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Fortification of wheat and maize flour with folic acid for population health outcomes (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Fortification of wheat and maize flour with folic acid for population health outcomes

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the health benefits and safety of folic acid fortification of wheat and maize flour (alone or in combination with other micronutrients) on folate status and health outcomes in the overall population, with emphasis on populations at risk.

For the purposes of this review, a fortified wheat product includes any food prepared from fortified wheat flour; a fortified maize flour product includes any food prepared from fortified corn meal or maize flour. We will include composite flours that contain more than 50% wheat or maize within the definition of flour in this review.

BACKGROUND

Description of the condition

Folate is an essential nutrient that plays a key role in cell division, DNA repair, and tissue growth (Ulrich 2008). Folate and folic acid are forms of the water-soluble vitamin B9. Folate is present in legumes, leafy green vegetables, and some citrus fruits; lower folate intakes are common where the staple diet consists of unfortified cereals, and intake of folate-rich legumes, vegetables, and fruit is low (Allen 2008; de Benoist 2008). Folic acid is the synthetic and most stable form of folate, and is often used in supplements and fortified foods. Folic acid bioavailability is approximately 70% higher than folate naturally contained in foods, although there are wide variations depending on the method of assessment (McNulty 2004; Yetley 2011). Folate is mainly stored in the liver, and can be assessed in serum, plasma, or red blood cells (RBC) via microbiological assay, liquid chromatography-tandem mass spectrometry (LC-MS/MS), radioisotope competitive binding or enzyme-linked or chemiluminescence assays (Yetley 2011). Red blood cell folate is an indicator of longer-term folate status, while serum folate is influenced by recent folate intake.

The classic presentation of folate deficiency is hematological: macrocytic anaemia. Inadequate dietary intake of folate decreases erythrocyte folate and serum folate concentrations, and leads to megaloblastic changes in bone marrow and macrocytosis in circulating red blood cells (Stabler 2010).

Folate concentrations lower than 100 ng/mL (less than 226.5 nmol/L) in erythrocytes and lower than 3 ng/mL (less than 6.8 nmol/L) in serum are associated with increased risk of macrocytic anaemia, but inadequate folate status is also linked to several other adverse health outcomes (WHO 2015a).

Folate insufficiency during the periconceptional period has been associated with a number of early developmental fetal anomalies, most notably neural tube defects. Neural tube defects comprise a collection of neurodevelopmental abnormalities that arise when the neural folds fail to fuse entirely during early embryogenesis, which include anencephaly, spina bifida, and encephalocoele (Botto 1999; WHO/CDC/ICBDSR 2014). Neural tube defects are among the most common structural congenital anomalies worldwide, with an estimated 300,000 cases per year (Lo 2014; WHO/CDC/ICBDSR 2014), and contribute to 10% of deaths during the first 28 days of life (WHO 2012; WHO/CDC/ICBDSR 2014). It is estimated that up to 70% of neural tube defects can be prevented by increasing folic acid intake during the periconceptional period (Czeizel 1992; Czeizel 2013; De-Regil 2015; MRC 1991).

Folate insufficiency also has severe consequences throughout the life cycle. For example, inadequate folate status during pregnancy has been associated with increased risk of low birth weight (less than 2500 g) (Molloy 2008; van Uitert 2013); congenital heart defects, orofacial clefts, and cleft palate (Czeizel 2000); and placental abruption, spontaneous abortion, preterm delivery, small-for-gestational age, and stillbirth (Molloy 2008; van Uitert 2013). Inadequate folate status has also been associated with increased risk of non-communicable diseases in studies in men and postmenopausal women, including cancers (e.g., lymphoma, leukaemia; colorectal, breast, and prostate cancer), cardiovascular disease (e.g., hypertension, stroke), depression, and cognitive dysfunction (Bailey 2015). Studies in children and adolescents have also noted an age-related decline in folate status biomarkers, which suggests higher metabolic demands for growth (Bailey 2015). Together, these findings suggest that the safety and efficacy of folate fortification interventions need to be evaluated at the population level.

Low folate intake is also associated with impairments in other biomarkers in one-carbon metabolism, including circulating vitamin B12 and functional biomarkers, methylmalonic acid and total homocysteine (tHcy) (Yetley 2011). The World Health Organization (WHO) recently published guidelines for optimal red blood cell folate and serum folate concentrations in women of reproductive age for prevention of neural tube defects (WHO 2015b). The recommended cut-offs for prevention of neural tube defects are red cell folate concentrations below 906 nmol/L (less than 400 ng/mL), an indicator of longer-term folate status (WHO 2015b).

Description of the intervention

The association between low maternal folate status and increased risk of neural tube defects was first reported over 40 years ago (Hibbard 1965; Smithells 1976). Adequate periconceptional maternal folate status is critical for embryonic development and prevention of neural tube defects. Clinical trials have established that periconceptional folic acid supplementation prevents the occurrence and recurrence of neural tube defects by up to 70% (Czeizel 1992; MRC 1991). Then, the United States Public Health Service recommended that all women capable of becoming pregnant should consume 400 µg of folic acid daily (MRC 1991). Since approximately half of all pregnancies in the USA are unplanned (Finer 2006), in 1998 the U.S. Food and Drug Administration (US FDA) mandated that folic acid be added to the flour supply to target women of reproductive age and ensure adequate intake of folic acid (US Preventive Services Task Force 2009).

Folate fortification of flour has since been rapidly scaled up worldwide, and is thought to be one of the most efficacious and cost-effective public health interventions to date (WHO/FAO 2006). Over 80 countries have adopted mandatory fortification of wheat (*Triticum spp.*) flour with folic acid, or iron, or both. Fourteen countries have adopted mandatory fortification of maize (*Zea mays* subsp Mays) flour or meal with folic acid, or iron, or both (Peña-Rosas 2014). Fortification of grains with folic acid has substantially reduced the prevalence of neural tube defects in the USA and a number of other countries (Castillo-Lancellotti 2013). Several studies have noted a decrease in neural tube defects ranging from 19% to 32% following fortification, with the greatest reduction in the year immediately following fortification (Crider 2011). A recent systematic review of 27 studies assessed the impact of folic acid fortification on the prevalence of neural tube defects from 2000 to 2011 in nine countries, and revealed a significant reduction in all countries (Castillo-Lancellotti 2013).

Fortification is a promising, sustainable, and cost-effective approach to combat micronutrient deficiencies. It has been defined as "the addition of one or more essential nutrients to a food, whether or not it is normally contained in the food, for the purpose of preventing or correcting a demonstrated deficiency of one or more nutrients in the general population or specific population groups" (WHO/FAO 2006). This process usually takes place during the processing of staple foods at a central level so that it reaches a considerable proportion of the at-risk populations without requiring their active participation. While there are different definitions for enrichment, for the purposes of this Cochrane review we will use enrichment and fortification interchangeably.

Cereals are the major source of food supplies for direct human consumption. Of the 2.4 billion tonnes of cereals currently produced, approximately 1.1 billion tonnes are destined for food use, and the remainder is used for animal feed, industrial use, seed, or is wasted.

