WHO GUIDELINE:

FORTIFICATION OF MAIZE FLOUR AND CORN MEAL WITH VITAMINS AND MINERALS

World Health Organization

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PUBLICATION HISTORY

This guideline, *Fortification of maize flour and corn meal with vitamins and minerals,* is a partial update of, and supersedes, the recommendations related to maize flour only in the 2009 WHO guideline, *Recommendations on wheat and maize flour fortification. Meeting report: interim consensus statement,* which was published during the interim period of the adoption of the evidence-informed guideline development process in WHO. The focus is on the use of this intervention as a public health strategy. Given the many types of maize flour and corn meal consumed in various countries in Africa and in the Americas as food vehicles for fortification, a separate guideline for this food vehicle was deemed necessary. In order to produce this guideline, the rigorous procedures described in the *WHO handbook for guideline development* were followed. This guideline complements the WHO/FAO (Food and Agriculture Organization of the United Nations) *Guidelines on food fortification with micronutrients* (2006) and the Pan American Health Organization (PAHO) publication, *Iron compounds for food fortification: guidelines for Latin America and the Caribbean* (2002). The overall direct evidence is limited but supports the use of maize flour and corn meal as a food vehicle for micronutrients where these foods are staples. This document expands the sections on dissemination and updates the summary of evidence used for the guideline, based on the most recent systematic reviews on the topic.

ACKNOWLEDGEMENTS

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Donors do not fund specific guidelines and do not participate in any decision related to the guideline development process, including the composition of research questions, membership of the guideline groups, conduct and interpretation of systematic reviews, or formulation of the recommendations.

WHO GUIDELINE[1]: FORTIFICATION OF MAIZE FLOUR AND CORN MEAL WITH VITAMINS AND MINERALS

EXECUTIVE SUMMARY

Fortification of industrially processed flour, when appropriately implemented, is an efficient, simple and inexpensive strategy for supplying vitamins and minerals to the diets of large segments of the population. Maize, also referred to as corn,[2] is cultivated in most parts of the world, as it grows in diverse climates. Industrial fortification of maize flour and corn meal with at least iron has been practised for many years in several countries in the Americas and Africa, where these ingredients are used in the preparation of many common national dishes.

Decisions about which nutrients to add to fortified white or yellow maize flour, and how much of each nutrient to use, should be based on the nutritional needs and intake gaps of the target populations; the usual level of consumption of maize flour, corn meal and products made from these staples; the sensory and physical effects of the fortificant on white and yellow maize flour, corn meal and flour products; the fortification of other food vehicles; the population use of vitamin and mineral supplements; costs; feasibility; and acceptability.

Maize flour can be fortified with several micronutrients, such as iron, folic acid and other B-complex vitamins, vitamin A and zinc – some used for restitution of nutritional contents and others used for preventing micronutrient deficiencies of public health significance in several countries.

PURPOSE OF THE GUIDELINE

This guideline aims to help Member States and their partners to make informed decisions on the appropriate nutrition actions to achieve the Sustainable Development Goals and the global targets set in the *Comprehensive implementation plan on maternal, infant and young child nutrition*.

The recommendations in this guideline are intended for a wide audience, including policy-makers, their expert advisers, economists, and technical and programme staff in ministries and organizations involved in the design, implementation and scaling-up of nutrition actions for public health, particularly in the design and implementation of appropriate food-fortification programmes, as part of a comprehensive food-based strategy for combating micronutrient deficiencies.

These recommendations supersede the previous WHO recommendation on fortification of maize flour.[3] The guideline complements the WHO/FAO (Food and Agriculture Organization of the United Nations) *Guidelines on food fortification with micronutrients*[4] and the Pan American Health Organization (PAHO) 2002 document, *Iron compounds for food fortification: guidelines for Latin America and the Caribbean*.[5]

[1] This publication is a World Health Organization (WHO) guideline. A WHO guideline is any document, whatever its title, containing WHO recommendations about health interventions, whether they be clinical, public health or policy interventions. A recommendation provides information about what policy-makers, health-care providers or patients should do. It implies a choice between different interventions that have an impact on health and that have ramifications for the use of resources. All publications containing WHO recommendations are approved by the WHO guidelines Review Committee.

[2] The terms maize and corn are used synonymously throughout this guideline.

[3] Recommendations on wheat and maize flour fortification. Meeting report: interim consensus statement. Geneva: World Health Organization; 2009 (WHO/NMH/NHD/MNM/09.1); (http://apps.who.int/iris/bitstream/10665/111837/1/WHO_NMH_NHD_MNM_09.1_eng.pdf?ua=1&ua=1).

[4] Allen L, de Benoist B, Dary O, Hurrell R, editors. Guidelines on food fortification with micronutrients. Geneva: World Health Organization and Food and Agriculture Organization of the United Nations; 2006 (http://www.who.int/nutrition/publications/micronutrients/9241594012/en/).

[5] Dary O, Freire W, Kim S. Iron compounds for food fortification: guidelines for Latin America and the Caribbean 2002. Nutr Rev. 2002;60:S50–61.

GUIDELINE DEVELOPMENT METHODOLOGY

WHO developed the present evidence-informed recommendations using the procedures outlined in the *WHO handbook for guideline development*. The steps in this process included: (i) identification of priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations, including research priorities; and planning for (v) dissemination; (vi) implementation, equity and ethical considerations; and (vii) impact evaluation and updating of the guideline. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was followed, to prepare evidence profiles related to preselected topics, based on up-to-date systematic reviews.

The guideline development group consisted of content experts, methodologists and representatives of potential stakeholders and beneficiaries. One guideline group participated in a meeting concerning this guideline, held in Geneva, Switzerland on 22–25 February 2010, where the guideline was scoped. A second guideline group participated in a meeting held in Cancun, Mexico, on 3–6 November 2014, to discuss the evidence and finalize the recommendations. External experts, as resource persons, assisted the guideline development group during the guideline development process, in presenting the evidence and identifying research priorities. Seven technical experts were invited to peer-review the draft guideline.

AVAILABLE EVIDENCE

Eight systematic reviews on the effect on critical nutrition- and health-related outcomes of fortification of staple foods, including maize flour and corn meal, with vitamins and minerals, served to inform this guideline. These showed positive effects on nutritional status of using fortified foods to supply sufficient amounts of micronutrients that are otherwise inadequate in the diet, compared to no intervention. Evidence on the effect of fortified maize flour or maize-flour products was scarce for vitamin A, zinc, vitamin D and calcium, or it was not possible to isolate the effect of the intake of fortified maize flour on the outcomes, as was the case for programmes in Brazil and Venezuela where more than one food item was fortified simultaneously.

Evidence on fortification of maize flour with folic acid or iron showed a positive effect on health outcomes in the general population. Fortification of maize flour with iron, in combination with other micronutrients, reduced the risk of iron deficiency but had no effect on anaemia in children. Addition of folic acid to wheat and maize flour in the United States of America (USA) and other countries has had a significant impact on multiple measures, including folate intake, blood folate concentrations and the prevalence of neural tube defects and, for some subpopulations, fortification of nixtamalized maize flour with folic acid could potentially reduce the disparity in folate intake that is common between Latino women living in the USA and white populations.

The overall quality of the direct evidence for fortification of maize flour and corn meal with vitamins and minerals as a strategy to improve the health of populations was very low[1] for the critical outcomes of iron status, iron deficiency anaemia and folate status. There was no direct evidence for the critical outcomes of iron deficiency anaemia, neural tube defects and other congenital anomalies, zinc status and deficiency, growth, and adverse effects in children, including constipation, nausea, vomiting, heartburn or diarrhoea, as measured by trialists.

[1] According to GRADE, very low-quality evidence indicates that we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of effect.

RECOMMENDATIONS

- Fortification of maize flour and corn meal with iron is recommended to prevent iron deficiency in populations, particularly vulnerable groups such as children and women (*very low-quality evidence*).[2]
- Fortification of maize flour and corn meal with folic acid is recommended to reduce the risk of occurrence of births with neural tube defects (*very low-quality evidence*).[2]

Note: Although evidence in maize flour or corn meal is rather limited, addition of other vitamins and minerals in fortification of maize flour and corn meal is a common and optional practice. The remarks section includes important considerations that can be used to inform design and implementation.

REMARKS

The remarks in this section are intended to give some considerations for implementation of the recommendations, based on the discussion of the guideline development group.

- Although limited direct evidence was found from fortification of maize flour or corn meal to supply effective amounts of micronutrients, there is documented evidence from several countries that fortification of other staple foods with zinc, vitamin A, folic acid, vitamin D and calcium is associated with significant reductions in the incidence of deficiency-related outcomes, and improvements in the health status of populations.
- Countries can integrate fortification of maize flour and corn meal as part of their national programmes for prevention and control of micronutrient deficiencies and insufficiences. The choice and concentration of nutrients for fortification of maize flour or corn meal should be considered in the context of the strategy, including consideration of the vitamin and mineral nutritional needs and intake gaps of the target populations; the usual level of consumption of maize flour, corn meal and products made from these staples; the sensory and physical effects of the fortificant on white and yellow maize flour, corn meal and flour products; the fortification of other food vehicles; the population use of vitamin and mineral supplements; other ongoing nutrition interventions; costs; feasibility; and acceptability.
- Since some of the B-complex vitamins naturally present in the maize grain are removed during milling and degerming, the restoration of niacin, riboflavin and thiamine in maize flour should remain a regular practice in fortification, especially niacin for non-nixtamalized maize flour. This strategy has contributed to the virtual elimination of beriberi and pellagra in many countries.
- Countries that fortify maize flour also frequently fortify wheat flour. A combined fortification strategy using multiple vehicles appears to be a suitably effective option for reaching all segments of the population. In this context, selection of a combined fortification formula that is applicable to both types of flour may be appropriate.

[2] This is a conditional recommendation. A *conditional recommendation* is one for which the guideline development group concludes that the desirable effects of adherence probably outweigh the undesirable effects, although the trade-offs are uncertain. Implications of a conditional recommendation for populations are that, while many people would desire fortification of maize flour and corn meal with vitamins and minerals, a considerable proportion would not. With regard to policy-makers, a conditional recommendation means that there is a need for substantial debate and involvement from stakeholders before considering the adoption of fortification of maize flour and corn meal with these vitamins and minerals in each setting.

- The choice of iron compound is a compromise between cost, bioavailability, micronutrient interactions and the acceptance of texture, taste, smell and/or colour. Nixtamalized flour (lime treated), commonly used in the Americas, is more reactive to ferrous compounds. The use of electrolytic iron does not appear to be effective in fortification of nixtamalized maize flour.
- The addition of vitamin C and the removal of phytates in maize flour and corn meal could increase the bioavailability of iron.
- Food fortification should be guided by national standards, with quality-assurance and quality-control systems to ensure quality fortification. Continuous programme monitoring should be in place as part of a process to ensure high-quality implementation.

RESEARCH GAPS

Discussions between the members of the WHO guideline development group and the external review group highlighted the limited evidence available in some knowledge areas, meriting further research on the fortification of maize flour and corn meal, particularly in the following areas:

- the bioavailability of different iron compounds for use in maize flour and corn meal produced with different technological processing, including mixtures of different compounds;
- the bioavailability and stability of folic acid and vitamin A in maize flour and corn meal with different methods of processing (e.g. nixtamalized maize flour);
- evaluation of the efficacy and effectiveness of programmes for fortification of maize flour and corn meal, either alone or in combination with wheat-flour fortification, in all age groups;
- determination of appropriate levels and combinations of nutrients and their interactions, the stability of micronutrient compounds, and their physical properties and acceptability to consumers;
- biomarkers of individual micronutrient status under different conditions of infection and inflammation;
- the impact of maize use for biofuel production on food security and on the sustainability of programmes for fortification of maize flour and corn meal;
- the feasibility of small-scale fortification of maize flour and corn meal for public health programmes.

WHO GUIDELINE[1]: FORTIFICATION OF MAIZE FLOUR AND CORN MEAL WITH VITAMINS AND MINERALS

SCOPE AND PURPOSE

This guideline provides global, evidence-informed recommendations on the fortification of maize flour and corn meal with micronutrients as a strategy to increase the supply of vitamins and minerals that are present in inadequate diets, and therefore contributing to improvement of the health status of populations.

The guideline aims to help Member States and their partners in their efforts to make informed decisions on the appropriate nutrition actions to achieve the Sustainable Development Goals (SDGs) *(1),* in particular, Goal 2: End hunger, achieve food security and improved nutrition and promote sustainable agriculture and Goal 3: Ensure healthy lives and promote well-being for all at all ages. It will also support Member States in their efforts to achieve the global targets of the *Comprehensive implementation plan on maternal, infant and young child nutrition (2)* and *The global strategy for women's, children's and adolescents' health (2016–2030) (3).*

The recommendations in this guideline are intended for a wide audience, including policy-makers, their expert advisers, economists, and technical and programme staff in ministries and organizations involved in the design, implementation and scaling-up of nutrition actions for public health, particularly in the design and implementation of appropriate food-fortification programmes, as part of a comprehensive food-based strategy for combating micronutrient deficiencies.

This guideline is intended to contribute to discussions among stakeholders when selecting or prioritizing interventions to be undertaken in their specific context. The document presents the key recommendations and a summary of the supporting evidence.

BACKGROUND

Cereals are the major source of energy and other nutrients for most societies worldwide. Wheat, maize and rice represent the most important cereal crops, accounting for 94% of the total cereal consumption worldwide *(4)*. Maize, also referred to as corn,[2] is cultivated in most parts of the world, as it is able to grow in diverse climates. In 2012, the total world production of maize was over 875 million tonnes, with the United States of America (USA), Brazil and China producing the vast majority of the total volume *(5, 6)*. Currently, about 55% of the world's consumption of coarse grains is used for animal feed, but in many countries, mainly in sub-Saharan Africa and Latin America, they are directly used for human consumption.

