemoglobin higher than 90 g/L and not taking nutritional supplements containing iron were randomly assigned to one of two groups: group 1 received a micronutrient powder containing 2.5 mg elemental iron (as NaFeEDTA), 2.5 mg of zinc (as zinc oxide), and 60 mg vitamin C, as well as a phytase and other 14 micronutrients; group 2 received the unfortified carrier added just before consumption to a daily bowl of 250 g a sweetened high-phytate maize porridge 5 days a week for a period of 23 weeks. Primary outcomes were iron and zinc status and a secondary outcome was somatic growth The participants are school age children 5-11 years of age and are outside the scope of this review
Wijaya-Erhardt 2007	Randomised controlled trial conducted in children aged between 6 and 12 months in rural Indonesia, that assessed the efficacy and safety of 3 types of food like tablets (foodlets) given for 23 weeks, compared to placebo. The foodlets were given as daily iron (ferrous sulphate), daily multiple micronutrients (14 nutrients: vitamins A, D, E, K, vitamin C, thiamine, riboflavin, Vitamin B_{12}, niacin, folate, iron, zinc, copper, iodine) and weekly multiple micronutrient (same 14 nutrients). Results showed an increase in iron stores in the daily

(*Continued*)

	iron and daily multiple micronutrients group, but not in the weekly multiple micronutrients group. Side effects observed were vomiting and diarrhoea, with no significant difference between intervention groups The study was excluded because Foodlets are not an intervention within the scope of this review
Zlotkin 2001	Randomised controlled trial with 557 anaemic children aged between 6 and 18 months from rural Ghana. It assessed the efficacy of home fortification with MNP containing 80 mg of elemental iron (microencapsulated ferrous fumarate) + 50 mg of ascorbic acid added to weaning foods compared to iron drops (40 mg of elemental iron given 3 times/d) given for two months. Outcomes included anaemia, ferritin, serum zinc and growth concentration. Anaemia was successfully treated in the two groups in 58% and 56% of children. There were no significant differences in side effects between the groups. Diarrhea was reported in 14.5% and 12.8% of the participants receiving drops or MNP, respectively. The study was excluded because the MNP formulation tested in this study include only two micronutrients. These interventions do not comply with the definition used in this review of MNP requiring three or more micronutrients with at least iron, vitamin A and zinc
Zlotkin 2003a	Randomised trial with 437 Ghanaian non-anaemic children aged 8-20 months, who were ingesting a weaning food in addition to breast milk. Participants were randomised individually to one of four groups: group 1 (n=110) received a micronutrient powder (with iron only) containing 40 mg elemental iron (as microencapsulated ferrous fumarate) daily; group 2 (n=107) received a micronutrient powder (with iron and vitamin A) containing 40 mg elemental iron (as microencapsulated ferrous fumarate), and 600 μg retinol equivalents (as retinyl acetate) daily; group 3 (n=112) received 12.5 mg elemental iron (as ferrous sulphate iron drops) daily; and group 4 (n=108) received placebo in powder form. Primary outcome measures were change in haemoglobin and anaemic status at baseline and end of the study. Prophylactic supplementation was provided to children for six months (Oct 1999-March 2000) and children who maintained Hb of 100 g/L or above at the end of the intervention were reassessed at 12 months post-intervention Acceptability of the powders was better in comparison to the iron drops. No significant changes were seen in mean haemoglobin, ferritin or serum retinol values from baseline to the end of the supplementation period among the groups. The study area was considered a setting where intestinal parasites, malaria and infectious diarrhoea are common. the supplementation period began at the end of the rainy season and had finished by the end of the dry season when the burden of malaria is lower. Iron and haematological status were maintained equally well among all groups, including micronutrient powders and placebo The study was excluded because the trial evaluated the provision of micronutrient powders formulated with only one or two micronutrients. These interventions do not comply with the definition used in this review of MNP requiring three or more micronutrients with at least iron, vitamin A and zinc
Zlotkin 2003b	Randomised controlled trial with 304 anaemic children aged between 6 and 18 months from rural Ghana. It compared the efficacy of home fortification with "multiple micronutrient powders" including 80 mg of elemental iron (as microencapsulated ferrous fumarate) + 50 mg ascorbic acid with that of 80 mg of elemental iron (as microencapsulated ferrous fumarate) and 5 mg zinc (as gluconate) over two months. Outcomes included anaemia, ferritin, serum zinc and growth concentration. Both formulations were successful in treating anaemia. There was not an effect on zinc status and growth The study was excluded because the interventions evaluated in this study include micronutrient powders with only one or two micronutrients. These interventions do not comply with the definition used in this review of MNP requiring three or more micronutrients with at least iron, vitamin A and zinc. In addition MNP were not compared with a placebo or any other supplements

Characteristics of studies awaiting assessment *[ordered by study ID]*

Bilenko 2010

Methods	A two-arm open-labelled cluster-randomised controlled clinical trial. randomisation at individual level
Participants	621 infants (328 Bedouin and 293 Jewish) aged 6 months old, living in the Negev, who belonged to families attending Mother and Child Health clinics during 2005-2007
Interventions	The MNP arm received sachets with iron, vitamins A and C, folic acid and zinc, and the control arm received standard treatment (liquid iron and vitamins A and D) Intervention and follow-up were conducted for babies aged 6-12 months
Outcomes	Haematologic and nutritional indicators, growth parameters, morbidity rates were evaluated at 12 and 18 months
Notes	This study is awaiting assessment because it only includes the background information of the trial

Neufeld 2008

Methods	Cluster-randomised trial, implemented in the context of Oportunidades programme, a conditional cash transfer programme implemented in rural areas in 1997 and urban areas in 2002 with authorization of Oportunidades officials at the federal, state and local level, national Institute of Public Health Ethics Commission, in Mexico. The study was designed to guide decisions within the programme to compare the efficacy of three nutritional supplements with identical multiple micronutrient content (syrup, Nutrisano, multiple micronutrient powder Sprinkles*)* on child growth, development and micronutrient status in Mexican children 6 to 12 mo of age at baseline
Participants	927 children 6 to 12 mo of age, beneficiaries of the Oportunidades programme from communities (18 per supplement) were randomly assigned to receive a fortified food, syrup or multiple micronutrient powder Sprinkles. Supplements were delivered daily (6 mo)
Interventions	Communities were randomly assigned (18 communities per supplement) to one of three interventions: group 1 (n= 265 infants) received 44 g of daily supplement Nutrisano (fortified food) containing 10 mg elemental iron (as ferrous gluconate), 400 μg vitamin A, 10 mg zinc, 50 mg vitamin C, 50 μg (0.05 mg) folic acid, 6 mg vitamin E, 0.8 mg vitamin B_2 and 0.7 μg vitamin B_{12} and also provided energy, protein, lipids, carbohydrates and sodium; group 2 (n= 323 infants) received 5 ml of a syrup daily containing 10 mg elemental iron (as ferrous gluconate),400 μg vitamin A, 10 mg zinc, 50 mg vitamin C, 50 μg (0.05 mg) folic acid, 6 mg vitamin E, 0.8 mg vitamin B_2 and 0.7 μg vitamin B_{12}; and group 3 (n=339 infants) received 1 g of micronutrient powder (Sprinkles) containing 10 mg elemental iron (as ferous fumarate), 400 μg vitamin A, 10 mg zinc, 50 mg vitamin C, 50 μg (0.05 mg) folic acid, 6 mg vitamin E, 0.8 mg vitamin B_2 and 0.7 μg vitamin B_{12}.
Outcomes	Haemoglobin concentration, anaemia after 4 and 10 mo of supplementation and at 24 and 30 mo of age
Notes	Statistical analysis: Estimates were made using multilevel modelling, with cluster as level one, children as level two and the measurement (for example, Hb concentration) as level three, using the gllamm command in Stata Preliminary results indicate After 4 mo supplementation, the prevalence of anaemia was significantly (P<0.05) higher in the children receiving the *Nutrisano* (fortified food) in comparison with the multiple micronutrient powder and syrup. At 24 mo of age the anaemia had decreased in three groups (p<0.001), but remained slightly higher in the Nutrisano (fortified food) group (fortified food:12.3%, syrup :8.8%, multiple micronutrient powder: 9.2%). The large decrease and the low prevalence at 24 mo suggests that all supplements were similarly efficacious to prevent and cure anaemia; with the effect observed slower in the children who received the fortified food

	Attrition was 20%, not different between groups, no differences in characteristics of those lost to follow-up and those who completed the trial. The main reasons for attrition were: dislike or perceived reacted to supplements (43%), migrated out of community (18%); but were not different between groups

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

Fitzsimons 2009

Trial name or title	Early childhood development: a cluster-randomised controlled trial to identify successful interventions and the mechanisms behind them
Methods	4 arm cluster-randomised controlled parallel group trial
Participants	Children 12 and 24 months from households eligible for the Colombian conditional cash transfer programme 'Familias en Accion' and parental or caregiver informed consent; Exclusion criteria: 1. Children outside the 12-24 month age range at the start of the intervention 2. Children with serious congenital abnormalities 3. Twins
Interventions	Community-based intervention to promote early childhood development. 96 clusters in total. 1. Stimulation group 24 clusters will receive stimulation through weekly home visits - lasting around one hour - to mothers/primary caregivers of children aged between 12 and 24 months, for a period of 18 months. The "home visitors" will interact with caregivers and children and will discuss the importance of psychosocial stimulation for child development with the caregiver. The home visitors will be drawn from local female elected representatives, and will receive extensive guidance and preparation for their role. 2. Nutrition group 24 clusters will receive micronutrients in the form of 'Nutritional Anemia Formulation MNP' to children between 12 and 24 months at the start of the study, also for a duration of 18 months. Sprinkles are sachets containing a blend of micronutrients in powder form, which are easily sprinkled onto foods prepared in the home. Any homemade food can be instantly fortified by adding Sprinkles. Coating of the iron prevents changes to the taste, colour or texture of the food to which Sprinkles are added. Sprinkles were developed by the Sprinkles Global Health Initiative to prevent and treat micronutrient deficiencies among young children and other vulnerable groups at risk. 3. Stimulation and nutrition group 24 clusters will receive both home visits and Sprinkles. This set up will allow us to test whether the intervention is more likely to be successful if children's nutrition is also targeted - an important ongoing debate. 4. Control group 24 clusters will receive no intervention. Total duration of interventions: 18 months (2 periods of 3 months of data collection will precede and follow the interventions)

Fitzsimons 2009 (*Continued*)

Outcomes	Primary: 1. Children's motor and mental development measured using the Bayley Scales of Infant and Toddler Development, third edition 2. Children's nutritional status, measured by collecting height and weight, haemoglobin levels (using capillary blood specimens from finger prick samples), and children's consumption of iron rich food Secondary: 1. Maternal depression measured using the 10-item CESD Scale 2. Investigate the constraints that poor households face when making choices relevant to their children's development, and ultimately to investigate why the intervention works or not
Starting date	01/01/2010
Contact information	Dr Emla Fitzsimons Institute for Fiscal Studies 7 Ridgmount Street London, WC1E 7AE United Kingdom
Notes	Sponsors: 1. Economic and Social Research Council (ESRC) (UK) 2. Inter-American Development Bank (International) 3. International Growth Centre (UK)

Jack 2008

Trial name or title	
Methods	Randomised controlled trial. Cluster-randomised study. One cluster = one health centre catchment area. 20 Health Centres in Svay Rieng Operational District. List of 20 Health Centres randomised into the intervention group by a statistician not involved in the day to day running of the study. For sub-sample for blood testing, anthropometry and survey questionnaire. Listing of all eligible infants will be made at village level. Sub-sample from list will be randomly selected by a statistician not involved in the day to day running of the study
Participants	All 6 month old infants (rolling recruitment from March 2008- August 2008) residing in Svay Rieng Operational District, Svay Rieng Province, Cambodia. Children with severe acute malnutrition (<-3 Z-score weight for length) or severe anaemia (<70 g/L) were excluded
Interventions	Infant and young child feeding practices promotion through one on one and group education by village health volunteers using behaviour change communication including flip charts; multiple micronutrient powder in-home fortification (MNP formulation: 12.5 mg of elemental iron (as microencapsulated ferrous fumarate); 10 mg zinc (as zinc gluconate); 300 µg vitamin A (as retinol acetate); 90 µg iodine; 0.5 mg vitamin B1; 0.5 mg vitamin B_2; 0.5 mg vitamin B_6; 0.9 µg vitamin B12; 6 mg niacin 6mg; 160 µg (0.16 mg) folic acid; 30 mg vitamin C (as ascorbic acid); 0.3 mg copper; 5 µg vitamin D; 6 IU once daily, sprinkled on complementary food, for 6 months
Outcomes	Anaemia (complete blood count, haemoglobin concentration, mean cell volume, blood film). Anaemia <110 g/L ; iron status (serum transferrin receptor concentration); zinc status (serum zinc concentration); vitamin A status (serum retinol binding protein concentration); growth (anthropometry: length, weight, head circum-

Jack 2008 (*Continued*)

	ference and mid upper arm circumference) at baseline (aged 6 months), after 6 months of intervention (aged 12 months) and after a further 6 months post intervention (aged 18 months)
Starting date	
Contact information	Dr Susan Jack, C/- World Health Organization, Cambodia177-179 St 51, Phnom Penh, Cambodia. Tel: 855 12 506911. Email: jacks@wpro.who.int
Notes	

