GUIDELINE:
FORTIFICATION OF WHEAT FLOUR WITH VITAMINS AND MINERALS AS A PUBLIC HEALTH STRATEGY
# CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acknowledgements</td>
<td>v</td>
</tr>
<tr>
<td>Financial support</td>
<td>v</td>
</tr>
<tr>
<td>Executive summary</td>
<td>1</td>
</tr>
<tr>
<td>Purpose of the guideline</td>
<td>1</td>
</tr>
<tr>
<td>Guideline development methodology</td>
<td>2</td>
</tr>
<tr>
<td>Summary of the evidence</td>
<td>3</td>
</tr>
<tr>
<td>Recommendations</td>
<td>4</td>
</tr>
<tr>
<td>Key remarks</td>
<td>4</td>
</tr>
<tr>
<td>Evidence gaps</td>
<td>7</td>
</tr>
<tr>
<td>Plans for updating the guideline</td>
<td>7</td>
</tr>
<tr>
<td>Scope and purpose</td>
<td>8</td>
</tr>
<tr>
<td>Background</td>
<td>8</td>
</tr>
<tr>
<td>Objectives</td>
<td>12</td>
</tr>
<tr>
<td>Summary of the evidence</td>
<td>13</td>
</tr>
<tr>
<td>Wheat flour fortification and population micronutrient status and health-related outcomes</td>
<td>13</td>
</tr>
<tr>
<td>Recommendations</td>
<td>17</td>
</tr>
<tr>
<td>Remarks</td>
<td>17</td>
</tr>
<tr>
<td>Summary of the considerations for determining the direction and strength of the recommendations</td>
<td>20</td>
</tr>
<tr>
<td>Evidence gaps</td>
<td>21</td>
</tr>
<tr>
<td>Dissemination, implementation and ethical considerations</td>
<td>22</td>
</tr>
<tr>
<td>Dissemination</td>
<td>22</td>
</tr>
<tr>
<td>Equity, human rights and implementation considerations</td>
<td>23</td>
</tr>
<tr>
<td>Regulatory considerations</td>
<td>25</td>
</tr>
<tr>
<td>Ethical considerations</td>
<td>26</td>
</tr>
<tr>
<td>Monitoring and evaluation of guideline implementation</td>
<td>27</td>
</tr>
<tr>
<td>Guideline development process</td>
<td>28</td>
</tr>
<tr>
<td>Scope of the guideline, evidence appraisal and decision-making</td>
<td>29</td>
</tr>
<tr>
<td>Management of competing interests</td>
<td>31</td>
</tr>
<tr>
<td>Plans for updating the guideline</td>
<td>32</td>
</tr>
<tr>
<td>References</td>
<td>33</td>
</tr>
<tr>
<td>Annex</td>
<td>Title</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------------------------------</td>
</tr>
<tr>
<td>1.</td>
<td>GRADE summary of findings tables</td>
</tr>
<tr>
<td>2.</td>
<td>Questions in population, intervention, control, outcomes (PICO) format</td>
</tr>
<tr>
<td>3.</td>
<td>Summary of the considerations of the members of the guideline development group – nutrition actions 2013-2014 for determining the strength of the recommendations</td>
</tr>
<tr>
<td>4.</td>
<td>Logic model for fortification of maize flour and corn meal with vitamins and minerals in public health</td>
</tr>
<tr>
<td>5.</td>
<td>WHO steering committee for food fortification</td>
</tr>
<tr>
<td>6.</td>
<td>WHO guideline development groups</td>
</tr>
<tr>
<td></td>
<td>A. Guideline development group – micronutrients 2010–2011</td>
</tr>
<tr>
<td></td>
<td>B. WHO guideline development group – nutrition actions 2013–2014</td>
</tr>
<tr>
<td></td>
<td>(attended the 2020 meeting)</td>
</tr>
<tr>
<td>7.</td>
<td>Systematic reviews teams</td>
</tr>
<tr>
<td>8.</td>
<td>Peer-reviewers</td>
</tr>
<tr>
<td>9.</td>
<td>WHO Secretariat</td>
</tr>
<tr>
<td></td>
<td>WHO regional offices</td>
</tr>
</tbody>
</table>
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Donors did 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.
GUIDELINE:
FORTIFICATION OF WHEAT FLOUR WITH VITAMINS AND MINERALS
AS A PUBLIC HEALTH STRATEGY

EXECUTIVE SUMMARY

Anaemia and iron, folate, zinc, vitamin A and iodine deficiencies are the most studied and more prevalent nutritional problems, constituting serious public health problems that particularly affect young children and women. The most common causes of micronutrient deficiencies are related to inadequate intakes, utilization or increased losses.

Fortification of industrially processed flour, when appropriately designed and implemented, is an efficient, simple and inexpensive strategy for supplying vitamins and minerals to the diets of large segments of the population. Wheat is cultivated and consumed in many parts of the world and its domestication contributed to the development of farming and human civilization. Industrial fortification of wheat flour with at least iron has been practised for many years in several countries where the flour is used in the preparation of different types of bread and national dishes.

Decisions about which nutrients to add to fortified wheat 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 wheat flour and products made from this staple; the sensory and physical effects of the fortificant on the flour and on flour products; the type of wheat and the extraction rate\(^1\) of the flour; the availability and coverage of fortification of other staple food vehicles in addition to other commercially available fortified products; the population use of vitamin and mineral supplements; costs; feasibility; and acceptability of the fortified product by the consumers.

Wheat flour can be fortified with several micronutrients, such as iron, folic acid and other B-complex vitamins\(^2\), vitamin A and zinc. Some micronutrients are incorporated for restitution of the original nutritional contents of unrefined wheat flour, and others are used for correcting inadequacies and associated deficiencies of public health significance. The bioavailability of the added micronutrients will partially depend on the grain type and the extraction rate of the flour.

PURPOSE OF THE GUIDELINE

The main objective of this guideline is to provide locally adaptable, clear, evidence-informed global recommendations on the fortification of wheat flour with vitamins and minerals as a public health strategy to improve the micronutrient status of populations, which are grounded in gender, equity and human rights approaches with the aim of leaving no one behind. The focus of this document is on the use of this intervention as a public health strategy and not on market-driven fortification of wheat flour or products\(^3\).

This guideline aims to help Member States and their partners to make informed decisions on the appropriate nutrition actions to achieve the 2030 Sustainable Development Goals and the global targets set in the World Health Organization (WHO) Comprehensive implementation plan on maternal, infant and young child nutrition.

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\(^1\) The production of wheat flour is a multi-step process to isolate the endosperm and subsequent sifting into flour. The extraction rate of a flour is the extent to which it has been sifted to separate the fine-grain endosperm, with a higher extraction rate indicating higher retention of the bran and germ.

\(^2\) The B-complex vitamins include B\(_1\), thiamine; B\(_2\), riboflavin; B\(_3\), niacin; B\(_6\), pyridoxine; B\(_9\), folate; and B\(_12\), cyanocobalamin. Thiamine, riboflavin, niacin and folic acid are commonly referred to by name, and their names are used throughout this document; the others are referred to by vitamin number.

\(^3\) Market-driven fortification refers to the situation where the food manufacturer takes the initiative to add one or more micronutrients to processed foods, usually within regulatory limits, to increase sales and profitability. Fortification as a public health strategy refers to the practice of deliberately increasing the content of an essential micronutrient, i.e. vitamins and minerals (including trace elements), in a food to improve the nutritional quality of the food supply and provide a public health benefit with minimal risk to health.
The recommendations in this guideline are intended for a wide audience, including policymakers, expert advisers, and technical and programme staff in ministries and organizations involved in the design, implementation and scaling-up of nutrition actions for public health. The recommendations are particularly relevant to the design and implementation of appropriate food-fortification programmes, as part of a comprehensive food-based strategy for combating micronutrient inadequacies and deficiencies.

These recommendations supersede the previous WHO recommendation on fortification of wheat flour. The guideline complements the WHO/FAO (Food and Agriculture Organization of the United Nations) Guidelines on food fortification with micronutrients and the Pan American Health Organization (PAHO) iron compounds for food fortification: guidelines for Latin America and the Caribbean. These two documents are not WHO standard guidelines but contain information still current that is not covered in this guideline. Because of the important aspects covered, the WHO Nutrition and Food Safety Department plans to update both documents.

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 the 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), equity, human rights, implementation, regulatory and ethical considerations; as well as (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 and other narrative syntheses of the evidence.

The guideline development group consisted of content experts, methodologists and representatives of potential beneficiaries. One guideline group participated in a meeting where the guideline was scoped, and a second WHO guideline development group – nutrition actions, was convened to discuss the evidence and finalize the recommendations. The members of the first guideline development group meeting identified five priority areas for guidelines on food fortification: wheat, maize, rice, sugar, and oil and condiments. For each item the group prioritized the nutrients based on the prevalence of deficiency and the feasibility of fortification based on nutrients to add and the characteristics of the food vehicle(s). For wheat flour the group prioritized iron, folic acid and zinc.

4 The GRADE approach defines the overall rating of confidence in the body of evidence from systematic reviews as the extent to which one can be confident of an estimate of effect across all outcomes considered critical to the recommendation. Each critical outcome had a confidence rating based on certainty of evidence – high, moderate, low or very low. High-certainty evidence indicates that we are very confident that the true effect lies close to that of the estimate of the effect. Moderate-certainty evidence indicates that we are moderately confident in the effect estimate and that the true estimate is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low-certainty evidence indicates that our confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect. Very low-certainty 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.
Systematic reviews team members participated in the guideline development process as resource persons by presenting evidence and identifying research priorities. While developing recommendations, the guideline development group considered additional factors in the implementation of wheat flour fortification as a public health strategy, including equitable access and universal coverage. Four technical experts were invited to peer-review the draft guideline.

**SUMMARY OF THE EVIDENCE**

Several systematic reviews were included in the evidence to decision document presented to the guidelines development group to inform recommendations.

- For iron, seven systematic reviews were included that aimed to determine the benefits and harms of wheat flour fortification with iron on anaemia, iron status and health-related outcomes.
- For folic acid, one systematic review was commissioned to evaluate the effect of fortification of wheat and maize flour with folic acid on population health outcomes.
- For zinc, two systematic reviews evaluated the effects of the fortification of staple foods on health-related outcomes and biomarkers of zinc status in the general population.
- For vitamin A, one systematic review assessed the effects of fortifying staple foods on vitamin A deficiency and health-related outcomes in the general population.

**IRON**

A systematic review was commissioned to determine the benefits and harms of wheat flour fortification, with iron alone or with other vitamins and minerals, on anaemia, iron status and health-related outcomes. Ten trials, involving 3319 participants, were included in the review and assessment of different iron compounds, doses and duration of fortification. In comparison to unfortified flour, wheat flour fortified with iron alone or with other micronutrients may reduce anaemia and probably makes little or no difference in the risk of iron deficiency. The effect of wheat flour fortified with iron on haemoglobin concentrations is uncertain.

**FOLIC ACID**

A systematic review from 2019 concluded that fortification of wheat flour with folic acid alone or with other micronutrients may increase erythrocyte and serum/plasma folate concentrations and may reduce the risk of neural tube defects compared to unfortified flour.

**ZINC**

Two systematic reviews aimed to evaluate the beneficial and adverse effects of fortification of staple foods with zinc on health-related outcomes and biomarkers of zinc status in the general population. Both reviews show that zinc may improve the serum zinc status of populations, reducing the prevalence of zinc deficiency and may provide health and functional benefits, including a reduced incidence of diarrhoea.