The way in which maize is processed and consumed varies from country to country. Two basic categories of industrial processing are employed for transforming maize into products for human consumption, known as wet and dry milling. In the wet-milling process, maize is separated into relatively pure chemical compound classes of starch, protein, oil and fibre. Because wet milling of maize separates much of its nutrient content from the starch component, this type of milling is not used for small-scale production or for direct consumption *(7, 8)*. Dry milling reduces the particle size

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[2] The terms maize and corn are used synonymously throughout this guideline

of clean whole maize, with or without screening. The main products obtained from dry milling of corn are corn meal, flour, precooked meal and nixtamalized products (dry masa and hominy flour, which differ essentially in particle size) *(7, 9)*. Although there is no globally recognized terminology for dry-milled maize products, attempts have been made to classify and define the products of maize processing. The commonly accepted terms used, according to ranges of particle size, include grits (600–1400 µm), corn meal (300–600 µm), fine meal (212–300 µm) and flour (less than 212 µm). Some have subdivided the definition of maize meal into smaller size categories, to include coarse meal (730–1190 µm), medium meal (420–730 µm) and fine meal or cones (212–420 µm) *(10)*.

In some countries, maize kernels undergo pre-processing steps before milling, which result in differences in appearance, taste and final preparations. One of these pre-processing steps is called nixtamalization, which is characterized by cooking maize kernels in a dilute alkali solution of calcium hydroxide that is made by dissolution of calcium oxide in water (traditionally, limewater, ash or lye). After washing, the grain/kernel is dehulled by removing the pericarp, leaving the endosperm and germ *(11, 12)*. Precooking is another procedure that may be applied to maize before milling, in which the kernel is sequentially dehulled, degermed, precooked, dried, flaked and milled *(7, 13)*.

The maize food products most commonly fortified are maize flour and corn meal. The composition of maize flour and corn meal varies by regional preferences, with some preferring whole ground maize rather than degermed or partially degermed maize products. The nutrient composition, including vitamins, minerals and anti-nutrient factors, such as phytate, is influenced by those local product preferences, which include not only the way the corn product is consumed, but also what other food items or additives are part of a complete meal *(7)*. Maize colour is also important to specific consumer groups. In Latin America and Africa, white maize is preferred for human consumption, while yellow varieties are used for animal feeding. In the eastern USA, corn meal, grits and hominy are white, while in the northern USA, maize meal and maize products used for breakfast cereals and snack foods are manufactured with yellow maize *(4)*.

Fortification of maize flour, corn meal and products made from them has been implemented in several settings around the world. When appropriately implemented, this is an efficient, simple and inexpensive strategy for supplying vitamins and minerals to the diets of large segments of the population *(14, 15)*. These maize products can be fortified with several micronutrients, such as iron, folic acid and other B-complex vitamins, vitamin A and zinc – some used for restitution of nutritional contents and others used for the prevention of micronutrient deficiencies of public health significance in several countries. Industrial fortification of maize flour with at least iron has been practised for many years in several countries in the Americas and Africa *(6)*. As of August 2016, the fortification of maize flour or corn meal has been voluntarily introduced in Lesotho, Namibia and Nicaragua, while mandatory fortification is in place in Brazil, Burundi, Costa Rica, El Salvador, Guatemala, Kenya, Malawi, Mexico, Mozambique, Nigeria, Rwanda, South Africa, the United Republic of Tanzania, Uganda, the USA and Venezuela *(16)*. Folic-acid fortification of corn masa flour, a staple food product within the Hispanic community in the USA, can potentially reduce the disparity in intake of folic acid *(17)*.

In many cases, procedures for fortification of wheat and maize flour have been viewed and managed similarly, and many of the conclusions on the impact of fortification programmes are based on experiences with wheat flour, or on programmes simultaneously fortifying wheat and maize flour *(18)*. It is now recognized that there is much more variability in processing maize flour than wheat flour, and that the principles that apply to the fortification of wheat flour may not necessarily apply to the fortification of maize flour *(6)*.

Fortified blended foods, blends of partially precooked and milled cereals (e.g. corn and soy) fortified with micronutrients, are often used in food-assistance programmes for moderately malnourished children as well as other vulnerable groups (pregnant and lactating women and people who are chronically ill with HIV/AIDS or tuberculosis). When prepared with corn, they contain 20–25% soybeans, 75–80% corn and a micronutrient premix *(19)*.

Decisions about which nutrients to add and the appropriate amounts to add to fortify maize flour and meal should be based on the nutritional needs and intake gaps of the target populations; the usual level of consumption of maize flour, corn meal and products made from these staples; the sensory and physical effects of the fortificant on white and yellow maize flour, corn meal and flour products; the fortification of other food vehicles; the population use of vitamin and mineral supplements; costs; feasibility; and acceptability *(14, 15, 20)*. Fortification programmes should include appropriate quality-assurance and quality-control programmes at mills, as well as regulatory and public health monitoring of the nutrient content of fortified foods and assessment of the nutritional and health impacts of the fortification strategies. There are also specific country or community settings to evaluate and decisions to make. For example, as part of quality-control systems, it is desirable that milling is centralized in few mills, although people who mainly consume locally produced, unprocessed maize meal are less likely to benefit from an industrial, large-scale, maize-fortification programme.

This guideline provides information on the health impact of the fortification of maize flour and corn meal with micronutrients.

OBJECTIVES

The recommendations in this guideline supersede the previous WHO recommendation on fortification of maize flour *(18)*. The guideline complements the WHO/FAO (Food and Agriculture Organization of the United Nations) *Guidelines on food fortification with micronutrients* *(15)* and the Pan American Health Organization (PAHO) 2002 document, *Iron compounds for food fortification: guidelines for Latin America and the Caribbean* *(21)*.

SUMMARY OF AVAILABLE EVIDENCE

Eight systematic reviews were commissioned to inform this guideline on the effect of fortification of maize flour and corn meal with vitamins and minerals on critical nutrition and health-related outcomes *(22–29)*. The main results related to maize flour and corn meal are summarized. A GRADE summary of findings tables for the critical outcomes and their quality of evidence are provided in Annex 1. The outcomes of fortification of maize flour and corn meal that were considered by the WHO guideline development group to be critical for decision-making were iron status (as defined by trialists), iron deficiency and anaemia, neural tube defects and other congenital anomalies, folate status (as measured by serum or red cell folate concentrations) in women of reproductive age and older adults, zinc deficiency, zinc status (as measured by plasma zinc concentrations) and growth (as defined by stunting, wasting or underweight) (see Annex 2).

Although the initial scoping did not aim to consider the effects of fortification of maize flour and corn meal with vitamins A and D, calcium or other vitamins and minerals, it was decided by the group that this evidence should be reported, as, in practice, the fortification of staple foods, including maize flour and corn meal, involves several micronutrients in the premix, depending on the contextual needs. The various systematic reviews that informed this guideline and the review teams can be found in Annex 3.

FORTIFICATION OF MAIZE FLOUR AND CORN MEAL WITH VITAMINS AND MINERALS

IRON

Regarding studies with maize flour and corn meal, a systematic review following the methods described in the *Cochrane handbook for systematic reviews of interventions* *(30)* was undertaken, to determine the benefits and harms of iron fortification of maize flour, corn meal and fortified maize-flour products for anaemia and iron status among the general population. The Cochrane review describing the methods and results has been submitted *(22)*. For the purpose of the review, a fortified maize-flour product included any food prepared from fortified corn meal or maize flour fortified with iron and other minerals or vitamins, versus no intervention. The search strategy identified 236 trials (15 September 2016); however, only five trials evaluated a fortified maize-flour product. Three of these studies were randomized trials involving 2610 participants and two were observational studies (pre and post interventions without a control group) involving 849 participants. All included studies (*31–34*; Villalpando, personal communication, 2002) compared maize flour or maize-flour products fortified with iron plus other vitamins and minerals versus unfortified maize flours or maize-flour products (not containing iron or any other vitamins or minerals). Two studies were undertaken in children aged 3–8 years *(31)*, and 6–11 years (Villalpando, personal communication, 2002), one in children and adolescents aged 7–14 years *(32)*, one in young children (6–59 months of age), adolescents (10–19 years of age) and women (20–49 years of age) *(33)*, and one in adult women *(34)*. Two studies evaluated the effects on nixtamalized maize flour (*34*; Villalpando, personal communication, 2002); two studies used whole-maize milled meal *(31, 33)*; and another used degermed-maize milled meal *(32)*.

One study *(31)* provided porridge (*uji*) prepared with whole maize flour sweetened with sugar. The maize flour was fortified (per kg of flour) with 56 mg or 28 mg elemental iron (as NaFeEDTA or electrolytic iron) and vitamin A (2500 µg), thiamine (3.5 mg), riboflavin (4 mg) and niacin (45 mg), in comparison to unfortified porridge in children. Another study *(34)* provided 20 kg monthly of fortified maize flour, containing (per 100 g of flour): 1.5 g soy protein, 42.4 mg elemental iron (as ferrous fumarate), 120 µg vitamin A, 548 µg folic acid, 33.3 mg zinc and 6.5 mg niacin, in comparison to providing unfortified maize flour to women. The other study, in children (Villalpando, personal communication, 2002), also provided nixtamalized corn flour fortified with elemental iron (as reduced iron or NaFeEDTA), and (per kg of flour) 5 mg thiamine, 3 mg riboflavin, 35 mg niacin, 2 mg folic acid and 40 mg zinc, in comparison to unfortified nixtamalized flour.

The pre–post study in Brazil (32) provided children and adolescents with sweet and savoury products (biscuits, cakes and pies) derived from 100 g of corn flour fortified with 9.8 mg elemental iron powder (as reduced iron) and 350 µg (0.35 mg) folic acid during 6 months, while the pre–post study in the refugee camp in Kenya *(33)* provided 97%-extraction fortified maize meal containing (per kg of flour) 2100 µg retinol equivalents, 4.4 mg thiamine, 2.6 mg riboflavin, 35 mg nicotinamide, 2.5 mg vitamin B_6, 10 mg vitamin B_{12}, 1500 µg (1.5 mg) folic acid, 35 mg elemental iron and 20 mg zinc, in addition to provision of a food ration containing 120 g pulses (beans or peas), 20 g vegetable oil and 10 g salt. The maize grain included in the pre-intervention ration was replaced by the fortified maize meal during the period of the intervention.

In comparison to unfortified maize flour, fortification of maize-flour products with iron and other vitamins and minerals reduced the risk of iron deficiency in children (risk ratio [RR]: 0.53; 95% confidence interval [CI]: 0.40 to 0.69; 2 studies, *n* = 1277; *very low-quality evidence*) and had no effect on anaemia (RR: 0.89; 95% CI: 0.57 to 1.39; 2 studies, *n* = 1359; *very low-quality evidence*), haemoglobin (mean difference [MD]: 0.42 g/L; 95% CI: –2.47 to 3.31 g/L; 2 studies, *n* = 1325; *very low-quality evidence*) or ferritin (MD: 0.00 µg/L; 95% CI: –0.27 to 0.27 µg/L; 2 studies, *n* = 758; *very low-quality evidence)* in children *(22)*. One randomized controlled trial involving 308 Mexican women aged 14–64 years reported a change in haemoglobin concentration from 131 to 133 g/L in a group receiving fortified flour and from 131 to 132 g/L in the control group (no reported measures of dispersion of data) after 10 months of receiving fortified maize flour *(34)*. One of the studies reported on iron deficiency anaemia and none reported on adverse effects. The review authors concluded that, in comparison to no intervention, fortification of maize flour or corn meal with iron in combination with other micronutrients can reduce the risk of iron deficiency, but has no effect on anaemia in children. There are publications on fortification of precooked maize flour in Brazil and Venezuela but these countries initiated the fortification of maize and wheat flour simultaneously, rendering it impossible to separate the effect of each staple food *(35–38)*. A GRADE summary of findings table for meta-analysis of included studies with maize flour or maize-flour products fortified with iron plus other vitamins and minerals versus unfortified maize flour or maize-flour products (not containing iron or any other vitamins or minerals) is presented in Annex 1A.

Another systematic review conducted in 2012 focused on the effects of iron fortification in different food vehicles on haemoglobin and serum ferritin concentrations and the prevalence of iron deficiency and anaemia in the general population *(23)*. The review included 60 studies, 36 of which were on cereals and 19 on wheat and rice, without mentioning maize flour specifically. The review showed that iron fortification of foods resulted in a significant increase in haemoglobin (weighted mean difference [WMD]: 4.2 g/L; 95% CI: 0.28 to 0.56 g/L; 60 trials) and serum ferritin (WMD: 1.36 µg/L; 95% CI: 1.23 to 1.52 µg/L; 33 studies, *n* = 12 150) and a reduced risk of anaemia (RR 0.59; 95% CI: 0.48 to 0.71; 33 studies, *n* = 13 331) and iron deficiency (RR: 0.48; 95% CI: 0.38 to 0.62; 21 studies, *n* = 5765). A significant improvement in haemoglobin was shown in a post-hoc analysis of the subgroup of trials conducted on cereals (*n* = 33). The largest effect size in this subset was with NaFeEDTA, and the response with sulfate, pyrophosphate or fumarate salts was lower but statistically significant.