Wheat is the third most-produced cereal after maize and rice, but ranks second to rice in terms of dietary intake (FAO 2012). With an ability to grow in diverse climates, maize - the world's primary coarse grain - is cultivated in most parts of the world, although most production is concentrated in the Americas, particularly in the USA where genetically-modified maize accounts for 85% of plantings (USDA 2014). Currently, approximately 55% of world consumption of coarse grains is used for animal feed, but in many countries (mainly in Sub-Saharan Africa and Latin America) they are also directly used for human consumption. At the global level, approximately 17% of consumption of coarse grains is devoted to food, but this rises to as much as 80% in sub-Saharan Africa (FAO 2012).

Flour is defined as a powder that is made by grinding cereal grains, other seeds, or roots (e.g., cassava). Wheat flour is one of the most important foods in Europe, North America, Middle East, India, and North Africa, and is the defining ingredient in most types of breads and pastries. Maize (*Zea mays*) flour has been important in Mesoamerican cuisine since ancient times, and remains a staple in Latin American and Africa (Ranum 2014).

Wheat processing and products

Wheat kernels are comprised of three parts: bran, endosperm, and germ. The bran is the hard, brownish, outer protective skin that surrounds the germ and the endosperm. It consists of seven layers that are a concentrated source of dietary fibre. The endosperm is the inner part of the grain, which contains 8% to 18% protein and 50% to 75% starch. The germ contains the plant embryo and accounts for most of the wheat kernel's fat and vitamin E content. Raw wheat can be ground into flour or semolina, germinated and dried to create malt, crushed or cut into cracked wheat, and par-boiled, dried, crushed, and de-branned into bulgur. Wheat flour is a powder made from ground wheat and used for human consumption. White flour is made from the endosperm only; whole grain flour is made from the entire grain, including bran, endosperm, and germ; and germ flour is made from the endosperm and germ. Extraction rate describes the composition of flour, and is the percent of flour extracted from the grain compared to the weight of grain.

Maize processing and products

Maize kernels are comprised of several components: the outer cover (pericarp and aleurone); the endosperm, which comprises the largest fraction of the kernel; and the germ which consists of the embryo and scutellum. Genetic background, variety, environmental conditions, plant age, and geographic location can impact kernel composition within and between maize varieties (Nuss 2010). The nutritional properties of maize are located in distinct though overlapping components of the kernel. Maize contains approximately 72% starch (endosperm), 10% protein (endosperm and germ), and 3% to 6% oils.

Following harvest, maize undergoes several initial processing steps. Cobs are dried, hulled, and shelled to remove kernels prior to wet or dry milling (ILO 1984). Some maize products use whole maize, while others use degerminated kernels. In many settings, maize grains undergo nixtamalization or precooking prior to milling. All of these processes may impact its overall nutritional content. Maize meal or flour derived from dry milling is used in different ways throughout the world (Herbst 2001), such as polenta in Italy, angu in Brazil, mamaliga in Romania, mush in the USA, and sadza, nshima, and ugali in African countries. Corn flakes are also derived from corn meal that has undergone extrusion (Nuss 2010). Fermentation of milled kernels is also common in African and South American countries: derived products, including bread and alcohol, may have improved bioavailability of niacin, and fermented maize gruel has been used as a fluid for replacement of electrolytes in acute diarrhoea for children in resource-limited settings (Yartey 1995).

The definitions of corn flour and corn meal vary widely. The U.S. Food and Drug Administration defines corn flour and corn meal as products obtained from the grinding of dried yellow or white corn grains. These regulations define the size, moisture content, and amount of fibre and fat that is retained in the product. Maize meal and flour may also be included as part of a composite flour in combination with other products, such as tubers (e.g., yam, cassava, sweet potato), legumes (e.g., soy, peanut), and cereals (e.g., maize, rice, wheat), to enhance the nutritional content and bioavailability (Seibel 2006).

Fortification of maize flour and other products (e.g., porridges, breakfast cereals, tortillas, tamales, arepas) produced from maize has been implemented in several settings around the world. Although folic acid fortification of maize flour is less common than wheat flour, mass fortification of maize flour with at least iron has been practiced for many years in several countries in the Americas (Dary 2002; García-Casal 2002) and sub-Saharan Africa (FFI 2014; Peña-Rosas 2014). Maize flour and corn meal products vary worldwide, based on local and regional practices (Ranum 2014). Additionally, the legislative (Makhumula 2014), dietary (Fiedler 2014; Guamuch 2014), logistical and economic (Fiedler 2014), risk population (Hamner 2014), and equity (Zamora 2014) contexts need to be considered to evaluate the feasibility and long-term sustainability of folic acid fortification of maize flour.

How the intervention might work

The WHO recommends fortification of wheat and maize flour with folic acid in doses ranging form 1 ppm to 5 ppm, depending on the average per capita flour availability per day, a proxy measure of dietary intake (WHO 2009; WHO/CDC/ICBDSR 2014).

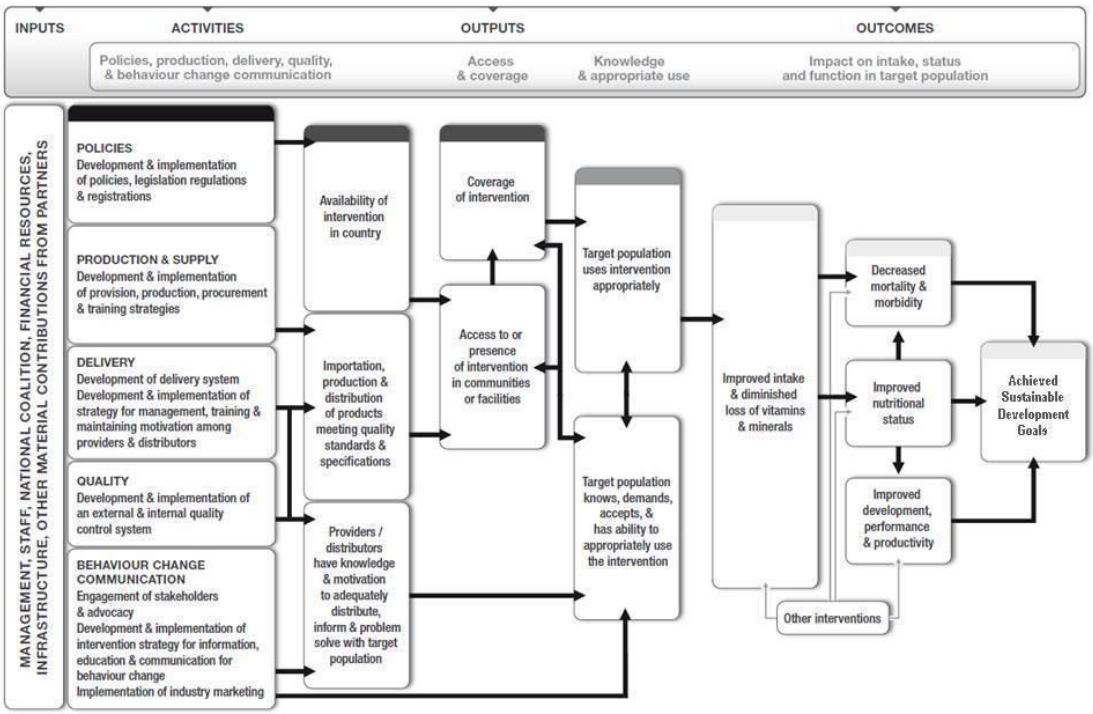
Fortification of wheat and maize flour with folic acid increases daily intake and absorption of folic acid to meet the existing intake gap, improves folate status, and reduces the risk of neural tube defects and other adverse health outcomes. In addition to

the general population, in countries where folate intake is insufficient, population groups that are at highest risk of deficiency (i.e., women of reproductive age, infants, preschool children) are of interest in this review. Fortification of grains with folic acid has reduced the prevalence of neural tube defects in several countries, including the USA, Canada, Chile, Australia, and South Africa (Bower 2009; Castillo-Lancellotti 2013; De Wals 2007; Honein 2001; López-Camelo 2005; Sayed 2008). Additionally, in different age groups, folic acid fortification has been associated with a reduced risk of cardiovascular disease, cancer, and depression (Cavalli-Sforza 2005; Cui 2010; Feng 2006; Rimm 1998; Wald 2002) and macrocytic anaemia (Odewole 2013; Ganji 2009).