Ribeiro Da Costa 2009

Trial name or title	The Impact of the use of zinc supplementation and other micronutrients on the occurrence of diarrhoea diseases and respiratory infections in children of daycare centres
Methods	Double-blind placebo-controlled trial. Masking: double blind (subject, caregiver) Primary purpose: prevention
Participants	120 healthy children 6 months to 4 years of age attending day care in Salvador, Bahia, Brazil. The study will be conducted at the Fima Lifshitz Metabolic Research Center, Department of Pediatrics, Universidade Federal Da Bahia, Salvador-Bahia, Brazil over a period of 18 months
Interventions	Participants will be randomised into 2 groups of 60 children each. The intervention group will receive MNP containing zinc (as zinc gluconate) while the control group will receive micronutrient powder without zinc
Outcomes	The primary outcome variables of interest are zinc status, stool zinc losses and diarrhoea duration. Both groups of infants will be monitored at monthly intervals for an initial duration of 180 days for zinc status, diarrhoea episodes, respiratory illness and growth Secondary: respiratory infections.
Starting date	July 2009.
Contact information	Hugo Ribeiro Da Costa, MD, PhD, Universidade Federal da Bahia, Complexo Hospitalar Universitário. Email: hugocrj@gmail.com. Professor Edgar Santos, Centro de Pesquisa Fima Lifshitz, Salvador, Bahia, Brazil
Notes	Sponsor: Federal University of Bahia, Brazil.

van der Kam 2010

Trial name or title	Effectiveness of Nutritional Supplementation (RUTF and Multi Micronutrient) in Preventing Malnutrition in Children 6-59 Months With Infection (Malaria, Pneumonia, Diarrhoea), a randomised Controlled Trial in Nigeria
Methods	Randomised controlled trial comparing multiple micronutrient powder to iron only powder

van der Kam 2010 (*Continued*)

Participants	Children 6 to 59 months of age, both sexes.
Interventions	Dietary supplement: Nutrition supplement with RUTF, MNP or placebo to micronutrients
Outcomes	Negative nutritional outcome" of a child. For children with no malnourishment at time of entry into study, "negative nutritional outcome" is defined as progression to moderate or severe malnourishment. For children with moderate malnourishment at time of entry into study, "negative nutritional outcome" is defined as loss of ³10% of baseline weight or progression to severe malnourishment, whichever is reached first Secondary Outcome Measures: Number of new events of a malaria, diarrhoea, and LRTI
Starting date	August 2010
Contact information	saskia.vd.kam@amsterdam.msf.org
Notes	Not yet recruiting

Zavaleta 2010

Trial name or title	Efficacy of the nutritional supplement powders with zinc and micronutrients on anaemia and acute diarrhoea in Peruvian children
Methods	Randomised controlled trial comparing a powder with multiple micronutrient to iron only powder
Participants	Healthy born at term infants and children 6-17 months of age living in Villa El Salvador, Lima, Peru 3 with birth weight equal or higher than 2500g and haemoglobin > 80 g/L. Written informed consent from parents or care-givers is required.
Interventions	Participants will be randomly assigned to one of two groups: group 1 will receive an oral micronutrient supplement powder containing 12.5 mg elemental iron (as ferrous fumarate), 10 mg zinc (as zinc oxide), 160 μg (0.16 mg) folic acid, 300mcg RE vitamin A (as retinol palmitate), 30 mg ascorbic acid; and group 2 will receive an oral micronutrient supplement powder containing 12.5 mg elemental iron (as ferrous fumarate) only for a period of 6 months. The iron portion of the powder is lipid encapsulated to prevent changing the taste, texture, or colour of the food. Each child will receive 30 sachets monthly of the corresponding supplement, to be consumed as one sachet per day mixed with a part of the main meal
Outcomes	1. Anaemia. 2. Diarrhoea. 3. Incidence of severe diarrhoea. 4. Duration of diarrhoea. 5. Compliance
Starting date	Jan 7 2010. Ongoing.
Contact information	Dr. Nelly Zavaleta Principal Investigator Instituto de Investigacion Nutricional Av. La Molina 1885, P.O. Box 18-0191

	Lima 12, Peru Email: nzavalet@iin.sld.pe
Notes	Financial support from: United Nations Children's Fund (UNICEF) (USA) http://apps.who.int/trialsearch/Trial.aspx?TrialID=ISRCTN39244429

Zimmermann 2010

Trial name or title	The effect of iron fortification of complementary foods on iron status and infant gut microbiota in Kenya
Methods	Subgroup (n=160) of a larger double-blind controlled feeding trial
Participants	330 apparently healthy infants 5.5- 6.5 months of age, with a mother of at least 15 years of age, long-term residence in study site and anticipating residing in the area for at least 3 years, who speak a Mjikenda language or Kiswahili in the home and who approves to provide blood samples during clinic visits. will be randomised to receive a micronutrient powder containing either 2.5 mg iron or no iron for one year. In this sub study, the infants will be studied only over the first 6 months of the 1 year intervention Exclusion criteria: haemoglobin <70 g/L for infants; these infants will be referred for treatment at the local health clinic/hospital; acute or chronic pulmonary, cardiovascular, hepatic, renal or neurological condition or any other finding that in the opinion of the PI or co-researchers that would increase risk of participating in the study; and other conditions that in the opinion of the principal investigator or co-researchers would jeopardize the safety or rights of a participant in the trial or would render the participant unable to comply with the protocol
Interventions	Group 1: multiple micronutrient powder (MixMe®) containing 2.5 mg elemental iron; copper 0.34 mg; 30 µg iodine; 7 µg selenium; 2.5 mg Zinc; 100 µg vitamin A; vitamin D 5 µg; 5 mg tocopherol Equivalent; 30 µg vitamin K1; 10.5 mg thiamine; 0.5 mg riboflavin; 0.5 mg pyridoxine; 90 µg (0.9 mg) folic acid anhydrous; 6 mg niacinamide; 60 mg vitamin C and 0.9 µg vitamin B_{12} daily. Group 2: multiple micronutrient powder (MixMe®) with no iron; containing copper 0.34 mg; 30 µg iodine; 7 µg selenium; 2.5 mg zinc; 100 µg vitamin A; vitamin D 5 µg; 5 mg tocopherol Equivalent; 30 µg vitamin K1; 10.5 mg thiamine; 0.5 mg riboflavin; 0.5 mg pyridoxine; 90 µg (0.9 mg) folic acid anhydrous; 6 mg niacinamide; 60 mg vitamin C and 0.9 µg vitamin B_{12} daily.
Outcomes	Primary: gut microbiota composition. Stool samples (2 at baseline before intervention, 6 throughout the study and additional samples in case of diarrhoea) will be obtained for analysis of the gut microbiota secondary: iron status. Blood samples, taken at baseline and after 6 months will be used to define the iron status and the anaemia level of the infants. In the entire study (n=330), we will measure changes in iron status over 1 year
Starting date	February 2010
Contact information	Prof. Dr.med. Michael Zimmermann Laboratory for Human Nutrition Swiss Federal Institute of Technology (ETH) Zürich ETH Zentrum, Schmelzbergstrasse 7, LFV E19 CH - 8092 Zürich, Switzerland Tel. +41-44-632-8657 / Fax. +41-44-632-1470 email: michael.zimmermann@ilw.agrl.ethz.ch

Zimmermann 2010 (*Continued*)

	Principal investigator: Jane Kvalsvig, PhD, Department of Public Health Medicine, Nelson Mandela School of Medicine, South Africa
Notes	Sponsor: Swiss Federal Institute of Technology, University of KwaZulu, University of Nairobi, The Eunice Kennedy Shriver National Institute of Child Health and Human Development

Zlotkin 2010

Trial name or title	Treatment of iron deficiency anaemia in malaria endemic Ghana
Methods	Community-based blinded randomised controlled trial with 2 study arms
Participants	Afebrile infants 6-24 months ingesting weaning food in addition to breast milk, free from malaria or other major illnesses living in Brong Ahafo Region of Ghana for duration of intervention and follow-up Exclusion criteria: severe anaemia (haemoglobin less than 70 g/L); weight-for-height <-3 Z-score (severe wasting); kwashiorkor (defined as evidence of edema); congenital abnormality; treatment with iron supplements within the past 6 months; presence of any chronic illness
Interventions	The study will be conducted in two phases: Phase I will take place during the dry season (December to April), when malaria transmission rates are lower. Eligible subjects (one per household) will be individually randomised to receive a daily dose of either a powdered vitamin/mineral fortificant containing 12.5 mg of iron (plus ascorbic acid, vitamin A and zinc), or a placebo (containing all micronutrients excluding iron), added to complementary foods, for 5 months Phase II will take place during the wet season (June to October), when malaria transmission rates are higher. Eligible subjects, who did not participate in Phase I, will be individually randomised to one of the two study arms as described above and followed for 5 months
Outcomes	Primary: incidence of clinical malaria Secondary: changes in anaemia status (blood levels of: haemoglobin (Hb), ferritin; severity of clinical malaria (blood parasite count); cerebral malaria; hospitalisation; pneumonia; diarrhoea; dehydration
Starting date	November 2009
Contact information	Stanley Zlotkin CM, MD, PhD, FRCPC Senior Scientist, Programme in Child Health and Evaluative Sciences, Research Institute, Hospital for Sick Children, Director, Sprinkles Global Health Initiative, Hospital for Sick Children, Research Fellow, Centre for International Health, University of Toronto, Head, Division of Gastroenterology, Hepatology and Nutrition, Hospital for Sick Children, Toronto CANADA Email: stanley.zlotkin@sickkids.ca
Notes	Sponsors: The Hospital for Sick Children and The Eunice Kennedy Shriver National Institute of Child Health and Human Development

DATA AND ANALYSES

Comparison 1. Provision of multiple micronutrient powders versus no intervention or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Anaemia (ALL)	6	1447	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.60, 0.78]
2 Anaemia (SUBGROUPS)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 By anaemia at baseline: anaemic	1	125	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.38, 0.76]
2.2 By anaemia at baseline: non anaemic	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 By anaemia at baseline: mixed/unknown	5	1322	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.64, 0.79]
2.4 By iron status at baseline: iron deficient	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 By iron status at baseline: non iron deficient	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.6 By iron status at baseline: mixed/unknown	6	1447	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.60, 0.78]
2.7 By age at baseline: 6 to 11 months	3	345	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.43, 0.75]
2.8 By age at baseline: 12-23 months	1	126	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.32, 0.90]
2.9 By age at baseline: mixed/unknown	2	976	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.63, 0.86]
2.10 By refugee status: yes	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.11 By refugee status: no	6	1447	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.60, 0.78]
2.12 By frequency: daily	5	1028	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.59, 0.74]
2.13 By frequency: weekly	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.14 By frequency: flexible	1	419	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.66, 1.00]
2.15 By duration of the intervention: less than 6 months	3	709	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.61, 0.78]
2.16 By duration of the intervention: 6 months or more	3	738	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.48, 0.89]
2.17 By iron content: 12.5 mg or less	6	1447	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.60, 0.78]
2.18 By iron content:: more than 12.5 mg	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.19 By zinc content: less than 5 mg	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.20 By zinc content:: 5 mg or more	6	1447	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.60, 0.78]
2.21 By malaria status of the area at baseline: yes	4	864	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.49, 0.83]
2.22 By malaria status of the area at baseline: no	2	961	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.63, 0.77]

3 Iron deficiency (ALL)	4	586	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.35, 0.67]
4 Iron deficiency (SUBGROUPS)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 By anaemia at baseline: anaemic	1	125	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.14, 0.52]
4.2 By anaemia at baseline: non anaemic	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 By anaemia at baseline: mixed/unknown	3	487	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.43, 0.73]
4.4 By iron status at baseline: iron deficient	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.5 By iron status at baseline: non iron deficient	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.6 By iron status at baseline: mixed/unknown	4	586	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.35, 0.67]
4.7 By age at baseline: 6 to 11 months	3	321	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.26, 0.75]
4.8 By age at baseline: 12-23 months	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.9 By age at baseline: mixed/unknown	1	265	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.37, 0.86]
4.10 By refugee status: yes	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.11 By refugee status: no	4	586	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.35, 0.67]
4.12 By frequency: daily	3	321	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.26, 0.75]
4.13 By frequency: weekly	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.14 By frequency: flexible	1	265	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.37, 0.86]
4.15 By duration of the intervention: less than 6 months	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.16 By duration of the intervention: 6 months or more	3	321	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.26, 0.75]
4.17 By iron content: 12.5 mg or less	4	586	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.35, 0.67]
4.18 By iron content:: more than 12.5 mg	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.19 By zinc content: less than 5 mg	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.20 By zinc content:: 5 mg or more	4	612	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.38, 0.67]
4.21 By malaria status of the area at baseline: yes	4	586	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.35, 0.67]
4.22 By malaria status of the area at baseline: no	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Haemoglobin (g/L) (ALL)	6	1447	Mean Difference (IV, Random, 95% CI)	5.87 [3.25, 8.49]
6 Haemoglobin (g/L) (SUBGROUPS)	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 By anaemia at baseline: anaemic	1	125	Mean Difference (IV, Random, 95% CI)	7.90 [4.17, 11.63]
6.2 By anaemia at baseline: non anaemic	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 By anaemia at baseline: mixed/unknown	5	1321	Mean Difference (IV, Random, 95% CI)	5.32 [2.08, 8.56]