FOLIC ACID

A systematic review and meta-analysis of the prevalence of spina bifida by countries/areas, according to the fortification of any staple product with folic acid, geographic region and study population, identified 179 studies for the systematic review and 123 studies for the meta-analysis *(24)*. In studies of live births, period prevalence estimates of spina bifida from 1985 to 2010 were lower in regions with mandatory (33.86 per 100 000 live births) versus voluntary (48.35 per 100 000 live births) folic-acid fortification. Period prevalence estimates of spina bifida were also lower in studies of live births, stillbirths and terminations of pregnancy, with mandatory (35.22 per 100 000 live births) compared to voluntary (52.29 per 100 000 live births) fortification. In studies of live births, stillbirths and terminations of pregnancy, the lowest pooled prevalence estimate was in North America (38.70 per 100 000 live births) *(24)*. Folic-acid fortification of wheat flour in the USA has had a significant impact on multiple measures, including folate intake, blood folate concentrations and the prevalence of neural tube defects *(17)*. However, some subpopulations, including Hispanic populations, exhibit higher rates of neural tube defects and lower total folate intakes. Folic-acid fortification of nixtamalized maize flour, a staple food product within the Hispanic community, can potentially reduce the disparity in folate intake that is common between Latino women living in the USA and white populations *(17)*. Mexican American women generally have a lower mean total folic acid intake than non-Hispanic white women (244 µg and 332 µg, respectively) *(39)*.

A Cochrane systematic review was commissioned to specifically 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 *(25)*. The search strategy (6 September 2016) identified 2407 records, of which 1827 records were considered after de-duplication. From this search three randomized controlled studies were identified *(40–42)*, but only two contributed relevant data for the quantitative analysis on the critical outcomes *(40, 41)*.

One randomized controlled trial involved 45 non-anaemic pregnant women attending the lodging facility of the Charles Johnson Memorial Hospital at Nqutu, South Africa during a 3-week period *(40)*. All participants received iron supplementation from the date of their first antenatal visit and were randomly assigned to one of two groups: group 1 (*n* = 24) to receive a soft porridge maize meal prepared with 30 g maize flour fortified with folic acid (as synthetic pteroylglutamic acid) and milk and sugar and group 2 (*n* = 14) received no additional intervention. Other than the provision of the fortified porridge, the two groups received the same diet. Participants received daily fortified meal during 10–50 days, for a mean of 26.4 days. Each fortified maize meal contained 1000 µg (1 mg) of folic acid before cooking; the authors estimated that it would account for a daily dose of 300 µg (0.3 mg) folic acid per meal. In comparison to no intervention, pregnant women receiving maize porridge fortified with folic acid had higher erythrocyte folate concentrations: MD: 239.07 nmol/L (95% CI: 226.43 to 251.71 nmol/L; 1 study, 38 participants, *very low-quality evidence*). Serum folate levels were significantly higher: MD: 14.98 nmol/L (95% CI: 14.67 to 15.29 nmol/L; 1 study, 38 participants, *very low-quality evidence*). There were no data on other critical outcomes (see Annex 1B).

A longitudinal study performed in 2011 in Mexico compared the effect of intake of maize flour fortified with folic acid versus unfortified flour and folic-acid supplementation, on blood folate levels in non-pregnant women of reproductive age *(41)*. Forty-five women without a history of previous birth defects, were randomly assigned to one of three groups: group 1 (*n* = 18) received folic-acid-fortified maize flour (50 µg/100 g flour); group 2 (*n* = 17) received unfortified flour; and group 3 (*n* = 10) received supplements containing 5000 µg (5 mg) of oral folic acid per week for 3 months. Supplementation significantly increased plasma and erythrocyte folic acid, while consumption of maize flour, fortified or not, significantly increased plasma folate concentrations. The studies did not report on the other critical outcomes of neural tube defects or other adverse events. Participants receiving the folic-acid-fortified maize flour had no significant changes in erythrocyte folate concentrations in comparison to those receiving the unfortified flour (MD: –61.60 nmol/L; 95% CI: –52.98 to 29.38 nmol/L; 1 study, 35 participants, very low-quality evidence) or in plasma folate concentrations (MD: 2.00 nmol/L; 95% CI: –0.33 to 4.33 nmol/L; 1 study, 35 participants, very low-quality evidence). There were serious doubts about the reference values and the units used for reporting plasma folate concentrations, and the quality of evidence for this outcome was considered very low. There were no data on other critical outcomes. (see Annex 1C).

One randomized controlled trial *(42)* aimed to evaluate the impact of corn flour enriched with soy and other micronutrients on the nutritional status and haemoglobin levels of indigenous women aged 14–64 years, from communities classified as highly marginalized and rural. A total of 308 participants in Mexico were randomly assigned to one of two groups: group 1 (*n* = 155) received maize flour fortified with (per 100 g flour) 548 µg (0.54 mg) folic acid and 1.5 g soy protein, 42.4 mg ferric fumarate, 120 µg vitamin A, 33.3 mg zinc and 6.5 mg niacin and provided monthly (20 kg); group 2 (*n* = 153) received unfortified maize flour. This study did not contribute any data for this review.

No studies on other population groups of interest were identified.

VITAMIN A

A systematic review following the methods described in the *Cochrane handbook for systematic reviews of interventions* *(30)* was carried out to assess the benefits and harms of fortifying staple foods with vitamin A on vitamin A status and health-related outcomes in the general population. The Cochrane review describing the methods and study results has been submitted *(26)*. The search strategy (21 April 2016) identified 10 683 records after duplicates had been removed. The comparisons included staple foods fortified with vitamin A versus no intervention and versus the same unfortified staple foods, as well as staple foods fortified with vitamin A plus other micronutrients versus no intervention and versus the same unfortified staple foods. The outcomes of interest were related to changes in retinol levels, subclinical and clinical evidence of vitamin A deficiency, morbidity and mortality. Twenty-two studies were included. The studies were conducted in lower-middle income countries (Bangladesh, India, Philippines, South Africa, Zambia) and upper-middle income countries (Brazil, China, Mexico, Thailand). The duration of intervention ranged from 3 to 36 months and participants included individuals with vitamin A deficiency, those vulnerable to micronutrient deficiencies, and apparently healthy individuals.

Only two included studies referred specifically to maize flour or meal fortified with vitamin A and other micronutrients in comparison to unfortified maize flour. In one of the two studies, 44 1–3-year-old malnourished children who had weight-for-age or height-for-age below the 5th percentile of the National Center for Health Statistics reference were recruited from a well-baby clinic and formal crèche in Oukasie, South Africa *(43)*. The participants were randomly allocated to one of two groups: group 1 (*n* = 21) consumed maize meal fortified with 1700 international units (IU) vitamin A, 0.61 mg thiamine, 0.62 mg riboflavin and 0.56 mg pyridoxine for each 150 g of raw maize flour; group 2 (*n* = 23) consumed unfortified maize meal. All children regularly consumed maize porridge, as either soft porridge with milk or stiff porridge with a relish, two to four times a day. The 12–18-month-old children were occasionally breastfed. After 12 months, there was a significantly higher increase in body weight in the children receiving fortified porridge compared to children in the control group (4.6 kg versus 2.0 kg), and non-significant increases in haemoglobin and serum retinol. The second trial referring to maize flour was conducted in Zambia and provided fortified and unfortified maize flour to 212 adolescents (10–19 years), 157 children (aged 6–59 months) and 118 women (aged 20–49 years) in the Nangweshi refugee camp *(33)*. Each household received a 400 g ration of 97%-extraction, fortified maize meal per registered refugee, irrespective of age, throughout the duration of the intervention period, which lasted from November 2003 until June 2004. The ration supplied by a food-aid agency also included 120 g pulses (beans or peas), 20 g vegetable oil and 10 g salt, per person per day. The maize grain included in the pre-intervention ration was replaced by the fortified maize flour during the period of the intervention. The fortificant formulation contained 2100 IU (0.63 mg) vitamin A, 4.4 mg thiamine, 2.6 mg riboflavin, 35 mg nicotinamide, 2.5 mg vitamin B_6 10 mg vitamin B_{12}, 1500 µg (1.5 mg) folic acid, 35 mg elemental iron and 20 mg zinc per kg of maize meal. The fortificants were added to the maize meal at the flour stage; the meal was then blended, bagged and stored for a maximum of 4 weeks prior to distribution. There was a significant increase in haemoglobin concentrations in children and adolescents (8.7 g/L; $P < 0.001$ and 2.4 g/L; $P < 0.043$, respectively) and a 23.4% decrease in anaemia in children ($P < 0.001$), compared to the pre-intervention period, but no significant change in the prevalence of anaemia in adolescents. In adolescents, serum retinol increased significantly by 0.16 µmol/L and vitamin A deficiency decreased by 26.1% *(33)*. The data from other food vehicles fortified with vitamin A provided evidence that fortification of staple foods with vitamin A and other micronutrients reduces subclinical vitamin A deficiency in populations.

ZINC

A Cochrane systematic review was commissioned to assess the efficacy of fortifying staple foods, including maize flour or corn meal, with zinc alone or in combination with other vitamins and minerals *(27)*. The search strategy (8 April 2015) identified 6582 references (after removing duplicates) for possible inclusion, 6337 through international databases and the remaining through regional databases and other resources. Eight studies were included, involving 709 participants. None of the studies involved the use of maize flour or corn meal as a food-fortification vehicle.

Nonetheless, the cereals studied included wheat bread, taftoon bread, biscuits and wheat products, breakfast cereals and rice. Doses of elemental zinc varied from 3 to 40 mg per 100 g of food as different zinc salts. Four trials compared the effect of zinc-fortified staple foods to unfortified foods and four compared zinc-fortified staple foods in combination to other nutrients/factors with the same foods containing other nutrients or factors without zinc. The duration of intervention was between 1 and 9 months. Foods fortified with zinc increased the serum or plasma zinc levels in comparison to foods without added zinc (MD: 2.12; 95% CI: 1.25 to 3.00 µmol/L; 3 studies, $n = 158$; *low-quality evidence*). Individuals consuming foods fortified with zinc, compared to individuals consuming the same food without zinc, had a similar risk of underweight (RR: 3.10; 95% CI: 0.52 to 18.38; 2 studies, $n = 397$) and stunting (RR: 0.88; 95% CI: 0.36 to 2.13; 2 studies, $n = 397$). Fortification of foods with zinc improved the serum zinc status of populations if zinc was the only micronutrient used for fortification. The zinc status did not improve significantly if zinc was added to foods in combination with other micronutrients. Effects of the fortification of foods with zinc on any other outcome, including children's growth, cognition, work capacity of adults or haematological indicators, were unclear, as no studies reported on these outcomes.

VITAMIN D AND CALCIUM

A systematic review following the methods described in the *Cochrane handbook for systematic reviews of interventions* *(30)* assessed the impact of food fortification with vitamin D and/or calcium on health outcomes in the general population. The Cochrane protocol describing the methods has been published *(28)*. The search strategy (20 May 2016) identified a total of 1203 records. After removing duplicates, a total of 876 abstracts were screened for possible inclusion and a total of 62 full-text articles were further assessed for eligibility. The review included 37 trials (*n* = 5563) in the meta-analysis. The included studies were divided into three separate analyses for fortification with calcium only, vitamin D only, or a combination of vitamin D and calcium. Primary outcomes included the effect of fortification on morbidity and mortality, while secondary outcomes included effects on serum or plasma concentrations of vitamin D, calcium and parathyroid hormone (PTH); bone mineral density; markers of bone resorption; and associated adverse effects. The meta-analysis included 34 trials. The most commonly used fortification vehicles were dairy products and fruit juice.

None of the studies included maize flour or corn meal as the fortification vehicle.

Data were analysed separately by calcium-only fortification, vitamin-D-only fortification and combined fortification with vitamin D and calcium. There was a significant impact of vitamin D fortification, alone or in combination with calcium, on serum vitamin D levels, serum PTH levels and total body bone mineral density in selected population groups, although the quality of the evidence was low. Fortification with vitamin D alone showed a significant impact on serum vitamin D concentrations (standardized mean difference [SMD]: 1.55; 95% CI: 0.99 to 2.11; 5 studies, *n* = 925) and PTH levels (SMD: –0.71; 95% CI: –1.34 to –0.08; 3 studies, *n* = 216). Fortification with both vitamin D and calcium resulted in higher serum vitamin D concentrations (SMD: 3.64; 95% CI: 3.22 to 4.06; 1 study, *n* = 235) and PTH levels (SMD: –0.51; 95% CI: –0.76 to –0.27; 2 studies, *n* = 265) in prepubertal girls but not in postmenopausal women.

ALL FOODS AND WHOLE DIETS WITH MICRONUTRIENTS

A systematic review was conducted in 2013 to assess the effect of fortification of any type of food (staples, condiments, processed foods) with one, two or a combination of micronutrients on health outcomes and relevant biochemical indicators of women and children (i.e. haemoglobin, ferritin, retinol, vitamin D, vitamin A status, zinc, urinary iodine, copper and folate concentrations); twinning; and incidence of neural tube defects, anencephaly and spina bifida) *(29)*. The review included 201 studies and showed improvements in serum concentrations of micronutrients and increased haemoglobin concentrations when a food was fortified with vitamin A, iron and multiple micronutrients. Iron fortification led to a significant increase in serum ferritin and haemoglobin concentrations. Eleven randomized controlled trials in women showed a significant effect of iron fortification on haemoglobin concentration (SMD: 0.64; 95% CI: 0.30 to 0.97), serum ferritin concentrations (SMD: 0.41; 95% CI: 0.23 to 0.60) and prevalence of anaemia (RR: 0.68; 95% CI: 0.49 to 0.93). Folate fortification significantly reduced the incidence of congenital anomalies, such as neural tube defects, without increasing the incidence of twinning. The number of studies pooled for zinc and multiple micronutrients for women was low, though the evidence suggested a benefit *(29)*. Five randomized controlled trials studied the impact of a combination of micronutrients (from 3 to 20) in woman of reproductive age, pregnant women and postmenopausal women. Women receiving fortified foods showed a significant improvement in haemoglobin concentrations (SMD: 0.31; 95% CI: 0.13 to 0.48), serum ferritin (SMD: 0.47; 95% CI: 0.36 to 0.58), serum zinc (SMD: 0.50; 95% CI: 0.38 to 0.61) and serum retinol concentrations (SMD: 0.47; 95% CI: 0.30 to 0.65), and similar prevalence of anaemia (RR: 0.76; 95% CI: 0.48 to 1.21). The authors highlighted that these findings should be interpreted with caution, since few studies were pooled for each outcome.