Despite the success of this public health intervention, folic acid fortification has not fully eliminated neural tube defects (CDC 2004; CDC 2010), and has raised concerns regarding potential unintended consequences of elevated intake (Cole 2007; Wien 2012), including cancer (Van Guelpen 2006), unmetabolized folic acid in serum (Boilson 2012; Kelly 1997; Morris 2010; Troen 2006), and potential adverse impact in the context of vitamin B12 deficiency. For example, higher folate status in combination with vitamin B12 deficiency may be associated with increased risk of adverse pregnancy outcomes (Dwarkanath 2013).

In addition to demonstrated benefits on health outcomes, the success of wheat and maize flour fortification with folic acid as a public health intervention will likely be determined by several factors such as: availability of resources, existence of appropriate policies and legislation, production and supply, the development and implementation of delivery systems, external and internal quality control systems, and strategies for information, education, and communication for consumer behaviour change. Figure 1 presents an overall logic model for micronutrient interventions that depicts the programme theory and the potential relationships between inputs and anticipated changes in health and outcomes that can be adapted to the context of each setting (De-Regil 2013; WHO/CDC 2011).

Figure 1. Adapted from WHO/CDC 2011.



Why it is important to do this review

Vitamin and mineral deficiencies are important public health problems worldwide. Among the potential strategies to address these deficiencies, mass fortification is a promising, sustainable, and cost-effective approach to combat micronutrient deficiencies and improve development, as it leverages existing market and delivery systems, and does not require the active participation of vulnerable populations to increase food intake or dietary diversity. Wheat and maize represent suitable vehicles for fortification as they are considered staple foods in most of the world, particularly in regions where micronutrient deficiencies are common.

Wheat or maize flour fortification with folic acid and other micronutrients has demonstrated promising results in reducing anaemia, cardiovascular disease, and neural tube defects (Castillo-Lancellotti 2013). As a result, an increasing number of countries across the world are rapidly adopting fortification of wheat and maize to target micronutrient deficiencies. In 2004, 33 countries had mandatory wheat flour fortification with folic acid. In 2013, there were 77 countries with legislation for mandatory fortification of wheat or maize flour, and 11 required both to be fortified (CDC 2008). The access to fortified wheat flour by women aged 15 to 60 years increased by 167 million from 2004 to 2007, while the number of births that potentially benefited from flour fortification increased by at least 14 million (Castillo-Lancellotti 2013; CDC 2008).

Despite the benefits of fortification of maize and wheat flour with folic acid, current fortification programmes have not fully eliminated neural tube defects (Honein 2001; Williams 2002). The recent WHO guidelines suggest that optimal red blood cell folate (906 nmol/L) and serum folate (15.9 nmol/L) concentrations in women of reproductive age for prevention of neural tube defects are considerably higher than previously estimated (WHO 2015b). However, there are some concerns regarding universal population-based fortification to prevent neural tube defects, including potential unintended consequences of elevated folic acid intake particularly in populations not at risk for neural tube defects. A systematic review of the benefits and possible adverse effects of this intervention is needed to inform policy makers.

There is considerably more variability in processing maize flour and corn meal compared to wheat flour; therefore the evidence and principles of wheat flour fortification may not necessarily apply to maize flour or corn meal fortification (Gwirtz 2014; Peña-Rosas 2014). There are limited studies that have evaluated the stability of folic acid and other micronutrients during storage, processing, preparation, and cooking of maize flour and corn meal (Dunn 2014). Available evidence suggests that folic acid and encapsulated retinyl ester offer adequate bioavailability, which is likely independent of food vehicle, and that bioavailability of folic acid in fortified maize flour and corn meal products may be similar to those of fortified wheat products (Moretti 2014). However, some studies have noted significant losses in folic acid and other B-vitamins during manufacturing, distribution, and cooking of maize products, which warrants investigation (Dunn 2014).

This Cochrane review will complement the findings of several systematic reviews that explore the effects of interventions that may improve folate status and health-related outcomes. Two Cochrane systematic reviews have been conducted to assess the effects of folic acid supplementation during the periconceptional period (De-Regil 2015) and pregnancy (Lassi 2013). Other related Cochrane systematic reviews include the combined effects of iron and folic acid supplementation among menstruating women (Fernández-Gaxiola 2011; Pasricha 2012), pregnant women (Peña-Rosas 2015a; Peña-Rosas 2015b), and post-partum women (Neufeld 2012), and the effect of oral iron and folic acid supplementation on the prevention and treatment of anaemia in children (up to 19 years of age) in malaria-endemic areas (Okebe 2011). A Cochrane review on the use of folate to fortify rice is currently also in progress (Ashong 2012).

OBJECTIVES

To evaluate the health benefits and safety of folic acid fortification of wheat and maize flour (alone or in combination with other micronutrients) on folate status and health outcomes in the overall population, with emphasis on populations at risk.

For the purposes of this review, a fortified wheat product includes any food prepared from fortified wheat flour; a fortified maize flour product includes any food prepared from fortified corn meal or maize flour. We will include composite flours that contain more than 50% wheat or maize within the definition of flour in this review.

METHODS

Criteria for considering studies for this review

Types of studies

Fortification of wheat, maize flour or corn meal is an intervention that aims to reach the entire population of a country or large sections of the population and is frequently delivered through the market system. We anticipate, therefore, that we will not be able to assess the benefits and potential harms of flour fortification with folic acid if we only include randomised trials; thus in addition to randomised trials, we plan to examine data from other study designs.

We will include the following types of trials.

- Randomised controlled trials (RCTs), with randomisation at either individual or cluster level.

- Quasi-RCTs (where allocation of treatment has been made, for example, by alternate allocation, date of birth, alphabetical order, etc).
- Non-RCTs.
- Observational studies that are prospective and have a control group:
    - cohort studies (prospective and retrospective);
    - controlled before-and-after studies;
    - interrupted time series (ITS) with at least three measurement points both before-and-after intervention.

Although we plan to include both RCTs and non-randomised studies, we will not pool results from RCTs together with those from non-randomised studies in meta-analysis; instead we will use separate meta-analysis estimates for different study designs.
In addition to the above-mentioned study designs, we will also consider before-and-after studies without a control group for inclusion in this review. We will present results from these studies in a table but will not include them in a meta-analysis.