6.4 By iron status at baseline: iron deficient	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.5 By iron status at baseline: non iron deficient	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.6 By iron status at baseline: mixed/unknown	6	1446	Mean Difference (IV, Random, 95% CI)	5.87 [3.25, 8.49]
6.7 By age at baseline: 6 to 11 months	3	345	Mean Difference (IV, Random, 95% CI)	6.05 [3.42, 8.68]
6.8 By age at baseline: 12-23 months	1	126	Mean Difference (IV, Random, 95% CI)	3.90 [-0.91, 8.71]
6.9 By age at baseline: mixed/unknown	2	975	Mean Difference (IV, Random, 95% CI)	6.41 [0.05, 12.78]
6.10 By refugee status: yes	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.11 By refugee status: no	5	1028	Mean Difference (IV, Random, 95% CI)	6.66 [4.06, 9.25]
6.12 By frequency: daily	5	1028	Mean Difference (IV, Random, 95% CI)	6.66 [4.06, 9.25]
6.13 By frequency: weekly	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.14 By frequency: flexible	1	418	Mean Difference (IV, Random, 95% CI)	3.0 [-0.68, 6.68]
6.15 By duration of the intervention: less than 6 months	3	709	Mean Difference (IV, Random, 95% CI)	6.57 [2.19, 10.95]
6.16 By duration of the intervention: 6 months or more	2	319	Mean Difference (IV, Random, 95% CI)	6.23 [2.72, 9.75]
6.17 By iron content: 12.5 mg or less	6	1446	Mean Difference (IV, Random, 95% CI)	5.87 [3.25, 8.49]
6.18 By iron content:: more than 12.5 mg	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.19 By zinc content: less than 5 mg	6	1446	Mean Difference (IV, Random, 95% CI)	5.87 [3.25, 8.49]
6.20 By zinc content:: 5 mg or more	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.21 By malaria status of the area at baseline: yes	4	863	Mean Difference (IV, Random, 95% CI)	4.87 [2.60, 7.14]
6.22 By malaria status of the area at baseline: no	2	961	Mean Difference (IV, Random, 95% CI)	8.13 [3.47, 12.79]
7 Iron status (ferritin concentrations in μg/L) (ALL)	2	264	Mean Difference (IV, Random, 95% CI)	20.38 [6.27, 34.49]
8 Weight-for-age (in Z-scores) (ALL)	2	304	Mean Difference (IV, Random, 95% CI)	0.00 [-0.37, 0.37]
9 Length-for-age (in Z-scores)	2	304	Mean Difference (IV, Random, 95% CI)	0.04 [-0.15, 0.23]
10 Weight-for-length (in Z-scores)	2	304	Mean Difference (IV, Random, 95% CI)	0.04 [-0.44, 0.52]
11 Any cause morbidity	1	127	Risk Ratio (M-H, Random, 95% CI)	1.91 [0.60, 6.02]
12 Malaria smears	1	194	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.05, 1.12]
13 Diarrhoea (ALL)	1	206	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.00, 1.78]
14 Recurrent diarrhoea (not pre-specified)	1	127	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.51, 5.42]
15 Upper respiratory infections	1	127	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.34, 4.24]
16 Serum zinc	1	125	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.95, 0.55]
17 Walking independently	1	179	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.02, 2.46]

Comparison 2. Provision of multiple micronutrient powders versus iron supplements

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Anaemia (ALL)	1	145	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.58, 1.39]
2 Haemoglobin (g/L) (ALL)	2	278	Mean Difference (IV, Random, 95% CI)	-2.36 [-10.30, 5.58]
3 Diarrhoea (ALL)	1	262	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.38, 0.72]
4 Diarrhoea episodes (ALL) (not pre-specified)	2	389	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.16, 1.30]
5 Vomiting (ALL) (not pre-specified)	1	262	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.35, 0.95]
6 Staining of teeth (ALL) (not pre-specified)	2	395	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.16, 0.82]
7 Stool discolouration (ALL) (not pre-specified)	2	395	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.66, 0.98]
8 Cough (ALL) (not pre-specified)	1	130	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.53, 1.03]
9 Cold (ALL) (not pre-specified)	1	262	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.73, 0.97]
10 Fever (ALL) (not pre-specified)	1	262	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.42, 0.82]
11 Recurrent diarrhoea (3 or more episodes) (ALL) (not pre-specified)	1	262	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.10, 0.73]

Analysis 1.1. Comparison 1 Provision of multiple micronutrient powders versus no intervention or placebo, Outcome 1 Anaemia (ALL).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 1 Provision of multiple micronutrient powders versus no intervention or placebo

Outcome: 1 Anaemia (ALL)

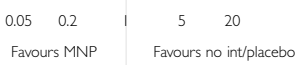
Study or subgroup	MNP n/N	no int/placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Adu-Afarwuah 2007	18/98	31/96		6.1 %	0.57 [0.34, 0.95]
Giovannini 2006	25/65	43/60		12.1 %	0.54 [0.38, 0.76]
Lundeen 2010	148/283	206/274		45.9 %	0.70 [0.61, 0.79]
Menon 2007	18/76	22/50		6.0 %	0.54 [0.32, 0.90]
Sharieff 2006a	5/13	6/13		2.0 %	0.83 [0.34, 2.06]
Suchdev 2011	88/205	113/214		27.8 %	0.81 [0.66, 1.00]
Total (95% CI)	**740**	**707**		**100.0 %**	**0.69 [0.60, 0.78]**

Total events: 302 (MNP), 421 (no int/placebo)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.17$, df = 5 (P = 0.29); $I^2 = 19\%$

Test for overall effect: Z = 5.65 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Provision of multiple micronutrient powders versus no intervention or placebo, Outcome 2 Anaemia (SUBGROUPS).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 1 Provision of multiple micronutrient powders versus no intervention or placebo

Outcome: 2 Anaemia (SUBGROUPS)

Study or subgroup	MNP n/N	no int/placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 By anaemia at baseline: anaemic					
Giovannini 2006	25/65	43/60		100.0 %	0.54 [0.38, 0.76]
Subtotal (95% CI)	**65**	**60**		**100.0 %**	**0.54 [0.38, 0.76]**
Total events: 25 (MNP), 43 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.52 (P = 0.00043)					
2 By anaemia at baseline: non anaemic					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (MNP), 0 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 By anaemia at baseline: mixed/unknown					
Menon 2007	18/76	22/50		4.2 %	0.54 [0.32, 0.90]
Adu-Afarwuah 2007	18/98	31/96		4.2 %	0.57 [0.34, 0.95]
Lundeen 2010	148/283	206/274		63.8 %	0.70 [0.61, 0.79]
Suchdev 2011	88/205	113/214		26.5 %	0.81 [0.66, 1.00]
Sharieff 2006a	5/13	6/13		1.3 %	0.83 [0.34, 2.06]
Subtotal (95% CI)	**675**	**647**		**100.0 %**	**0.71 [0.64, 0.79]**
Total events: 277 (MNP), 378 (no int/placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.80, df = 4 (P = 0.43); I^2 =0.0%					
Test for overall effect: Z = 6.37 (P < 0.00001)					
4 By iron status at baseline: iron deficient					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (MNP), 0 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
5 By iron status at baseline: non iron deficient					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (MNP), 0 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
6 By iron status at baseline: mixed/unknown					

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Study or subgroup	MNP n/N	no int/placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Giovannini 2006	25/65	43/60		12.1 %	0.54 [0.38, 0.76]
Menon 2007	18/76	22/50		6.0 %	0.54 [0.32, 0.90]
Adu-Afarwuah 2007	18/98	31/96		6.1 %	0.57 [0.34, 0.95]
Lundeen 2010	148/283	206/274		45.9 %	0.70 [0.61, 0.79]
Suchdev 2011	88/205	113/214		27.8 %	0.81 [0.66, 1.00]
Sharieff 2006a	5/13	6/13		2.0 %	0.83 [0.34, 2.06]
Subtotal (95% CI)	**740**	**707**		**100.0 %**	**0.69 [0.60, 0.78]**
Total events: 302 (MNP), 421 (no int/placebo)					
Heterogeneity: Tau² = 0.01; Chi² = 6.17, df = 5 (P = 0.29); I² =19%					
Test for overall effect: Z = 5.65 (P < 0.00001)					
7 By age at baseline: 6 to 11 months					
Giovannini 2006	25/65	43/60		62.1 %	0.54 [0.38, 0.76]
Adu-Afarwuah 2007	18/98	31/96		28.8 %	0.57 [0.34, 0.95]
Sharieff 2006a	5/13	6/13		9.1 %	0.83 [0.34, 2.06]
Subtotal (95% CI)	**176**	**169**		**100.0 %**	**0.57 [0.43, 0.75]**
Total events: 48 (MNP), 80 (no int/placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 0.79, df = 2 (P = 0.67); I² =0.0%					
Test for overall effect: Z = 4.06 (P = 0.000048)					
8 By age at baseline: 12-23 months					
Menon 2007	18/76	22/50		100.0 %	0.54 [0.32, 0.90]
Subtotal (95% CI)	**76**	**50**		**100.0 %**	**0.54 [0.32, 0.90]**
Total events: 18 (MNP), 22 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.38 (P = 0.017)					
9 By age at baseline: mixed/unknown					
Lundeen 2010	148/283	206/274		62.5 %	0.70 [0.61, 0.79]
Suchdev 2011	88/205	113/214		37.5 %	0.81 [0.66, 1.00]
Subtotal (95% CI)	**488**	**488**		**100.0 %**	**0.74 [0.63, 0.86]**
Total events: 236 (MNP), 319 (no int/placebo)					
Heterogeneity: Tau² = 0.00; Chi² = 1.65, df = 1 (P = 0.20); I² =39%					
Test for overall effect: Z = 3.99 (P = 0.000066)					
10 By refugee status: yes					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (MNP), 0 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
11 By refugee status: no					
Giovannini 2006	25/65	43/60		12.1 %	0.54 [0.38, 0.76]

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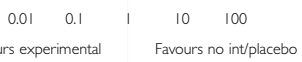
Study or subgroup	MNP n/N	no int/placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Menon 2007	18/76	22/50		6.0 %	0.54 [0.32, 0.90]
Adu-Afarwuah 2007	18/98	31/96		6.1 %	0.57 [0.34, 0.95]
Lundeen 2010	148/283	206/274		45.9 %	0.70 [0.61, 0.79]
Suchdev 2011	88/205	113/214		27.8 %	0.81 [0.66, 1.00]
Sharieff 2006a	5/13	6/13		2.0 %	0.83 [0.34, 2.06]
Subtotal (95% CI)	**740**	**707**		**100.0 %**	**0.69 [0.60, 0.78]**
Total events: 302 (MNP), 421 (no int/placebo)					
Heterogeneity: Tau² = 0.01; Chi² = 6.17, df = 5 (P = 0.29); I² =19%					
Test for overall effect: Z = 5.65 (P < 0.00001)					
12 By frequency: daily					
Giovannini 2006	25/65	43/60		11.0 %	0.54 [0.38, 0.76]
Menon 2007	18/76	22/50		5.0 %	0.54 [0.32, 0.90]
Adu-Afarwuah 2007	18/98	31/96		5.1 %	0.57 [0.34, 0.95]
Lundeen 2010	148/283	206/274		77.3 %	0.70 [0.61, 0.79]
Sharieff 2006a	5/13	6/13		1.6 %	0.83 [0.34, 2.06]
Subtotal (95% CI)	**535**	**493**		**100.0 %**	**0.66 [0.59, 0.74]**
Total events: 214 (MNP), 308 (no int/placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 3.29, df = 4 (P = 0.51); I² =0.0%					
Test for overall effect: Z = 7.04 (P < 0.00001)					
13 By frequency: weekly					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (MNP), 0 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
14 By frequency: flexible					
Suchdev 2011	88/205	113/214		100.0 %	0.81 [0.66, 1.00]
Subtotal (95% CI)	**205**	**214**		**100.0 %**	**0.81 [0.66, 1.00]**
Total events: 88 (MNP), 113 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.01 (P = 0.045)					
15 By duration of the intervention: less than 6 months					
Menon 2007	18/76	22/50		6.0 %	0.54 [0.32, 0.90]
Lundeen 2010	148/283	206/274		92.1 %	0.70 [0.61, 0.79]
Sharieff 2006a	5/13	6/13		1.9 %	0.83 [0.34, 2.06]
Subtotal (95% CI)	**372**	**337**		**100.0 %**	**0.69 [0.61, 0.78]**
Total events: 171 (MNP), 234 (no int/placebo)					



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Study or subgroup	MNP n/N	no int/placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau² = 0.0; Chi² = 1.10, df = 2 (P = 0.58); I² =0.0%					
Test for overall effect: Z = 5.87 (P < 0.00001)					
16 By duration of the intervention: 6 months or more					
Giovannini 2006	25/65	43/60		32.7 %	0.54 [0.38, 0.76]
Adu-Afarwuah 2007	18/98	31/96		22.0 %	0.57 [0.34, 0.95]
Suchdev 2011	88/205	113/214		45.3 %	0.81 [0.66, 1.00]
Subtotal (95% CI)	**368**	**370**		**100.0 %**	**0.66 [0.48, 0.89]**
Total events: 131 (MNP), 187 (no int/placebo)					
Heterogeneity: Tau² = 0.04; Chi² = 4.97, df = 2 (P = 0.08); I² =60%					
Test for overall effect: Z = 2.71 (P = 0.0068)					
17 By iron content: 12.5 mg or less					
Giovannini 2006	25/65	43/60		12.1 %	0.54 [0.38, 0.76]
Menon 2007	18/76	22/50		6.0 %	0.54 [0.32, 0.90]
Adu-Afarwuah 2007	18/98	31/96		6.1 %	0.57 [0.34, 0.95]
Lundeen 2010	148/283	206/274		45.9 %	0.70 [0.61, 0.79]
Suchdev 2011	88/205	113/214		27.8 %	0.81 [0.66, 1.00]
Sharieff 2006a	5/13	6/13		2.0 %	0.83 [0.34, 2.06]
Subtotal (95% CI)	**740**	**707**		**100.0 %**	**0.69 [0.60, 0.78]**
Total events: 302 (MNP), 421 (no int/placebo)					
Heterogeneity: Tau² = 0.01; Chi² = 6.17, df = 5 (P = 0.29); I² =19%					
Test for overall effect: Z = 5.65 (P < 0.00001)					
18 By iron content:: more than 12.5 mg					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (MNP), 0 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
19 By zinc content: less than 5 mg					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (MNP), 0 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
20 By zinc content:: 5 mg or more					
Giovannini 2006	25/65	43/60		12.1 %	0.54 [0.38, 0.76]
Menon 2007	18/76	22/50		6.0 %	0.54 [0.32, 0.90]
Adu-Afarwuah 2007	18/98	31/96		6.1 %	0.57 [0.34, 0.95]
Lundeen 2010	148/283	206/274		45.9 %	0.70 [0.61, 0.79]