**VITAMIN A**

A systematic review assessed the effects of fortifying staple foods with vitamin A for reducing vitamin A deficiency and improving health-related outcomes in the general population older than
2 years of age. Out of ten studies, two were on wheat flour and showed that vitamin A, with or without other micronutrients, made little or no difference to the serum retinol levels in children and adolescents after six months of intervention.

RECOMMENDATIONS

Overarching principle for recommendations – Fortification of cereal flours, in this case industrially processed/produced wheat flour fortification, should be considered when wheat flour is regularly consumed by large population groups in a country. The fortification scheme in terms of which nutrients to add and in what amounts should be based on the nutritional needs of the population, usual consumption of fortifiable flour, sensory and physical effects of the added nutrients on flour and flour products, type of wheat and the extraction rate of flour, other fortified food items or ongoing micronutrient programmes, and fortification costs, feasibility and acceptance.

Based on available evidence, the recommendations to fortify wheat flour are as follows.

- Fortification of wheat flour with highly bioavailable iron is recommended as a public health strategy to improve haemoglobin concentrations and iron status, and to prevent anaemia and iron deficiency in populations, particularly for vulnerable groups such as children and women (strong recommendation, low certainty of evidence).

- Fortification of wheat flour with folic acid is recommended as a public health strategy to reduce the risk of occurrence of pregnancies affected by neural tube defects among women of reproductive age and to improve folate status in populations (strong recommendation, low and very low certainty of evidence).

- Fortification of wheat flour with zinc may be used as a public health strategy to improve serum/plasma zinc status of populations (conditional recommendation, low certainty of evidence).

KEY REMARKS

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

- When vitamin A deficiency constitutes a public health problem and no other/insufficient strategies to address it are in place, fortification of wheat flour with vitamin A could be considered as a public health strategy to improve vitamin A status or to reduce the risk of subclinical vitamin A deficiency.

- In countries with a high prevalence of vitamin B₁₂ depletion and deficiency, the inclusion of vitamin B₁₂ could be considered when staples are fortified with folic acid, to prevent unintended consequences of imbalances caused by the addition of folic acid alone.

- Since some of the B-complex vitamins naturally present in the wheat kernel are removed during milling, especially with low-extraction (i.e. refined) wheat flour, the restoration of thiamine, riboflavin, niacin and pyridoxine in wheat flour could be considered as a regular practice in fortification.

- The choice of iron compound is a compromise between cost, bioavailability, micronutrient interactions and the acceptance of texture, taste, smell and/or colour.
• The removal of phytates in wheat flour could increase the bioavailability of iron and zinc.

• Addition of vitamins and minerals to wheat flour should be based on evidence about inadequacy of micronutrient intakes and/or the prevalence of deficiency. This pre-fortification data will also serve for measuring impact of the fortification programme.

• Countries that fortify wheat flour may also fortify other food items. A combined fortification strategy using multiple vehicles appears to be a suitably effective option for reaching all segments of the population. Fortification of wheat flour should be integrated and monitored as part of their national programmes for prevention and control of micronutrient deficiencies and insufficiencies.

• 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. Monitoring consumption patterns and evaluation of micronutrient status in the population can inform adjustment of fortification levels over time.

• Populations should be encouraged to receive adequate nutrition, which is best achieved through consumption of a healthy balanced diet. Fortified foods only complement the diet when feasible and required.

• Although evidence is limited, fortification of wheat flour could potentially decrease inequity in population access to and consumption of micronutrient required to achieve good health and to prevent adverse health outcomes.

• The following table contains a list of nutrients and levels that could be added to wheat flour for fortification and/or restitution of contents based on extraction rate, chemical form and estimated per capita flour consumption.

### TABLE 1. Average level of nutrients to consider adding to fortified wheat flour based on extraction rate, fortificant compound, and estimated per capita flour consumption

<table>
<thead>
<tr>
<th>Nutrient*</th>
<th>Flour extraction rate(b)</th>
<th>Chemical form of the compound</th>
<th>Amount of nutrient to be added in (mg/kg wheat flour) based on estimated average per capita wheat flour consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron(d)</td>
<td>Low</td>
<td>NaFeEDTA</td>
<td>40 40 20 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ferrous sulfate</td>
<td>40 40 30 20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ferrous fumarate</td>
<td>60 60 30 20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Electrolytic iron</td>
<td>NR NR 60 40</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>NaFeEDTA</td>
<td>40 40 20 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ferrous sulfate</td>
<td>5.0 2.6 1.3 1.0</td>
</tr>
<tr>
<td>Folate</td>
<td>Low or high</td>
<td>Folic acid</td>
<td>95 55 40 30</td>
</tr>
<tr>
<td>Zinc(c)</td>
<td>Low</td>
<td>Zinc oxide</td>
<td>100 100 80 70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zinc sulfate</td>
<td>55 55 40 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zinc acetate</td>
<td>40 40 30 70</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Zinc oxide</td>
<td>100 100 80 70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zinc sulfate</td>
<td>55 55 40 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zinc acetate</td>
<td>40 40 30 70</td>
</tr>
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GUIDELINE: FORTIFICATION OF WHEAT FLOUR WITH VITAMINS AND MINERALS AS A PUBLIC HEALTH STRATEGY

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Amount of nutrient to be added in (mg/kg wheat flour) based on estimated average per capita wheat flour consumption</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>&lt;75 g/day</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Low or high</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>Low or high</td>
</tr>
</tbody>
</table>

For restitution of content lost during milling of refined flours:

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Amount of nutrient to be added in (mg/kg wheat flour) based on estimated average per capita wheat flour consumption</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>&lt;75 g/day</td>
</tr>
<tr>
<td>Vitamin B1 (thiamine)</td>
<td>Low or high</td>
</tr>
<tr>
<td>Vitamin B2 (riboflavin)</td>
<td>Low or high</td>
</tr>
<tr>
<td>Vitamin B3 (niacin)</td>
<td>Low or high</td>
</tr>
<tr>
<td>Vitamin B6 (pyridoxine)</td>
<td>Low or high</td>
</tr>
</tbody>
</table>

Other nutrients:

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Amount of nutrient to be added in (mg/kg wheat flour) based on estimated average per capita wheat flour consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;75 g/day</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Low or high</td>
</tr>
<tr>
<td>Calcium</td>
<td>Low or high</td>
</tr>
</tbody>
</table>

NaFeEDTA: sodium iron ethylenediaminetetraacetate; NR: not recommended.

Note: This table is for general guidance and is partially based on the 2009 Recommendations on wheat and maize flour fortification. The number and amounts of nutrients should be adapted according to the needs of the country. These estimated target levels consider only wheat flour as the main fortification vehicle in a public health programme. If other large-scale food fortification programmes are implemented effectively, these suggested fortification levels may need to be adjusted downwards as needed.

- Nutrient levels were adapted from the 2009 Recommendations on wheat and maize flour fortification and the evidence presented and discussed at the guideline development group meeting.
- High-extraction flour (>80%) is also known as whole flour. It retains high levels of natural phytates, which inhibit the body’s ability to absorb iron and zinc. High-extraction flours contain a naturally higher content of vitamins and minerals than low-extraction flours.
- Estimated per capita consumption of <75 g/day does not allow for the addition of sufficient amounts of fortificant to cover the needs of some micronutrients for women of reproductive age. Fortification of additional food vehicles and other interventions may need to be considered.
- The amounts of micronutrients such as iron, zinc and calcium presented here are in mg of the elemental micronutrient. The amount of a micronutrient compound to add should be calculated depending on the molecular weight of the compound.
- These amounts of zinc fortification assume 5 mg zinc intake and no additional phytate intake from other dietary sources. As with iron, the phytate concentration of high-extraction flour will affect the bioavailability of zinc.
- Consider fortifying wheat flour with vitamin A when deficiency constitutes a public health problem or when wheat flour is fortified with folic acid.
- Inclusion of vitamin B12 is recommended when its deficiency is a public health problem or when wheat flour is fortified with folic acid.
- Restitution of some B-complex vitamins should be achieved as a regular practice in all settings. The B-vitamins contents vary between types of whole wheat flours.
- Compounds and amounts indicated in this section are seldom used and constitute only rough estimates. Including them will depend on country needs, wheat type and other ongoing nutrition programmes.
- Level used in Jordan and Mongolia, with consumptions above 300 g/day. For lower levels of wheat flour consumption, consider increasing the amount of vitamin D.
EVIDENCE GAPS

The WHO guideline development groups and the systematic reviews teams highlighted the limited evidence available in some areas. Further research on wheat flour fortification is merited, particularly in:

- the bioavailability of different iron compounds for use in wheat flour fortification, including mixtures of different compounds;
- the bioavailability and stability of added folic acid, vitamin A and vitamin D in wheat flour;
- fortification of wheat flour with zinc only in comparison with fortification with a mix of micronutrients;
- the effects of different phytate contents on the absorption of iron and zinc from the premix formulation;
- biomarkers of individual micronutrient status under different conditions of infection and inflammation;
- stability of different micronutrients and compounds in different cooking processes that are context specific;
- relative bioavailability among different chemical forms of various micronutrients that can be used in wheat flour fortification, including nutrient-nutrient interactions;
- the most appropriate delivery platforms of the fortified flour/fortified flour products for reaching the intended target population;
- the impact of wheat flour fortification on micronutrient status and health outcomes to prevent excessive supplies of micronutrients to certain groups and identify situations where complementary interventions are needed to reduce inequity in populations.

PLANS FOR UPDATING THE GUIDELINE

The WHO Secretariat will continue to follow research developments in wheat flour fortification, particularly for questions in which the certainty of evidence was found to be low or very low. If the guideline merits an update, or if there are concerns about the validity of the guideline, the Department of Nutrition and Food Safety, in collaboration with other WHO departments or programmes, will coordinate the guideline update, following the formal procedures of the WHO handbook for guideline development.
SCOPE AND PURPOSE

WHO is committed to increasing the impact of public health measures in every country, ensuring healthy lives and promoting well-being for all at all ages. As part of its unique normative function in public health, WHO aims to provide global, evidence-informed recommendations on the fortification of wheat flour with vitamins and minerals to improve health outcomes associated with micronutrient status. This guideline will support the work of WHO regional and country offices and will help Member States and their partners to make evidence-informed decisions on the appropriate actions in their efforts to improve access to quality essential health services, support countries to be prepared for health emergencies, and address the determinants of health. It will also help in increasing capacity in the countries to respond to their needs on improving micronutrient status and to prioritize essential nutrition actions in national health policies, strategies and plans.

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 2030 Sustainable Development Goals (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 policymakers, their expert advisers and technical and programme staff at ministries and organizations involved in the design, implementation and scaling-up of nutrition actions for public health. 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. Further details of the evidence base are provided in Annex 1 and other documents listed in the references.

BACKGROUND

The most studied and more prevalent nutritional problems – anaemia and iron, folate, zinc, vitamin A and iodine deficiencies – are serious public health issues that particularly affect young children and women. The most common causes of micronutrient deficiencies are related to inadequate intakes, utilization or increased losses.

Anaemia is a condition in which the number of red blood cells or the haemoglobin concentration within them is lower than normal. The most common causes of anaemia include nutritional deficiencies, particularly of iron, although deficiencies in folate, vitamin B₁₂ and vitamin A are also important causes; inherited haemoglobinopathies; and infectious diseases, such as malaria, tuberculosis, HIV and parasitic infections. Anaemia is a serious global public health problem that particularly affects young children and pregnant women. WHO estimates that 40% of children aged 6–59 months and 37% of pregnant women worldwide are anaemic (4).
Low folate status in women of reproductive age can lead to adverse health consequences of public health significance, such as megaloblastic anaemia (folate deficiency) and an increased risk of pregnancies affected by neural tube defects. A review, which involved searching eight databases and the WHO Micronutrients Database, identified surveys of population prevalence of folate deficiency or insufficiency in women of reproductive age. Between 2000 and 2014, 45 relevant surveys in 39 countries were published. Prevalence of folate deficiency was >20% in many countries with lower-income economies but was typically <5% in countries with higher-income economies. Eleven surveys reported the prevalence of folate insufficiency, which was >40% in most countries (5).