Types of participants

We will include participants from the general population, who are older than two years of age (including pregnant women), and are from any country. We will exclude studies of interventions targeted toward participants with critical illnesses or severe co-morbidities.

Types of interventions

We will include trials in which wheat flour, maize flour, or corn meal have been centrally fortified with folic acid, irrespective of the fortification technology used. Interventions to be included in the review are those in which wheat flour is fortified with folic acid alone or in combination with other micronutrients, irrespective of the fortification technology used and those in which maize flours, or maize subproducts, or both have been fortified with folic acid alone or in combination with other micronutrients.
Maize flour refers to white or yellow maize (corn) flour or maize (corn) meal that is produced by grinding dried maize grains (FDA 2011). We will also include nixtamalized dehydrated corn flour, also known as 'masa flour' or precooked corn flour. We will include composite flours that contain more than 70% wheat for wheat flours or more than 50% maize for maize flours within the definitions of either predominantly maize or wheat flour in this review. Wheat flour products include products prepared from wheat flour (e.g., bread, pasta, crackers, cakes). Maize flour products include all products derived from fortified corn meal and flour (e.g., breads, cereals, polenta, porridges, grits, or *arepas*). We will include studies where fortification of the flour (wheat flour, maize flour, or corn meal) occurs during the flour production.
We will include trials of any form of folic acid fortification of wheat flour, maize flour, or corn meal, with or without other micronutrients, with or without complementary interventions, compared to no fortification, fortification without folic acid, or other strategies to improve folate status and reduce folate deficiency in the wider population.
We will consider any form of wheat flour or maize flour fortification independently of length of intervention, extraction rate of wheat flour, compounds used, preparation of the folic acid-flour premix, and fortification levels achieved in the wheat flour, maize flour, or derivative foods.
We will consider any wheat flour for direct human consumption prepared from common wheat, *Triticum aestivum* L., or club wheat, *Triticum compactum* Host., or mixtures thereof (Codex Alimentarius 1995a); durum wheat semolina, including whole durum wheat semolina and durum wheat flour prepared from durum wheat (*Triticum durum* Desf.) (Codex Alimentarius 1995b), as well as products prepared with these flours.
Maize flour refers to white or yellow maize (corn) flour or maize (corn) meal flour or meal produced from maize or corn (*Zea mays* subsp. Mays that is produced by grinding dried maize grains (Codex Alimentarius 1985a; Codex Alimentarius 1985b; FDA 2011). This includes nixtamalized dehydrated corn flour, also known as 'masa flour', as well as precooked corn flour.
We will exclude studies with wheat flour destined for use as a brewing adjunct or for the manufacture of starch, or gluten, or both; or flours whose protein content had been reduced or had been submitted after the milling process to a special treatment other than drying or bleaching. We will exclude studies that evaluate products derived from wet milling of maize, including corn starch (which is often called 'corn flour' in the UK and Australia), and products that are fortified after recomposition of the flour. For example, if maize flour is used to prepare a bread product, and fortification occurs at the level of bread or tortilla production, then we will exclude this study.
We will only include studies where the fortification occurred at the flour stage. We will exclude studies where fortification occurred at the dough or masa stage. For example, if wheat or maize flour were used to prepare a bread product or biscuit, and fortification occurred at the level of bread or biscuit preparation, we will exclude this study.
We plan to make the following comparisons.

Combined wheat and maize flour fortification

- Wheat and maize flour or products fortified with folic acid alone vs. no intervention.
- Wheat and maize flour or products fortified with folic acid plus other vitamins and minerals vs. no intervention.
- Wheat and maize flour or products fortified with folic acid alone vs. unfortified wheat and maize flours or flour products (not containing folic acid nor any other vitamin and minerals).
- Wheat and maize flour or products fortified with folic acid plus other vitamins and minerals vs. unfortified wheat and maize flours or flour products (not containing folic acid nor any other vitamin and minerals).

Wheat flour

- Wheat flour or wheat flour products fortified with folic acid alone vs. no intervention.
- Wheat flour or wheat flour products fortified with folic acid plus other vitamins and minerals vs. no intervention.
- Wheat flour or wheat flour products fortified with folic acid alone vs. unfortified wheat flours or wheat flour products (not containing folic acid nor any other vitamin and minerals).
- Wheat flour or wheat flour products fortified with folic acid plus other vitamins and minerals vs. unfortified wheat flours or wheat flour products (not containing folic acid nor any other vitamin and minerals).

Maize flour

- Maize flour or maize flour products fortified with folic acid alone vs. no intervention.
- Maize flour or maize flour products fortified with folic acid plus other vitamins and minerals vs. no intervention.
- Maize flour or maize flour products fortified with folic acid alone vs. unfortified maize flours or maize flour products (not containing folic acid nor any other vitamin and minerals).
- Maize flour or maize flour products fortified with folic acid plus other vitamins and minerals vs. unfortified maize flours or maize flour products (not containing folic acid nor any other vitamin and minerals).

We will include studies with co-interventions (e.g., fortified flour with education) only if all compared groups receive the same co-intervention (e.g., education). We will exclude studies that compare flour fortification vs. other forms of micronutrient interventions, such as micronutrient supplementation, biofortification, point-of-use fortification with multiple micronutrient powders or lipid-based nutrient supplements, or other forms of micronutrient interventions. These are currently the subjects of other Cochrane systematic reviews.

Types of outcome measures

Primary outcomes

We will consider the primary outcomes across all populations of folate biomarkers (erythrocyte folate, serum/plasma folate), haemoglobin (Hb) concentrations, and the presence of anaemia, neural tube defects, and any type of cancer. Additional primary outcomes of interest differ by participant group, and we have listed these below by participant group.

Primary outcomes across all populations

- Erythrocyte folate concentrations (nmol/L) (continuous, deficiency, and insufficiency as defined by the study authors).
- Serum/plasma folate concentrations (nmol/L) (continuous, deficiency, and insufficiency as defined by the study authors).
- Hb concentrations (g/L).
- Anaemia (defined as Hb concentrations below the cut-off for age, adjusted by altitude in g/L).
- Neural tube defects (e.g., anencephaly, spina bifida, meningocoele).
- Any type of cancer (as defined by the study authors).

Children (two to 11.9 years of age)

- Erythrocyte folate concentrations (nmol/L) (continuous, deficiency, and insufficiency as defined by the study authors).
- Serum/plasma folate concentrations (nmol/L) (continuous, deficiency, and insufficiency as defined by the study authors).
- Anaemia (defined as Hb below 110 g/L or 115 g/L, adjusted for altitude as appropriate, as defined by the study authors).
- Hb concentrations (in g/L).
- Childhood cancers (as defined by the study authors).

Adolescent girls and boys (12 to 18.9 years of age)

- Erythrocyte folate concentrations (nmol/L) (continuous, deficiency, and insufficiency as defined by the study authors).
- Serum/plasma folate concentrations (nmol/L) (continuous, deficiency, and insufficiency as defined by the study authors).
- Anaemia (defined as Hb below 115 g/L or 120 g/L, adjusted for altitude and smoking as appropriate, as defined by the study authors).
- Hb concentrations (in g/L).