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Study or subgroup	MNP n/N	no int/placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Suchdev 2011	88/205	113/214		27.8 %	0.81 [0.66, 1.00]
Sharieff 2006a	5/13	6/13		2.0 %	0.83 [0.34, 2.06]
Subtotal (95% CI)	**740**	**707**		**100.0 %**	**0.69 [0.60, 0.78]**
Total events: 302 (MNP), 421 (no int/placebo)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.17$, df = 5 (P = 0.29); $I^2 = 19\%$					
Test for overall effect: Z = 5.65 (P < 0.00001)					
21 By malaria status of the area at baseline: yes					
Giovannini 2006	25/65	43/60		26.7 %	0.54 [0.38, 0.76]
Menon 2007	18/76	22/50		17.1 %	0.54 [0.32, 0.90]
Adu-Afarwuah 2007	18/98	31/96		17.2 %	0.57 [0.34, 0.95]
Suchdev 2011	88/205	113/214		39.0 %	0.81 [0.66, 1.00]
Subtotal (95% CI)	**444**	**420**		**100.0 %**	**0.64 [0.49, 0.83]**
Total events: 149 (MNP), 209 (no int/placebo)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 6.03$, df = 3 (P = 0.11); $I^2 = 50\%$					
Test for overall effect: Z = 3.41 (P = 0.00064)					
22 By malaria status of the area at baseline: no					
Lundeen 2010	248/474	346/461		98.8 %	0.70 [0.63, 0.77]
Sharieff 2006a	5/13	6/13		1.2 %	0.83 [0.34, 2.06]
Subtotal (95% CI)	**487**	**474**		**100.0 %**	**0.70 [0.63, 0.77]**
Total events: 253 (MNP), 352 (no int/placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.15$, df = 1 (P = 0.70); $I^2 = 0.0\%$					
Test for overall effect: Z = 7.02 (P < 0.00001)					

Analysis 1.3. Comparison 1 Provision of multiple micronutrient powders versus no intervention or placebo, Outcome 3 Iron deficiency (ALL).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 1 Provision of multiple micronutrient powders versus no intervention or placebo

Outcome: 3 Iron deficiency (ALL)

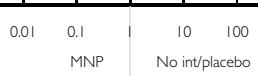
Study or subgroup	MNP n/N	no int/placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Adu-Afarwuah 2007	28/98	39/72		39.2 %	0.53 [0.36, 0.77]
Giovannini 2006	9/65	31/60		19.3 %	0.27 [0.14, 0.52]
Sharieff 2006a	3/13	4/13		6.1 %	0.75 [0.21, 2.71]
Suchdev 2011	19/73	88/192		35.4 %	0.57 [0.37, 0.86]
Total (95% CI)	**249**	**337**		**100.0 %**	**0.49 [0.35, 0.67]**

Total events: 59 (MNP), 162 (no int/placebo)

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 4.34$, df = 3 (P = 0.23); $I^2 = 31\%$

Test for overall effect: Z = 4.30 (P = 0.000017)

Test for subgroup differences: Not applicable



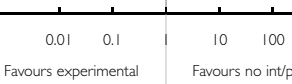
Analysis 1.4. Comparison 1 Provision of multiple micronutrient powders versus no intervention or placebo, Outcome 4 Iron deficiency (SUBGROUPS).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 1 Provision of multiple micronutrient powders versus no intervention or placebo

Outcome: 4 Iron deficiency (SUBGROUPS)

Study or subgroup	MNP n/N	no int/placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 By anaemia at baseline: anaemic					
Giovannini 2006	9/65	31/60		100.0 %	0.27 [0.14, 0.52]
Subtotal (95% CI)	**65**	**60**		**100.0 %**	**0.27 [0.14, 0.52]**
Total events: 9 (MNP), 31 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.95 (P = 0.000079)					
2 By anaemia at baseline: non anaemic					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (MNP), 0 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 By anaemia at baseline: mixed/unknown					
Adu-Afarwuah 2007	28/98	39/72		50.0 %	0.53 [0.36, 0.77]
Sharieff 2006a	3/13	4/13		4.3 %	0.75 [0.21, 2.71]
Sharieff 2006a	3/13	4/13		4.3 %	0.75 [0.21, 2.71]
Suchdev 2011	19/73	88/192		41.3 %	0.57 [0.37, 0.86]
Subtotal (95% CI)	**197**	**290**		**100.0 %**	**0.56 [0.43, 0.73]**
Total events: 53 (MNP), 135 (no int/placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.50, df = 3 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 4.24 (P = 0.000022)					
4 By iron status at baseline: iron deficient					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (MNP), 0 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
5 By iron status at baseline: non iron deficient					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (MNP), 0 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
6 By iron status at baseline: mixed/unknown					
Adu-Afarwuah 2007	28/98	39/72		39.2 %	0.53 [0.36, 0.77]



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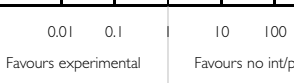
Study or subgroup	MNP n/N	no int/placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Giovannini 2006	9/65	31/60		19.3 %	0.27 [0.14, 0.52]
Sharieff 2006a	3/13	4/13		6.1 %	0.75 [0.21, 2.71]
Suchdev 2011	19/73	88/192		35.4 %	0.57 [0.37, 0.86]
Subtotal (95% CI)	**249**	**337**		**100.0 %**	**0.49 [0.35, 0.67]**
Total events: 59 (MNP), 162 (no int/placebo)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 4.34, df = 3 (P = 0.23); I^2 =31%					
Test for overall effect: Z = 4.30 (P = 0.000017)					
7 By age at baseline: 6 to 11 months					
Adu-Afarwuah 2007	28/98	39/72		52.0 %	0.53 [0.36, 0.77]
Giovannini 2006	9/65	31/60		34.2 %	0.27 [0.14, 0.52]
Sharieff 2006a	3/13	4/13		13.9 %	0.75 [0.21, 2.71]
Subtotal (95% CI)	**176**	**145**		**100.0 %**	**0.44 [0.26, 0.75]**
Total events: 40 (MNP), 74 (no int/placebo)					
Heterogeneity: Tau^2 = 0.11; Chi^2 = 3.79, df = 2 (P = 0.15); I^2 =47%					
Test for overall effect: Z = 3.02 (P = 0.0025)					
8 By age at baseline: 12-23 months					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (MNP), 0 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
9 By age at baseline: mixed/unknown					
Suchdev 2011	19/73	88/192		100.0 %	0.57 [0.37, 0.86]
Subtotal (95% CI)	**73**	**192**		**100.0 %**	**0.57 [0.37, 0.86]**
Total events: 19 (MNP), 88 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.66 (P = 0.0077)					
10 By refugee status: yes					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (MNP), 0 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
11 By refugee status: no					
Adu-Afarwuah 2007	28/98	39/72		39.2 %	0.53 [0.36, 0.77]
Giovannini 2006	9/65	31/60		19.3 %	0.27 [0.14, 0.52]
Sharieff 2006a	3/13	4/13		6.1 %	0.75 [0.21, 2.71]
Suchdev 2011	19/73	88/192		35.4 %	0.57 [0.37, 0.86]
Subtotal (95% CI)	**249**	**337**		**100.0 %**	**0.49 [0.35, 0.67]**
Total events: 59 (MNP), 162 (no int/placebo)					



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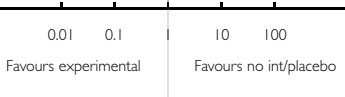
Study or subgroup	MNP n/N	no int/placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau² = 0.03; Chi² = 4.34, df = 3 (P = 0.23); I² =31%					
Test for overall effect: Z = 4.30 (P = 0.000017)					
12 By frequency: daily					
Adu-Afarwuah 2007	28/98	39/72		52.0 %	0.53 [0.36, 0.77]
Giovannini 2006	9/65	31/60		34.2 %	0.27 [0.14, 0.52]
Sharieff 2006a	3/13	4/13		13.9 %	0.75 [0.21, 2.71]
Subtotal (95% CI)	**176**	**145**		**100.0 %**	**0.44 [0.26, 0.75]**
Total events: 40 (MNP), 74 (no int/placebo)					
Heterogeneity: Tau² = 0.11; Chi² = 3.79, df = 2 (P = 0.15); I² =47%					
Test for overall effect: Z = 3.02 (P = 0.0025)					
13 By frequency: weekly					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (MNP), 0 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
14 By frequency: flexible					
Suchdev 2011	19/73	88/192		100.0 %	0.57 [0.37, 0.86]
Subtotal (95% CI)	**73**	**192**		**100.0 %**	**0.57 [0.37, 0.86]**
Total events: 19 (MNP), 88 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.66 (P = 0.0077)					
15 By duration of the intervention: less than 6 months					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (MNP), 0 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
16 By duration of the intervention: 6 months or more					
Adu-Afarwuah 2007	28/98	39/72		52.0 %	0.53 [0.36, 0.77]
Giovannini 2006	9/65	31/60		34.2 %	0.27 [0.14, 0.52]
Sharieff 2006a	3/13	4/13		13.9 %	0.75 [0.21, 2.71]
Subtotal (95% CI)	**176**	**145**		**100.0 %**	**0.44 [0.26, 0.75]**
Total events: 40 (MNP), 74 (no int/placebo)					
Heterogeneity: Tau² = 0.11; Chi² = 3.79, df = 2 (P = 0.15); I² =47%					
Test for overall effect: Z = 3.02 (P = 0.0025)					
17 By iron content: 12.5 mg or less					
Adu-Afarwuah 2007	28/98	39/72		39.2 %	0.53 [0.36, 0.77]
Giovannini 2006	9/65	31/60		19.3 %	0.27 [0.14, 0.52]
Sharieff 2006a	3/13	4/13		6.1 %	0.75 [0.21, 2.71]



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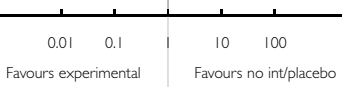
Study or subgroup	MNP n/N	no int/placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Suchdev 2011	19/73	88/192		35.4 %	0.57 [0.37, 0.86]
Subtotal (95% CI)	**249**	**337**		**100.0 %**	**0.49 [0.35, 0.67]**
Total events: 59 (MNP), 162 (no int/placebo)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 4.34, df = 3 (P = 0.23); I^2 =31%					
Test for overall effect: Z = 4.30 (P = 0.000017)					
18 By iron content:: more than 12.5 mg					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (MNP), 0 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
19 By zinc content: less than 5 mg					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (MNP), 0 (no int/placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
20 By zinc content:: 5 mg or more					
Adu-Afarwuah 2007	28/98	39/72		39.3 %	0.53 [0.36, 0.77]
Giovannini 2006	9/65	31/60		16.7 %	0.27 [0.14, 0.52]
Sharieff 2006a	3/13	4/13		4.8 %	0.75 [0.21, 2.71]
Sharieff 2006a	3/13	4/13		4.8 %	0.75 [0.21, 2.71]
Suchdev 2011	19/73	88/192		34.4 %	0.57 [0.37, 0.86]
Subtotal (95% CI)	**262**	**350**		**100.0 %**	**0.50 [0.38, 0.67]**
Total events: 62 (MNP), 166 (no int/placebo)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 4.72, df = 4 (P = 0.32); I^2 =15%					
Test for overall effect: Z = 4.73 (P < 0.00001)					
21 By malaria status of the area at baseline: yes					
Adu-Afarwuah 2007	28/98	39/72		39.2 %	0.53 [0.36, 0.77]
Giovannini 2006	9/65	31/60		19.3 %	0.27 [0.14, 0.52]
Sharieff 2006a	3/13	4/13		6.1 %	0.75 [0.21, 2.71]
Suchdev 2011	19/73	88/192		35.4 %	0.57 [0.37, 0.86]
Subtotal (95% CI)	**249**	**337**		**100.0 %**	**0.49 [0.35, 0.67]**
Total events: 59 (MNP), 162 (no int/placebo)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 4.34, df = 3 (P = 0.23); I^2 =31%					
Test for overall effect: Z = 4.30 (P = 0.000017)					
22 By malaria status of the area at baseline: no					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (MNP), 0 (no int/placebo)					
Heterogeneity: not applicable					



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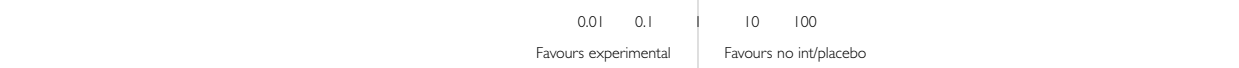
Study or subgroup	MNP n/N	no int/placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: not applicable					



Analysis 1.5. Comparison 1 Provision of multiple micronutrient powders versus no intervention or placebo, Outcome 5 Haemoglobin (g/L) (ALL).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 1 Provision of multiple micronutrient powders versus no intervention or placebo

Outcome: 5 Haemoglobin (g/L) (ALL)

Study or subgroup	MNP N	Mean(SD)	no int/placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Sharieff 2006a	13	103 (8)	13	99 (12)		8.1 %	4.00 [-3.84, 11.84]
Menon 2007	76	104.4 (12.74)	50	100.5 (13.96)		14.7 %	3.90 [-0.91, 8.71]
Adu-Afarwuah 2007	98	110 (15.15)	96	105.7 (14.7)		16.7 %	4.30 [0.10, 8.50]
Giovannini 2006	65	107.6 (11)	60	99.7 (10.3)		18.3 %	7.90 [4.17, 11.63]
Suchdev 2011	205	110 (16.6)	214	107 (21.6)		18.5 %	3.00 [-0.68, 6.68]
Lundeen 2010	283	108.1 (13.2)	274	98.6 (14.6)		23.7 %	9.50 [7.19, 11.81]
Total (95% CI)	**740**		**707**			**100.0 %**	**5.87 [3.25, 8.49]**

Heterogeneity: $Tau^2 = 6.14$; $Chi^2 = 12.91$, df = 5 (P = 0.02); $I^2 = 61\%$

Test for overall effect: Z = 4.39 (P = 0.000011)

