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# Effects of micronutrient supplementation and fortification interventions on the health and nutritional status of young children: a systematic review

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## **Title of the review**

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Effects of micronutrient supplementation and fortification interventions on the health and nutritional status of young children: a systematic review

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## **Background**

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Malnutrition in childhood continues to be a pervasive problem in low- and middle-income countries (LMICs). In these settings, low consumption and poor quality and diversity of available foods mean that diets are not able to meet the nutrients required for rapid growth, making infants and children the most vulnerable group to micronutrient malnutrition. Globally, it is estimated that 42% of children under-five have anemia (Stevens, 2013) and 190 million (33%) preschool-aged children are deficient in vitamin A (WHO, 2009). Multiple deficiencies frequently occur simultaneously, and can be associated with negative physical, developmental, and cognitive consequences, increased mortality, and poor health and productivity later in life (WHO, 2001; Lozoff, 2007; Sanghvi, 2007; Black, 2008). Undernutrition, including deficiencies of essential vitamins and minerals, stunting, and wasting, is estimated to cause 45% of deaths in children under-five, resulting in 3.1 million deaths per year (Black, 2013).

Interventions to prevent and treat micronutrient malnutrition come in several forms, including the promotion of breastfeeding for infants and children up to two years of age, dietary diversification, biofortification of staple crops, fortification of complementary and staple foods, and the provision of micronutrient tablets or powders (Bhutta, 2008). While the potential benefits of each of these interventions have been well-established through proof-of-principle studies, implementation is not always successful due to programmatic barriers such as low compliance, lack of supply, and poor coverage.

This review aims to update the evidence that exists from trials as well as collate relevant data from evaluations of existing programmes for child undernutrition. As such, we will provide an overall assessment of the effectiveness of micronutrient supplementation and fortification interventions for improving child health and nutrition. This evidence will be critical to inform policy and programmatic decision-making in LMICs.

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## **Objectives**

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1. What is the effectiveness of micronutrient interventions (single, multiple, micronutrient powders) on child health and nutritional status?
  2. What is the effectiveness of lipid-based nutrient supplementation on child health and nutritional status?
  3. What is the effectiveness of targeted or large-scale food fortification on child health and nutritional status?
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## **Existing reviews**

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### **Objective 1: Micronutrient interventions**

Imdad A, Ahmed Z, Bhutta ZA. Vitamin A supplementation for the prevention of morbidity and mortality in infants one to six months of age. *Cochrane Database Syst Rev* 2016, Issue 9. Art. No: CD007480. doi:10.1002/14651858.CD007480.pub3.

Imdad A, Mayo-Wilson E, Herzer K, Bhutta ZA. Vitamin A supplementation for preventing morbidity and mortality in children from six months to five years of age. *Cochrane Database Syst Rev* 2017, Issue 3. Art. No: CD008524. doi:10.1002/14651858.CD008524.pub3.

De-Regil LM, Jefferds ME, Sylvetsky AC, Dowswell T. Intermittent iron supplementation for improving nutrition and development in children under 12 years of age. *Cochrane Database Syst Rev* 2011, Issue 12. Art. No: CD009085. doi:10.1002/14651858.CD009085.pub2.

Sachdev H, Gera T, Nestel P. Effect of iron supplementation on mental and motor development in children: systematic review of randomised controlled trials. *Public Health Nutr* 2005;8(2):117-32.

Mayo-Wilson E, Junior JA, Imdad A, Dean S, Chan XH, Chan ES, Jaswal A, Bhutta ZA. Zinc supplementation for preventing mortality, morbidity, and growth failure in children aged 6 months to 12 years of age. *Cochrane Database Syst Rev* 2014, Issue 5. Art. No: CD009384. doi:10.1002/14651858.CD009384.pub2.

Brown KH, Peerson JM, Baker SK, Hess SY. Preventive zinc supplementation among infants, preschoolers, and older prepubertal children. *Food Nutr Bull* 2009;30(1):S12-40.

Gogia S, Sachdev HS. Zinc supplementation for mental and motor development in children. *Cochrane Database Syst Rev* 2012 Dec 12;12:CD007991. doi:10.1002/14651858.CD007991.pub2.

Yakoob MY, Salam RA, Khan FR, Bhutta ZA. Vitamin D supplementation for preventing infections in children under five years of age. *Cochrane Database Syst Rev* 2016, Issue 11. Art. No: CD008824. doi:10.1002/14651858.CD008824.pub2.

Allen LH, Peerson JM, Olney DK. Provision of multiple rather than two or fewer micronutrients more effectively improves growth and other outcomes in micronutrient-deficient children and adults. *J Nutr* 2009;139(5):1022-30. doi:10.3945/jn.107.086199.

Ramakrishnan U, Nguyen P, Martorell R. Effects of micronutrients on growth of children under 5 y of age: meta-analyses of single and multiple nutrient interventions. *Am J Clin Nutr* 2009; 89(1):191-203. doi:10.3945/ajcn.2008.26862.

De-Regil LM, Jeffards MD, Pena-Rosas J. Powdered vitamins and minerals added to foods at the point-of-use reduces anaemia and iron deficiency in preschool- and school-age children. *Cochrane Database Syst Rev* 2017, Issue 11. Art. No.: DC009666. DOI: 10.1002/14651858.CD009666.pub2.