Pregnant women (any age)

- Erythrocyte folate concentrations (nmol/L) (continuous, deficiency, and insufficiency as defined by the study authors).
- Serum/plasma folate concentrations (nmol/L) (continuous, deficiency, and insufficiency as defined by the study authors).
- Anaemia (defined as Hb below 110 g/L at any trimester of pregnancy, adjusted for altitude and smoking as appropriate, as defined by the study authors).
- Hb concentrations (in g/L).
- Neural tube defects (e.g., anencephaly, spina bifida, or meningocoele).
- Low birth weight (less than 2500 g).
- Other adverse pregnancy outcomes (as reported by the study authors, including low birth weight (less than 2500g), preterm delivery (less than 37 weeks of gestational age), and other congenital anomalies).

Adult males and females (19 years of age to less than 59 years of age)

- Erythrocyte folate concentrations (nmol/L) (continuous, deficiency, and insufficiency as defined by the study authors).

- Serum/plasma folate concentrations (nmol/L) (continuous, deficiency, and insufficiency as defined by the study authors).
- Anaemia (defined as Hb below 120 g/L or 130 g/L, adjusted for altitude and smoking as appropriate, as defined by the study authors).
- Hb concentrations (in g/L).

Older persons (60 years of age and older)

- Erythrocyte folate concentrations (nmol/L) (continuous, deficiency, and insufficiency as defined by the study authors).
- Serum/plasma folate concentrations (nmol/L) (continuous, deficiency, and insufficiency as defined by the study authors).
- Anaemia (defined as Hb below 120 g/L or 130 g/L, adjusted for altitude and smoking as appropriate, as defined by the study authors).
- Hb concentrations (in g/L).
- Cognitive function/decline (as defined by the study authors).
- Any type of cancer (as defined by the study authors).

Secondary outcomes

We will consider the following secondary outcomes.

- Serum/plasma homocysteine concentrations (μmol/L) (adjusted for renal function, vitamin B12 as defined by the study authors).
- Serum/plasma methylmalonic acid (μmol/L) (adjusted for renal function, vitamin B12 as defined by the study authors).
- Depression (as defined by the study authors).
- Cognitive function (as defined by study authors, e.g., formal tests addressing intelligence, memory, attention, and other cognitive domains). We will accept any measure of cognitive function that has been previously validated as an appropriate test in this domain.
- Pernicous anaemia (as defined by the study authors).
- Urinary folic acid, 5-Methyltetrahydrofolate (5MTHF), and catabolite concentrations (nmol/L) (adjusted for renal function, as defined by study authors).
- Unmetabolized blood folic acid (nmol/L).
- Malaria (as defined by the study authors).
- Colorectal cancer/polyps (as defined by the study authors).
- Cardiovascular disease (as defined by the study authors).
- Any adverse side effects (as measured by the study authors, including but not limited to abdominal pain, vomiting, nausea, heartburn, diarrhoea, and constipation).

Search methods for identification of studies

We have designed and piloted a structured search strategy. We will conduct this search strategy, starting from January 1960 to date, in electronic databases and we will handsearch relevant journals and publications to identify relevant primary studies. We will also contact study authors for unpublished/ongoing studies, as needed, and consult institutions, agencies, and experts in the field regarding the results of our search and for any additional data.

Electronic searches

We will search the following international and regional sources.

International databases

- The Cochrane Central Register of Controlled Trials (CENTRAL).
- MEDLINE.
- MEDLINE® In Process.
- EMBASE.
- Web of Science (both the Social Science Citation Index and the Science Citation Index).
- CINAHL.
- POPLINE.
- AGRICOLA (http://agricola.nal.usda.gov/).
- BIOSIS.
- Food Science and Technology Abstracts (FSTA).

Regional databases

- IBECS (http://ibecs.isciii.es/).
- Scielo (http://www.scielo.br/).
- Global Index Medicus - AFRO (includes African Index Medicus); EMRO (includes Index Medicus for the Eastern Mediterranean Region).
- LILACS.
- PAHO (Pan American Health Library).
- WHOLIS (WHO Library).
- WPRO (includes Western Pacific Region Index Medicus).
- IMSEAR, Index Medicus for the South-East Asian Region.
- IndMED, Indian medical journals (http://indmed.nic.in/).
- Native Health Research Database (https://hscssl.unm.edu/nhd/).

We will also contact the Information Specialist of the Cochrane Public Health Group to search the Cochrane Public Health Group Specialised Register.

The search will use keyword and controlled vocabulary (when available), and the search terms set out in Appendix 1. We will adapt them as appropriate for each database. We will not apply any language or date restrictions.

We will handsearch the five journals with the highest number of included studies in the last 12 months to capture any article that may not have been indexed in the databases at the time of the search. As maize fortification technologies are not novel, we will not apply time restrictions for all databases. We will contact the authors of included studies and check reference lists of included papers for identification of additional records.

We will search the WHO International Clinical Trials Registry Platform (ICTRP) for any ongoing or planned trials, and contact

the authors of such studies to obtain further information or eligible data if available.

If we identify articles written in a language other than English, we will commission their translations into English. If this is not possible, we will seek advice from the Cochrane Public Health Group. We will store such articles in the 'Awaiting assessment' section of the review until a translation is available.

Searching other resources

For assistance in identifying ongoing or unpublished studies, we will contact the Departments of Nutrition for Health and Development, Reproductive Health and Research and Maternal, Newborn, Child and Adolescent Health as well as the regional offices from the WHO, Centers for Disease Control and Prevention (CDC), the nutrition section of the United Nations Children's Fund (UNICEF), the World Food Programme (WFP), the Micronutrient Initiative (MI), Global Alliance for Improved Nutrition (GAIN), and the Food Fortification Initiative (FFI).

Data collection and analysis

Selection of studies

Two review authors will independently screen the titles and abstracts of articles retrieved by each search to assess eligibility, as determined by the inclusion and exclusion criteria listed above. We will retrieve full-text copies of all eligible papers. When we cannot reject a title or abstract with certainty, we will obtain the full-text article for further evaluation. If we cannot obtain the full-text article, we will attempt to contact the authors to obtain further details of the study. Failing this, we will classify studies as 'awaiting assessment' until further information is published or made available to us. We will resolve any disagreements at any stage of eligibility assessment process through discussion and we will consult a third review author where necessary.

Data extraction and management

Two review authors will independently extract data using data extraction forms based on those from the Cochrane Public Health Group (Cochrane PHG 2010) and the Cochrane Effective Practice and Organisation of Care (EPOC) Group.

All review authors will be involved in piloting the form. We will use a subset of articles to enhance consistency amongst review authors and, based on this, we will modify the form if necessary. We will collect information on study design, study setting and participants (number and characteristics), and provide a full description of the interventions examined. We will extract details of outcomes measured (including a description of how and when outcomes were measured) and results.

We will design the form so that we are able to record results for our prespecified outcomes and for other (non-prespecified) outcomes (although such outcomes will not underpin any of our conclusions). We will extract additional items relating to study recruitment and the implementation of the intervention; these will include number of sites for an intervention, whether recruitment was similar at different sites, whether there were protocol deviations, levels of compliance/use of flours in different sites within studies, resources required for implementation, as well as findings from process evaluations conducted.