Test for subgroup differences: Not applicable

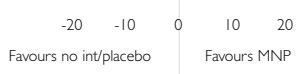
Analysis 1.6. Comparison 1 Provision of multiple micronutrient powders versus no intervention or placebo, Outcome 6 Haemoglobin (g/L) (SUBGROUPS).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 1 Provision of multiple micronutrient powders versus no intervention or placebo

Outcome: 6 Haemoglobin (g/L) (SUBGROUPS)

Study or subgroup	MNP N	Mean(SD)	no int/placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 By anaemia at baseline: anaemic							
Giovannini 2006	65	107.6 (11)	60	99.7 (10.3)		100.0 %	7.90 [4.17, 11.63]
Subtotal (95% CI)	**65**		**60**			**100.0 %**	**7.90 [4.17, 11.63]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.15 (P = 0.000034)							
2 By anaemia at baseline: non anaemic							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
3 By anaemia at baseline: mixed/unknown							
Adu-Afarwuah 2007	98	110 (15.15)	96	105.7 (14.7)		20.6 %	4.30 [0.10, 8.50]
Lundeen 2010	283	108.1 (13.2)	274	98.6 (14.6)		27.2 %	9.50 [7.19, 11.81]
Menon 2007	76	104.4 (12.74)	50	100.5 (13.96)		18.6 %	3.90 [-0.91, 8.71]
Sharieff 2006a	13	103 (8)	13	99 (12)		11.1 %	4.00 [-3.84, 11.84]
Suchdev 2011	205	110 (16.6)	213	107 (21.6)		22.4 %	3.00 [-0.68, 6.68]
Subtotal (95% CI)	**675**		**646**			**100.0 %**	**5.32 [2.08, 8.56]**
Heterogeneity: Tau^2 = 8.65; Chi^2 = 12.48, df = 4 (P = 0.01); I^2 =68%							
Test for overall effect: Z = 3.22 (P = 0.0013)							
4 By iron status at baseline: iron deficient							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
5 By iron status at baseline: non iron deficient							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
6 By iron status at baseline: mixed/unknown							
Adu-Afarwuah 2007	98	110 (15.15)	96	105.7 (14.7)		16.7 %	4.30 [0.10, 8.50]
Giovannini 2006	65	107.6 (11)	60	99.7 (10.3)		18.3 %	7.90 [4.17, 11.63]
Lundeen 2010	283	108.1 (13.2)	274	98.6 (14.6)		23.8 %	9.50 [7.19, 11.81]



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Study or subgroup	MNP N	Mean(SD)	no int/placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Menon 2007	76	104.4 (12.74)	50	100.5 (13.96)		14.7 %	3.90 [-0.91, 8.71]
Sharieff 2006a	13	103 (8)	13	99 (12)		8.1 %	4.00 [-3.84, 11.84]
Suchdev 2011	205	110 (16.6)	213	107 (21.6)		18.5 %	3.00 [-0.68, 6.68]
Subtotal (95% CI)	**740**		**706**			**100.0 %**	**5.87 [3.25, 8.49]**
Heterogeneity: Tau^2 = 6.14; Chi^2 = 12.89, df = 5 (P = 0.02); I^2 =61%							
Test for overall effect: Z = 4.39 (P = 0.000011)							
7 By age at baseline: 6 to 11 months							
Adu-Afarwuah 2007	98	110 (15.15)	96	105.7 (14.7)		39.2 %	4.30 [0.10, 8.50]
Giovannini 2006	65	107.6 (11)	60	99.7 (10.3)		49.6 %	7.90 [4.17, 11.63]
Sharieff 2006a	13	103 (8)	13	99 (12)		11.2 %	4.00 [-3.84, 11.84]
Subtotal (95% CI)	**176**		**169**			**100.0 %**	**6.05 [3.42, 8.68]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.87, df = 2 (P = 0.39); I^2 =0.0%							
Test for overall effect: Z = 4.51 (P < 0.00001)							
8 By age at baseline: 12-23 months							
Menon 2007	76	104.4 (12.74)	50	100.5 (13.96)		100.0 %	3.90 [-0.91, 8.71]
Subtotal (95% CI)	**76**		**50**			**100.0 %**	**3.90 [-0.91, 8.71]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.59 (P = 0.11)							
9 By age at baseline: mixed/unknown							
Lundeen 2010	283	108.1 (13.2)	274	98.6 (14.6)		52.5 %	9.50 [7.19, 11.81]
Suchdev 2011	205	110 (16.6)	213	107 (21.6)		47.5 %	3.00 [-0.68, 6.68]
Subtotal (95% CI)	**488**		**487**			**100.0 %**	**6.41 [0.05, 12.78]**
Heterogeneity: Tau^2 = 18.66; Chi^2 = 8.57, df = 1 (P = 0.003); I^2 =88%							
Test for overall effect: Z = 1.98 (P = 0.048)							
10 By refugee status: yes							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
11 By refugee status: no							
Adu-Afarwuah 2007	98	110 (15.15)	96	105.7 (14.7)		20.0 %	4.30 [0.10, 8.50]
Giovannini 2006	65	107.6 (11)	60	99.7 (10.3)		22.5 %	7.90 [4.17, 11.63]
Lundeen 2010	283	108.1 (13.2)	274	98.6 (14.6)		31.6 %	9.50 [7.19, 11.81]
Menon 2007	76	104.4 (12.74)	50	100.5 (13.96)		17.2 %	3.90 [-0.91, 8.71]
Sharieff 2006a	13	103 (8)	13	99 (12)		8.7 %	4.00 [-3.84, 11.84]
Subtotal (95% CI)	**535**		**493**			**100.0 %**	**6.66 [4.06, 9.25]**
Heterogeneity: Tau^2 = 4.17; Chi^2 = 8.06, df = 4 (P = 0.09); I^2 =50%							
Test for overall effect: Z = 5.03 (P < 0.00001)							

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Study or subgroup	MNP N	Mean(SD)	no int/placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
12 By frequency: daily							
Adu-Afarwuah 2007	98	110 (15.15)	96	105.7 (14.7)		20.0 %	4.30 [0.10, 8.50]
Giovannini 2006	65	107.6 (11)	60	99.7 (10.3)		22.5 %	7.90 [4.17, 11.63]
Lundeen 2010	283	108.1 (13.2)	274	98.6 (14.6)		31.6 %	9.50 [7.19, 11.81]
Menon 2007	76	104.4 (12.74)	50	100.5 (13.96)		17.2 %	3.90 [-0.91, 8.71]
Sharieff 2006a	13	103 (8)	13	99 (12)		8.7 %	4.00 [-3.84, 11.84]
Subtotal (95% CI)	**535**		**493**			**100.0 %**	**6.66 [4.06, 9.25]**
Heterogeneity: Tau² = 4.17; Chi² = 8.06, df = 4 (P = 0.09); I² =50%							
Test for overall effect: Z = 5.03 (P < 0.00001)							
13 By frequency: weekly							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
14 By frequency: flexible							
Suchdev 2011	205	110 (16.6)	213	107 (21.6)		100.0 %	3.00 [-0.68, 6.68]
Subtotal (95% CI)	**205**		**213**			**100.0 %**	**3.00 [-0.68, 6.68]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.60 (P = 0.11)							
15 By duration of the intervention: less than 6 months							
Lundeen 2010	283	108.1 (13.2)	274	98.6 (14.6)		47.3 %	9.50 [7.19, 11.81]
Menon 2007	76	104.4 (12.74)	50	100.5 (13.96)		32.9 %	3.90 [-0.91, 8.71]
Sharieff 2006a	13	103 (8)	13	99 (12)		19.9 %	4.00 [-3.84, 11.84]
Subtotal (95% CI)	**372**		**337**			**100.0 %**	**6.57 [2.19, 10.95]**
Heterogeneity: Tau² = 9.17; Chi² = 5.38, df = 2 (P = 0.07); I² =63%							
Test for overall effect: Z = 2.94 (P = 0.0033)							
16 By duration of the intervention: 6 months or more							
Adu-Afarwuah 2007	98	110 (15.15)	96	105.7 (14.7)		46.3 %	4.30 [0.10, 8.50]
Giovannini 2006	65	107.6 (11)	60	99.7 (10.3)		53.7 %	7.90 [4.17, 11.63]
Subtotal (95% CI)	**163**		**156**			**100.0 %**	**6.23 [2.72, 9.75]**
Heterogeneity: Tau² = 2.37; Chi² = 1.58, df = 1 (P = 0.21); I² =37%							
Test for overall effect: Z = 3.47 (P = 0.00052)							
17 By iron content: 12.5 mg or less							
Adu-Afarwuah 2007	98	110 (15.15)	96	105.7 (14.7)		16.7 %	4.30 [0.10, 8.50]
Giovannini 2006	65	107.6 (11)	60	99.7 (10.3)		18.3 %	7.90 [4.17, 11.63]
Lundeen 2010	283	108.1 (13.2)	274	98.6 (14.6)		23.8 %	9.50 [7.19, 11.81]
Menon 2007	76	104.4 (12.74)	50	100.5 (13.96)		14.7 %	3.90 [-0.91, 8.71]

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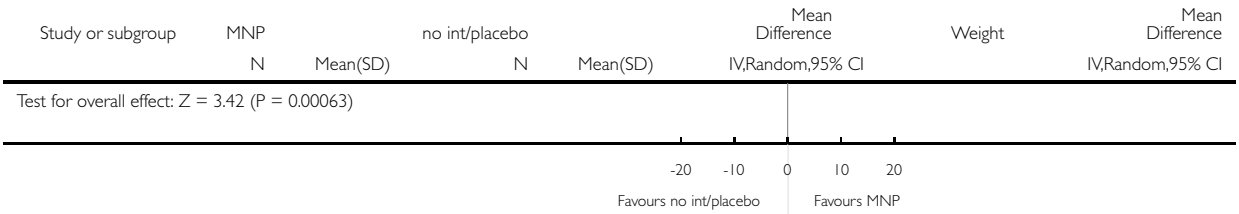
Study or subgroup	MNP N	Mean(SD)	no int/placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Sharieff 2006a	13	103 (8)	13	99 (12)		8.1 %	4.00 [-3.84, 11.84]
Suchdev 2011	205	110 (16.6)	213	107 (21.6)		18.5 %	3.00 [-0.68, 6.68]
Subtotal (95% CI)	**740**		**706**			**100.0 %**	**5.87 [3.25, 8.49]**
Heterogeneity: Tau² = 6.14; Chi² = 12.89, df = 5 (P = 0.02); I² =61%							
Test for overall effect: Z = 4.39 (P = 0.000011)							
18 By iron content:: more than 12.5 mg							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
19 By zinc content: less than 5 mg							
Adu-Afarwuah 2007	98	110 (15.15)	96	105.7 (14.7)		16.7 %	4.30 [0.10, 8.50]
Giovannini 2006	65	107.6 (11)	60	99.7 (10.3)		18.3 %	7.90 [4.17, 11.63]
Lundeen 2010	283	108.1 (13.2)	274	98.6 (14.6)		23.8 %	9.50 [7.19, 11.81]
Menon 2007	76	104.4 (12.74)	50	100.5 (13.96)		14.7 %	3.90 [-0.91, 8.71]
Sharieff 2006a	13	103 (8)	13	99 (12)		8.1 %	4.00 [-3.84, 11.84]
Suchdev 2011	205	110 (16.6)	213	107 (21.6)		18.5 %	3.00 [-0.68, 6.68]
Subtotal (95% CI)	**740**		**706**			**100.0 %**	**5.87 [3.25, 8.49]**
Heterogeneity: Tau² = 6.14; Chi² = 12.89, df = 5 (P = 0.02); I² =61%							
Test for overall effect: Z = 4.39 (P = 0.000011)							
20 By zinc content:: 5 mg or more							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
21 By malaria status of the area at baseline: yes							
Adu-Afarwuah 2007	98	110 (15.15)	96	105.7 (14.7)		23.6 %	4.30 [0.10, 8.50]
Giovannini 2006	65	107.6 (11)	60	99.7 (10.3)		28.5 %	7.90 [4.17, 11.63]
Menon 2007	76	104.4 (12.74)	50	100.5 (13.96)		18.8 %	3.90 [-0.91, 8.71]
Suchdev 2011	205	110 (16.6)	213	107 (21.6)		29.1 %	3.00 [-0.68, 6.68]
Subtotal (95% CI)	**444**		**419**			**100.0 %**	**4.87 [2.60, 7.14]**
Heterogeneity: Tau² = 1.07; Chi² = 3.74, df = 3 (P = 0.29); I² =20%							
Test for overall effect: Z = 4.21 (P = 0.000025)							
22 By malaria status of the area at baseline: no							
Lundeen 2010	474	108.1 (13.2)	461	98.6 (14.6)		75.1 %	9.50 [7.71, 11.29]
Sharieff 2006a	13	103 (8)	13	99 (12)		24.9 %	4.00 [-3.84, 11.84]
Subtotal (95% CI)	**487**		**474**			**100.0 %**	**8.13 [3.47, 12.79]**
Heterogeneity: Tau² = 6.71; Chi² = 1.80, df = 1 (P = 0.18); I² =44%							

(*Continued* . . .)