Suchdev PS, Peña-Rosas JP, De-Regil LM. Multiple micronutrient powders for home (point-of-use) fortification of foods in pregnant women. *Cochrane Database Syst Rev* 2015, Issue 6. Art. No.: CD011158. doi:10.1002/14651858.CD011158.pub2.

De-Regil LM, Suchdev PS, Vist GE, Walleser S, Peña-Rosas JP. Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age. *Cochrane Database Syst Rev* 2011, Issue 9. Art. No.: CD008959.

De-Regil LM, Jefferds MED, Peña-Rosas JP. Point-of-use fortification of foods with micronutrient powders containing iron in children of preschool and school age. *Cochrane Database Syst Rev* 2012, Issue 2. Art. No.: CD009666. doi:10.1002/14651858.CD009666.

De-Regil LM, Suchdev PS, Vist GE, Walleser S, Pena-Rosas J. 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. *Cochrane Database Syst Rev* 2011, Issue 9. Art. No.: CD008959. doi:10.1002/14651858.CD008959.

Salam RA, MacPhail C, Das JK, Bhutta ZA. Effectiveness of micronutrient powders (MNP) in women and children. *BMC Public Health* 2013;13(3):S22. doi:10.1186/1471-2458-13-S3-S22.

## **Objective 2: Lipid-based nutrient supplementation**

Das JK, Salam RA, Weise PZ, et al. Provision of preventive lipid-based nutrient supplements given with complementary foods to infants and young children 6 to 23 months of age for health, nutrition and developmental outcomes. 2017 *Cochrane (review protocol)*.

## **Objective 3: Large-scale food fortification**

Keats EC, Neufeld L, Garrett, G, Bhutta, ZA (2017) Large-Scale Fortification: What Works in Low and Middle Income Settings? Evidence from a Systematic Review and Meta-Analysis (in preparation).

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## **Intervention**

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The following interventions will be included:

- Single micronutrient supplementation (iodine, iron, vitamin A, zinc, vitamin D)
- Multiple micronutrient supplementation
- Lipid-based nutrient supplementation
- Large-scale food fortification interventions (i.e. fortified staple foods and condiments)
- Targeted fortification for infants/young children (e.g. complementary foods, formula)
- Point of use fortification with micronutrient powders

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## **Population**

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The target population is healthy children (i.e. non-diseased) from 1 month up to 5 years of age living in low- and middle-income countries (as defined by the World Bank). We will exclude antenatal maternal supplementation trials that have included newborn/child health outcomes (i.e. supplementation was not given to the child).

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## **Outcomes**

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Primary outcomes:

- All-cause mortality
- Cause-specific mortality
  - Diarrhea
  - Meningitis
  - Measles
  - Acute lower respiratory infection, including pneumonia
  - Malaria
  - Other
- Nutritional status
  - Anemia prevalence
  - Stunting (-2 z-score or lower)
  - Wasting (-2 z-score or lower)
  - Underweight (-2 z-score or lower)

## Secondary outcomes:

- Morbidity (as defined by study authors), including hospitalization
- Micronutrient deficiencies
  - Vitamin A (serum/plasma retinol)
  - Iron (serum/plasma ferritin, plasma TfR)
  - Serum/plasma folate
  - Serum/plasma zinc
  - Serum/plasma vitamin D
  - Hemoglobin concentration
- Growth
  - Height (cm or height-for-age z-score)
  - Weight (kg or weight-for-age z-score)
- Mental and motor skill development (as assessed by study authors e.g. Bayley Mental Development Index, Bayley Psychomotor Development Index, Stanford-Binet Test, DENVER II Developmental Screening Test)
- Adverse effects
  - Gastrointestinal (vomiting, diarrhea, stomach ache, constipation)
  - Irritability
  - Fever
  - Headache
  - Stained teeth
  - Bulging fontanelle
  - Kidney stones
  - Other

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## Study designs

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We will include primary studies, including large-scale programme evaluations, which assess the efficacy and/or effectiveness of interventions using experimental and quasi-experimental study designs that allow for causal inference:

- Studies where participants were randomly assigned, individually or in clusters, to intervention and comparison groups.
- Studies where non-random assignment to intervention and comparison groups is based on other known allocation rules, including a threshold on a continuous variable (regression discontinuity designs) or exogenous geographical variation in the treatment allocation (natural experiments).
- Controlled before-after studies in which allocation to intervention and control groups was not made by study investigators, and outcomes were measured in both intervention and control groups at baseline, and appropriate methods were used to control for selection bias and confounding, such as statistical matching (e.g.,

propensity score matching, or covariate matching) or regression adjustment (e.g., difference-in-differences, instrumental variables).

- Interrupted time series (ITS) studies in which outcomes were measured in the intervention group at least three time points before the intervention was implemented and at least three time points after.

Evidence from efficacy trials and programme evaluations will be grouped and analysed separately.

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## **Roles and responsibilities**

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Emily Keats and Jai Das have methodological, statistical, and information retrieval expertise. Zulfiqar Bhutta has content expertise. All additional team members (to be determined) will receive training in systematic review methods.

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## **Potential conflicts of interest**

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The authors are not aware of any conflicts of interest arising from financial or researcher interests.

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## **Preliminary timeframe**

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- Date you plan to submit a draft protocol: 15 January 2018
- Date you plan to submit a draft review: 30 June 2018