We will use the equity checklist to record whether or not data have been reported by socio-demographic characteristics (PROGRESS - place of residence, race/ethnicity, occupation, gender, religion/culture, education, socio-economic status, social capital) known to be important from an equity perspective (Ueffing 2011). We will also record whether or not studies included specific strategies to address diversity or disadvantage. We will extract data on the costs of the implementation of the intervention where available. We will document this data in the 'Characteristics of included studies' table in the review.

For eligible studies, two review authors will independently extract data using the agreed form. Two authors will enter data into Review Manager (RevMan) software (RevMan 2014) and two other review authors will carry out checks for accuracy. We will resolve any discrepancies through discussion.

When information regarding any aspect of study design or results is unclear, we will attempt to contact the authors of the original reports, and will ask them to provide further details.

Assessment of risk of bias in included studies

We will use the Cochrane EPOC 'Risk of bias' tool for studies with a separate control group to assess the risk of bias of all included studies (EPOC 2009). This tool examines five domains of bias: selection, performance, attrition, detection, and reporting, as well as an 'other' bias category to capture other potential threats to validity.

Two review authors (LMD, JLF) will independently assess the risk of bias for each included study. We will resolve any disagreements by discussion or we will involve a third review author (JP).

Assessing risk of bias in RCTs

1. Sequence generation (checking for possible selection bias)

We will assess RCTs as at one of the following levels of bias.

- Low risk of bias if there is a random component in the sequence generation process (any truly random process, e.g., random number table; computer random number generator).
- High risk of bias if the trial authors use a non-random approach (any non-random process, e.g., odd or even date of birth; hospital or clinic record number).

- Unclear.

2. Allocation concealment (checking for possible selection bias)

We will assess trials as one of the following.

- Low risk of bias if participants and investigators that enrolled participants could not foresee assignment because an appropriate method is used to conceal allocation (e.g., telephone or central randomisation; consecutively numbered sealed opaque envelopes). We will give this rating to studies where the unit of allocation was by institution and allocation was performed on all units at the start of the study.
- High risk of bias if participants and investigators that enrolled participants could possibly foresee assignments and potentially introduce selection bias (e.g., open random allocation; unsealed or non-opaque envelopes).
- Unclear.

3. Similarity of baseline outcome measurements (checking for confounding, a potential consequence of selection bias)

We will assess studies as at one of the following levels of bias.

- Low risk of bias if outcomes were measured prior to the intervention, and no important differences were present across intervention groups.
- High risk of bias if important differences in outcomes between groups were present prior to intervention and were not adjusted for in analysis.
- Unclear risk of bias if there was no baseline measure of outcome (note: if 'high' or 'unclear' but there is sufficient information to do an adjusted analysis, the assessment should be 'low').

4. Similarity of baseline characteristics (checking for confounding, a potential consequence of selection bias)

We will assess studies as follows.

- Low risk of bias if baseline characteristics are reported and similar across intervention groups.
- High risk of bias if baseline characteristics are not reported or if there are differences across groups.
- Unclear risk of bias if it is not clear (e.g., characteristics mentioned in text but no data presented).

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, and protocol deviations)

We will assess the outcomes in each included study as one of the following.

- Low risk of bias due to incomplete outcome data could be either that there was no missing outcome data or the missing outcome data was unlikely to bias the results based on the following considerations: study authors provided transparent documentation of participant flow throughout the study, the proportion of missing data was similar in the intervention and control groups, the reasons for missing data were provided and balanced across intervention and control groups, the reasons for missing data were unlikely to bias the results (e.g., moving house).
- High risk of bias if missing outcome data was likely to bias the results. We will give studies this rating if an 'as-treated (per protocol)' analysis is performed with substantial differences between the intervention received and that assigned at randomisation, or if potentially inappropriate methods for imputation have been used.
- Unclear risk of bias.

6. Blinding (checking for possible performance and detection bias)

We will assess the risk of performance bias associated with blinding as follows.

1. Low, high, or unclear risk of bias for participants.
2. Low, high, or unclear risk of bias for personnel.
3. Low, high, or unclear risk of bias for outcome assessors.

We will assess the risk of detection bias associated with blinding as follows.

- Low, high, or unclear risk of bias for outcome assessors.

Whilst assessed separately, we will combine the results into a single evaluation of risk of bias associated with blinding as follows.

- Low risk of bias if there was blinding of participants and key study personnel and it was unlikely to have been broken, or the outcomes are objective. We will also give this rating to studies where either participants and key study personnel were not blinded but outcome assessment was blinded and the non-blinding of others was unlikely to introduce bias.
- High risk of bias if there was no blinding or incomplete blinding, or if there was blinding that was likely to have been broken, and the outcome or outcome assessment was likely to be influenced by a lack of blinding.
- Unclear risk of bias.

7. Contamination (checking for possible performance bias)

We will assess included studies as follows.

- Low risk of bias if allocation was by community, institution, or practice and it is unlikely that the control group received the intervention.
- High risk of bias if it is likely that the control group received the intervention.
- Unclear risk of bias if it is possible that contamination occurred but the risk of this happening is unclear.

8. Selective reporting bias

For each included study we will describe how we investigated the possibility of selective outcome reporting bias and what we found. We will assess studies for this domain as follows.

- Low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported).
- High risk of bias (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest were reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported).
- Unclear risk of bias.

9. Other sources of bias

We will describe other possible sources of bias for each included study and we will give a rating of either low, high, or unclear risk of bias for this item.

Assessing risk of bias in ITS studies

We will assess the risk of bias for ITS studies using the Cochrane EPOC 'Risk of bias' tool for ITS study designs, which includes items (5), (6), (8), and (9) from the EPOC 'Risk of bias' tool above (EPOC 2010), as well as the following additional items.

- Was the intervention independent of other changes?
  - low risk of bias if there are compelling arguments that the intervention occurred independently of other changes over time and the outcome was not influenced by other confounding variables/historical events during the study period;
  - high risk of bias if it is reported or if there are grounds to suspect that the intervention was not independent of other changes over the time period of the study;
  - unclear risk of bias if it is unclear from the information provided.
- Was the shape of the intervention effect prespecified?
  - low risk of bias if the point of analysis is the point of intervention or a rational explanation for the shape of the intervention effect was provided;
  - hIgh risk of bias if it clear that these conditions were not met;
  - unclear risk of bias if it is unclear from the information provided.
- Was the intervention unlikely to affect data collection?
  - low risk of bias if it is reported that the intervention itself was unlikely to affect data collection (e.g., sources and methods of data collection were the same before and after the intervention);
  - high risk of bias if the intervention itself was likely to affect data collection;
  - unclear risk of bias if it is unclear from the information provided.

Overall risk of bias

For all included studies, we will summarise the overall risk of bias by primary outcome across studies. Studies at high risk of bias will be those with high or unclear risk of bias in the following domains: allocation concealment, similarity of baseline outcome measurements, and completeness of outcome data. We will also take into account the likely magnitude and direction of bias and whether it is likely to impact on the study findings.

If there is insufficient information in study reports to enable us to assess risk of bias, studies will await assessment until further information is published, or made available to us.