SUMMARY OF DIRECT EVIDENCE

Direct evidence (specifically on maize flour and corn meal as food vehicles) on the fortification with iron showed that, in comparison to unfortified maize flour, fortification of maize-flour products with iron and other vitamins and minerals reduced the risk of iron deficiency in children (RR: 0.53; 95% CI: 0.40 to 0.69; 2 studies, *n* = 1277; *very low-quality evidence*) and had no effect on anaemia (RR: 0.89; 95% CI: 0.57 to 1.39; 2 studies, *n* = 1359; *very low-quality evidence*), haemoglobin (MD: 0.42 g/L; 95% CI: –0.47 to 3.31 g/L; 2 studies, *n* = 1325; *very low-quality evidence*) or ferritin (MD: 0.00 µg/L; 95% CI: –0.27 to 0.27 µg/L; 2 studies, *n* = 758; *very low-quality evidence*) *(22)*. One of the studies reported on iron deficiency anaemia and none on adverse effects. Two studies, conducted in Mexico and South Africa, reported the effect of folic-acid fortification of maize flour or corn meal *(40, 41)*. Consumption of maize flour, fortified or not, significantly increased plasma folic-acid concentrations, compared to baseline determinations. No studies were found that reported on the effect of zinc fortification of maize flour or corn meal *(27)*.

The quality of the direct evidence for the critical outcomes ranged from low to very low, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology *(44, 45)*;[1] there was no direct evidence (specifically on maize flour and corn meal as food vehicle) for the critical outcomes of iron deficiency anaemia, neural tube defects and other congenital anomalies, zinc status and deficiency, growth, and adverse effects in children, including constipation, nausea, vomiting, heartburn or diarrhoea, as measured by trialists. The GRADE summary of findings table for the fortification of maize flour and corn meal is shown in Annex 1. In addition to the direct and indirect evidence (delivered using food vehicles other than maize flour and corn meal) and its overall quality, other considerations were taken into account by the guideline development group to define the direction and strength of the recommendations. They included values and preferences of the populations related to fortification of maize flour and corn meal in different settings, trade-off between benefits and harms and costs and feasibility (see Annex 4).

RECOMMENDATIONS

- Fortification of maize flour and corn meal with iron is recommended to prevent iron deficiency in populations, particularly vulnerable groups such as children and women (*very low-quality evidence*).[2]
- Fortification of maize flour and corn meal with folic acid is recommended to reduce the risk of occurrence of births with neural tube defects (*very low-quality evidence*).[2]

Note: Although evidence in maize flour or corn meal is rather limited, addition of other vitamins and minerals in fortification of maize flour and corn meal is a common and optional practice. The remarks section includes important considerations that can be used to inform design and implementation.

[1] According to GRADE, very low-quality evidence indicates that we have very little confidence in the effect estimate and the true effect is likely to be substantially difference from the estimate of effect.

[2] This is a conditional recommendation. *A conditional recommendation* is one for which the guideline development group concludes that the desirable effects of adherence probably outweigh the undesirable effects, although the trade-offs are uncertain. Implications of a conditional recommendation for populations are that, while many people would desire fortification of maize flour and corn meal with vitamins and minerals, a considerable proportion would not. With regard to policy-makers, a conditional recommendation means that there is a need for substantial debate and involvement from stakeholders before considering the adoption of fortification of maize flour and corn meal with these vitamins and minerals in each setting.

REMARKS

The remarks in this section are intended to give some considerations for implementation of the recommendations, based on the discussion of the guideline development group.

- Although limited direct evidence was found from fortification of maize flour or corn meal to supply effective amounts of micronutrients, there is documented evidence that fortification of other staple foods with zinc, vitamin A, folic acid, vitamin D and calcium is associated with significant reductions in the incidence of deficiency-related outcomes and improvements in the health status of populations.
- Countries can integrate fortification of maize flour and corn meal as part of their national programmes for prevention and control of micronutrient deficiencies and insufficiencies. The choice and concentration of nutrients for fortification of maize flour or corn meal should be considered in the context of the strategy, including consideration of the vitamin and mineral nutritional needs and intake gaps of the target populations; the usual level of consumption of maize flour, corn meal and products made from these staples; the sensory and physical effects of the fortificant on white and yellow maize flour, corn meal and flour products; the fortification of other food vehicles; the population use of vitamin and mineral supplements; other ongoing nutrition interventions; costs; feasibility; and acceptability *(15, 46, 47)*. A general guidance scheme that could help with implementation and decision-making is presented in Table 1.
- Since some of the B-complex vitamins naturally present in the maize grain are removed during milling and degerming, the restoration of niacin, riboflavin and thiamine in maize flour should remain a regular practice in fortification, especially niacin for non-nixtamalized maize flour. This strategy has contributed to the virtual elimination of beriberi and pellagra in many countries *(15)*.
- Countries that fortify maize flour also frequently fortify wheat flour. A combined fortification strategy using multiple vehicles appears to be a suitably effective option for reaching all segments of the population *(48)*. In this context, selection of a combined fortification formula that is applicable to both types of flour may be appropriate.
- The choice of iron compound is a compromise between cost, bioavailability, micronutrient interactions and the acceptance of texture, taste, smell and/or colour. Nixtamalized flour (lime treated), commonly used in the Americas, is more reactive to ferrous compounds. The use of electrolytic iron does not appear to be effective in fortification of nixtamalized maize flour *(18)*.
- The addition of vitamin C and the removal of phytates in maize flour and corn meal could increase the bioavailability of iron *(4, 15, 49)*.
- Food fortification should be guided by national standards, with quality-assurance and quality-control systems to ensure quality fortification. Continuous programme monitoring should be in place as part of a process to ensure high-quality implementation.

TABLE 1. Levels of nutrients to consider for adding to fortified maize flour and corn meal, when it is the only micronutrient intervention, based on extraction rate, chemical form and estimated per capita consumption[a]

			Nutrient concentration to be added by estimated availability/consumption (mg nutrient/kg maize flour)[d]		
Nutrient[b]	Flour-extraction rate[c]	Compound	<75 g/day[e]	75–149 g/day	150–300 g/day
Iron[f]	Low	NaFe-EDTA	40	40	20
		Ferrous sulfate	60	60	30
		Ferrous fumarate	60	60	30
		Electrolytic iron	NR	NR	60
	High	NaFe-EDTA	40	40	40
		Ferrous sulfate	60	60	60
		Ferrous fumarate	60	60	60
		Electrolytic iron	NR	NR	NR
Folic acid	Low or high	Folic acid	5.0	2.6	1.3
Vitamin A	Low or high	Vitamin A palmitate	6.0	3.0	1.5
Zinc	Low	Zinc sulfate/zinc oxide[3]	95	55	40
	High	Zinc sulfate/zinc oxide	100	100	80
Vitamin B_{12}[h]	Low or high	Cyanocobalamin	0.04	0.02	0.01
For restitution of content lost during milling[i]					
Thiamine	Low or high	Thiamine hydrochloride	3.9	3.9	3.9
Riboflavin	Low or high	Riboflavin	2.0	2.0	2.0
Niacin	Low or high	Niacinamide	36	36	36
Pyridoxine	Low or high	Pyridoxine hydrochloride	6.2	6.2	6.2
Pantothenic acid	Low or high	Calcium pantothenate	4.2	4.2	4.2

NaFeEDTA: ferric sodium ethylenediaminetetraacetate; NR: not recommended

[a] This is a table to be used as a general guidance, and the number and amounts of nutrients should be adapted according to the needs of the country. These estimated levels consider only maize flour or corn meal as the main fortification vehicle in a public health programme. If other fortification programmes with other food vehicles and other micronutrient interventions are jointly implemented effectively, these suggested fortification levels need to be adjusted downwards as necessary.

[b] Nutrient levels were adapted from reference (*18*). In studies with maize flour, NaFeEDTA, encapsulated iron salts and ferrous bisglycinate have shown high bioavailability with high-extraction flours *(15, 50, 51)*. Other iron compounds for use with high-extraction flour are included for increasing the variety of choices during the decision-making process. The addition of iron compounds at low levels of maize-flour or corn-meal consumption will depend on the organoleptic characteristics of the final product, after testing if feasible at industrial level *(21)*.

[c] High-extraction flour (>80%) is also known as whole flour. It retains high levels of natural maize phytates, which inhibit the body's ability to absorb iron and zinc *(4)*. For maize flour, nixtamalization is a process that yields high-extraction flour, while degermination and precooking produce low-extraction flour *(7)*.

[d] Consumption of maize flour and corn meal varies widely in different countries, ranging from around 50 g/person/day in Ghana, Haiti and Uganda, to 300 g/person/day in Lesotho and Malawi *(7)*.

[e] Estimated per capita consumption of <75 g/day does not allow for the addition of sufficient amounts of fortificant to cover the micronutrient needs for women of childbearing age. Fortification of additional food vehicles and other interventions may need to be considered.

[f] The amounts of iron presented here are in milligrams of elemental iron. The amount of a particular iron compound should be calculated depending on the molecular weight of the compound.

[g] Both zinc sulfate and zinc oxide could be used for maize fortification, although zinc oxide is cheaper *(52, 53)*. As with iron, the phytate concentration (high flour-extraction rate) will affect the bioavailability of zinc *(53, 54)*. These amounts of zinc fortification assume 5 mg zinc intake and no additional phytate intake from other dietary sources *(18)*.

[h] The prevalence of vitamin B_{12} depletion and deficiency is high in all age groups, reaching 50% in some countries *(55, 56)*. Also, inclusion of vitamin B_{12} is recommended when flour is fortified with folic acid *(56, 57)*.

[i] Restitution of some B-complex vitamins should be achieved as a regular practice in all settings. The content in flour from white maize is: thiamine 3.9 mg/kg, riboflavin 2.0 mg/kg, niacin 36 mg/kg, pyridoxine 6.2 mg/kg and pantothenic acid 4.2 mg/kg *(7)*.

RESEARCH GAPS

Discussions between the WHO guideline development group and the external review group highlighted the limited evidence available in some knowledge areas, meriting further research on the fortification of maize flour and corn meal, particularly in the following areas:

- the bioavailability of different iron compounds for use in maize flour and corn meal produced with different technological processing, including mixtures of different compounds;
- the bioavailability and stability of folic acid and vitamin A in maize flour and corn meal with different methods of processing (e.g. nixtamalized maize flour);
- evaluation of the efficacy and effectiveness of programmes for fortification of maize flour and corn meal, either alone or in combination with wheat-flour fortification, in all age groups;
- determination of appropriate levels and combinations of nutrients and their interactions, the stability of micronutrient compounds, and their physical properties and acceptability to consumers;
- biomarkers of individual micronutrient status under different conditions of infection and inflammation;
- the impact of maize use for biofuel production on food security and on the sustainability of programmes for fortification of maize flour and corn meal;
- the feasibility of small-scale fortification of maize flour and corn meal for public health programmes.

DISSEMINATION, IMPLEMENTATION AND ETHICAL CONSIDERATIONS

DISSEMINATION

This guideline will be disseminated through electronic media such as slide presentations and the World Wide Web, through the WHO Nutrition mailing lists, social media, the WHO Nutrition website *(58)*, or the WHO e-Library of Evidence for Nutrition Actions (eLENA) *(59)*. eLENA compiles and displays WHO guidelines related to nutrition, along with complementary documents such as systematic reviews and other evidence that informed the guidelines; biological and behavioural rationales; and additional resources produced by Member States and global partners. In addition, the guideline will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, universities, other United Nations agencies and nongovernmental organizations. Derivative products that are useful for end-users, such as summaries and collation of recommendations related to food fortification, may be developed.

Particular attention will be given to improving access to these guidelines for stakeholders that face more, or specific, barriers in access to information, or to those that play a crucial role in the implementation of the guideline recommendations, for example, policy-makers and decision-makers at subnational level that disseminate the contents of the guideline. Disseminated information may emphasize the benefits of food-fortification programmes in populations or regions where micronutrient deficiencies and their consequences are of public health significance. This is particularly important in rural communities or highly isolated settings where access to fortified foods is limited or difficult.

EQUITY, HUMAN RIGHTS AND IMPLEMENTATION CONSIDERATIONS

This guideline provides Member States with evidence-informed recommendations on the effects and safety of fortifying maize flour and corn meal with micronutrients, as a strategy to improve the health status of populations, specifically for the prevention of iron deficiency in populations and reduction of the risk of occurrence of births with neural tube defects. This guideline is intended to help Member States make informed decisions about what interventions are best suited to their context, needs, resources and ongoing programmes, observing existing human rights standards and pursuing health equity.[1] Currently, fortification of maize flour and corn meal with micronutrients is already taking place in several Member States, and up to 16 countries have developed mandatory legislation: Brazil, Burundi, Costa Rica, El Salvador, Guatemala, Kenya, Malawi, Mexico, Mozambique, Nigeria, Rwanda, South Africa, Uganda, the United Republic of Tanzania, USA and Venezuela *(16)*. If Member States decide to adopt the recommendations contained in this guideline at either the national or subnational level, a thorough assessment of the policy implications concerning this decision is needed. The following illustrative implications seek to support Member States that are considering fortification of maize flour and corn meal with micronutrients.