Zinc deficiency is largely related to inadequate intake or absorption of zinc from the diet, although excess losses of zinc during diarrhoea may also contribute. Severe zinc deficiency was defined in the early 1900s as a condition characterized by short stature, hypogonadism, impaired immune function, skin disorders, cognitive dysfunction, and anorexia. Estimates based on food availability data indicate that zinc inadequacy (i.e. intakes that do not satisfy the nutrient requirements) affects about one third of the world's population, with estimates ranging from 4% to 73% across subregions. Although severe zinc deficiency is rare, mild-to-moderate zinc deficiency is quite common throughout the world. At least 17% of the world's population is at risk of inadequate zinc intake with the highest risk occurring in sub-Saharan Africa and south Asia (6). Worldwide, it is estimated that zinc deficiency is associated with approximately 16% of lower respiratory tract infections, 18% of malaria and 10% of diarrhoeal disease.

Vitamin A deficiency is the leading cause of preventable blindness in children and increases the risk of disease and death from severe infections. In pregnant women, vitamin A deficiency causes night blindness and may increase the risk of maternal mortality. Vitamin A deficiency is a public health problem in more than half of all countries, especially in Africa and south-east Asia, affecting young children and pregnant women in low-income countries the most (7).

Emerging, unexpected situations that affect health, food safety or trade have a deep impact on micronutrient status, especially of vulnerable populations such as children, women and elderly people. The COVID-19 pandemic is likely worsening the already high prevalence of micronutrient deficiencies worldwide. Lockdowns and physical distancing may lead to decreased family income and reduced access to crops, food, services, health care and social protection programmes that could result in increased rates of malnutrition and micronutrient deficiency. Modelling predicts that the COVID-19 pandemic will have a significant impact on maternal and child undernutrition and child mortality in the current generation, with large long-term negative consequences on productivity (8).

Wheat is cultivated and consumed in many parts of the world, and its domestication contributed to the development of farming and human civilization. It was first cultivated 9000 years ago in the Euphrates Valley of the Middle East. An estimated 65% of the global wheat crop is used for human consumption, 17% is used for animal feed and 12% is used in industrial applications, including biofuel production (9). China, India and the Russian Federation are the top three producers of wheat (10). Low-income countries consume 77% of wheat produced globally and are generally wheat importers, with wheat accounting for 24% of imported food commodities in these countries (11, 12). In 2019, the annual production of wheat was 765 769 635 tonnes, being the second most produced cereal after maize and before rice (12).
Wheat is a staple in many countries due to its agronomic adaptability, ease of grain storage and milling, and suitability for making edible, palatable, acceptable and satisfying foods (13). Doughs produced from wheat flour differ from those made from other cereals in their unique viscoelastic properties. Wheat varieties, including hard/soft, winter/spring, and red, white and durum, are grown at a variety of altitudes and in various types of soil throughout the world.

All types of wheat belong to the genus *Triticum aestivum*, subspecies *vulgare*. In addition, three other species are cultivated and traded: *T. durum*, *T. compactum* and *T. spelta*. Because of its quality, durum wheat is used by the pasta industry, and non-durum wheat is used for milling, livestock feed or ethanol production. Wheat kernels have three components: bran, germ, and endosperm. Most wheat is milled into flour through mechanical extraction of the endosperm, the core part of the kernel containing mainly carbohydrates and some proteins (14, 15). The nutrient-rich germ and bran are usually removed in refined flours and therefore the micronutrient content of these flours is lower than that of whole wheat flour.

The production of wheat flour is a multi-step process to isolate the endosperm and subsequent sifting into flour (16). The extraction rate of a flour is the extent to which it has been sifted to separate the fine-grain endosperm, with a higher extraction rate indicating higher retention of the bran and germ. Most vitamins and minerals in wheat are found in the bran or germ, and flours of 80% or lower extraction rates have a significantly reduced micronutrient content (14). However, high-extraction flour also contains higher levels of phytates, which interfere with intestinal absorption of iron and other minerals as zinc and copper (17, 18).

Fortification is the practice of deliberately increasing the content of one or more micronutrients, i.e. vitamins and minerals, in a food to improve the nutritional quality of the food supply and provide a public health benefit with minimal risk to health. Fortification of staple foods is one of the strategies used to safely and effectively prevent vitamin and mineral inadequacies and their associated deficiencies in populations (19).

Fortification of industrially processed wheat flour, when appropriately designed and implemented, can be an efficient, simple and inexpensive strategy for supplying vitamins and minerals to the diets of large segments of the population. Industrial fortification of wheat flour has been practised for many years in several countries where the flour is used in the preparation of different types of bread and national dishes. Based on data from the Food Fortification Initiative, 86 countries in 2021 had legislation on fortification of wheat flour alone or in combination with other grains. Table 1 shows the most common levels and chemical forms of micronutrient compounds included in standards for wheat flour fortification around the world.

Decisions about which nutrients to add to fortified wheat flour and how much of each nutrient to use should be based on the nutritional needs and intake gaps of the target populations; usual level of consumption of wheat flour and products made from this staple; sensory and physical effects of the fortificant on the flour and on flour products; type of wheat and the extraction rate of the grain; availability and coverage of other fortified staple foods, in addition to other commercially available fortified products; population use of vitamin and mineral supplements; costs; feasibility; and acceptability by the producers and consumers (19–21).
Wheat flour can be fortified with several micronutrients, such as iron, folic acid and other B-complex vitamins, vitamin A and zinc. Some micronutrients are incorporated for restitution of original nutritional contents of unrefined wheat flour, and others are used for correcting inadequacies and their associated deficiencies of public health significance. The bioavailability of the added micronutrients will depend in part on the grain type and the extraction rate of the flour.

In many cases, procedures for the fortification of wheat and maize flours 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 (22). It is now recognized that there are differences and that the principles that apply to fortification of wheat flour may not necessarily apply to fortification of other flours (23).

Table 1. Contents and chemical forms of micronutrients included in wheat fortification standards

<table>
<thead>
<tr>
<th>Micronutrient</th>
<th>Range of levels used in standards (mg/kg)</th>
<th>Most commonly used level in legislations (mg/kg)</th>
<th>Number of countries with legislation or standards</th>
<th>Most commonly used chemical form of compounds (number of countries)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>15–120</td>
<td>30–60</td>
<td>78</td>
<td>Ferrous sulfate (64)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ferrous fumarate (63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Elemental iron (11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NaFeEDTA (10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Electrolytic iron (7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reduced iron (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ferric pyrophosphate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Carbonyl iron</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ferric citrate</td>
</tr>
<tr>
<td></td>
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<td>Ferric gluconate</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Ferric oxide</td>
</tr>
<tr>
<td>Folic acid</td>
<td>0.4–5.11</td>
<td>1.5–2.6</td>
<td>62</td>
<td>Folic acid (63)</td>
</tr>
<tr>
<td>Zinc</td>
<td>15–101</td>
<td>30–40</td>
<td>26</td>
<td>Zinc oxide (23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unspecified (3)</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>1–10</td>
<td>1–2</td>
<td>14</td>
<td>Retinyl palmitate (13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Retinyl palmitate and retinyl acetate (1)</td>
</tr>
<tr>
<td>Other nutrients commonly added not covered in this recommendation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B1 (thiamine)</td>
<td>1.3–10</td>
<td>6</td>
<td>56</td>
<td>Thiamine (28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thiamine mononitrate (27)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Thiamine hydrochloride (3)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unspecified (1)</td>
</tr>
<tr>
<td>Vitamin B2 (riboflavin)</td>
<td>1.3–6.5</td>
<td>3–5</td>
<td>54</td>
<td>Riboflavin (52)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Riboflavin 5’ phosphate sodium (1)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Unspecified (2)</td>
</tr>
<tr>
<td>Vitamin B3 (niacin)</td>
<td>6.7–60</td>
<td>50</td>
<td>54</td>
<td>Niacin (33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Niacinamide (37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unspecified (1)</td>
</tr>
</tbody>
</table>

1 The B-complex vitamins include B1, thiamine; B2, riboflavin; B3, niacin; B6, pyridoxine; B9, folate; and B12, cyanocobalamin. Thiamine, riboflavin, niacin and folic acid are commonly referred to by name, and their names are used throughout this document; the others are referred to by vitamin number.
GUIDELINE: FORTIFICATION OF WHEAT FLOUR WITH VITAMINS AND MINERALS AS A PUBLIC HEALTH STRATEGY

<table>
<thead>
<tr>
<th>Micronutrient</th>
<th>Range of levels used in standards (mg/kg)</th>
<th>Most commonly used level in legislations (mg/kg)</th>
<th>Number of countries with legislation or standards</th>
<th>Most commonly used chemical form of compounds (number of countries)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B6 (pyridoxine)</td>
<td>2.6</td>
<td>6.5</td>
<td>12</td>
<td>Pyridoxine (7) Pyridoxine hydrochloride (5)</td>
</tr>
<tr>
<td>Vitamin B12 (cyanocobalamin)</td>
<td>0.004–0.04</td>
<td>0.02</td>
<td>16</td>
<td>Cyanocobalamin (16)</td>
</tr>
<tr>
<td>Vitamin D (cholecalciferol)</td>
<td>0.01–0.03</td>
<td>0.02</td>
<td>3</td>
<td>D₃ cholecalciferol (3)</td>
</tr>
<tr>
<td>Calcium</td>
<td>1250–2112</td>
<td>1250</td>
<td>14</td>
<td>Unspecified (12) Calcium carbonate (3) Calcium phosphate (3) Other (2)</td>
</tr>
</tbody>
</table>

NaFeEDTA: sodium iron ethylenediaminetetraacetate.

Source: Based on data from legislations compiled by the Flour Fortification Initiative (21) and the Global Fortification Data Exchange.

The whole fortification process and supply chain in a given country is an intricate network of public and private entities that link farmers, collectors, traders, millers, retailers and food processors to the final consumers. Other stakeholders include transporters; companies that supply seeds, agrochemicals, and agricultural equipment; irrigation companies; inspection agencies; government departments of commerce, tax, and agriculture; and other state agencies that control the flow in this chain according to individual governmental policies (24).

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, from a quality-control point of view, it is desirable that milling is centralized in few mills, although this is not the case in some countries.

OBJECTIVES

The main objective of this guideline is to provide locally adaptable, clear, evidence-informed global recommendations on the fortification of wheat flour with vitamins and minerals as a public health strategy to improve the micronutrient status of populations, which are grounded in gender, equity and human rights approaches with the aim of leaving no one behind.

These recommendations supersede the previous WHO recommendation on fortification of wheat flour. The guideline complements the WHO/FAO Guidelines on food fortification with micronutrients (19) and the PAHO 2002 document, Iron compounds for food fortification: guidelines for Latin America and the Caribbean (25). These two documents are not WHO standard guidelines but contain information still current that is not covered in this guideline. Because of the important aspects covered, the WHO Nutrition and Food Safety Department plans to update both documents.

SUMMARY OF THE EVIDENCE

WHEAT FLOUR FORTIFICATION AND POPULATION MICRONUTRIENT STATUS AND HEALTH-RELATED OUTCOMES

Several systematic reviews were included in the evidence to decision document presented to the guidelines development group to inform recommendations.

- For iron, seven systematic reviews were included that aimed to determine the benefits and harms of wheat flour fortification with iron on anaemia, iron status and health-related outcomes. One of the reviews was commissioned, and results from six additional systematic reviews were discussed to complement findings from the commissioned review.