(. . . *Continued*)

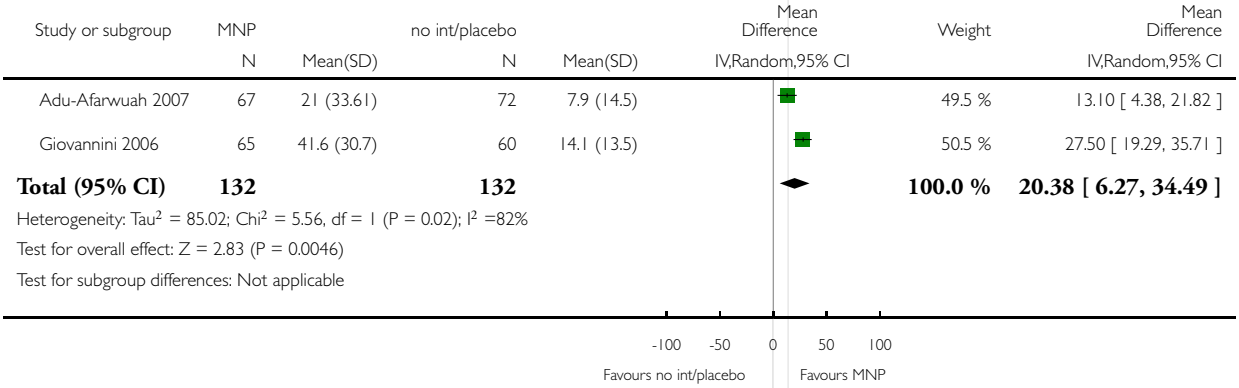


Analysis 1.7. Comparison 1 Provision of multiple micronutrient powders versus no intervention or placebo, Outcome 7 Iron status (ferritin concentrations in μg/L) (ALL).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 1 Provision of multiple micronutrient powders versus no intervention or placebo

Outcome: 7 Iron status (ferritin concentrations in μ g/L) (ALL)



Analysis 1.8. Comparison 1 Provision of multiple micronutrient powders versus no intervention or placebo, Outcome 8 Weight-for-age (in Z-scores) (ALL).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 1 Provision of multiple micronutrient powders versus no intervention or placebo

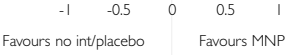
Outcome: 8 Weight-for-age (in Z-scores) (ALL)

Study or subgroup	MNP N	Mean(SD)	no int/placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Adu-Afarwuah 2007	96	-0.53 (1.1)	81	-0.74 (1.1)		45.6 %	0.21 [-0.12, 0.54]
Giovannini 2006	65	-1.25 (0.69)	62	-1.08 (0.68)		54.4 %	-0.17 [-0.41, 0.07]
Total (95% CI)	**161**		**143**			**100.0 %**	**0.00 [-0.37, 0.37]**

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 3.41$, df = 1 (P = 0.06); $I^2 = 71\%$

Test for overall effect: Z = 0.02 (P = 0.99)

Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1 Provision of multiple micronutrient powders versus no intervention or placebo, Outcome 9 Length-for-age (in Z-scores).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 1 Provision of multiple micronutrient powders versus no intervention or placebo

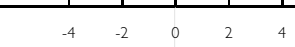
Outcome: 9 Length-for-age (in Z-scores)

Study or subgroup	MNP N	Mean(SD)	no int/placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Adu-Afarwuah 2007	96	-0.4 (1)	81	-0.4 (1)		43.1 %	0.0 [-0.30, 0.30]
Giovannini 2006	65	-1.56 (0.78)	62	-1.63 (0.7)		56.9 %	0.07 [-0.19, 0.33]
Total (95% CI)	**161**		**143**			**100.0 %**	**0.04 [-0.15, 0.23]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.12$, df = 1 (P = 0.73); $I^2 = 0.0\%$

Test for overall effect: Z = 0.40 (P = 0.69)

Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1 Provision of multiple micronutrient powders versus no intervention or placebo, Outcome 10 Weight-for-length (in Z-scores).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 1 Provision of multiple micronutrient powders versus no intervention or placebo

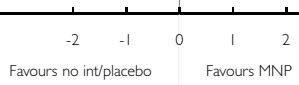
Outcome: 10 Weight-for-length (in Z-scores)

Study or subgroup	MNP N	Mean(SD)	no int/placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Adu-Afarwuah 2007	96	-0.45 (1.1)	81	-0.74 (1.1)		48.4 %	0.29 [-0.04, 0.62]
Giovannini 2006	65	-0.46 (0.76)	62	-0.26 (0.82)		51.6 %	-0.20 [-0.48, 0.08]
Total (95% CI)	**161**		**143**			**100.0 %**	**0.04 [-0.44, 0.52]**

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 5.08$, df = 1 (P = 0.02); $I^2 = 80\%$

Test for overall effect: Z = 0.15 (P = 0.88)

Test for subgroup differences: Not applicable

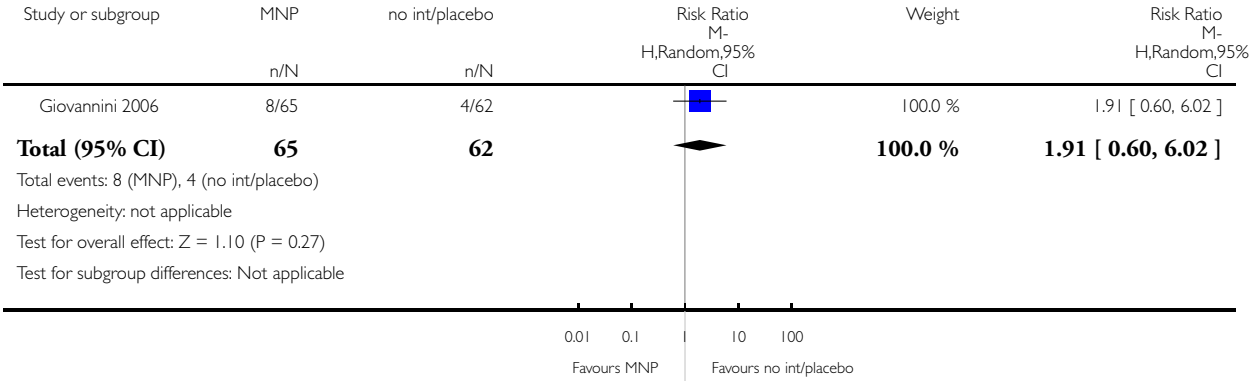


Analysis 1.11. Comparison 1 Provision of multiple micronutrient powders versus no intervention or placebo, Outcome 11 Any cause morbidity.

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 1 Provision of multiple micronutrient powders versus no intervention or placebo

Outcome: 11 Any cause morbidity

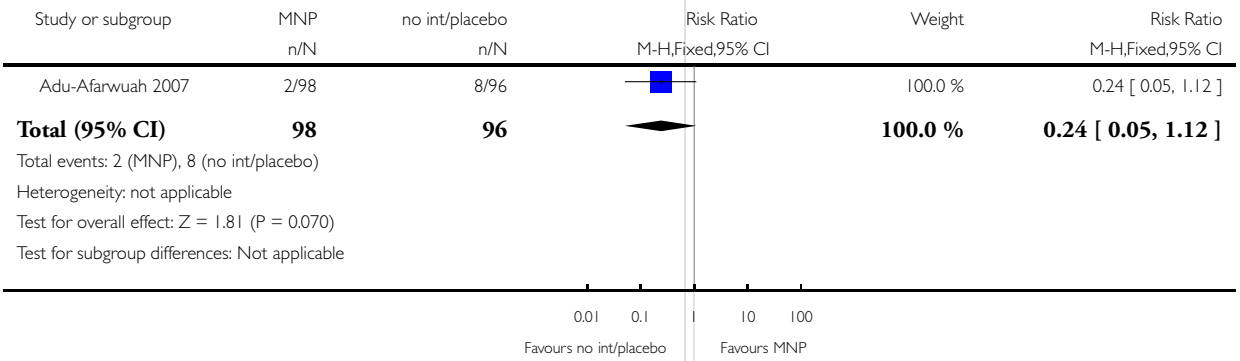


Analysis 1.12. Comparison 1 Provision of multiple micronutrient powders versus no intervention or placebo, Outcome 12 Malaria smears.

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 1 Provision of multiple micronutrient powders versus no intervention or placebo

Outcome: 12 Malaria smears

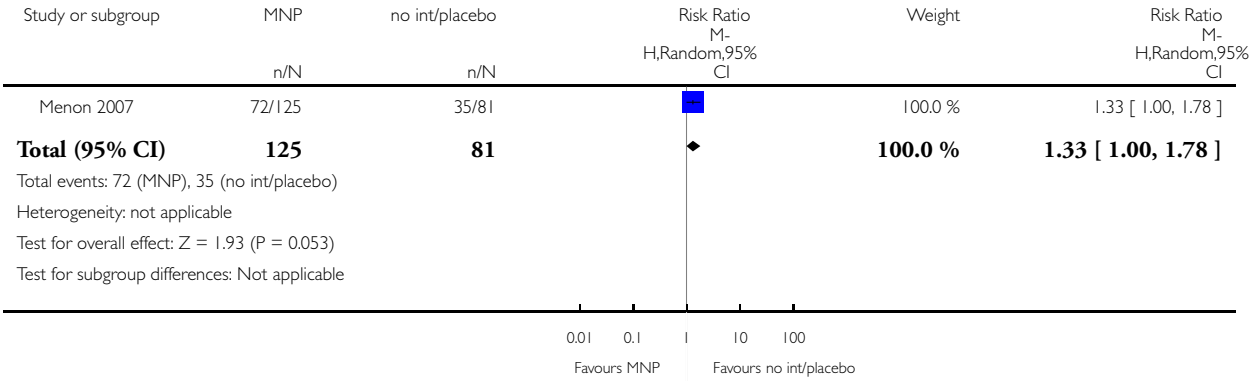


Analysis 1.13. Comparison 1 Provision of multiple micronutrient powders versus no intervention or placebo, Outcome 13 Diarrhoea (ALL).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 1 Provision of multiple micronutrient powders versus no intervention or placebo

Outcome: 13 Diarrhoea (ALL)

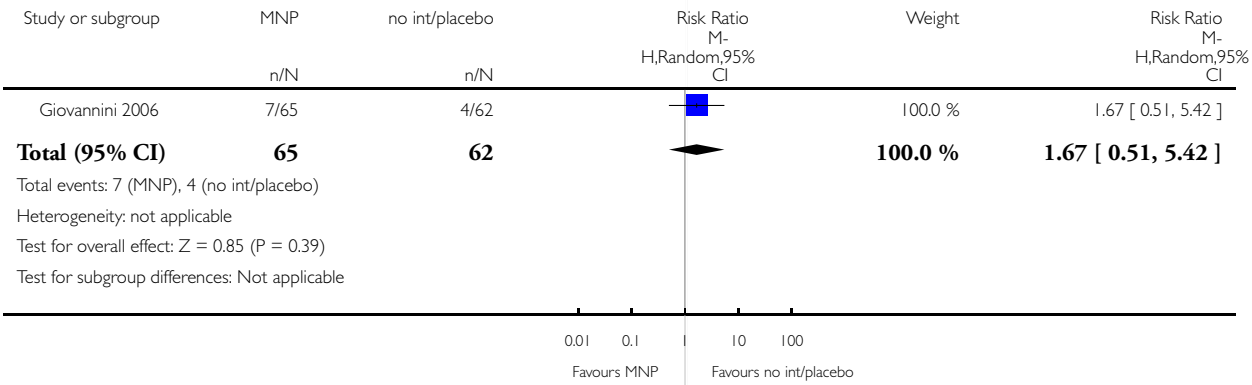


Analysis 1.14. Comparison 1 Provision of multiple micronutrient powders versus no intervention or placebo, Outcome 14 Recurrent diarrhoea (not pre-specified).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 1 Provision of multiple micronutrient powders versus no intervention or placebo

Outcome: 14 Recurrent diarrhoea (not pre-specified)



Analysis 1.15. Comparison 1 Provision of multiple micronutrient powders versus no intervention or placebo, Outcome 15 Upper respiratory infections.

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 1 Provision of multiple micronutrient powders versus no intervention or placebo

Outcome: 15 Upper respiratory infections

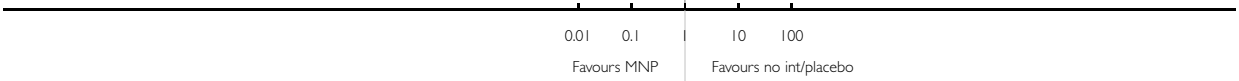
Study or subgroup	MNP	no int/placebo	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
Giovannini 2006	5/65	4/62		100.0 %	1.19 [0.34, 4.24]
Total (95% CI)	**65**	**62**		**100.0 %**	**1.19 [0.34, 4.24]**

Total events: 5 (MNP), 4 (no int/placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.27 (P = 0.79)

Test for subgroup differences: Not applicable

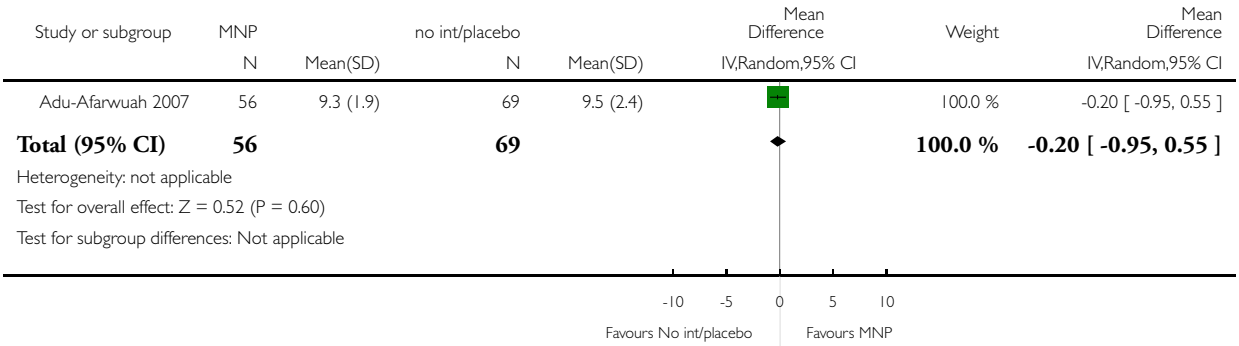


Analysis 1.16. Comparison 1 Provision of multiple micronutrient powders versus no intervention or placebo, Outcome 16 Serum zinc.