We will report the findings of the major outcomes in 'Summary of findings' tables, which we will prepare using (GRADEpro) software (GRADEpro 2015). We will list the primary outcomes for each comparison with estimates of relative effects, along with the number of participants and studies that contribute data for those outcomes. For each individual outcome, we will assess the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Balshem 2011). Factors that affect the quality of evidence include risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, risk of publication bias, dose effect responses, magnitude of effect, and issues around residual plausible confounding. The quality of evidence is expressed as one of four levels (high, moderate, low, or very low).

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present proportions. For two-group comparisons, we will present results as an average risk ratio or odds ratio with 95% confidence intervals (CIs).

Continuous data

We will report the results for continuous outcomes as the mean difference with 95% CIs if all included trials measure outcomes on the same scale. Where some studies report endpoint data and other report change from baseline data (with a measure of dispersion) we will combine these in the meta-analysis if the studies report the outcomes using the same scale.

We will use the standardised mean difference with 95% CIs to combine trials that measure the same outcome but use different methods.

If a sufficient number of studies do not meet the inclusion criteria, or we cannot pool studies, we will summarize the results in a narrative form.

Unit of analysis issues

Cluster-RCTs

We will combine results from both cluster- and individually-RCTs if there is little heterogeneity between the studies. If the authors of cluster-RCTs conducted their analyses at a different level to that of allocation and did not appropriately account for the cluster design in their analyses, we will calculate trials' effective sample size to account for the effect of clustering in data. We will utilise the intracluster correlation coefficient (ICC) derived from the trial (if available), or from another source (e.g., using the ICCs derived from other similar trials) and then calculate the design effect with the formula provided in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If we take this approach, we will report this and undertake sensitivity analysis to investigate the effect of variations in ICC.

Studies with more than two treatment groups

If we identify studies with more than two intervention groups (multi-arm studies), where possible we will combine groups to create a single pair-wise comparison or use the methods set out in the *Cochrane Handbook for Systematic Reviews of Interventions* to avoid double-counting study participants (Higgins 2011). For the subgroup analyses, when the control group is shared by two or more study arms, we will divide the control group (events and total population) over the number of relevant subgroups to avoid double counting the participants.

Cross-over trials

From cross-over trials, we will consider the first period of measurement only and we will analyse the results together with the parallel group studies.

Dealing with missing data

We will try to contact the authors if outcome data is missing, unclear, or has not been fully reported. We will capture the missing data in the data extraction form and report it in the 'Risk of bias' tables.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis (i.e., for RCTs, we will attempt to include all participants randomised to each group in the analyses). The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing. For non-randomised studies, where possible, we will analyse data according to initial group allocation irrespective of whether or not participants received or complied with the planned intervention.

When assessing adverse events, the principle of 'intention-to-treat' has more issues. Thus we will relate the results to the treatment received ('per protocol' or 'as observed'). This means that for the side effects we will base the analyses on the participants who actually received treatment and the number of adverse events reported in the included studies.

Assessment of heterogeneity

We will examine the forest plots from meta-analysis to visually assess the level of heterogeneity (in terms of the size or direction of treatment effect) among studies. We will use the I^2 and Tau^2 statistics, and the Chi^2 test to quantify the level of heterogeneity among the trials in each analysis. If we identify moderate or substantial heterogeneity, we will explore it by prespecified subgroup effects analysis.

Heterogeneity may be a particular concern in non-randomised studies. Where there is evidence of heterogeneity, we will summarise the findings using a forest plot but we will not present the pooled estimate**.**

We will take caution when we interpret results with high levels of unexplained heterogeneity.

Assessment of reporting biases

Where we suspect reporting bias (see 'Selective reporting bias' above), we will attempt to contact study authors and ask them to provide missing outcome data. Where this is not possible, and we consider that the missing data introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

If more than 10 studies reporting the same outcome of interest meet the inclusion criteria of the review, we will generate funnel plots in RevMan (RevMan 2014). We will visually examine them for asymmetry. Where we pool studies in meta-analysis we will order studies in terms of weight, so that a visual examination of forest plots may allow us to assess whether the results from smaller and larger studies are similar, or if there are any apparent differences (i.e., we will check that the effect size is similar in smaller and larger studies).

Data synthesis

We will perform meta-analysis to provide an overall estimate of treatment effect when more than one study examines the same intervention, provided that included studies use similar methods, and measure the same outcome in similar ways in similar populations. We will not combine results from RCTs and non-RCTs together in a meta-analysis, nor will we present pooled estimates for non-randomised studies with different types of study designs. Evidence on different outcomes may be available from different types of studies (e.g., it is likely that larger non-randomised studies will report data on less common adverse events). Where there is evidence on a particular outcome from both RCTs and non-randomised studies, we will use the evidence from trials that are at lower risk of bias to estimate treatment effect.

Where there is evidence from several RCTs, or good quality non-randomised studies, we will carry out statistical analysis using the RevMan software (RevMan 2014). We will use a random-effects meta-analysis for combining data, as we anticipate that there may be natural heterogeneity between studies attributable to the different doses, durations, populations, and implementation/delivery strategies. For continuous variables we will use the inverse variance method. For dichotomous variables we will use the one proposed by Mantel-Haenszel.

For non-randomised studies, where results are adjusted for possible confounding factors, we will use the generic inverse variance method in RevMan to carry out any meta-analysis (if included studies provide both adjusted and non-adjusted figures we will carry out a sensitivity analysis using the unadjusted figures to examine any possible impact on the estimate of treatment effect) (RevMan 2014).

We will also use narrative synthesis, guided by the data extraction form in terms of the ways in which studies may be grouped and summarised, to describe the outcomes, explore intervention processes, and describe the impact of interventions by socio-demographic characteristics known to be important from an equity perspective based on the PROGRESS framework, where this information is available.

Specifically, we will describe factors that determine the differential availability, accessibility, acceptability, and effective usage of fortified wheat or maize flour and corn meal among population groups and we will categorise them. We will define key areas of monitoring and suggest appropriate policy action to promote equity in access to these products. In addition, we will describe any financial issues related to the implementation of wheat or maize flour and corn meals fortification programmes, considering existing facilities, production, and considerations for implementation of fortifying wheat and maize flours and corn meals in countries with different levels of market development.

We will highlight the importance of a significant difference in folate status by fortifying wheat and maize flours or cornmeal for the health and nutritional implications in countries where wheat or maize are a staple food.

'Summary of findings' tables

We will summarize the body of evidence for dichotomous and continuous outcomes as recommended by the GRADE Working Group. We will present data in 'Summary of findings' tables for the primary outcomes (Guyatt 2013a; Guyatt 2013b) using GRADEprofiler software (GRADEpro 2015).

Subgroup analysis and investigation of heterogeneity

Where data are available we will perform the following subgroup analyses.

- By range of wheat or maize flour consumption patterns: less than 75 g/day, vs. 75 to 149 g/day, vs. 150 to 300 g/day, vs. great than 300 g/day.
- By dose of folic acid in parts per million (ppm): less than 1.5 ppm vs. 1.5 to 4.99 vs. 5 ppm or more (by dose per 100 g of product).
- By length of intervention: less than six months, six months to 12 months, more than 12 months.
- By baseline folate status (as defined by study authors): deficient vs. non-deficient or unknown/unreported.
- By malaria endemicity at the time that the trial was conducted malaria setting vs. non/unknown malaria setting (yes/no).