- For folic acid, one systematic review was commissioned to evaluate the effect of fortification of wheat and maize flour with folic acid on population health outcomes.

- For zinc, two systematic reviews evaluated the effects of the fortification of staple foods on health-related outcomes and biomarkers of zinc status in the general population.

- For vitamin A, one systematic review assessed the effects of fortifying staple foods on vitamin A deficiency and health-related outcomes in the general population.

The evidence from systematic reviews was used to prepare the evidence-to-decision framework and draft this guideline. The GRADE summary of findings tables for each of the critical outcomes were prepared from commissioned (Cochrane) systematic reviews.

IRON

A systematic review was commissioned to determine the benefits and harms of wheat flour fortification with iron alone or with other vitamins and minerals on anaemia, iron status and health-related outcomes (18). The systematic review included cluster and individual randomized controlled trials done among general populations in any country aged 2 years and above. Ten trials, involving 3319 participants, were included in the review. The duration of interventions varied from 3 to 24 months. In comparison to unfortified flour, wheat flour fortified with iron alone or with other micronutrients may reduce anaemia and probably makes little or no difference in iron deficiency. The effect of wheat flour fortified with iron increasing haemoglobin concentrations is uncertain (18).

A group of six systematic reviews on food fortification, which included wheat flour fortified with iron and other micronutrients were also reviewed (26–31). Studies of populations from all socioeconomic strata showed that fortification of flours with iron is an effective strategy to improve the iron status of populations (26); this includes large-scale food fortification programmes in low- and middle-income countries (27). The impact of flour fortification on iron status and anaemia has also been demonstrated government-supported fortification programmes in children and women of reproductive age, showing statistically significant decreases in the prevalence of anaemia and in low serum/plasma ferritin concentrations (28).

The review of randomized controlled trials on food fortification with iron, including wheat flour consumed as bread, snacks, noodles and biscuits in children aged <10 years, showed a significant increase of haemoglobin concentration in the fortification group compared with the control group (29). A systematic review of studies of the effect of fortification of staple foods in women of reproductive age and pregnant women reported a significant increase in serum ferritin...
and haemoglobin levels (30). Finally, a systematic review of 60 randomized and pseudorandomized controlled trials found that, compared with non-fortified food intake, consumption of foods fortified or biofortified with iron (31) resulted in significant improvements in haemoglobin, serum ferritin and iron status, and a reduced risk of remaining anaemic and iron deficient.

**FOLIC ACID**

A systematic review was commissioned to evaluate the effect of fortification of wheat and maize flour with folic acid on population health outcomes. Seven studies included fortified wheat flour (32). Adults consuming bread rolls made with wheat flour fortified with folic acid had higher erythrocyte folate (mean difference [MD] 0.66 nmol/L, 95% confidence interval [CI] 0.13 to 1.19; 1 study, 30 participants; very low-certainty evidence) and plasma folate (MD 27.00 nmol/L, 95% CI 15.63 to 38.37; 1 study, 30 participants; very low-certainty evidence) than those consuming bread made with unfortified flour. The authors conclude that folic acid, alone or with other micronutrients, may increase erythrocyte and serum/plasma folate concentrations. In one non-randomized controlled trial of women of reproductive age and pregnant women, wheat flour fortified with folic acid and other micronutrients was associated with significantly lower occurrence of total neural tube defects, spina bifida, and encephalocele compared to unfortified flour (total neural tube defects: risk ratio [RR] 0.32, 95% CI 0.21 to 0.48; 8037 births; low-certainty evidence) (32).

**ZINC**

A systematic review evaluated the beneficial and adverse effects of the fortification of staple foods with zinc on health-related outcomes and biomarkers of zinc status in the general population. Eight trials with 709 participants were included. Five of the included studies were on wheat flour or wheat products. The analysis of the wheat flour products showed the same trend as the main analysis: foods fortified with zinc increased the serum or plasma zinc levels in comparison to foods without added zinc (MD 2.46 µmol/L, 95% CI 2.05 to 2.87 µmol/L; 2 studies; 99 participants; low-certainty evidence). There was no difference in serum or plasma zinc levels in participants consuming foods fortified with zinc plus other micronutrients when compared with participants consuming the same foods with micronutrients but no added zinc (MD -0.01 µmol/L, 95% CI -1.01 to 0.98 µmol/L; 3 studies; 201 participants; low-certainty evidence). The authors concluded that fortification of foods with zinc may improve the serum zinc status of populations if zinc is the only micronutrient used for fortification. If zinc is added to foods in combination with other micronutrients, it may make little or no difference to serum zinc concentrations (33).

A 2021 systematic review on the effect of zinc fortification, alone or with multiple micronutrients, on zinc-related biomarkers showed that zinc fortification with and without multiple micronutrients increased plasma zinc concentrations (efficacy, \( n = 27 \): 4.68 \( \mu g/dL \); 95% CI: 2.62–6.75; effectiveness, \( n = 13 \): 6.28 \( \mu g/dL \); 95% CI: 5.03–7.77 \( \mu g/dL \)) and reduced the prevalence of zinc deficiency (efficacy, \( n = 11 \): odds ratio [OR]: 0.76, 95% CI: 0.60–0.96; effectiveness, \( n = 10 \): OR: 0.45, 95% CI: 0.31–0.64). There was no statistical difference in the effect on plasma zinc concentration or zinc deficiency by food vehicle group (cereal grains, beverages, and condiments). When analysing studies only on wheat flour/products, there was no effect of zinc fortification on prevalence of zinc deficiency (34).
**VITAMIN A**

A systematic review assessed the effects of fortifying staple foods with vitamin A for reducing vitamin A deficiency and improving health-related outcomes in the general population older than two years of age (35). The authors included interventions that fortified staple foods with vitamin A alone or in combination with other vitamins and minerals. Only two studies reported on wheat flour as the intervention vehicle for fortification – in chapati (36) and in wheat flour buns (37). The duration of interventions ranged from 3 to 9 months. In the study with chapati, the intervention made little or no difference to mean serum retinol levels in participants (1.06 µmol/L, standard deviation [SD] 0.27 [n = 105]) compared to those receiving unfortified chapati (0.94 µmol/L, SD 0.23 [n = 77]) (36). In the study of wheat flour bun fortified with vitamin A, the intervention made little or no difference to the serum retinol levels in children (1.32 µmol/L, SD 0.37 [n=396]) compared to those receiving unfortified buns (1.31 µmol/L, SD 0.4 [n = 439]) (37).

*Table 2* compiles the concentrations and chemical forms of compounds that were used both in the studies included in the systematic reviews described previously and by the WHO guideline development group as a base for discussions to establish the recommendations of this guideline.

The outcomes 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) in women of reproductive age and older adults, zinc deficiency, zinc status (as measured by plasma zinc), and growth (as defined by stunting, wasting or underweight). The presence of adverse effects was an outcome for all micronutrients (Annexes 1–3).

On application of the GRADE methodology, the certainty of the direct evidence for the critical outcomes was low and very low (38, 39). The GRADE summary of findings table for the fortification of wheat flour is shown in Annexes 1A to 1I. In addition to the direct and indirect evidence (delivered using food vehicles other than wheat flour) and its overall certainty, other considerations were taken into account by the guideline development group to define the direction and strength of the recommendations.
### Table 2. Concentrations and chemical forms of the compounds used to fortify wheat flour

<table>
<thead>
<tr>
<th>Micronutrient</th>
<th>Chemical form</th>
<th>Dosage</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Iron</strong></td>
<td>NaFeEDTA</td>
<td>40–80 mg Fe/kg</td>
<td>Field et al. Wheat flour fortification with iron for reducing anaemia and improving iron status in populations. 2020 (18).</td>
</tr>
<tr>
<td></td>
<td>Ferrous sulfate</td>
<td></td>
<td>Sadighi et al. Systematic review and metaanalysis of the effect of iron-fortified flour on iron status of populations worldwide. 2019 (26).</td>
</tr>
<tr>
<td></td>
<td>MnFeEDTA</td>
<td>Not reported</td>
<td>Das et al. Micronutrient fortification of food and its impact on woman and child health: a systematic review. 2013 (30).</td>
</tr>
<tr>
<td></td>
<td>Sodium ferrous sulfate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ferrous fumarate</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Reduced iron</td>
<td></td>
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<tr>
<td></td>
<td>Electrolytic iron</td>
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<tr>
<td></td>
<td>Ferric pyrophosphate</td>
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<td></td>
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<tr>
<td></td>
<td>Hydrogen-reduced iron</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heme</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Ferric orthophosphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amino acid chelates</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Ferrous gluconate</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Ferric ammonium citrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Folic Acid</strong></td>
<td>Folic acid</td>
<td>1.0–11.1 mg folic acid per kg</td>
<td>Centeno Tablante et al. Fortification of wheat and maize flour with folic acid for population health outcomes. Cochrane Database of Systematic Reviews 2019 (32).</td>
</tr>
<tr>
<td></td>
<td>Folic acid</td>
<td>0.4–5 mg folic acid per kg</td>
<td>Das et al. Micronutrient fortification of food and its impact on woman and child health: a systematic review. Systematic reviews. 2013 (30).</td>
</tr>
<tr>
<td><strong>Zinc</strong></td>
<td>Zinc sulfate</td>
<td>3–40 mg zinc per kg</td>
<td>Shah et al. Fortification of staple foods with zinc for improving zinc status and other health outcomes in the general population. Cochrane Database Syst Rev. 2016 (33).</td>
</tr>
<tr>
<td></td>
<td>Zinc chloride</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Zinc oxide</td>
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<td></td>
<td>Zinc acetate</td>
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<td></td>
<td>Zinc lactate</td>
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<tr>
<td></td>
<td>Zinc aminochlorate</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Zinc sulfate (n = 16)</td>
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<td></td>
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<tr>
<td></td>
<td>Zinc chloride (n = 16)</td>
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<td></td>
<td>Zinc oxide (n = 16)</td>
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<tr>
<td></td>
<td>Zinc glutamate (n = 3)</td>
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<td></td>
<td>Zinc chloride (n = 2)</td>
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<td></td>
<td>Zinc acetate (n = 2)</td>
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<tr>
<td></td>
<td>Other compounds used included zinc aminochlorate, dioxide and lactate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vitamin A</strong></td>
<td>Retinyl palmitate</td>
<td>3.03–6.00 mg retinol equivalents per kg</td>
<td>Hombali et al. Fortification of staple foods with vitamin A for vitamin A deficiency. Cochrane Database of Systematic Reviews. 2019 (33).</td>
</tr>
<tr>
<td></td>
<td>Microencapsulated retinyl acetate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Table compiles the concentrations and chemical forms of compounds used in included studies of the systematic reviews and by the WHO guideline development group to aid establishing the recommendations of this guideline.
RECOMMENDATIONS

The overarching principle of these recommendations is that fortification of cereal flours, in this case industrially processed/produced wheat flour fortification, should be considered when flour is regularly consumed by large population groups in a country. The fortification scheme, in terms of which nutrients to add and in what amounts, should be based on the nutritional needs of the population; usual consumption of fortifiable flour; sensory and physical effects of the added nutrients on flour and flour products; type of wheat and the extraction rate of flour; other fortified food items or ongoing micronutrient programmes; and fortification costs, feasibility and acceptance.

Based on available evidence the recommendations to fortify wheat flour are as follows.