The adoption and adaptation of this recommendation should be framed under the existing national strategy on prevention and control of micronutrient deficiencies. The choice of an intervention to prevent micronutrient deficiencies should be considered in the context of that strategy, including consideration of the costs, feasibility, accessibility and acceptability among the different stakeholders (e.g. decision-makers, law-makers, programme-managers, manufacturers, industry organizations, consumers' organizations, organizations with opposing views). A mapping exercise of the different stakeholders and their interests and form of involvement in the intervention is a useful practice *(60)*.

A robust baseline or database on the prevalence of micronutrient deficiencies across the population is the optimal foundation for any programme. Data should be disaggregated as much as possible, in order to identify health inequities across population groups, which is also needed for monitoring. Some of the most useful and common stratifiers include those grouped under the acronym PROGRESS-Plus: place of residence; race, ethnicity, culture and language; occupation; gender and sex; religion; socioeconomic status; and social capital; plus other relevant social determinants (e.g. age, disability status, migration status, health-system configuration, political environment). WHO has developed guidance on health equity, in order to support Member States in this respect: the WHO *Handbook on health inequality monitoring: with a special focus on low- and middle-income countries* *(61)* and the WHO *Health Equity Assessment Toolkit (HEAT)* *(62)*. These resources will assist Member States in the assessment of within-country health inequalities and can inform Member States adopting this guideline in the process of adaptation.

This guideline can be adapted to the specific national or subnational context, as long as the suggested levels of nutrients to consider adding to fortified maize flour and corn meal are followed, so the expected effect of the intervention is met by the intervention. Policy-makers and programme managers may consider appropriate measures to guarantee that the intervention is implemented as it was designed, so that fidelity[2] can also be measured and monitored.

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[1] Equity in health refers to the absence of unjust differences in health, which are avoidable by reasonable action *(59)*. Thus, the implementation of the interventions informed by this guideline should contribute to preventing or mitigating systematic differences in nutritional status across populations, including health inequities that may be exacerbated or created as a result of their implementation.

[2] "Fidelity" is an implementation outcome variable, which indicates the degree to which an intervention is or was implemented as it was designed in an original policy, plan or protocol *(62)*. A full description of different implementation outcomes (e.g. acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost, coverage and sustainability) can be found in reference *(62)*.

Likewise, during pre-implementation stages, an analysis is recommended of capacities for maize production and industrialization, the nutrients needed, and consumption of maize flour and corn meal. Accurate and robust data on the prevalence of micronutrient deficiencies in the population groups are needed for cost estimates, as this will inform the decision on the formulation of the fortification premix. Careful identification of pathways to benefit hard-to-reach populations, and the required distribution channels, is also recommended.

Access to and availability of fortified maize flour and corn meal should be promoted, irrespective of geographical, cultural or economic factors, including factors that arise as a result of the implementation of the programme, which must be corrected (e.g. poor planning of distribution channels; culturally irrelevant messages; weak monitoring standards). In the context of staple foods in particular, even slight changes in geographical placement, culturally adapted communication strategies, and variations in the price of the food could affect their accessibility. For example, in many low-income and rural settings, households may often purchase maize flour at local markets, or from local hammer or small mills, or grind their own *(63)*. Subsequently, these households may not benefit from large-scale fortification of maize flour and corn meal, if concurrent measures are not designed, especially within multisectoral efforts (e.g. awareness-raising campaigns, food subsidies, cash-transfer programmes directly distibuting fortified flours, and the use of other interventions such as point-of-use fortification or supplementation). These concurrent measures can contribute to prevent and mitigate health inequities that are produced as a result of differential access to fortified maize flour and corn meal.

As a means to prevent misconceptions, culturally appropriate communication strategies should be developed to disseminate accurate and evidence-based information on what fortified maize flour is and why it is important for health and nutrition *(60, 64)*. Likewise, programmes at national and subnational levels should be culturally appropriate to the target populations, so the intervention is accepted *(63)*, adopted and sustained, and should also identify any resistance, via actions or behaviours, based on well-established practices or social beliefs that affect adoption of and adherence to use of fortified maize products. In addition, populations should be informed about the need for fortification and benefits of the programme, especially in settings where maize constitutes one of the main sources of energy in the diet. For example, in areas where beliefs that fortified maize flour and corn meal contain poison or contraceptives to limit birth rates and family size, or conversely, that the fortified foods directly contribute to increasing sexual strength and birth rates *(63)*, it is important and necessary to disseminate accurate information on the rationale and purpose of food fortification. This is especially relevant in poor-resource settings and for populations with a low education level, since these groups are more likely to not understand the intervention and its benefits *(65)*. The involvement of local leaders and the use of local languages and culturally relevant representations is a reasonable strategy.

Acceptability and adoption are better achieved if they are accompanied by simple and easy-to-access information that can be understood by different population groups, including frontline health workers. Dissemination of information must be carried out in a manner that aims to ensure that these recommendations are perceived as appropriate by all actors involved, including the population expected to consume the fortified maize products, the industrials in charge of milling and fortifying the maize flour or meal, and the organizations in charge of measuring the impact of the programme and monitoring and evaluating it.

The programme should have well-defined objectives that take into account available resources, existing policies, suitable delivery platforms and suppliers, communication channels and potential stakeholders. Ideally, a programme for the fortification of maize flour and corn meal should be implemented as part of a coordinated and comprehensive programme aiming to address micronutrient deficiencies. A coordinated and comprehensive fortification programme may include several food items. The selection of the foods to be fortified and the levels of nutrients to be added to those different foods must be carried out in a coordinated manner. Some countries offer suitable case-studies, such as Costa Rica, where the national fortification programme includes a basket of foods: wheat flour, maize flour, rice, milk, sugar and salt. The levels of nutrients added to these foods are determined in a coordinated way *(66)*. While the present guideline offers suggested levels of nutrients to be considered for fortifying maize flour and corn meal (see Table 1), these are based on maize flour and corn meal alone and, therefore, national programmes considering the adoption of this recommendation should take into account any coexisting mass-fortification programmes and determine the levels of micronutrients for fortification accordingly.

Programmes fortifying maize flour and corn meal with iron and folic acid should be coordinated with antenatal care programmes that supplement pregnant women with these two micronutrients. Likewise, when a malaria-prevention and treatment programme is in place, the coexistence of a public health programme distributing iron is feasible, provided that coordinating measures between both programmes are formulated and observed, as has been pointed out by recent WHO guidelines *(67, 68)*.

With regard to public health programmes distributing folic acid, there have been concerns about the impact of folic acid on malaria treatment, which is dependent on administration of the antifolate sulfadoxine/pyrimethamine. Hence, in malaria-endemic settings, women may be provided with folic acid (through supplementation or fortified foods) to prevent neural tube defects, and also with antifolate medication to prevent malaria. Recent evidence, based on trials with pregnant women, suggests that the effect of folate supplementation on the efficacy of the antifolate malaria treatments is dose dependent and that the doses of folic acid required to prevent neural tube defects will not decrease antifolate activity *(69)*. Futher, concerns have also been raised about the potential effect of folic acid on the health and morbidities (e.g. cancer, fertility) of different population groups, such as elderly people (i.e. aged above 65 years) and adult men *(70, 71)*. The generation of evidence on the evaluation of these concerns keeps expanding; however, the robust evidence available to date confirms that fortifying foods with folic acid does not pose risks of harm to the entire population exposed, owing to the modest and safe amounts of folic acid in fortified foods *(72)*.

Moreover, food-fortification programmes should not be considered replacements for adequate varied diets; hence, food-fortification efforts should coincide with initiatives for the improvement of diets, especially in population groups with more monotonous diets, and with other dietary counselling programmes in place. In order to achieve this form of coordination, policy-makers need to determine what multisectoral approaches represent the most appropriate allocation of resources, produce the greatest benefits, and optimize the results of the programme objectives.

REGULATORY CONSIDERATIONS

WHO and FAO have developed guidelines on fortification that describe key functions of regulatory monitoring and that identify criteria for evaluating monitoring systems that include the role of national authorities in establishing procedures, methodologies and reporting requirements to evaluate the fortification programme; allocation of responsibilities between the different actors; and a monitoring mechanism *(15)*.

Regulations that include the creation of a general legal framework subordinated by technical regulations could be placed at different levels of the programme and contain considerations about recommended fortificant compounds; food standards providing levels and chemical forms of nutrients in the fortified foods; quality and compliance assurance; surveillance systems; evaluation tools; and enforcement measures to assure compliance *(73)*.

Governments should also consider regulations about trade. Mandatory fortification may impose trade restrictions on imported products, because either they are unfortified or they have been fortified differently. On the other hand, nations with similar needs may benefit from a common agreement on fortification policy and regulation that could be regionally adopted *(15, 73)*. Further information can be found in Chapter 11 of the WHO/FAO *Guidelines on food fortification with micronutrients* *(15)*.

ETHICAL CONSIDERATIONS

Ethics refers to standards of what is right or wrong and fair or unfair, which can advise people on what to do and not do in terms of rights, obligations and benefits to society and individuals. Ethics is central to science, research, policy-making and implementation. Every field of human action, including public health nutrition, is subject to facing ethical challenges.

The delivery of micronutrients to populations suffering from micronutrient deficiencies must be informed by the right to health, and duty-bearers should take into account the corresponding human-rights instruments when designing the intervention and also during its implementation. Mass fortification of a staple food may raise ethical challenges about how to best benefit populations, avoid unintended harms and promote the principles of equity and social justice.

For example, the question of whether food fortification should be voluntary or mandatory can be approached as an ethically challenging question: "which of the two policy options is the one to produce greater benefit in the population, reduce micronutrient deficiencies and be feasible within available resources, policy frameworks and supply and demand?" Member States may need to consider several issues when deciding on the type of fortification (i.e. mandatory or voluntary) of maize flour and corn meal *(73)*. For instance, the configuration of the industry within the country must be examined. Mandatory fortification is more feasible when the existing landscape consists of large and formal factories. Evidence suggests that in this type of configuration, producers prefer mandatory fortification because it establishes "a level playing field for the staple whose branding and specific additional values may not be the deciding factor for the consumer to purchase it" *(74)*. Conversely, when the configuration of the industry within a country consists mainly of small, formal and informal businesses, mandatory fortification becomes more difficult and the option of voluntary fortification may be feasible, although not optimal as, for instance, low demand may discourage greater uptake from the industry and, thus, create a persistent scenario of weak supply. The decision of mandatory versus voluntary fortification must also observe international agreements of the World Trade Organization, so countries that export maize may not claim that a mandatory standard or regulation is a technical barrier to trade *(73)*. A sound, ethically informed decision must thus be grounded in the consideration of all relevant factors.

As discussed in the section "Equity, human rights and implementation considerations", the provision of folic acid through food fortification to prevent neural tube defects may pose concerns about the safety of this intervention for other groups in the population not affected by folic-acid deficiency or insufficiency, thus triggering ethical questions on how to avoid causing harm. Similar ethical questions have been raised in the case of iron. Because the amount of folic acid in fortified foods is usually well below the recommended daily allowance, mass food fortification with iron and folic acid is not likely to pose a risk to an entire population. Nevertheless, a public health programme on fortification of maize flour and corn meal that includes iron and folic acid as added nutrients must be carefully designed so that the levels of iron and folic acid are within appropriate limits. Technical expertise and proper training is, hence, a necessity for all staff involved in the food-fortification programme. Likewise, coordination is fundamental between different food-fortification initiatives taking place in the same setting, and between public health programmes distributing micronutrients to the same populations.

Another concern that may arise is the potential effects of iron-fortified maize flour or corn meal on individuals suffering from thalassaemia. Since resemblance between thalassaemia and iron deficiency can confuse the diagnosis of either disorder *(75)*, appropriate clinical procedures and services should be designed to identify and treat individuals suffering from this condition. Usually, these inviduals are advised to refrain from taking standard iron supplements, and have been treated with regular blood transfusions. Iron overload in individuals suffering from thalassaemia comes from both their diet and the blood transfusions. Therefore, these individuals take iron chelators to remove exccessive iron from the body. Public authorities in charge of a public health programme providing added iron through fortified foods should make sure that food items with added iron are properly labelled, so that both patients with thalassaemia and the clinical staff treating them are provided with all the information they require to enable them to adapt their diet to reduce iron absorption and plan for the quality care they need *(76)*.

On the other hand, some claims on the effect of folic acid on male fertility have also been raised *(77, 78)*. Such claims point to the potential beneficial effect of folic acid on increasing sperm concentrations. However, the evidence is still limited and sometimes contested; therefore, cautious use of such claims should be part of an ethically informed approach to fortification of maize flour and corn meal. A good regulatory framework should also address the issue of health claims for fortified foods.