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 1 Provision of multiple micronutrient powders versus no intervention or placebo

Outcome: 16 Serum zinc

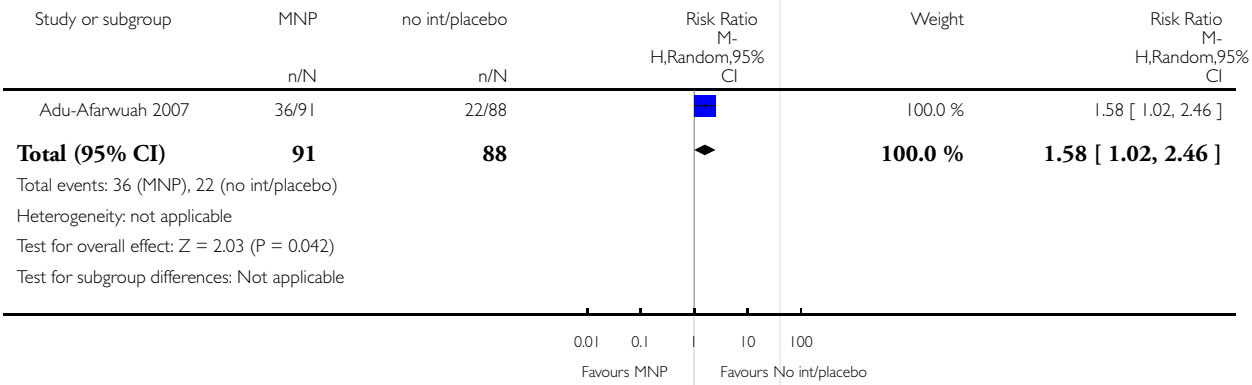


Analysis 1.17. Comparison 1 Provision of multiple micronutrient powders versus no intervention or placebo, Outcome 17 Walking independently.

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 1 Provision of multiple micronutrient powders versus no intervention or placebo

Outcome: 17 Walking independently

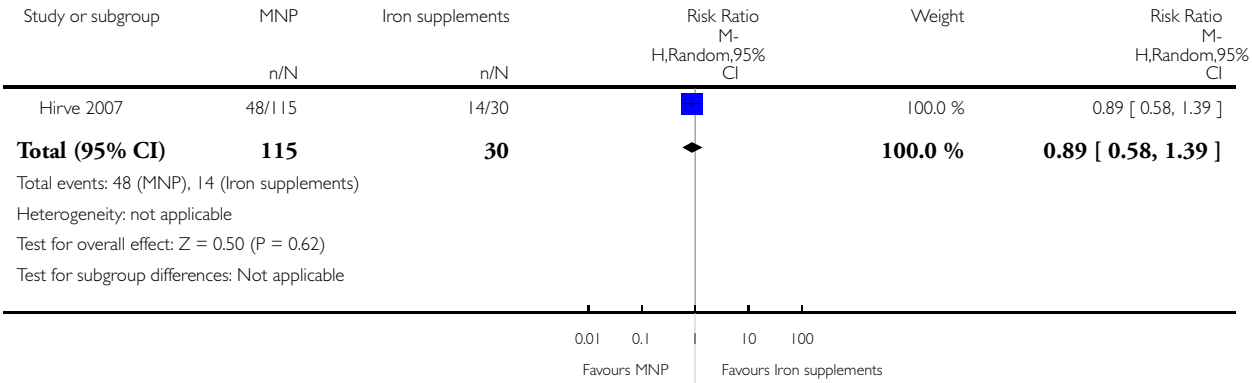


Analysis 2.1. Comparison 2 Provision of multiple micronutrient powders versus iron supplements, Outcome 1 Anaemia (ALL).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 2 Provision of multiple micronutrient powders versus iron supplements

Outcome: 1 Anaemia (ALL)

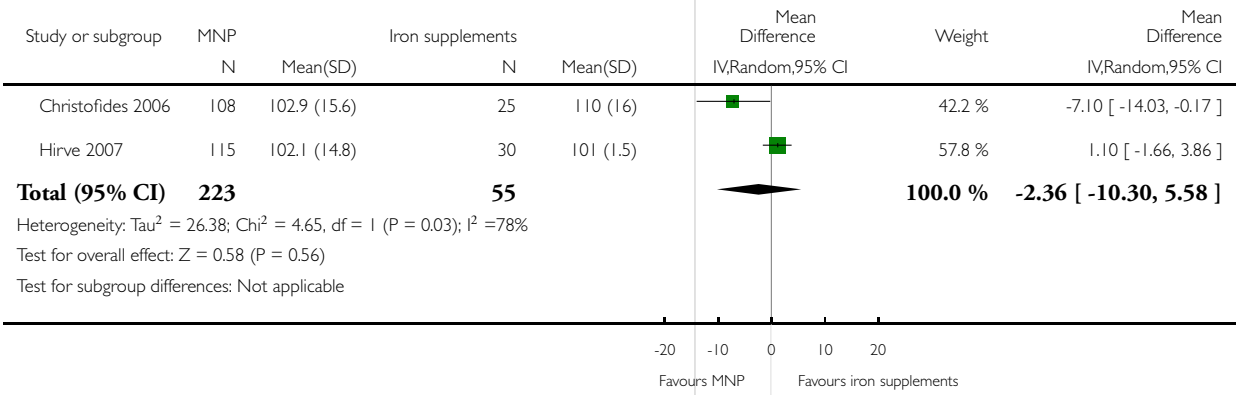


Analysis 2.2. Comparison 2 Provision of multiple micronutrient powders versus iron supplements, Outcome 2 Haemoglobin (g/L) (ALL).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 2 Provision of multiple micronutrient powders versus iron supplements

Outcome: 2 Haemoglobin (g/L) (ALL)



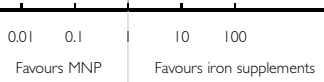
Analysis 2.3. Comparison 2 Provision of multiple micronutrient powders versus iron supplements, Outcome 3 Diarrhoea (ALL).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 2 Provision of multiple micronutrient powders versus iron supplements

Outcome: 3 Diarrhoea (ALL)

Study or subgroup	MNP n/N	Iron supplements n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Hirve 2007	59/207	30/55		100.0 %	0.52 [0.38, 0.72]
Total (95% CI)	**207**	**55**		**100.0 %**	**0.52 [0.38, 0.72]**
Total events: 59 (MNP), 30 (Iron supplements)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.93 (P = 0.000085)					
Test for subgroup differences: Not applicable					



Analysis 2.4. Comparison 2 Provision of multiple micronutrient powders versus iron supplements, Outcome 4 Diarrhoea episodes (ALL) (not pre-specified).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 2 Provision of multiple micronutrient powders versus iron supplements

Outcome: 4 Diarrhoea episodes (ALL) (not pre-specified)

Study or subgroup	MNP n/N	Iron supplements n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Christofides 2006	11/108	3/25		42.8 %	0.85 [0.26, 2.82]
Hirve 2007	9/203	8/53		57.2 %	0.29 [0.12, 0.72]
Total (95% CI)	**311**	**78**		**100.0 %**	**0.46 [0.16, 1.30]**

Total events: 20 (MNP), 11 (Iron supplements)

Heterogeneity: Tau² = 0.27; Chi² = 1.93, df = 1 (P = 0.16); I² =48%

Test for overall effect: Z = 1.46 (P = 0.14)

Test for subgroup differences: Not applicable

Analysis 2.5. Comparison 2 Provision of multiple micronutrient powders versus iron supplements, Outcome 5 Vomiting (ALL) (not pre-specified).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 2 Provision of multiple micronutrient powders versus iron supplements

Outcome: 5 Vomiting (ALL) (not pre-specified)

Study or subgroup	MNP n/N	Iron supplements n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Hirve 2007	37/207	17/55		100.0 %	0.58 [0.35, 0.95]
Total (95% CI)	**207**	**55**		**100.0 %**	**0.58 [0.35, 0.95]**

Total events: 37 (MNP), 17 (Iron supplements)

Heterogeneity: not applicable

Test for overall effect: Z = 2.18 (P = 0.029)

Test for subgroup differences: Not applicable

Analysis 2.6. Comparison 2 Provision of multiple micronutrient powders versus iron supplements, Outcome 6 Staining of teeth (ALL) (not pre-specified).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 2 Provision of multiple micronutrient powders versus iron supplements

Outcome: 6 Staining of teeth (ALL) (not pre-specified)

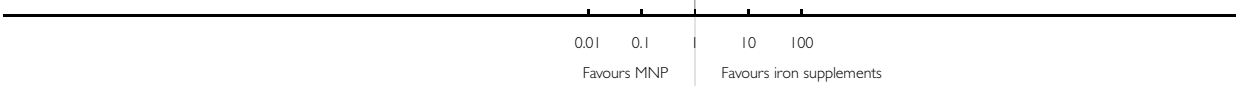
Study or subgroup	MNP n/N	Iron supplements n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Christofides 2006	5/108	3/25		35.7 %	0.39 [0.10, 1.51]
Hirve 2007	8/207	6/55		64.3 %	0.35 [0.13, 0.98]
Total (95% CI)	**315**	**80**		**100.0 %**	**0.37 [0.16, 0.82]**

Total events: 13 (MNP), 9 (Iron supplements)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.01$, df = 1 (P = 0.92); $I^2 = 0.0\%$

Test for overall effect: Z = 2.42 (P = 0.015)

Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2 Provision of multiple micronutrient powders versus iron supplements, Outcome 7 Stool discolouration (ALL) (not pre-specified).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 2 Provision of multiple micronutrient powders versus iron supplements

Outcome: 7 Stool discolouration (ALL) (not pre-specified)

Study or subgroup	MNP n/N	Iron supplements n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Christofides 2006	58/108	15/25		30.9 %	0.90 [0.62, 1.29]
Hirve 2007	101/207	35/55		69.1 %	0.77 [0.60, 0.98]
Total (95% CI)	**315**	**80**		**100.0 %**	**0.80 [0.66, 0.98]**

Total events: 159 (MNP), 50 (Iron supplements)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.48$, df = 1 (P = 0.49); $I^2 = 0.0\%$

Test for overall effect: Z = 2.11 (P = 0.035)

Test for subgroup differences: Not applicable

Analysis 2.8. Comparison 2 Provision of multiple micronutrient powders versus iron supplements, Outcome 8 Cough (ALL) (not pre-specified).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 2 Provision of multiple micronutrient powders versus iron supplements

Outcome: 8 Cough (ALL) (not pre-specified)

Study or subgroup	MNP n/N	Iron supplements n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Hirve 2007	51/103	18/27		100.0 %	0.74 [0.53, 1.03]
Total (95% CI)	**103**	**27**		**100.0 %**	**0.74 [0.53, 1.03]**

Total events: 51 (MNP), 18 (Iron supplements)

Heterogeneity: not applicable

Test for overall effect: Z = 1.76 (P = 0.078)

Test for subgroup differences: Not applicable

Analysis 2.9. Comparison 2 Provision of multiple micronutrient powders versus iron supplements, Outcome 9 Cold (ALL) (not pre-specified).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 2 Provision of multiple micronutrient powders versus iron supplements

Outcome: 9 Cold (ALL) (not pre-specified)

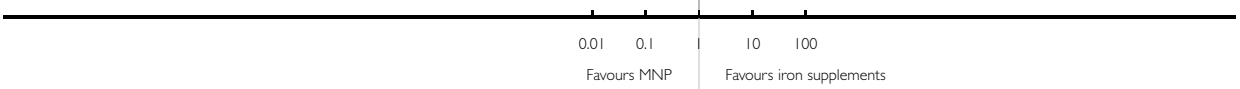
Study or subgroup	MNP n/N	Iron supplements n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Hirve 2007	149/207	47/55		100.0 %	0.84 [0.73, 0.97]
Total (95% CI)	**207**	**55**		**100.0 %**	**0.84 [0.73, 0.97]**

Total events: 149 (MNP), 47 (Iron supplements)

Heterogeneity: not applicable

Test for overall effect: Z = 2.43 (P = 0.015)

Test for subgroup differences: Not applicable

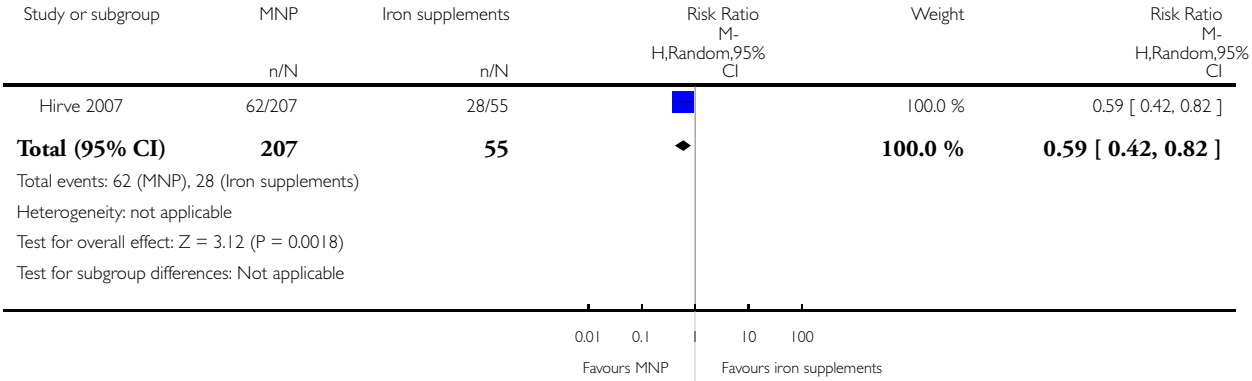


Analysis 2.10. Comparison 2 Provision of multiple micronutrient powders versus iron supplements, Outcome 10 Fever (ALL) (not pre-specified).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 2 Provision of multiple micronutrient powders versus iron supplements

Outcome: 10 Fever (ALL) (not pre-specified)

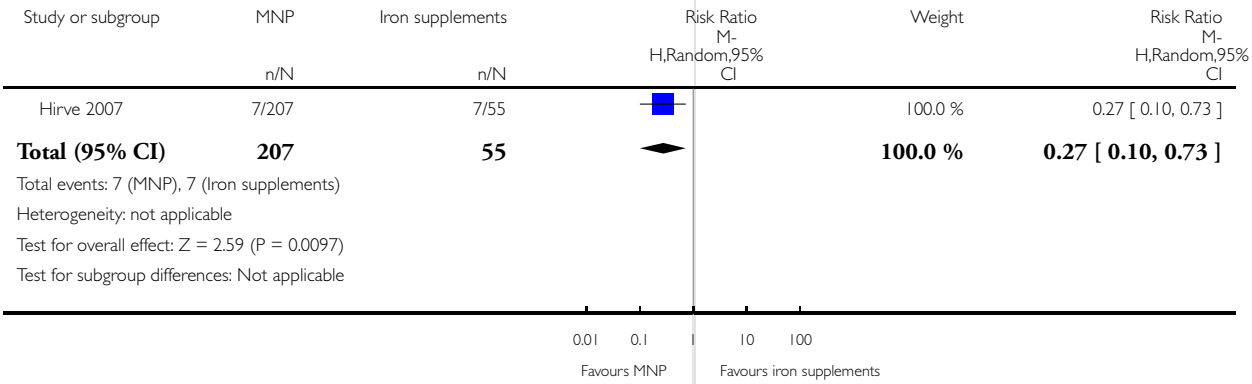


Analysis 2.11. Comparison 2 Provision of multiple micronutrient powders versus iron supplements, Outcome 11 Recurrent diarrhoea (3 or more episodes) (ALL) (not pre-specified).