- Fortification of wheat flour with highly bioavailable iron is recommended as a public health strategy to improve haemoglobin concentrations and iron status and to prevent anaemia and iron deficiency in populations, particularly in vulnerable groups such as children and women (strong recommendation, low certainty of evidence).
- Fortification of wheat flour with folic acid is recommended as a public health strategy to reduce the risk of occurrence of neural tube defects in pregnancies in women of reproductive age and to improve folate status in populations (strong recommendation, low and very low certainty of evidence).
- Fortification of wheat flour with zinc may be used as a public health strategy to improve serum/plasma zinc status of populations (conditional recommendation, low certainty of evidence).

The guideline development group considered wheat flour fortification with iron and folic acid as strong recommendations despite the low certainty of the evidence after discussing other considerations like the priority of the problem and the clear benefits of fortification. Other considerations included feasibility and acceptability of the intervention.

REMARKS

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

- When vitamin A deficiency constitutes a public health problem and no other/insufficient strategies to address it are in place, fortification of wheat flour with vitamin A could be considered as a public health strategy to improve vitamin A status or to reduce the risk of subclinical vitamin A deficiency.
- In countries with a high prevalence of vitamin B₁₂ depletion and deficiency, the inclusion of vitamin B₁₂ could be considered when staples are fortified with folic acid, to prevent unintended imbalances resulting from addition of folic acid alone.
- Since some of the B-complex vitamins naturally present in the wheat kernel are removed during milling, especially with low-extraction (i.e. refined) wheat flour, the restoration of thiamine, riboflavin, niacin and pyridoxine in wheat flour could be considered as a regular practice in fortification.
• The choice of iron compound is a compromise between cost; bioavailability; micronutrient interactions; and the acceptance of texture, taste, smell, and/or colour.

• The removal of phytates in wheat flour could increase the bioavailability of iron and zinc.

• Addition of vitamins and minerals in wheat flour should be based on evidence about inadequacy of micronutrient intakes and/or the prevalence of deficiency. These pre-fortification data are also used for measuring impact of the fortification programme.

• Countries that fortify wheat flour may also fortify other food items. A combined fortification strategy using multiple vehicles appears to be an effective option for reaching all segments of the population. Fortification of wheat flour should be integrated and monitored as part of national programmes for prevention and control of micronutrient deficiencies and insufficiencies.

• 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. Monitoring consumption patterns and evaluation of micronutrient status in the population can inform adjustment of fortification levels over time.

• Populations should be encouraged to receive adequate nutrition, which is best achieved through consumption of a healthy balanced diet. Fortified foods only complement the diet when feasible and required.

• Although evidence is limited, fortification of wheat flour could potentially decrease inequity in population access to and consumption of micronutrients required to achieve good health and to prevent adverse health outcomes.

• Table 3 contains a list of nutrients and levels that could be added to wheat flour for fortification and/or restitution of contents based on extraction rate, chemical form and estimated per capita flour consumption. This is a reference table based on a WHO interim consensus statement from 2009 (22); the levels used in included studies from the systematic reviews (Table 2); and in available standards from country legislations (Table 1).

<table>
<thead>
<tr>
<th>Nutrienta</th>
<th>Flour extraction rateb</th>
<th>Chemical form of the compound</th>
<th>Amount of nutrient to be added (in mg/kg of wheat flour) based on estimated average per capita wheat flour consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron1</td>
<td>Low</td>
<td>NaFeEDTA</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ferrous sulfate</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ferric fumarate</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Electrolytic iron</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>NaFeEDTA</td>
<td>40</td>
</tr>
<tr>
<td>Folate</td>
<td>Low or high</td>
<td>Folic acid</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Table 3. Average level of nutrients to consider adding to fortified wheat flour based on extraction rate, fortificant compound, and estimated per capita flour availability.
### Nutrient Fortification

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Flour extraction rate</th>
<th>Chemical form of the compound</th>
<th>Amount of nutrient to be added (in mg/kg of wheat flour) based on estimated average per capita wheat flour consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>Low</td>
<td>Zinc oxide</td>
<td>&lt;75 g/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zinc sulfate</td>
<td>75–149 g/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zinc acetate</td>
<td>150–300 g/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;300 g/day</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Low or high</td>
<td>Vitamin A palmitate</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitamin A acetate</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.5</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt;</td>
<td>Low or high</td>
<td>Cyanocobalamin</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**For restitution of content lost during milling of refined flours**

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Flour extraction rate</th>
<th>Chemical form of the compound</th>
<th>Amount of nutrient to be added (in mg/kg of wheat flour) based on estimated average per capita wheat flour consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B&lt;sub&gt;1&lt;/sub&gt; (thiamine)</td>
<td>Low or high</td>
<td>Thiamine</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thiamine mononitrato</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thiamine hydrochloride</td>
<td>3.0</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;2&lt;/sub&gt; (riboflavin)</td>
<td>Low or high</td>
<td>Riboflavin</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Riboflavin 5' phosphate</td>
<td>2.0</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;3&lt;/sub&gt; (niacin)</td>
<td>Low or high</td>
<td>Niacin</td>
<td>40.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Niacinamide</td>
<td>40.0</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;6&lt;/sub&gt; (pyridoxine)</td>
<td>Low or high</td>
<td>Pyridoxine</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pyridoxine hydrochloride</td>
<td>2.0</td>
</tr>
<tr>
<td>Other nutrients</td>
<td>Low or high</td>
<td>D&lt;sub&gt;3&lt;/sub&gt; cholecalcifer</td>
<td>0.02</td>
</tr>
<tr>
<td>Calcium</td>
<td>Low or high</td>
<td>Calcium carbonate</td>
<td>3125</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calcium phosphate</td>
<td>2112</td>
</tr>
</tbody>
</table>

Note: This table is for general guidance. The number and amounts of nutrients should be adapted according to the needs of the country. These estimated target levels consider only wheat flour as the main fortification vehicle in a public health programme. If other large-scale food fortification programmes are implemented effectively, these suggested fortification levels may need to be adjusted downwards as needed.

### Nutrient Fortification Details

- **Zinc**: High-extraction flour (>80%) is also known as whole flour. It retains high levels of natural phytates, which inhibit the body's ability to absorb iron and zinc. High-extraction flours contain a naturally higher content of vitamins and minerals than low-extraction flours.
- **Vitamin A**: Consider fortifying wheat flour with vitamin A when deficiency constitutes a public health problem and no other strategies to address it are in place.
- **Vitamin B<sub>12</sub>**: Inclusion of vitamin B<sub>12</sub> is recommended when its deficiency is a public health problem or when wheat flour is fortified with folic acid.
- **Calcium**: Restitution of some B-complex vitamins should be achieved as a regular practice in all settings. The B-vitamins contents vary between types of whole wheat flours (15, 41, 42).
- **Other nutrients**: Compounds and amounts indicated in this section are seldom used and constitute only rough estimates. Including them will depend on country needs, wheat type and other ongoing nutrition programmes.
- **Vitamin D**: Level used in Mongolia and Jordan, with consumptions above 300 g/day. For lower levels of wheat flour consumption, consider increasing the amount of vitamin D.

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NaFeEDTA: ferric sodium ethylenediaminetetraacetate; NR: not recommended.
SUMMARY OF THE CONSIDERATIONS TO DETERMINE THE DIRECTION AND STRENGTH OF THE RECOMMENDATIONS

In addition to the certainty of the scientific evidence described in the reviews, the other factors that the guideline development group considered in determining the strength and direction of the recommendations included: the priority of the problem, the balance of benefits and harms, equity and human rights, acceptability, feasibility and costs. Annex 3 presents a summary of these considerations.

CERTAINTY OF THE EVIDENCE

The certainty of direct evidence was moderate, low (for most of the included studies), and very low.

Two of the recommendations were considered strong and one was considered as moderate, although the certainty of the evidence was low or very low for the priority critical outcomes.

PRIORITY OF THE PROBLEM

All guideline development group members considered that micronutrient deficiencies are important public health problems and that health-care providers, policy-makers and family members in all settings are likely to place a high value on food fortification, especially with iron and folic acid, to combat micronutrient deficiencies.

BALANCE OF EFFECTS

Based on the available evidence, the guideline development group concluded that there are benefits in wheat flour fortification with iron, folic acid and zinc, while the benefits were uncertain for fortification with vitamin A. The evidence for undesirable effects was uncertain for iron, folic acid, zinc and vitamin A, since studies were limited in number and quality and some showed inconsistent results. The group concluded that the overall benefits for fortifying wheat flour outweighed the harms.

EQUITY AND HUMAN RIGHTS

The guideline development group discussed how flour fortification might affect equity and human rights and whether flour fortification could reduce inequalities and increase equity and accessibility. The group considered how the ability to choose fortified flour is affected by a person’s location (e.g. urban versus rural), educational attainment, and level of agency in making food choices.

The group concluded that effective interventions to improve nutrition in disadvantaged populations could help to reduce health inequalities. Strategies for fortification need to be aligned with relevant programmes, especially poverty reduction and other social interventions. In general, effective nutrition interventions are more likely to decrease health inequities only if they are accompanied by concurrent interventions that address the root cause of the problem.

Inequities in access to fortified flours, where these are staples, can perpetuate inequalities among communities and individuals with respect to cognitive abilities, work skills and capacities for protecting self and/or family health. Programmes to date may not favour increased equity, although the guideline development group considers they have potential to increase equity, especially if made mandatory.
ACCEPTABILITY

Acceptability is affected by several factors, such as who benefits from flour fortification and who may be harmed; who pays or who saves money as a result; and when the benefits, harms and costs occur. The group’s discussion was centered on acceptability to the end users, i.e. those who buy the flour and its products. Fortification requires less behaviour change than other interventions, thus acceptability and feasibility are favoured.

The group considered that wheat flour fortification is a well-accepted intervention, although the existence of sectors that are against adding anything to foods was recognized. Additionally, changes in organoleptic properties of the final product and acceptability by millers were also discussed as factors that could affect the overall acceptability of this intervention.

FEASIBILITY

Feasibility is influenced by the resources available, programmatic considerations, existing and additional necessary infrastructure and training, among other factors. Wheat flour fortification was considered a feasible intervention where implemented by millers and monitored by governments. The evidence is robust regarding feasibility where wheat flour is produced by a small number of large mills, but was recognized to be more complex and difficult for small millers. Education is important to enhance stakeholder value, and for this reason any intervention needs to be promoted and have an education component that does not increase consumption of the fortification vehicle.

COST

In comparison with other nutrition interventions, fortification represents a negligible cost to governments and might be affordable for the end users. The group recognized the need for investment at the milling/industry and government levels to implement and maintain fortification programmes.

For this guideline, the guideline development group was presented with the evidence-to-decision frameworks that considered the above-mentioned factors. This approach is in agreement with the WHO guideline development procedures, specifically with guidance on developing recommendations integrating evidence across multiple domains WHO handbook for guideline development (40).

EVIDENCE GAPS

The WHO guideline development groups and the systematic reviews teams highlighted the limited evidence available in some areas. Further research on wheat flour fortification is merited, particularly regarding:

- the bioavailability of different iron compounds for use in wheat flour fortification, including mixtures of different compounds;
- the bioavailability and stability of added folic acid, vitamin A and vitamin D in wheat flour;
- fortification of wheat flour with zinc only compared to fortification with a mix of micronutrients;
- the effects of different phytate contents on the absorption of iron and zinc from premix formulations;
biodata of individual micronutrient status under different conditions of infection and inflammation;

- stability of different micronutrients and compounds in different, context-specific, cooking processes;

- relative bioavailability among different chemical forms of various micronutrients that can be used in wheat flour fortification, including nutrient–nutrient interactions;

- the most appropriate delivery platforms for reaching the intended target population;

- the impact of wheat flour fortification on micronutrient status and health outcomes in preventing the need for excessive supplies of micronutrients to certain groups;

- identifying situations where complementary interventions are needed to reduce inequity in populations.