Other concerns that may arise when adopting fortification of maize flour and corn meal with iron and folic acid is their relationship with corn–soy blends (CSBs), which are the main form of fortified blended foods. CSBs are designed to provide protein to prevent and address micronutrient deficiencies *(79)*. They are mixed with water and cooked as porridge and are often used in food aid throughout the world, especially in emergency situations and settings *(79)*. The composition[1] of CSB usually includes iron and folic acid *(80)*. Therefore, in settings where CSBs are distributed to affected populations, careful coordination must be observed if fortified maize flour and corn meal also become available or are distributed, in order to avoid any potential risk of excessive intake, which is, nevertheless, likely to be within tolerable levels. Further, a human-rights-based approach

[1] The following is the usual nutritional value for fortified blended foods, including CSB; as per information from the World Food Programme *(79)*, 100 g CSB product contains energy, minimum 380 kcal; protein, minimum 18%; fat, minimum 6%; 4 mg iron (ferrous fumarate) or 2.5 mg (iron-sodium EDTA), 3460 IU vitamin A, 5 mg zinc, 110 µg folic acid, 362 mg calcium, 2 µg vitamin B_{12}, 0.2 mg thiamine, 1.4 mg riboflavin, 8 mg niacin, 1 mg pyridoxine, 1.6 mg pantothenic acid, 90 mg vitamin C, 441.6 IU vitamin D, 8.3 mg vitamin E, 30 µg vitamin K and 140 mg potassium, in a corn maltodextrin carrier. Variable levels of micronutrients naturally present in maize and soy may lead to variable amount of micronutrients in finished products.

to development suggests that the involvement of potential beneficiaries in nutrition interventions in emergency settings has been associated with improvements in their nutritional status *(81)*. Sound implementation of this guideline, as informed by these considerations, can contribute to systematic detection of facilitators and barriers to achieving the programme goals, and to better design of any scaling-up strategy *(81)*.

MONITORING AND EVALUATION OF GUIDELINE IMPLEMENTATION

A plan for monitoring and evaluation with appropriate indicators, including equity-oriented indicators, is encouraged at all stages *(61)*. The impact of this guideline can be evaluated within countries (i.e. monitoring and evaluation of the programmes implemented at national or regional scale) and across countries (i.e. the adoption and adaptation of the guideline globally). The WHO Department of Nutrition for Health and Development, Evidence and Programme Guidance Unit, jointly with the US Centers for Disease Control and Prevention's International Micronutrient Malnutrition Prevention and Control Programme (IMMPaCt), and with input from international partners, has developed a generic logic model for micronutrient interventions in public health *(82)*, to depict the plausible relationships between inputs and expected SDGs by applying the micronutrient programme evaluation theory. A logic model for fortification of maize flour and corn meal with vitamins and minerals as a public health strategy has been developed *(22)* (See Annex 5).

Member States can adjust the model and use it in combination with appropriate indicators, for designing, implementing, monitoring and evaluating the successful escalation of nutrition actions in public health programmes. Additionally, the WHO/CDC *eCatalogue of indicators for micronutrient programmes* *(83)*, which utilizes a logic model, can also be customized for programmes of fortification of maize flour or corn meal with vitamins and minerals in public health. This eCatalogue is a user-friendly and non-comprehensive web resource for those actively engaged in providing technical assistance in monitoring, evaluation and surveillance of public health programmes implementing micronutrient interventions. It provides potential indicators, with standard definitions that can be selected, downloaded and adapted to a local programme context. Indicators for programmes for fortification of maize flour or corn meal may include:

- key stakeholders' support of a programme for large-scale fortification of maize flour;
- the total amount of maize flour produced for domestic human consumption;
- sufficient resources to carry out regulatory monitoring of large-scale fortification of flour;
- the number of large-scale maize-flour mills in the country;
- legislation in place for mandatory large-scale fortification of maize flour;
- technical standards for large-scale fortification of maize flour;
- guidelines in place for large-scale inspection and standards enforcement of flour mills;
- the quantity of premix procured in line with the quantity of flour milled and fortified;
- whether premix meets national regulations and requirements for large-scale fortification;
- whether tested premix samples meet specifications for fortification according to country standards;
- quality-assurance and quality-control procedures in place at large-scale maize-flour mills;

- whether samples of flour from mills meet fortification specifications according to country standards;
- certificate of conformity for imported fortified flour or other foods made with fortified flour;
- whether samples of imported fortified maize flour tested meet fortification specifications;
- comparison of the planned and actual flour samples collected at mills for regulatory monitoring;
- whether retail and market samples of flour and products made from flour meet fortification specifications;
- consumer recognition of the logo for fortified maize flour;
- whether the target population knows key messages on fortification of maize flour
- whether labelling of packaged fortified flour or flour products at retail outlets follows standards;
- the percentage of fortified maize flour available on the national market;
- household coverage of fortified maize flour or fortified maize-flour products;
- consumption of fortified maize-flour products over the past 7 days;
- the intake of nutrients added to fortified maize flour.

Since 1991, WHO has hosted the Micronutrients Database as part of the Vitamin and Mineral Nutrition Information System (VMNIS) *(84)*. Part of WHO's mandate is to assess the micronutrient status of populations, monitor and evaluate the impact of strategies for the prevention and control of micronutrient malnutrition, and track related trends over time. The Evidence and Programme Guidance Unit of the Department of Nutrition for Health and Development manages the VMNIS Micronutrient Database through a network of regional and country offices, and in close collaboration with national health authorities.

For evaluation at the global level, the WHO Department of Nutrition for Health and Development has developed a web-based Global targets tracking tool *(85)* that allows users to explore different scenarios to achieve the rates of progress required to meet the 2025 global nutrition targets, including target 2: 50% reduction of anaemia in women of reproductive age *(86)*, as well as a centralized platform for sharing information on nutrition actions in public health practice implemented around the world By sharing programmatic details, specific country adaptations and lessons learnt, this platform will provide examples of how guidelines are being translated into actions. The Global database on the Implementation of Nutrition Actions (GINA) *(87)* provides valuable information on the implementation of numerous nutrition policies and interventions. The use of GINA has grown steadily since its launch in November 2012.

GUIDELINE DEVELOPMENT PROCESS

This guideline was developed in accordance with the WHO evidence-informed guideline development procedures, as outlined in the *WHO handbook for guideline development* *(88)*.

ADVISORY GROUPS

A WHO steering committee (see Annex 6), led by the Department of Nutrition for Health and Development, was established with representatives from relevant WHO departments and programmes with an interest in the provision of scientific nutrition advice. The steering committee guided and provided overall supervision of this guideline development process. Two additional groups were formed: a guideline development group and an external review group.

The WHO guideline development group – micronutrients, was established for the biennium 2010–2011 (see Annex 7A). Its role was to advise WHO on the choice of critical outcomes for decision-making within the scope of this guideline. Another guideline group, the WHO guideline development group – nutrition actions, established for the biennium 2013–2014 (see Annex 7B), reviewed the evidence and held deliberations on the interpretation of the evidence, and the recommendations. WHO guideline development groups include experts from various WHO expert advisory panels *(89)* and those identified through open calls for specialists, taking into consideration a balanced gender mix, multiple disciplinary areas of expertise and representation from all WHO regions. Efforts were made to include content experts, methodologists, representatives of potential stakeholders (such as managers and other health professionals involved in the health-care process) and technical staff from WHO and ministries of health from Member States. Representatives of commercial organizations may not be members of a WHO guideline group. External technical experts in food fortification and review authors participated only in the open meetings and recused themselves during the deliberations (see Annex 8).

The final draft guideline was peer-reviewed by six content experts, who provided technical feedback (see Annex 9). These peer-reviewers were identified through various expert panels within and outside WHO.

External peer-reviewers are not involved in the guideline development process *(88)* and are only asked to provide comments on the final draft guideline. Their role is to identify any errors or missing data and to comment on clarity, setting-specific issues and implications for implementation – not to change the recommendations formulated by the guideline development group. Reviews from such individuals or organizations on a draft guideline may be helpful in anticipating and dealing with controversy, improving the clarity of the final document and promoting engagement with all stakeholders. Peer-reviewers acting in their individual capacity need to complete a declaration-of-interests form, while reviewers representing organizations do not need to complete this form.

The names and affiliations of peer-reviewers are provided here as an acknowledgement and by no means indicate their endorsement of the recommendations in this guideline. The acknowledgement of the peer-reviewers does not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

This document is a WHO guideline and, after executive clearance, represents the decisions, policy or views of WHO.

SCOPE OF THE GUIDELINE, EVIDENCE APPRAISAL AND DECISION-MAKING

An initial set of questions (and the components of the questions) to be addressed in the guideline was the critical starting point for formulating the recommendations. The questions were drafted by technical staff at the Evidence and Programme Guidance Unit, Department of Nutrition for Health and Development, based on the policy and programme guidance needs of Member States and their partners. The population, intervention, control, outcomes (PICO) format was used (see Annex 2). The questions were discussed and reviewed by the WHO steering committee and the guideline development group – micronutrients 2010–2011, and were modified as needed. The guideline group scored the relative importance of each outcome from 1 to 9 (where 7–9 indicated that the outcome was critical for a decision, 4–6 indicated that it was important and 1–3 indicated that it was not important). The final key questions on this intervention, along with the outcomes that were identified as critical for decision-making, are listed in PICO format in Annex 2.

In April 2013, WHO, in collaboration with the Sackler Institute for Nutrition Science and the Food Fortification Initiative, convened a non-normative dialogue in New York, USA, on "Technical considerations for fortification of maize flour and corn meal in public health", to provide input to the guideline development process and discuss technical considerations of the fortification processes for maize flour and corn meal. The technical consultation brought together about 60 technical experts, researchers, producers, policy-makers, programme implementers, the private sector and civil society, to collate opinions on the technology, feasibility, economic impact and legislation related to fortification of maize flour and corn meal for the improvement of micronutrient status. The results of this meeting and the aspects covered during the meeting, the discussions and group conclusions were published in a volume of the *Annals of the New York Academy of Sciences* *(6)*.

To inform this guideline, WHO commissioned systematic reviews of the evidence, using the Cochrane methodology for systematic reviews of interventions *(30)*.[1] For identification of unpublished studies or studies still in progress, a standard procedure was followed, to contact more than 10 international organizations working on micronutrient interventions. In addition, the International Clinical Trials Registry Platform (ICTRP) *(90)*, hosted at WHO, was systematically searched for any trials still in progress. No language restrictions were applied in the search. Evidence summaries were prepared according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, to assess the overall quality of the evidence, by Dr Maria Nieves Garcia-Casal and Dr Juan Pablo Peña-Rosas *(44, 45)*. GRADE considers: the study design; the limitations of the studies in terms of their conduct and analysis; the consistency of the results across the available studies; the directness (or applicability and external validity) of the evidence with respect to the populations, interventions and settings where the proposed intervention may be used; and the precision of the summary estimate of the effect.

Both the systematic reviews and the GRADE summary of findings tables for each of the critical outcomes were used for drafting this guideline. The draft recommendations were discussed by the WHO steering committee and the guideline development group – nutrition actions, at a consultation, held on 3–6 November 2014 in Cancun, Mexico, where the guideline development group members received and filled out an online consensus-building form prepared using survey software (QuestionPro Inc.,

[1] As part of the Cochrane pre-publication editorial process, reviews are commented on by external peers (an editor and two referees external to the editorial team) and the group's statistical adviser (http://www.cochrane.org/what-is-cochrane-evidence). The *Cochrane handbook for systematic reviews of interventions* *(30)* describes in detail the process of preparing and maintaining Cochrane systematic reviews on the effects of health-care interventions.

San Francisco, USA). On this form, members could indicate their positions on the recommendation, and the judgements on harms and benefits. They also noted the strength of the recommendation, taking into account: (i) the desirable and undesirable effects of the intervention; (ii) the quality of the available evidence; (iii) values and preferences related to the intervention in different settings; and (iv) the cost and feasibility of the intervention in different settings (see Annex 4). These aspects were discussed openly in the meeting, followed by notation on individual forms of each member's primary considerations in these areas. Subsequent deliberations among the members of the guideline development group were of private character. The WHO Secretariat (see Annex 10) gathered and disclosed a summary of the results to the guideline development group. If there was no unanimous consensus (primary decision rule), more time was given for deliberations and a second round of online balloting took place. If no unanimous agreement was reached, a two-thirds vote of the guideline development group was required for approval of the proposed recommendations (secondary decision rule). Divergent opinions could be recorded in the guideline. The results from voting forms are kept on file by WHO for 5 years. Although there was no unanimous consensus, more than 80% of the voting members of the guideline development group decided that the recommendations were conditional. WHO staff present at the meeting, as well as other external technical experts (see Annex 8) involved in the collection and grading of the evidence, did not participate in the consensus-building process. The chairs had expertise in managing group processes and interpreting evidence and were nominated at the opening of each consultation. The guideline development group approved their nomination and appointment. Members of the WHO Secretariat were available at all times, to help guide the overall meeting process, but did not vote and did not have veto power.

MANAGEMENT OF COMPETING INTERESTS

According to the rules in the WHO *Basic documents* (*91*) and the processes recommended in the *WHO handbook for guideline development* (*88*), all experts participating in WHO meetings must declare any interest relevant to the meeting, prior to their participation. The responsible technical officer and the relevant departments reviewed the declarations-of-interest statements for all guideline development group members, before finalization of the group composition and invitation to attend a meeting of the guideline development group. All members of the guideline development group, and participants of the guideline development meetings, submitted a declaration-of-interests form, along with their curriculum vitae, before each meeting. Participants of these meetings participated in their individual capacity and not as institutional representatives. In addition, they verbally declared potential conflicts of interest at the beginning of each meeting. The procedures for management of competing interests strictly followed the WHO *guidelines for declaration of interests (WHO experts) (92)*. A public notice was published in the events sections of the WHO Nutrition website one month prior to the meeting in Mexico. The announcement included publication of the biographies of all members of WHO guideline development group – nutrition actions 2013–2014 able to participate in the meeting, together with a scope and purpose of the guideline development group meeting, describing the background and objectives of the meeting for which these individuals were being considered. The management of the perceived or real conflicts of interest declared by the members of the guideline development group that are relevant to this guideline is summarized next.[1]

[1] A conflict-of-interest analysis must be performed whenever WHO relies on the independent advice of an expert in order to take a decision or to provide recommendations to Member States or other stakeholders. The term "conflict of interest" means any interest declared by an expert that may affect or be reasonably perceived to affect the expert's objectivity and independence in providing advice to WHO. WHO's conflict-of-interest rules are designed to avoid potentially compromising situations that could undermine or otherwise affect the work of the expert, the committee or activity in which the expert is involved, or WHO as a whole. Consequently, the scope of the inquiry is any interest that could reasonably be perceived to affect the functions that the expert is performing.