We will only use the primary outcomes in subgroup analysis for those outcomes for which three or more trials contributed data. We will examine differences between subgroups by visual inspection of the subgroups' CIs; non-overlapping CIs suggesting a statistically significant difference in treatment effect between the subgroups. We will also formally investigate differences between two or more subgroups (Borenstein 2008). In the subgroup analyses we will provide totals and subtotals and we will assess subgroup differences by interaction tests available in RevMan (RevMan 2014). Where there is evidence of a difference between subgroups, we will report this in the text and present the results for the subgroup analyses quoting the Chi² statistic and P value, and the interaction I^2 statistic value. We will explore possible subgroup differences as a means of exploring heterogeneity.

Sensitivity analysis

We will conduct sensitivity analyses to examine the effects of removing studies at high risk of bias (e.g., those with high or unclear risk of bias for allocation concealment, lack of similarity of baseline outcome measurements, or incomplete outcome data) from the analysis. If cluster-RCTs meet the inclusion criteria of the review, we will conduct sensitivity analyses using a range of intracluster correlation values.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

We will use the following search strategies to search databases, and adapt these to other databases as necessary.

CENTRAL

#1 MESH DESCRIPTOR Folic Acid EXPLODE ALL TREES
#2 ((folic acid or folate or "vitamin b9" or "vitamin m" or folvite or folacin or pteroylglutamic acid)):TI,AB,KY
#3 #1 OR #2
#4 MESH DESCRIPTOR Flour
#5 MESH DESCRIPTOR Triticum
#6 MESH DESCRIPTOR Zea mays
#7 ((wheat or maize or mielies or mealies or corn or cornmeal or flour* or cornflour*)):TI,AB,KY
#8 #4 OR #5 OR #6 OR #7
#9 ((fortif* or enrich* or enhanc* or boost*)):TI,AB,KY
#10 MESH DESCRIPTOR Food, Fortified EXPLODE ALL TREES
#11 #9 OR #10
#12 #3 AND #8 AND #11

MEDLINE and MEDLINE in Progress (OVID)

1 exp Folic Acid/
2 (folic acid or folate or "vitamin b9" or "vitamin m" or folvite or folacin or pteroylglutamic acid).tw.
3 or/1-2
4 Flour/
5 Triticum/
6 Zea mays/
7 (wheat or maize or mielies or mealies or corn or cornmeal or flour* or cornflour*).tw.
8 4 or 5 or 6 or 7
9 (fortif* or enrich* or enhanc* or boost*).tw.
10 Food, Fortified/
11 9 or 10
12 3 and 8 and 11
13 exp animals/ not humans/
14 12 not 13

EMBASE (OVID)

1 exp Folic Acid/
2 (folic acid or folate or "vitamin b9" or "vitamin m" or folvite or folacin or pteroylglutamic acid).tw.
3 or/1-2
4 Flour/
5 Triticum/
6 Zea mays/
7 (wheat or maize or mielies or mealies or corn or cornmeal or flour* or cornflour*).tw.
8 4 or 5 or 6 or 7
9 (fortif* or enrich* or enhanc* or boost*).tw.
10 Food, Fortified/
11 9 or 10
12 3 and 8 and 11

13 exp animals/ not humans/
14 12 not 13
15 limit 14 to embase

CINAHL (EBSCO)

S11 (S3 AND S7 AND S10)
S10 S8 OR S9
S9 (MH "Food, Fortified")
S8 (fortif* or enrich* or enhanc* or boost*)
S7 S4 OR S5 OR S6
S6 (wheat or maize or mielies or mealies or corn or cornmeal or flour* or cornflour*)
S5 (MH "Corn")
S4 (MH "Wheat")
S3 S1 OR S2
S2 (folic acid or folate or "vitamin b9" or "vitamin m" or folvite or folacin or pteroylglutamic acid)
S1 (MH "Folic Acid+")

Web of Science (SCI, SSCI, CPCI, and CRCI-SSH)

#1 ((folic acid or folate or "vitamin b9" or "vitamin m" or folvite or folacin or pteroylglutamic acid))
#2 (Triticum)
#3 (Zea mays)
#4 (wheat or maize or mielies or mealies or corn or cornmeal or flour* or cornflour*)
#5 #4 OR #3 OR #2
#6 (fortif* or enrich* or enhanc* or boost*)
#7 #1 and #5 and #6

BIOSIS (ISI)

#1 ((folic acid or folate or "vitamin b9" or "vitamin m" or folvite or folacin or pteroylglutamic acid))
#2 (Triticum)
#3 (Zea mays)
#4 (wheat or maize or mielies or mealies or corn or cornmeal or flour* or cornflour*)
#5 #4 OR #3 OR #2
#6 (fortif* or enrich* or enhanc* or boost*)
#7 #1 and #5 and #6
#8 Refined by: MAJOR CONCEPTS: (NUTRITION) AND SUPER TAXA: (PRIMATES)

Popline

(fortif* or enrich* or enhanc* or boost*)
and
(folic acid or folate or "vitamin b9" or "vitamin m" or folvite or folacin or pteroylglutamic acid)
and
(wheat or maize or mielies or mealies or corn or cornmeal or flour* or cornflour* or Triticum or "zea mays")

IBECS, PAHO, WHOLIS, and LILACS (BIRME)

wheat or maize or mielies or mealies or corn or cornmeal or flour$ or cornflour$ or "zea mays" or triticum [Words] and fortif$ or enrich$ or enhanc$ or boost$ [Words] and folic acid or folate or "vitamin b9" or "vitamin m" or folvite or folacin or pteroylglutamic acid [Words]

SCIELO

(folic acid or folate or vitamin b9 or vitamin m or folvite or folacin or pteroylglutamic acid) and (wheat or flour$ or maize or mielies or mealies or corn or cornmeal or zea mays or triticum) and (fortif$ or enrich$ or enhanc$ or boost$)

WPRO, IMSEAR, AFRO, and EMRO (GLOBAL INDEX MEDICUS)

(folic acid or folate or "vitamin b9" or "vitamin m" or folvite or folacin or pteroylglutamic acid) and (fortif* or enrich* or enhanc* or boost*) and (wheat or maize or mielies or mealies or corn or cornmeal or flour* or cornflour* or "Zea mays" or Triticum)

INMED

wheat or flour or flours or maize or mielies or mealies or corn or cornmeal or zea mays or triticum
and
(folic acid or folate or vitamin b9 or vitamin m or folvite or folacin or pteroylglutamic acid)
and
(fortify or fortified or enrich or enriched or enhance or enhanced or boost or boosted or boosts)

Native Health Research Database

(folic acid) and (wheat or corn or maize)

CONTRIBUTIONS OF AUTHORS

Luz Maria De-Regil, Eva Hertampf, and Diego Gaitan drafted an initial protocol draft. Luz Maria De-Regil and Ingvil Saeterdal developed the protocol 'Methods' section. Julia Finkelstein and Juan Pablo Peña-Rosas revised the protocol. All protocol authors approved the final version of the protocol.

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