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 (43), or the WHO e-Library of Evidence for Nutrition Actions (eLENA) (44). 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 high, 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 often limited or difficult.

The executive summary of the guideline may be translated into the other five United Nations languages and disseminated through the WHO regional offices. Specialized technical assistance will be provided to any WHO regional office willing to translate the full guidelines into any of these languages and support countries in implementation for impact.
EQUITY, HUMAN RIGHTS AND IMPLEMENTATION CONSIDERATIONS

This guideline provides Member States with evidence-informed recommendations on the effects and safety of fortifying wheat flour with micronutrients, as a strategy to improve the health status of populations, specifically for reducing anaemia and the risk of occurrence of neural tube defects, and the improvement of iron, folate and zinc status. This guideline is intended to help Member States and their partners 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. Currently, fortification of wheat flour with micronutrients is already taking place in several Member States, and up to 86 countries have developed mandatory legislation to fortify wheat flour alone or in combination with other fortification vehicles (21). 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 considerations seek to support Member States that are considering fortification of wheat flour 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, farmers, manufacturers, industry organizations, importers, exporters, retailers, 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 (45).

Sound dietary intake data and a robust baseline or database on the prevalence of micronutrient inadequacies and 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) (46). The disaggregation of data is also useful for monitoring and evaluation of the programme. 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 (47) and the WHO Health equity assessment toolkit (HEAT) (48). 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.

An analysis is recommended during pre-implementation stages regarding capacities for wheat flour production, imports and industrialization, the nutrients needed and consumption of wheat flour/products. Accurate and robust data on the prevalence of micronutrient deficiencies in population groups is needed to inform cost estimates and the formulation of the fortification premix. It is also recommended the pathways and distribution channels required to reach and benefit hard-to-reach population groups should be carefully identified. Policy-makers and

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1 Equity in health refers to the absence of unjust differences in health, which are avoidable by reasonable action (45). Thus, the implementation of the interventions informed by this guideline should contribute to preventing or mitigating systematic difference in nutritional status across populations, including health inequities that may be exacerbated or created as a result of their implementation.
programme managers may consider appropriate measures to guarantee that the intervention is implemented as it was designed, so that fidelity\(^1\) can also be measured and monitored.

Access to and availability of fortified wheat flour should be promoted when the need is identified irrespective of geographical, cultural or economic factors. In the context of staple foods made from wheat flour, even slight changes in geographical placement, culturally adapted communication strategies, and variations in the price of the food could affect accessibility. For example, in low-income and rural settings, households may often purchase wheat flour at local markets, from local hammer or small mills, or grind their own. These households may not benefit from large-scale fortification of wheat flour. In that scenario, concurrent measures can contribute to prevent and mitigate health inequities that are produced as a result of differential access to fortified wheat flour. Those concurrent measures include awareness-raising campaigns, food subsidies, cash-transfer programmes, direct distribution of culturally appropriate fortified foods, and the coordinated use of other interventions such as point-of-use fortification or supplementation.

To counteract misunderstandings, culturally appropriate communication strategies should be developed to disseminate accurate and evidence-based information on what fortified wheat flour is and why it is important for health and nutrition. Likewise, programmes at national and subnational levels should be culturally appropriate to the target populations, to increase their acceptability, adoption and sustainability. Programmes should also identify any resistance, via actions or behaviours, based on well-established practices or social beliefs that affect adoption of and adherence to fortified wheat flour. The involvement of local leaders and use of local languages and culturally relevant representations is a reasonable strategy.

Acceptability and adoption are more likely if accompanied by simple and easy-to-access information that can be understood by different population groups. 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 fortified wheat flour products, the industries in charge of milling and fortifying the wheat, and the organizations in charge of measuring the impact of the programme and its monitoring and evaluation.

The programme should have well-defined objectives that consider available resources, existing policies, suitable delivery platforms and suppliers, communication channels and potential stakeholders. Ideally, a programme for the fortification of wheat flour should be implemented as part of a coordinated and comprehensive programme aiming to address micronutrient deficiencies. A 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 manner\(^{50}\). Fortification programmes should be coordinated with antenatal care programmes that supplement pregnant women with iron and folic acid. 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\(^{51, 52}\).

\(^1\) “Fidelity” is an implementation outcome variable that indicates the degree to which an intervention is or was implemented as designed in the original policy, plan or protocol. A full description of different implementation outcomes (e.g. acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost, coverage and sustainability) can be found in reference\(^{49}\).
Moreover, food-fortification programmes should not be considered as replacements for adequate and diverse 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. To achieve this form of coordination, policy-makers need to determine what multisectoral approaches represent the most appropriate allocation of resources, produce greater benefits, and optimize the results of the programme objectives.

REGULATORY CONSIDERATIONS

A general legislation framework and technical specifications, which are included in standards and regulations, could be placed at different levels of the wheat flour fortification programme. Regulations and standards might include (i) recommended nutrients, fortification target levels, minimum and/or maximum levels and chemical forms of nutrients in the fortified foods; (ii) labelling, claims and advertising; and (iii) regulatory monitoring, sampling procedures and enforcement measures to assure compliance. Other specifications might include physical, microbiological and contaminants limits (53). Several Codex Alimentarius standards provide general guidance that may be helpful to regulators, such as on the addition of essential nutrients; labelling and claims; and composition, quality and food safety factors in wheat flour (53, 54).

Competent authorities should determine whether the standards of fortification for wheat flour should be mandatory or voluntary. This decision may be based on the severity and extent of public health need. Input from all involved sectors when developing the regulations and standards, including producers, public institutions, academia, research organizations and consumer protection groups, will help to ensure a realistic approach.

The Code of practice for food premix operations was created by the Pan American Health Organization as a first step to assure premix quality for fortification programmes, not only in terms of adequate types and levels of nutrients added, but also in relation to hygiene, food safety, and good manufacturing practices, thereby assuring that the premix meets the minimum requirements for human consumption (55). Purity criteria for these compounds will also need to be stipulated and reference to texts such as the Food chemicals codex (56).

For implementing a wheat flour fortification programme, a well-designed regulatory monitoring system is an essential component to ensure nutrient, quality and safety standards are followed as set out in the regulations and standards. WHO and FAO have developed guidelines on fortification that describe key functions of regulatory monitoring and that identify criteria for evaluating monitoring systems, including 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 (19, 57). Regulatory monitoring encompasses all monitoring activities conducted at the production level, as well as monitoring at customs warehouses and at retail stores, by the relevant regulatory authorities as well as by producers themselves as part of self-regulation programmes. Production level regulatory monitoring comprises both internal and external monitoring and refers to the quality control and quality assurance practices conducted by producers, importers and packers. External monitoring refers to the inspection and auditing activities carried out by governmental authorities (19).

Governments should also consider regulations about trade. Mandatory fortification may impose trade restrictions on imported products based on health criteria, 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 policies and regulations that could be regionally adopted (19, 57, 58).

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 ethical challenges.

The delivery of micronutrients to populations with micronutrient deficiencies must be informed by the right to health, and duty-bearers should consider the corresponding human-rights instruments when designing the intervention and its implementation. Large-scale 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 application of food fortification standards should be voluntary or mandatory can be approached as an ethically challenging question: which of the two policy options is likely 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 wheat flour. For instance, the configuration of the industry within the country must be examined. Mandatory fortification is more feasible when the existing industry consists of large and formal mills (59). Data on wheat flour fortification around the world shows that mandatory fortification reaches a greater proportion of the population and is easier to monitor. Conversely, when the configuration of the industry within a country consists mainly of small, formal and informal businesses, mandatory fortification becomes more difficult. The decision of mandatory versus voluntary fortification must also observe international agreements of the World Trade Organization, so countries that export wheat flour may not claim that a mandatory standard or regulation is a technical barrier to trade. Therefore, mandatory fortification programmes must be supported by strong health criteria and epidemiological data. A sound, ethically informed decision must be grounded in the consideration of all relevant factors and robust evidence.

An additional ethical consideration could arise regarding the provision of iron through wheat flour fortification to groups in the population that are not affected by iron deficiency, raising questions on how to avoid causing harm. Large-scale food fortification with iron is not likely to pose a risk to an entire population because the amount of iron in fortified foods is usually well below the recommended daily allowance. Nevertheless, a public health programme on fortification of wheat flour must be carefully designed so that the selected contents are within appropriate limits. Thus, technical expertise and proper training are essential 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. The provision of folic acid through food fortification to prevent neural tube defects may also pose concerns about the safety of this intervention for other groups in the population not affected by folate deficiency or insufficiency, thus raising ethical questions on how to avoid causing harm.
Another concern that may arise is the potential effects of iron-fortified foods on individuals with thalassaemia. Since the resemblance between thalassaemia and iron deficiency can confuse the diagnosis of either disorder (60), appropriate clinical procedures and services should be designed to identify and treat individuals with this condition (61). Iron overload in individuals with thalassaemia comes from both their diet and the blood transfusions. Therefore, these individuals take iron chelators to remove excessive iron from the body. Public authorities in charge of a public health programme distributing iron through fortified foods should make sure that food items with added iron are properly labelled. This ensures that both patients with thalassaemia and the clinical staff treating them are provided with all the information needed to enable patients to adapt their diet to reduce iron absorption and clinicians to plan for quality care (62).

Other challenges that may arise when adopting fortification of wheat flour with iron is its relationship with corn-soy blends (CSBs), which are designed to provide protein to prevent malnutrition and address micronutrient deficiencies (63). They are mixed with water and cooked as porridge and are often used in food aid, especially in emergency settings (64). The composition of CSB usually includes iron, folic acid and other nutrients (63). Therefore, in settings where CSBs are distributed to affected populations, careful coordination is essential if fortified wheat flour or products become available or are distributed. The aim is to avoid the potential risk of excess intake, although this is likely to be within tolerable levels. Furthermore, a human-rights-based approach to development suggests that the involvement of potential beneficiaries in nutrition interventions in emergency settings has been associated with improvements in their nutritional status (65).

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 any scaling-up strategy (66).

**MONITORING AND EVALUATION OF GUIDELINE IMPLEMENTATION**

A plan for monitoring and evaluation with appropriate indicators, including equity-oriented indicators, is encouraged at all stages (67). 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 and Food Safety has developed a logic model for fortification of maize flour and corn meal with vitamins and minerals as a public health strategy to depict the plausible relationships between inputs and expected Sustainable Development Goals, especially goals 2 and 3, by applying the micronutrient-programme evaluation theory. This maize flour fortification logic model is adapted from the WHO/CDC logic model for micronutrient interventions and could be adapted and applied to wheat flour fortification (68) (Annex 4).

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 (69) and the manual of flour fortification (57) utilize this logic model, which can be customized for programmes of fortification of wheat flour with vitamins and minerals in public

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1. The following is the usual nutritional value for fortified blended foods, including CSB, as per information from the World Food Programme (59): energy, minimum 360 kcal; protein, minimum 18%; fat, minimum 6%; micronutrients, vitamins A, B₆, B₁₂, C, D, E, K, calcium, folic acid plus zinc, iron, niacin, pantothenic acid, potassium, riboflavin, thiamine.
health. This eCatalogue is a user-friendly, 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.

Since 1991, WHO has hosted the Micronutrients Database as part of the Vitamin and Mineral Nutrition Information System (VMNIS) (70). 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 WHO Department of Nutrition and Food Safety 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 Food Safety has developed a web-based WHO Global targets tracking tool (71) 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 (72), 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) (73) 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 (40).

The development of this guideline started in February 2010. The project included the development of guidelines on fortification of five staple foods (wheat, maize, rice, condiments, sugar and oil) and a group of micronutrients involved in maintaining health and development and whose deficiencies have severe consequences at the individual and the public health level (iron, folates, vitamin A, zinc, iodine). This fortification guideline is the third of this project. During this period, the Nutrition Department has published two fortification guidelines (maize and rice).