Dr Hector Bourges Rodriquez declared being chair of the Board of Directors of the Dannon Institute in Mexico (DIM), a non-profit organization promoting research and dissemination of scientific knowledge in nutrition, and receiving funds as chair honorarium from DIM. DIM is funded by Dannon Mexico, a food company and subsidiary of The Dannon Company, Inc. The main products of the Dannon group worldwide are dairy products, bottled water and baby products. Because Dannon does not manufacture products or make claims related to the fortification of maize flour and corn meal, it was agreed that he could participate fully in the deliberations and decision-making on this guideline.

Dr Luz Maria De-Regil works for an international nongovernmental agency, the Micronutrient Initiative, which supports food-fortification programmes. She also co-authored several systematic reviews and articles related to food fortification, which were discussed in the guideline development group meeting. She participated in the deliberations of the evidence used to inform the recommendations on the fortification of maize flour and corn meal but recused herself from voting on this guideline.

Dr Lynette Neufeld declared that her employer, the Global Alliance for Improved Nutrition supports food-fortification programmes and has led research and authored several publications in the area of food fortification. She participated in the deliberations of the evidence used to inform the recommendations on the fortification of maize flour and corn meal but recused herself from voting on this guideline.

Ms Carol Tom declared being employed by the United States Agency for International Development (USAID)/A2Z on a project related to child blindness and micronutrients, and being a consultant (technical and other adviser) for the East, Central and Southern African Health Community (ECSA-HC) on food fortification. It was felt that her employment did not present any conflict of interest for the meeting, as USAID is a US government agency and ECSA is a regional association of ministries of health, and it was agreed that she could participate fully in the deliberations and decision-making on this guideline.

External experts also declared their interest but did not participate in the deliberations or decision-making process.

PLANS FOR UPDATING THE GUIDELINE

The WHO Secretariat will continue to follow research developments in the area of fortification of maize flour and corn meal, particularly for areas in which the evidence was limited and the quality of evidence was found to be very low. If the guideline merits an update, or if there are concerns about the validity of the guideline, the Department of Nutrition for Health and Development will coordinate the guideline update, following the formal procedures of the *WHO handbook for guideline development* *(88)*. As the guideline nears the 10-year review period, the Department of Nutrition for Health and Development at the WHO headquarters in Geneva, Switzerland, along with its internal partners, will be responsible for conducting a search for appropriate new evidence.

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ANNEX 1

ANNEX 1. GRADE "SUMMARY OF FINDINGS" TABLES FOR META-ANALYSIS OF INCLUDED STUDIES WITH MAIZE FLOUR

A. MAIZE FLOUR OR MAIZE-FLOUR PRODUCTS FORTIFIED WITH IRON PLUS OTHER VITAMINS AND MINERALS VERSUS UNFORTIFIED MAIZE FLOUR OR MAIZE-FLOUR PRODUCTS (NOT CONTAINING IRON OR ANY OTHER VITAMINS OR MINERALS)

Patient or population: general population (including children above 2 years of age and adults)
Settings: all settings
Intervention: maize flour or maize-flour products fortified with iron plus other vitamins and minerals
Comparison: unfortified maize flour or maize-flour products (not containing iron or any other vitamins or minerals)

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
Anaemia in children (defined as haemoglobin below 110 g/L or 115 g/L, adjusted for altitude as appropriate)	RR 0.89 (0.57 to 1.39)	1359 (2 RCTs)	⊕⊖⊖⊖ VERY LOW[1,2,3]	
Iron deficiency in children (as defined by trialists, based on a biomarker of iron status)	RR 0.53 (0.40 to 0.69)	1277 (2 RCTs)	⊕⊖⊖⊖ VERY LOW[1,3]	
Haemoglobin concentration in children (g/L)	MD 0.42 higher (2.47 lower to 3.31 higher)	1325 (2 RCTs)	⊕⊖⊖⊖ VERY LOW[1,2,3]	
Ferritin in children (µg/L)	MD 0 (0.27 lower to 0.27 higher)	758 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1,3]	
Iron-deficiency anaemia in children (as defined by trialists)	RR 1.04 (0.58 to 1.88)	515 (1 RCT)	⊕⊖⊖⊖ VERY LOW[2,4]	
Any adverse side-effects (including constipation, nausea, vomiting, heartburn or diarrhoea in any population, as measured by trialists)	Not reported	(0 RCTs)	Not estimable	

CI: confidence interval; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio.
* **The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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 with high risk of bias, for randomization method, allocation concealment and unclear risk of bias for blinding (Villalpando, personal communication).
[2] Wide confidence interval crossing the line of no effect.
[3] High heterogeneity from one study (Villalpando, personal communication).
[4] Only one study deemed at low risk of bias contributed data to this outcome *(31).*

B. MAIZE FLOUR OR MAIZE-FLOUR PRODUCTS FORTIFIED WITH FOLIC ACID ALONE COMPARED TO NO INTERVENTION FOR POPULATION HEALTH OUTCOMES

Patient or population: general population (including children above 2 years of age and adults)
Settings: all settings
Intervention: Maize -flour or maize-flour products fortified with folic acid alone
Comparison: no intervention

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
Erythrocyte folate concentrations (nmol/L) in pregnant women	MD 239.07 higher (226.43 to 251.71 higher)	38 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1,2]	
Serum/plasma folate concentrations (nmol/L) in pregnant women	MD 14.98 (14.67 to 15.29 higher)	38 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1,2]	
Neural tube defects (e.g. anencephaly, spina bifida or meningocele)	Not reported	0	Not estimable	None of the included studies reported on this outcome

CI: confidence interval; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio.
[*] **The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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] Randomization was not clear; allocation concealment and blinding were not reported in the only study *(40)*.
[2] This is a study in pregnant women attending antenatal care.
[3] Few patients and few events in the only study included. Short period of study (10–50 days with average 26 days of intervention) *(40)*.

C. MAIZE FLOUR OR MAIZE-FLOUR PRODUCTS FORTIFIED WITH FOLIC ACID PLUS OTHER VITAMINS AND MINERALS VERSUS UNFORTIFIED MAIZE FLOURS OR MAIZE-FLOUR PRODUCTS (NOT CONTAINING FOLIC ACID OR ANY OTHER VITAMINS OR MINERALS)

Patient or population: general population (including children above 2 years of age and adults)
Settings: all settings
Intervention: maize flour or maize-flour products fortified with folic acid plus other vitamins and minerals
Comparison: unfortified maize flours or maize flour products (not containing folic acid or any other vitamins or minerals)

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
Erythrocyte folate concentrations (nmol/L) in non-pregnant women	−61.80 (−152.98 to 29.38)	35 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1,2]	
Serum/plasma folate concentrations (nmol/L) in non-pregnant women	RR 0 (0.00 to 0.00)	35 (1 RCT)	⊕⊖⊖⊖ VERY LOW[1,2,3]	The mean plasma folate was 20 nmol/L in the group receiving unfortified maize meal and 22 nmol/L in participants receiving the fortified maize meal
Neural tube defects (e.g. anencephaly, spina bifida or meningocele)	Not reported	0	Not estimable	None of the included studies reported on this outcome

CI: confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio.
* **The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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] Randomization was not clear; allocation concealment and blinding were not reported *(41)*.
[2] Few patients and few events *(41)*.
[3] Serious inconsistency about the reference values and the units of concentration used for reporting plasma folate concentrations *(41)*.

ANNEX 2. QUESTIONS IN POPULATION, INTERVENTION, CONTROL, OUTCOMES (PICO) FORMAT

EFFECTS AND SAFETY OF FORTIFICATION OF CORN/MAIZE FLOUR WITH MICRONUTRIENTS AS A PUBLIC HEALTH INTERVENTION

Could mass fortification of maize flour with iron improve health outcomes? If so, what fortificant(s) should be used and in what amounts?

POPULATION:	**General population** Subpopulations: *Critical* • By group: young children (24–59 months), school-age children (5–12 years), pregnant women, women of reproductive age (15–49 years) • By range of maize-flour consumption patterns: <75 g/day, 75–149 g/day, 150–300 g/day • By overall intake of dietary enhancers or inhibitors • By malaria transmission (four categories: no transmission or elimination achieved, susceptibility to epidemic malaria, year-round transmission with marked seasonal fluctuations, year-round transmission; with consideration of *Plasmodium falciparum* and/or *Plasmodium vivax*) • By the population prevalence of anaemia: countries with a public health problem (5–19.9%, mild; 20–39.9%, moderate, ≥40%, severe) versus no public health problem (<5%)
INTERVENTION:	Maize flour fortified with iron alone Maize flour fortified with iron plus other micronutrients Subgroup analyses *Critical* • By amount of iron added to the flour, and by the maize-flour-consumption groups
CONTROL:	Same maize flour without added iron, or no intervention
OUTCOMES:	*Critical* • Iron status (as defined by trialists) • Iron deficiency • Iron deficiency anaemia • Anaemia
SETTING:	All countries

Could mass fortification of maize flour with folic acid improve health outcomes? If so, what amounts should be used?

POPULATION:	**General population** Subpopulations: *Critical* • By group: young children (24–59 months), school-age children and adolescents (5–14 years), women of reproductive age (15–49 years), pregnant women, adult men (>19 years), older adults (≥50 years) • By range of patterns of maize-flour consumption: <75 g/day, 75–149 g/day, 150–300 g/day • By populations receiving supplements containing folic acid versus no folic-acid supplementation
INTERVENTION:	Maize flour fortified with folic acid alone Maize flour fortified with folic acid plus iron Maize flour fortified with folic acid plus other micronutrients Subgroup analyses *Critical* • By amount of folic acid added to the flour, and by the maize-flour-consumption groups
CONTROL:	Same maize flour without added folic acid, or no intervention
OUTCOMES:	*Critical* • Neural tube defects • Other congenital anomalies • Folate status (as measured by serum or red cell folate) in women of reproductive age and older adults (≥50 years)
SETTING:	All countries

Could mass fortification of maize flour with zinc improve health outcomes? If so, what zinc fortificant(s) should be used and in what amounts?

POPULATION:	**General population** Subpopulations: *Critical* • By group: young children (24–59 months), school-age children and adolescents (5–14 years), women of reproductive age (15–49 years), pregnant and lactating women, older adults (≥50 years) • By range of maize-flour-consumption patterns: <75 g/day, 75–149 g/day, 150–300 g/day • By risk of zinc deficiency in the population (as defined by inadequate zinc intakes or high prevalence of zinc deficiency)
INTERVENTION:	Maize flour fortified with zinc alone Maize flour fortified with zinc plus other micronutrients Subgroup analyses *Critical* • By amount of zinc added to the flour, and by the maize-flour-consumption groups
CONTROL:	Same maize flour without added zinc, or no intervention
OUTCOMES:	*Critical* • Zinc deficiency • Zinc status (as measured by plasma zinc) • Growth (as defined by stunting, wasting or underweight)
SETTING:	All countries

ANNEX 3. SYSTEMATIC REVIEWS AND AUTHOR TEAMS

SYSTEMATIC REVIEW 1

FORTIFICATION OF MAIZE FLOUR WITH IRON FOR PREVENTING ANAEMIA AND IRON DEFICIENCY IN POPULATIONS

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Note: We report in this document a summary of the results from a recent update of a systematic review (October 2016) first published as a protocol in the Cochrane Database of Systematic Reviews in 2012 *(22)*. The systematic review has been updated and is undergoing editorial process with the Cochrane Public Health Group. Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Database of Systematic Reviews should be consulted for the most recent version of the full review. A pre-publication summary can be obtained by contacting the Department of Nutrition for Health and Development, World Health Organization, Geneva, Switzerland (nutrition@who.int).

SYSTEMATIC REVIEW 2

EFFECT OF IRON-FORTIFIED FOODS ON HEMATOLOGIC AND BIOLOGICAL OUTCOMES: SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS (23)

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SYSTEMATIC REVIEW 3

GLOBAL BIRTH PREVALENCE OF SPINA BIFIDA BY FOLIC ACID FORTIFICATION STATUS: A SYSTEMATIC REVIEW AND META-ANALYSIS (24)

Callie AM Atta[1], Kirsten M Fiest[1,2,4], Alexandra D Frolkis4, Nathalie Jette[1,2,4], Tamara Pringsheim[1,3,4], Christine St Germaine-Smith[1], Thilinie Rajapakse[3], Gilaad G Kaplan[4], Amy Metcalfe[5]

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SYSTEMATIC REVIEW 4

FORTIFICATION OF WHEAT AND MAIZE FLOUR WITH FOLIC ACID FOR POPULATION HEALTH OUTCOMES

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Note: We report in this document a summary of the results from a recent update of a systematic review (October 2016) first published as a protocol in the Cochrane Database of Systematic Reviews in 2016 *(25)*. The systematic review has been updated and is undergoing final edits for submission to the Cochrane Public Health Group. Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Database of Systematic Reviews should be consulted for the most recent version of the full review. A pre-publication summary can be obtained by contacting the Department of Nutrition for Health and Development, World Health Organization, Geneva, Switzerland (nutrition@who.int).