Review: Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age

Comparison: 2 Provision of multiple micronutrient powders versus iron supplements

Outcome: 11 Recurrent diarrhoea (3 or more episodes) (ALL) (not pre-specified)



APPENDICES

Appendix 1. Search strategies

CENTRAL

1 MeSH descriptor Micronutrients, this term only
2 MeSH descriptor Trace Elements, this term only
3 MeSH descriptor Zinc, this term only
4 MeSH descriptor Vitamin A, this term only
6 MeSH descriptor Iron, Dietary, this term only
7 MeSH descriptor Ferric Compounds, this term only
8 MeSH descriptor Ferrous Compounds, this term only
9 micronutrient* or micro-nutrient* or micro next nutrient*
#10 multinutrient* or multi next nutrient* or multi* nutrient*
#11 multimicronutrient* or multimicro next nutrient*
#12 multivitamin* or multi* next vitamin*
#13 multimineral* or multi* next mineral*
#14 trace NEXT (element* or mineral* or nutrient*)
#15 iron or ferric* or ferrous* or Fe or zinc or Zn or (vit* next A) or retinol*
#16 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17 MeSH descriptor Food, Fortified, this term only
#18 MeSH descriptor Dietary Supplements, this term only
#19 MeSH descriptor Foods, Specialized explode all trees
#20 ((food* or meal* or drink* or beverage* or diet* or snack* or breakfast* or break-fast* or lunch* or dinner*) near/5 (fortif* or enrich* or supplement*))
#21 "point of use"
#22 home near/5 fortif*
#23 (in NEXT home or at NEXT home) near/5 (fortif*)
#24 mix* or powder* or supplement* or sachet* or packet* or powder* or MNP or MNPs
#25 (#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)
#26 Sprinkles Or Vita NEXT Shakti or Rahama or Anuka or Chispitas or BabyFer or Bebe NEXT Vanyan or Supplfer or Supplefem
#27 (#16 AND #25)
#28 (#26 OR #27)
#29 (baby or babies or infant* or toddler* or preschool* or pre-school* or child*)
#30 MeSH descriptor Infant explode all trees
#31 child near Mesh
#32 (#29 OR #30 OR #31)
#33 (#28 AND #32)

MEDLINE

1 micronutrients/
2 iron/ or zinc/ or vitamin A/
3 (micronutrient$ or micro-nutrient$).tw.
4. (multinutrient$ or multi-nutrient$ or multi$ nutrient$).tw.
5 (multimicro-nutrient$ or multimicronutrient$).tw.
6 (multivitamin$ or multi-vitamin$).tw.
7 (multimineral$ or multi-mineral$).tw.
8 Trace elements/
9 (trace adj (element$ or mineral$ or nutrient$)).tw.
10 iron,dietary/
11 ferric compounds/ or ferrous compounds/
12 (iron or Fe or ferric$ or ferrous$ or zinc or Zn or vit$ A or retinol$).mp.
13 or/1-12
14 food, fortified/

15 dietary supplements/
16 food,specialized/
17 ((food$ or meal$ or drink$ or beverage$ or diet$ or snack$ or breakfast$ or break-fast$ or lunch$ or dinner$) adj5 (fortif$ or enrich$ or supplement$)).tw.
18 "point of use".tw.
19 (home adj5 fortif$).tw.
20 ((in-home or at-home) adj5 fortif$).tw.
21 (mix$ or powder$ or supplement$ or sachet$ or packet$ or powder$ or MNP or MNPs).tw.
22 or/14-21
23 13 and 22
24 (Sprinkles or Vita Shakti or Rahama or Anuka or Chispitas or BabyFer or Bebe Vanyan or Supplefer or Supplefem).tw.
25 or/23-24
26 (baby or babies or infant$ or toddler$ or preschool$ or pre-school$ or child$).tw.
27 exp child/ or infant/
28 26 or 27
29 25 and 28

EMBASE

1 exp trace element/
2 vitamin mixture/
3 (trace adj (element$ or mineral$ or nutrient$)).tw.
4 iron/ or ZINC/ or retinol/
5 (iron or Fe or ferrous$ or ferric$ or zinc or Zn or vit$ A or retinol$).mp.
6 iron derivative/
7 iron intake/
8 ferric ion/ or ferrous ion/
9 (micronutrient$ or micro-nutrient$).tw.
10 (multinutrient or multi-nutrient or multi$ nutrient$).tw.
11 (multimicronutrient$ or multi-micronutrient$).tw.
12 (multivitamin$ or multi-vitamin$).tw.
13 (multimineral$ or multi-mineral$).tw.
14 or/1-13
15 diet supplementation/
16 ((food$ or meal$ or drink$ or beverage$ or diet$ or snack$ or breakfast$ or break-fast$ or lunch$ or dinner$) adj5 (fortif$ or enrich$ or supplement$)).tw.
17 "point of use".tw.
18 (home$ adj5 fortif$).tw
19 ((in-home or at-home) adj5 fortif$).tw.
20 (mix$ or powder$ or packet$ or supplement$ or sachet$ or powder$ or MNP or MNPs).tw.
21 or/15-20
22 14 and 21
23 (Sprinkles or Vita Shakti or Rahama or Anuka or Chispitas or BabyFer or Bebe Vanyan or Supplefer or Supplefem).tw.
24 22 or 23
25 exp child/
26 infant/
27 (baby or babies or infant$ or toddler$ or preschool or pre-school$ or child$).tw.
28 25 or 26 or 27
29 24 and 28

CINAHL

S28 S24 and S27
S27 S25 or S26
S26 baby or babies or infant* or toddler* or pre-school* or preschool* or child*
S25 AG Infant, Newborn: birth-1 month OR Infant: 1-23 months or Child,Preschool: 2-5 years
S24 S22 or S23

S23 (Sprinkles or Vita Shakti or Rahama or Anuka or Chispitas or BabyFer
or Bebe Vanyan or Supplefer or Supplefem)
S22 S13 and S21
S21 S14 or S15 or S16 or S17 or S18 or S19 or S20
S20 mix* or powder* or supplement* or sachet* or packet* or powder* or MNP or MNPs
S19 at-home N5 fortif*
S18 in-home N5 fortif*
S17 home N5 fortif*
S16 "point of use"
S15 (food* or meal* or drink* or beverage* or diet* or snack* or breakfast* or break-fast* or lunch* or dinner*) AND (fortif* or enrich* or supplement*)
S14 (MH "Food, Fortified") OR (MH "Dietary Supplements")
S13 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12
S12 iron or "Fe" or ferric* or ferrous* or zinc or "Zn" or "vit* A" or retinol*
S11 trace element* or trace mineral* or trace nutrient*
S10 (MH "Trace Elements")
S9 (MH "Ferric Compounds") OR (MH "Ferrous Compounds")
S8 multimineral* or multi-mineral*
S7 multivitamin* or multi-vitamin*
S6 (MH "Vitamin A")
S5 multimicro-nutrient* or multimicronutrient*
S4 multinutrient* or multi-nutrient* or multi* nutrient*
S3 micronutrient* or micro-nutrient*
S2 (MH "Iron") OR (MH "Iron Compounds") OR (MH "Zinc")
S1 (MH "Micronutrients")

Science Citation Index

12 #11 AND #10
11 TS= (baby or babies or infant or toddler* or pre-school* or preschool* or child*)
10 #1or #9
9 #8 SAME #7
8 #2 or #3
7 #6 OR #5 OR #4
6 TS=(home fortif* or at-home fortif* or in-home fortif*)
5 TS= point of use
4 TS=((food* or meal* or drink* or beverage* or diet* or snack* or breakfast* or break-fast* or lunch* or dinner*) SAME (fortif* or enrich* or supplement*))
3 TS=(iron or Fe or ferric* or ferrous* or zinc or Zn or vit* A or retinol*)
2 TS= (micronutrient* or micro-nutrient* or multinutrient* or multi-nutrient* or multi* nutrient* or multimicro-nutrient* or multimicronutrient* or multivitamin* or multi-vitamin*)
1 TS= (Sprinkles or Vita Shakti or Rahama or Anuka or Chispitas or BabyFer or Bebe Vanyan or Supplefer or Supplefem)

Conference Proceedings Citation Index - Science (CPCI-S)

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2 TS= (micronutrient* or micro-nutrient* or multinutrient* or multi-nutrient* or multi* nutrient* or multimicro-nutrient* or multimicronutrient* or multivitamin* or multi-vitamin*)
1 TS= (Sprinkles or Vita Shakti or Rahama or Anuka or Chispitas or BabyFer or Bebe Vanyan or Supplefer or Supplefem)

LILACS

micronutrient$ or multinutrien$ or micro-nutrient$ or multi-nutrient$ [Words] and home$ or fortif$ or point-of-use [Words] or sprinkles or MNP or MNPs [Words]

African Index Medicus

sprinkles OR micronutrients OR multimicronutrients OR mnp OR bebe vanyan or supplefer or vita shakti or babyfer or chispitas or anuka or rahama [Key Word]

POPline

((micronutrient* /micro-nutrient*/multinutrient/ multi-nutrient*/ multi* nutrient*) & (home fortif*/ point of use)) /sprinkles

ClinicalTrials.gov

sprinkles OR "multinutrient powder" OR multimicronutrients OR mnp OR mnps | Child

metaRegister of Clinical Trials

sprinkles or multinutrients or multimicronutrients or MNP or MNPs

WHO ICTRP

Intervention: sprinkles or multinutrients or multimicronutrients or MNP or MNPs
AND Clinical trials in children

HISTORY

Protocol first published: Issue 1, 2011

Review first published: Issue 9, 2011

CONTRIBUTIONS OF AUTHORS

All authors contributed to the development of the review.

DECLARATIONS OF INTEREST

Luz Maria De-Regil - none known.

Parminder S Suchdev - is the principal investigator in an effectiveness study of micronutrient powders among preschool children in Western Kenya (Suchdev 2011).

Gunn E Vist - none known.

Silke Walleser - none known.

Juan Pablo Peña-Rosas - none known.

Disclaimer: Juan Pablo Pena-Rosas and Luz Maria De-Regil are full-time staff members of the World Health Organization. Parminder Singh Suchdev is a staff member of the US Centers for Disease Control and Prevention (CDC). The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the official position, decisions, policy or views of these organizations.

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

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- Micronutrient Initiative (MI), Canada.

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- Global Alliance for Improved Nutrition (GAIN), Switzerland.

WHO acknowledges the Global Alliance for Improved Nutrition (GAIN) for their financial support to the Micronutrients Unit for conducting systematic reviews on micronutrients interventions.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In comparison with the protocol, this review has various differences in the following sections.

- Type of interventions: in our protocol we stated that the comparison groups would include no intervention, placebo, or usual supplementation. We decided to list the specific comparisons in order to make them explicit for the reader. Also, for clarity we decided to specify the type of interventions that are out of the scope of this review.

- Types of outcome measures: this section has various changes, 1) we added 'iron deficiency' as primary outcome as we have included previously iron status as a continuous variable but not a variable to diagnose the actual deficiency; 2) we moved 'all-cause mortality' from the secondary to the primary outcomes to be consistent with our objective and be able to evaluate the safety of this intervention; 3) we deleted 'growth' in one of the primary outcomes as it may refer to several indicators; we replaced it with 'weight-for-age Z-score (WAZ)' which is one of the variables to evaluate growth; 4) for the secondary outcomes, 'adverse effects (any)' was changed to 'side effects' and the definition was complemented with some examples such as staining of teeth, vomiting, fever, coughing or stool discolouration; 5) 'constipation' was included as a side effect and thus is no longer specified as an independent secondary outcome; and 6) we changed the order of the secondary outcomes proposed in the protocol to improve the legibility of the text.

- Searching other resources: we added the International Clinical Trials Registry Platform (ICTRP) as source of data to find information about ongoing trials.

- Assessment of risk of bias in included studies: we included a paragraph to summarize the use of the GRADE approach to generate the 'Summary of findings' tables.

- Unit of analysis issues: in the protocol we said that we were not going to combine cluster and individually randomised trial results; however as the direction and magnitude of the effect were consistent among trials at either level of randomisation we deemed convenient to combine the results. The methods used to combine the trials are clearly described.

- Subgroup analysis: given the small number of trials, the definition of malaria setting was changed from a four category to two categories.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; *Food, Fortified; Anemia, Iron-Deficiency [diet therapy]; Cooking [*methods]; Deficiency Diseases [*diet therapy]; Micronutrients [*administration & dosage; deficiency]; Powders; Randomized Controlled Trials as Topic; Trace Elements [administration & dosage]

MeSH check words

Humans; Infant