A WHO steering committee (Annex 5), led by the Department of Nutrition and Food Safety, was established with representatives from relevant WHO departments with an interest in the provision of scientific nutrition advice. The steering committee guided and provided overall supervision to the guideline development process. Two additional groups were formed: a guideline development group and a systematic reviews team.

The WHO guideline development group – micronutrients, was established for the biennium 2010–2011 (Annex 6A). 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 (Annex 6B) was convened for a second guideline development group meeting held virtually on 16 and 17 September 2020, to discuss the evidence and finalize the recommendations. WHO guideline development groups include experts from various WHO expert
advisory panels (74) 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. Systematic review teams participated only in the open meetings and were not allowed to participate in the decision-making process. (Annex 7).

The final draft guideline was peer-reviewed by four content experts, who provided technical feedback (Annex 8). These peer-reviewers were identified through various expert panels within and outside WHO.

Peer-reviewers are not involved in the guideline development process (40) 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; they may not 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.

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 starting point for formulating the recommendations. The questions were drafted by technical staff at the Department of Nutrition and Food Safety, based on the policy and programme guidance needs of Member States and their partners. The population, intervention, control, outcomes (PICO) format was used. 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 development 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.

This guideline builds on a body of previous work. The Flour Fortification Initiative, CDC and the Mexican Institute of Public Health held a first technical workshop entitled: “Wheat flour fortification: current knowledge and practical applications”, in Cuernavaca, Mexico in December 2004. A follow-up technical workshop entitled: “Wheat flour fortification: practical recommendations for national application”, was held in Stone Mountain, GA, United States of America in April 2008 by WHO, in collaboration with nearly 100 leading nutrition, pharmaceutical and cereal scientists and milling experts from the public and private sectors worldwide (22). The purpose of this second workshop was to provide guidance on national fortification of wheat and maize flours, milled in industrial roller mills (i.e. >20 metric tons/day milling capacity), with iron, zinc, folic acid, vitamin B₁₂ and vitamin A and to develop guidelines on formulations of premix based on common ranges of flour consumption. Expert work groups prepared technical documents that reviewed published efficacy
and effectiveness studies as well as the form and levels of fortificants currently being added to flour in different countries. The full reviews were published in a supplement of the *Food and Nutrition Bulletin* in 2010 (75).

To inform this guideline, and as detailed in the available evidence section, WHO commissioned Cochrane systematic reviews of the evidence to determine the benefits and harms of wheat flour fortification with vitamins and minerals (iron, folic acid, zinc or vitamin A) on micronutrient status and health-related outcomes in the general population. The Cochrane methodology for systematic reviews of interventions' (76) was followed. For identification of unpublished studies or studies still in progress, a standard procedure was followed to contact more than ten international organizations working on micronutrient interventions. In addition, clinicaltrials.gov (National Library of Medicine, United States of America) and the *International Clinical Trials Registry Platform* (77), hosted at WHO, were systematically searched for any trials still in progress. No language restrictions were applied in the search. Evidence summaries were prepared according to the GRADE approach, to assess the overall certainty of the evidence (38, 39). 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 review and the GRADE summary of findings tables for each of the critical outcomes were used for drafting this guideline (Annex 1). The draft recommendations were discussed by the WHO steering committee and the guideline development group, at a second guideline development group meeting, held virtually on 16–17 September 2020, where the guideline development group members received and filled out an online consensus-building form prepared using survey software (QuestionPro Inc., San Francisco, United States of America). 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 certainty 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 (Annex 3). 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 private. The WHO Secretariat (Annex 9) 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 up to 5 years. WHO staff present at the meeting, as well as the systematic reviews teams involved in the collection and grading of the evidence, did not participate in the consensus-building process. Two co-chairs with expertise in managing group processes and interpreting evidence were nominated at the opening of each consultation, and the guideline development group approved their

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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. The *Cochrane handbook for systematic reviews of interventions* (76) describes in detail the process of preparing and maintaining Cochrane systematic reviews on the effects of health-care interventions.
nomination. Members of the WHO Secretariat were always available to help guide the overall meeting process but did not vote and did not have veto power.

**MANAGEMENT OF COMPETING INTERESTS**

According to the processes recommended in the *WHO handbook for guideline development* (40), 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 declaration-of-interest statements for all guideline development group members, before finalization of the group composition and invitation to attend a guideline development group meeting. All participants, members of the guideline development group, and systematic reviews teams 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 any interests that could be perceived to affect their objectivity and independence in providing advice to WHO at the beginning of each meeting. The procedures for management of competing interests strictly followed the WHO *Guidelines for declaration of interests* (78). 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

**Dr Hector Bourges Rodriguez** declared being chair of the Board of Directors of the Danone 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 Danone Mexico, a food company and subsidiary of The Danone Company, Inc. The main products of the Danone group worldwide are dairy products, bottled water and baby products. Because Danone does not manufacture products or make claims related to the fortification of wheat flour, it was agreed that he could participate fully in the deliberations and decision-making on this guideline.

**Dr Luz Maria De-Regil** worked for an international nongovernmental agency, Nutrition International (formerly Micronutrient Initiative), which supports food-fortification programmes and was also a Member of the Executive Management Team of the Food Fortification Initiative. For the second guideline development group meeting she participated fully in decision making but was asked to verbally disclose to the other meeting participants at the start of the meeting, her previous employment at Nutrition International and her participation as member of the Executive Management Team of the Food Fortification Initiative at the start of the meeting.

**Dr Maria Elena del Socorro Jefferds** works for the International Micronutrient Malnutrition Prevention and Control Program (IMMPaCt), that financially supports the secretariat of the Food Fortification Initiative whose work includes supporting wheat flour fortification with vitamin and minerals. The leaders of her Division also participate as observers on the Executive Management Team of the Food Fortification Initiative. For the second guideline development group meeting, Dr Jefferds fully participated in decision making and was asked to verbally disclose to the other

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 the 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.**
meeting participants her employer’s involvement in financial support to the secretariat of the Food Fortification Initiative and the participation as observers in the Executive Management Team.

**Dr Lynette Neufeld** declared that her employer, the Global Alliance for Improved Nutrition, supports food-fortification programmes and that she has led research and authored several publications in the area of food fortification. For the second guideline development group meeting, Dr Neufeld declared that the organization she works for has received funding for research and programming related to food fortification, but she was not leading any of these initiatives, although she has publications in the area of food fortification. For the second guideline development group meeting Dr Neufeld fully participated in decision making and was asked to verbally disclose to the other meeting participants her personal interests in food fortification and her employer’s involvement in projects related to food fortification.

**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 government agency of the United States of America and ECSA-HC 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.

The systematic reviews teams also declared that they had no conflict of interest and 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 wheat fortification, 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 and Food Safety, in collaboration with other WHO departments or programmes, will coordinate the guideline update, following the formal procedures of the *WHO handbook for guideline development* (40).
REFERENCES


### ANNEX 1. GRADE SUMMARY OF FINDINGS TABLES

#### 1A. IRON-FORTIFIED WHEAT FLOUR WITH OR WITHOUT OTHER MICRONUTRIENTS ADDED COMPARED TO WHEAT FLOUR (NO ADDED IRON) WITH OR WITHOUT OTHER MICRONUTRIENTS ADDED FOR REDUCING ANAEMIA AND IMPROVING IRON STATUS IN POPULATIONS

**Patient or population:** general population above 2 years of age  
**Setting:** any country (settings of studies providing data for this comparison: Brazil, India, Kuwait, Pakistan, Philippines, South Africa, Sri Lanka)  
**Intervention:** iron-fortified wheat flour with or without other micronutrients added  
**Comparison:** wheat flour (no added iron) with or without other micronutrients added

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Risk with wheat flour (no added iron) with or without other micronutrients added</th>
<th>Risk with iron-fortified wheat flour with or without other micronutrients added</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia (defined as haemoglobin below WHO cut-off for age and adjusted for altitude as appropriate) follow-up: range 3 months to 24 months</td>
<td>231 per 1000&lt;sup&gt;a&lt;/sup&gt; 169 per 1000 (127 to 224)</td>
<td>RR 0.73 (0.55 to 0.97) 2315 (5 RCTs)</td>
<td>⊕⊕⊕⊕ ⊙ ⊙ ⊙ ⊙ Low a, b</td>
<td>Included studies: Barbosa 2012 (C); Cabalda 2009; Dad 2017; Muthayya 2012; Nestel 2004 (C) Data for Barbosa 2012 (C); Nestel 2004 (C) are adjusted for clustering effect</td>
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<tr>
<td>Iron deficiency (as defined by study authors, based on a biomarker of iron status) follow-up: range 5.5 months to 8 months</td>
<td>543 per 1000&lt;sup&gt;a&lt;/sup&gt; 250 per 1000 (109 to 563)</td>
<td>RR 0.46 (0.20 to 1.04) 748 (3 RCTs)</td>
<td>⊙ ⊙ ⊙ ⊙ Very low a, b</td>
<td>Included studies: Biebinger 2009; Cabalda 2009; Muthayya 2012</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin concentration (g/L) follow-up: range 3 months to 24 months</td>
<td>The mean haemoglobin concentration (g/L) was 122.63 g/L&lt;sup&gt;a&lt;/sup&gt;</td>
<td>MD 2.62 higher (0.71 lower to 4.80 higher) 2831 (8 RCTs)</td>
<td>⊙ ⊙ ⊙ ⊙ Very low a, b</td>
<td>Included studies: Amalrajan 2012; Barbosa 2012 (C); Biebinger 2009; Cabalda 2009; Dad 2017; Muthayya 2012; Nestel 2004 (C); Van Stuijvenberg 2008 (C); Data for Barbosa 2012 (C); Nestel 2004 (C) are adjusted for clustering effect</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Infection or inflammation as measured by CRP (only in children 2 to 11 years of age) follow-up: mean 7 months</td>
<td>The CRP (only in children 2 to 11 years of age) was 125.5 mg/L&lt;sup&gt;a&lt;/sup&gt;</td>
<td>MD 0.04 higher (0.02 lower to 0.11 higher) 558 (2 RCTs)</td>
<td>⊙ ⊙ ⊙ ⊙ Moderate a</td>
<td>Included studies: Amalrajan 2012; Muthayya 2012</td>
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</tbody>
</table>

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

**GRADE Working Group grades of evidence**

**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect  
**Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

**Low certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect  
**Moderate certainty:** 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

<sup>a</sup> Mean of control group values across studies included in the meta-analysis.  
<sup>b</sup> Downgraded 1 level for limitations in the study design or execution (risk of bias). Two studies included for this outcome were at low overall risk of bias and three studies were at high risk.  
<sup>c</sup> Downgraded 1 level for indirectness. Of the five studies contributing data for this outcome, three were conducted in children or adolescents. Only one study was conducted among pre-school-age children (9–71 months of age); school-age children (6–11 years of age); adult, non-pregnant women.  
<sup>d</sup> Downgraded 1 level for limitations in the study design and execution (risk of bias). Most of the information from results came from studies at overall high risk of bias, which lowers our confidence in the estimate of the effect.  
<sup>e</sup> Downgraded 1 level for inconsistency (heterogeneity measured as I^2 > 80%).  
<sup>f</sup> Downgraded 1 level for imprecision (wide confidence intervals consistent with the possibility of either a decrease or increase in the outcome).  
<sup>g</sup> Downgraded 1 level for limitations in the study design or execution (risk of bias). Most of the information from this outcome came from studies considered to have an overall high risk of bias sufficient to affect the interpretation. Two studies were at low overall risk of bias, but five studies were at high risk.  
<sup>h</sup> Downgraded 1 level for indirectness. The prevalence of anaemia at baseline varied among the trials, being low (<20%) in one trial; moderate 20–39%) in three trials; and high in two trials. One trial did not specify the prevalence of anaemia at baseline. Most studies were conducted in children.  
<sup>i</sup> Downgraded 1 level for limitations in the study design and execution. Only two studies provided information for this assessment and one was considered to have overall high risk of bias, lowering our confidence in the results.
18. IRON-FORTIFIED WHEAT FLOUR WITH OTHER MICRONUTRIENTS ADDED COMPARED TO UNFORTIFIED WHEAT FLOUR (NO MICRONUTRIENTS ADDED) FOR REDUCING ANAEMIA AND IMPROVING IRON STATUS IN POPULATIONS