SYSTEMATIC REVIEW 5

FORTIFICATION OF STAPLE FOODS WITH VITAMIN A FOR PREVENTING VITAMIN A DEFICIENCY

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SYSTEMATIC REVIEW 6

FORTIFICATION OF STAPLE FOODS WITH ZINC FOR IMPROVING ZINC STATUS AND OTHER HEALTH OUTCOMES IN THE GENERAL POPULATION (27)

Dheeraj Shah[1], Harshpal S Sachdev[2], Tarun Gera[3], Luz Maria De-Regil[4], Juan Pablo Peña-Rosas[5]

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SYSTEMATIC REVIEW 7

FOOD FORTIFICATION WITH CALCIUM AND VITAMIN D: IMPACT ON HEALTH OUTCOMES

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Note: we report in this document a summary of the results from a recent update of a systematic review (September 2016) first published as a protocol in the Cochrane Database of Systematic Reviews in 2012 *(28)*. The systematic review has been finalized and is undergoing editorial process with the Cochrane Public Health Group. Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Database of Systematic Reviews should be consulted for the most recent version of the full review. A pre-publication summary can be obtained by contacting the Department of Nutrition for Health and Development, World Health Organization, Geneva, Switzerland (nutrition@who.int).

SYSTEMATIC REVIEW 8

MICRONUTRIENT FORTIFICATION OF FOOD AND ITS IMPACT ON WOMAN AND CHILD HEALTH: A SYSTEMATIC REVIEW (29)

Jai K Das[1], Rehana A Salam[1], Rohail Kumar[1], Zulfiqar A Bhutta[1]

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ADDITIONAL COMMISSIONED REVIEWS ON VARIOUS ASPECTS OF FORTIFICATION OF MAIZE FLOUR

These narrative reviews are available in a special supplement that includes all commissioned reviews that summarize other aspects related to fortification of maize flour and corn meal. They were useful for consideration of the guideline development group in the guideline development process. This issue, "*Technical considerations for maize flour and corn meal fortification in public health*", was published in Ann N Y Acad Sci. 2014;1312:1–112, edited by Juan Pablo Peña-Rosas, Maria Nieves Garcia-Casal and Helena Pachón.

TECHNICAL CONSIDERATIONS FOR MAIZE FLOUR AND CORN MEAL FORTIFICATION IN PUBLIC HEALTH: CONSULTATION RATIONALE AND SUMMARY *(6)*

Juan Pablo Peña-Rosas, Maria Nieves Garcia-Casal, Helena Pachón, Mireille Seneclauze Mclean, Mandana Arabi

FORTIFICATION OF CORN MASA FLOUR WITH FOLIC ACID IN THE UNITED STATES: AN OVERVIEW OF THE EVIDENCE *(17)*

Heather C Hamner, Sarah C Tinker

STABILITY OF KEY MICRONUTRIENTS ADDED TO FORTIFIED MAIZE FLOURS AND CORN MEAL *(46)*

Michael L Dunn, Vijaya Jain, Barbara P Klein

MAIZE FLOUR FORTIFICATION IN AFRICA: MARKETS, FEASIBILITY, COVERAGE, AND COSTS *(74)*

John L Fiedler, Ronald Afidra, Gladys Mugambi, John Tehinse, Gladys Kabaghe, Rodah Zulu, Keith Lividini, Marc-Francois Smitz, Vincent Jallier, Christophe Guyondet, Odilia Bermudez

EQUITY IN ACCESS TO FORTIFIED MAIZE FLOUR AND CORN MEAL *(64)*

Gerardo Zamora, Luz Maria De-Regil

BIOAVAILABILITY OF IRON, ZINC, FOLIC ACID, AND VITAMIN A FROM FORTIFIED MAIZE *(47)*

Diego Moretti, Ralf Biebinger, Maaike J Bruins, Birgit Hoeft, Klaus Kraemer

PROCESSING MAIZE FLOUR AND CORN MEAL FOOD PRODUCTS *(7)*

Jeffrey A Gwirtz, Maria Nieves Garcia-Casal

MODEL FOR ESTIMATING NUTRIENT ADDITION CONTENTS TO STAPLE FOODS FORTIFIED SIMULTANEOUSLY: MEXICO AND KAMPALA DATA *(48)*

Monica Guamuch, Omar Dary, Zo Rambelson, Vanessa de la Cruz, Salvador Villalpando, Carol Tom, Ronald Afidra, Phillip Makhumula

LEGISLATIVE FRAMEWORKS FOR CORN FLOUR AND MAIZE MEAL FORTIFICATION *(73)*

Phillip Makhumula, Omar Dary, Monica Guamuch, Carol Tom, Ronald Afidra, Zo Rambeloson

GLOBAL MAIZE PRODUCTION, UTILIZATION, AND CONSUMPTION *(4)*

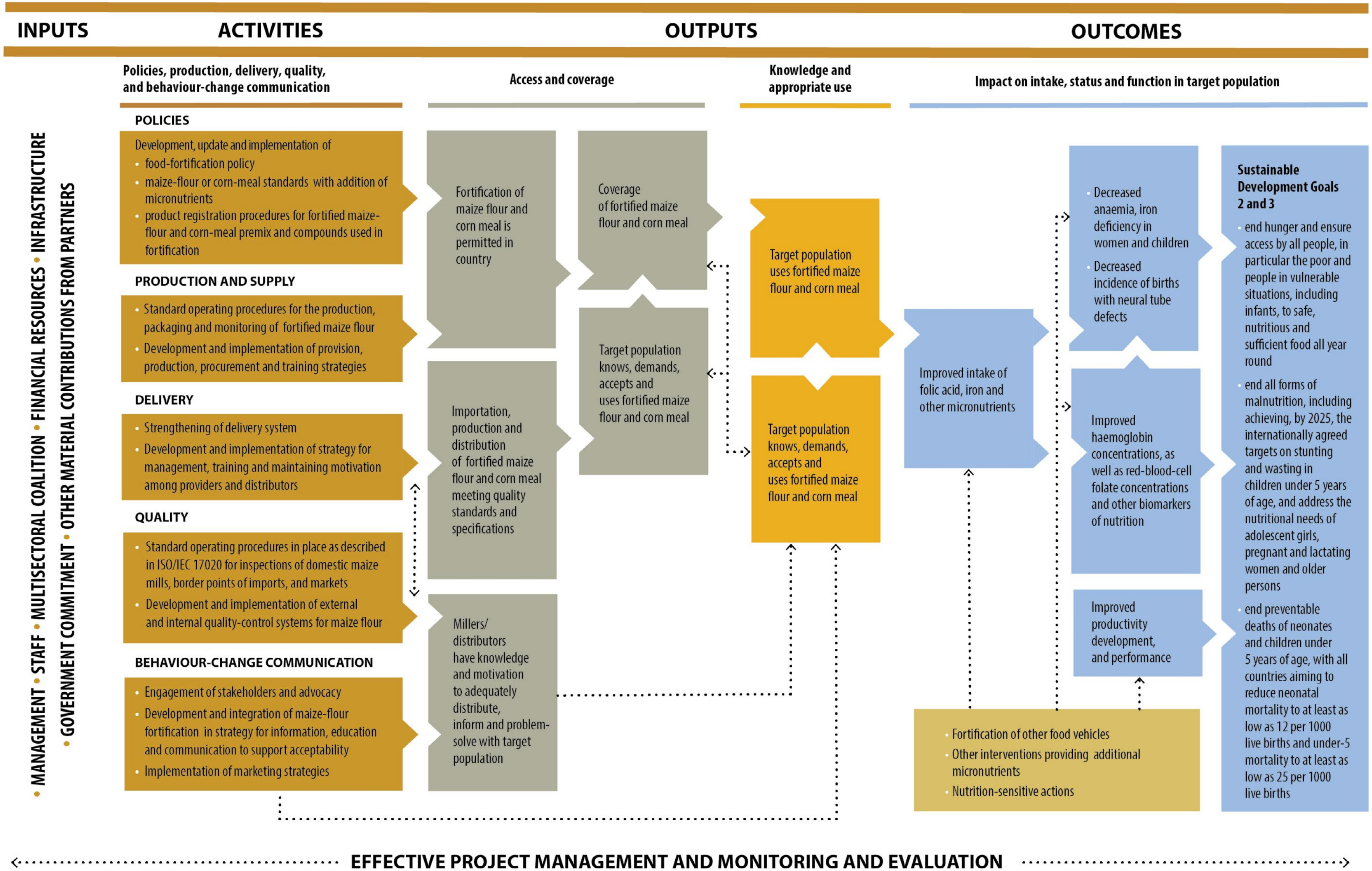
Peter Ranum, Juan Pablo Peña-Rosas, Maria Nieves Garcia-Casal

ANNEX 4. SUMMARY OF THE CONSIDERATIONS OF THE MEMBERS OF THE GUIDELINE DEVELOPMENT GROUP – NUTRITION ACTIONS FOR DETERMINING THE DIRECTION AND THE STRENGTH OF THE RECOMMENDATIONS

QUALITY OF EVIDENCE:	• The quality of direct evidence overall was very low, as most of the studies are pre and post studies without control groups. There are very few randomized controlled trials (RCTs), and the few studies there are have assessed a fortified flour with premix of various micronutrients, as this is the way it has been done in practice. The experience from other food vehicles such as wheat flour can be extrapolated with care to other cereal such as maize, with special considerations. • Few studies on iron; indirect evidence for folic acid; no studies on zinc. Maize flour may be a staple only in some countries but not all countries. In these countries, fortification of this food vehicle may help in filling the dietary gap of some micronutrients, as needed. • No RCTs for individual micronutrients. For multiple micronutrients, two RCTs show only reduction in iron deficiency and the remaining are observational studies. • There is no evidence from the systematic review in response to iron status, iron deficiency or iron deficiency anaemia. Only a few studies at the country level show the public health impact of fortification of maize and wheat flour: a significant difference in reduction of neural tube defects and increase in haemoglobin. However, there was no significant difference in improvement of iron status. • Findings indicate significant losses in B vitamins (B_1, B_2, B_3, B_6, B_9 and B_{12}) during manufacturing, distribution and cooking. Vitamins A and D_3 are recent additions to fortification premixes for maize and have not been well studied. In terms of minerals, iron, zinc and calcium are low in maize and maize/corn products, with small losses occurring during milling.
VALUES AND PREFERENCES:	• Values about the importance of iron deficiency at the population level vary among settings. Also values and preferences vary about whether a general population strategy is better, or a more targeted strategy. • The main products obtained from dry milling of corn are meal, flour, precooked meal and dry nixtamalized or hominy flour, differing essentially in particle size. • Benefits are uncertain and small, if any. Costs are involved. Will the public sector be willing to absorb the costs? • It is essential to consider consumer acceptability and consumers should be made aware of the potential benefits and costs. It is important that the fortified version does not change the characteristics of the flour or the products made with the maize flour. • In many settings, maize kernels undergo a pre-processing step before milling. This process is called nixtamalization and refers to cooking maize kernels in a dilute alkali solution (traditionally, limewater, ash or lye). The type of flour needs to be considered, to ensure that the fortified flour is efficacious and there is no change in colour or taste. • Fortification of maize flour and corn meal in countries where these are staples and are widely distributed and consumed could potentially improve the nutritional status of a large proportion of the population, and guidelines for its use in public health are required.

TRADE-OFF BETWEEN BENEFITS AND HARMS:	• No adverse effects were reported in the studies presented. • Apparent harms are related to the cost of fortification and the provision of micronutrients to those who do not need them. • The potential benefits of preventing anaemia and neural tube defects are considered to be greater than any potential harms, for which there is no evidence. • Fortification of maize flour and corn meal must be designed in the context of fortification (both voluntary and mandatory) of other food vehicles (i.e. salt, wheat flour, rice), in order to improve efficiencies while assuring safety.
COSTS AND FEASIBILITY:	• The presumed benefits are worth the cost, considering that, in general, fortification of maize flour is a low-cost intervention. • The long-term sustainability of fortification programmes is assured when consumers are willing and able to bear the additional cost of fortified foods. • In contexts of extreme and extended poverty and lack of opportunities, guaranteeing access to fortified maize flour requires addressing the factors that allow for the continuation of exclusion and poverty, which are socially determined and thus modifiable. • Although there is less experience with fortification of maize flour than of wheat flour, industrial fortification of maize flour with at least iron has been practised for many years in several countries in the Americas and Africa. • By 2014, voluntary fortification had been introduced in Ghana, Malawi, and Mauritania, whereas Brazil, Costa Rica, El Salvador, Kenya, Mexico, Nigeria, Rwanda, South Africa, the United Republic of Tanzania, Uganda, the United States of America and Venezuela have mandatory fortification. Up to 2016, more countries have enacted laws or are already allowing voluntary fortification of maize flour or corn meal. • The capacity of industrial technology varies in different parts of globe. Maize consumption is not global and maize products are staple only in some parts of the world, mainly in Africa, and Central and South America. • Fortification could be feasible in settings where maize is a staple. The way in which corn is processed and consumed varies from country to country. • There are several processes applied to maize before and after milling. These processes affect particle size, nutrient losses and contents, which are relevant in the fortification process. Milling degermed maize involves different processes than those for obtaining precooked refined maize flour, dehydrated nixtamalized flour, fermented maize flour and other products.

ANNEX 5. LOGIC MODEL FOR ORTIFICATION OF MAIZE FLOUR AND CORN MEAL WITH VITAMINS AND MINERALS IN PUBLIC HEALTH *(22)*



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ANNEX 7. WHO GUIDELINE DEVELOPMENT GROUPS

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