**Patient or population:** general population above 2 years of age

**Setting:** any country (settings of studies providing data for this comparison: Bangladesh, Kuwait, Philippines, South Africa)

**Intervention:** iron-fortified wheat flour with other micronutrients added

**Comparison:** unfortified wheat flour (no micronutrients added)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia (defined as haemoglobin below WHO cut-off for age and adjusted for altitude as appropriate) follow-up: range 6 months to 8 months</td>
<td>Risk with unfortified wheat flour (no micronutrients added) 281 per 1000a</td>
<td>Risk with iron-fortified wheat flour with other micronutrients added 216 per 1000 (115 to 410)</td>
<td>RR 0.77 (0.41 to 1.46)</td>
<td>317 (2 RCTs)</td>
<td>⊕⊕⊕⊝ VERY LOW b, c, d</td>
</tr>
<tr>
<td>Iron deficiency (as defined by study authors, based on a biomarker of iron status) follow-up: range 5.5 months to 8 months</td>
<td>355 per 1000a</td>
<td>259 per 1000 (192 to 352)</td>
<td>RR 0.73 (0.54 to 0.99)</td>
<td>382 (3 RCTs)</td>
<td>⊕⊕⊕⊝ MODERATE *</td>
</tr>
<tr>
<td>Haemoglobin concentration (g/L) follow-up: range 5.5 months to 8 months</td>
<td>The mean haemoglobin concentration (g/L) was 123.08 g/La</td>
<td>MD 2.5 higher (0.38 lower to 5.39 higher)</td>
<td>-</td>
<td>532 (4 RCTs)</td>
<td>⊕⊕⊕⊝ VERY LOW e, f</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

(C): denotes cluster RCT; CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: risk ratio.

**GRADE Working Group grades of evidence**

**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty:** 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 certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

**Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

* Mean of control group values across studies included in the meta-analysis.

* Downgraded 1 level for limitations in the study design or execution (risk of bias). The two studies contributing information were considered as having overall high risk of bias.

* Downgraded 1 level for indirectness. The studies were conducted in children, in settings with high or moderate prevalence of anaemia.

* Downgraded 1 level for imprecision (wide confidence intervals consistent with the possibility of either a decrease or increase in the outcome).

* Downgraded 1 level for limitations in the study design or execution (risk of bias). All three studies contributing information were considered to have overall high risk of bias sufficient to affect the interpretation of the results.

* Downgraded 1 level for indirectness. One study included adult participants who were already iron-deficient and another on children who were already anaemic.
### 1C. WHEAT FLOUR OR WHEAT FLOUR PRODUCTS FORTIFIED WITH FOLIC ACID ALONE COMPARED TO UNFORTIFIED WHEAT FLOURS OR WHEAT FLOUR PRODUCTS (NOT CONTAINING FOLIC ACID NOR ANY OTHER VITAMINS AND MINERALS) FOR POPULATION HEALTH OUTCOMES

**Patient or population:** general population above two years of age  
**Setting:** any country (location for study providing data for this comparison: Canada)  
**Intervention:** wheat flour or wheat flour products fortified with folic acid alone  
**Comparison:** unfortified wheat flours or wheat flour products (no micronutrients added)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte folate concentrations (nmol/L)</td>
<td>The mean erythrocyte folate concentrations (nmol/L) was 0</td>
<td>MD 0.66 higher (0.13 lower to 1.19 higher)</td>
<td>-</td>
<td>30 (1 RCT)</td>
<td>⊕⊝⊝⊝ INCLUDED STUDY: GREEN 2013</td>
</tr>
<tr>
<td>Iron deficiency (as defined by study authors, based on a biomarker of iron status) follow-up: range 5.5 months to 8 months</td>
<td>The mean plasma folate concentrations (nmol/L) was 0</td>
<td>MD 27 higher (15.63 lower to 38.37 higher)</td>
<td>-</td>
<td>30 (1 RCT)</td>
<td>⊕⊝⊝⊝ INCLUDED STUDY: GREEN 2013</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CIs: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: risk ratio.

**GRADE Working Group grades of evidence**

**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect  
**Moderate certainty:** 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 certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect  
**Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

* Downgraded 1 level for limitations in the study design or execution (risk of bias).  
* Downgraded 1 level for indirectness, the participants were healthy men and women, aged 18–45 years who received a high dose of folic acid (400 µg [0.4 mg] folic acid/bread) which is not commonly used by the general population.  
* Downgraded 1 level for imprecision; only one study informing these outcomes with few patients and few events, wide confidence intervals.
### 1D. WHEAT FLOUR OR WHEAT FLOUR PRODUCTS FORTIFIED WITH FOLIC ACID PLUS OTHER VITAMINS AND MINERALS COMPARED TO UNFORTIFIED WHEAT FLOURS OR WHEAT FLOUR PRODUCTS (NOT CONTAINING FOLIC ACID NOR ANY OTHER VITAMINS AND MINERALS) FOR POPULATION HEALTH OUTCOMES

**Patient or population:** general population above two years of age  
**Setting:** any country (location of the study providing data for this comparison: Bangladesh)  
**Intervention:** folic acid-fortified wheat flour or wheat flour products plus other vitamins and minerals  
**Comparison:** unfortified wheat flour (no micronutrients added)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Risk with unfortified wheat floors or wheat flour products (not containing folic acid nor any other vitamins and minerals)</th>
<th>Risk with wheat flour or wheat flour products fortified with folic acid alone</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia (as defined by trialists)</td>
<td>245 per 1000 (181 to 379)</td>
<td>262 per 1000 (181 to 379)</td>
<td>RR 1.07 (0.74 to 1.55)</td>
<td>334 (1 RCT)</td>
<td>⬤مسلسل</td>
<td>LOW a,b</td>
<td>Included study: Rahman 2015 (C)</td>
</tr>
<tr>
<td>Haemoglobin concentrations (g/L)</td>
<td>The mean haemoglobin concentrations (g/L), randomized studies was 0</td>
<td>MD 0 (2.08 lower to 2.08 higher)</td>
<td>-</td>
<td>334 (1 RCT)</td>
<td>⬤مسلسل</td>
<td>LOW a,b</td>
<td>Included study: Rahman 2015 (C)</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

(C): denotes cluster RCT; CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: risk ratio.

**GRADE Working Group grades of evidence**

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
- **Moderate certainty:** 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 certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
- **Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

---

a Downgraded 1 level for indirectness, the only study informing this outcome included children aged 6 to 15 years who received daily chapatis made with wheat flour fortified with folic acid and other nutrients and minerals; food intake was supervised by an adult.

b Downgraded 1 level for imprecision, there was only one study informing this outcome, and wide confidence intervals.
### Anticipated absolute effects* (95% CI)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects</th>
<th>Risk with unfortified wheat flours or wheat flour products (not containing folic acid nor any other vitamins and minerals)</th>
<th>Risk with wheat flour or wheat flour products fortified with folic acid alone</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neural tube defects (e.g. total neural tube defects; anencephaly, spina bifida, encephalocele, meningocoele)</td>
<td>23 per 1000</td>
<td>7 per 1000</td>
<td>RR 0.32 (0.21 to 0.48)</td>
<td>8037 (1 non-RCT)</td>
<td></td>
<td>⊕ ⊕ ⊕ ⊕ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝</td>
<td>Included study: Wang 2016</td>
</tr>
<tr>
<td>Plasma folate concentrations (nmol/L)</td>
<td>The mean serum folate (nmol/L) was 19.33 nmol/L</td>
<td>MD 2.92 nmol/L higher</td>
<td></td>
<td></td>
<td>657 (2 non-RCTs)</td>
<td>⊕ ⊕ ⊕ ⊕ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝</td>
<td>Included studies: Wang 2016, Huo 2011</td>
</tr>
<tr>
<td>Anaemia (as defined by trialists)</td>
<td>35–70 per 1000</td>
<td>1000 per 1000</td>
<td>RR 0.87 (0.68 to 1.11)</td>
<td>657 (2 non-RCTs)</td>
<td></td>
<td>⊕ ⊕ ⊕ ⊕ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝ ⊝</td>
<td>Included studies: Huo 2011, Huo 2012</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).  
CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: risk ratio.  
GRADE Working Group grades of evidence  
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.  
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.  
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.  

* Downgraded 2 level limitations in the study design or execution (risk of bias). There was no evidence of randomization, the clustering effect was not taken into consideration in the statistical analysis or outcome blinding.  
* Downgraded once for indirectness due to wide confidence intervals.
1F. ZINC-FORTIFIED WHEAT FLOUR WITH ZINC ALONE COMPARED TO SAME WHEAT FLOUR WITHOUT ADDED ZINC FOR IMPROVING ZINC STATUS AND OTHER HEALTH OUTCOMES IN THE GENERAL POPULATION

Patient or population: general population above 2 years of age

Setting: any country (settings of studies providing data for this comparison: Iran, Turkey)

Intervention: zinc-fortified wheat flour with zinc alone (no other micronutrients added)

Comparison: same wheat flour without added zinc (no other micronutrients added)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum or plasma zinc (in µmol/L)</td>
<td>Risk with same foods without added zinc</td>
<td>Risk with foods fortified with zinc alone</td>
<td>-</td>
<td>99 (2 RCTs)</td>
<td>LOW **</td>
</tr>
<tr>
<td></td>
<td>The mean serum or plasma zinc (in µmol/L) was 0</td>
<td>MD 2.46 higher (2.05 lower to 2.87 higher)</td>
<td>-</td>
<td>99 (2 RCTs)</td>
<td>LOW **</td>
</tr>
<tr>
<td>All-cause morbidity</td>
<td>Risk with all-cause morbidity was 0</td>
<td>Risk with foods fortified with zinc alone</td>
<td>-</td>
<td>24 (1 RCT)</td>
<td>MODERATE*</td>
</tr>
<tr>
<td></td>
<td>The mean all-cause morbidity was 0</td>
<td>MD 1.3 lower (2.34 higher to 0.26 lower)</td>
<td>-</td>
<td>24 (1 RCT)</td>
<td>MODERATE*</td>
</tr>
<tr>
<td>Adverse effect (iron status measured as serum ferritin in µg/L) (Ln transformed)</td>
<td>Risk with serum ferritin level in µg/L</td>
<td>Risk with foods fortified with zinc alone</td>
<td>-</td>
<td>24 (1 RCT)</td>
<td>MODERATE*</td>
</tr>
<tr>
<td></td>
<td>The mean adverse effect (iron status measured as serum ferritin in µg/L (Ln transformed) was 0</td>
<td>MD 0.29 higher (0.02 lower to 0.6 higher)</td>
<td>-</td>
<td>24 (1 RCT)</td>
<td>MODERATE*</td>
</tr>
<tr>
<td>Adverse effect (copper status as measured by serum or plasma copper level in µg/dL)</td>
<td>Risk with copper status</td>
<td>Risk with foods fortified with zinc alone</td>
<td>-</td>
<td>24 (1 RCT)</td>
<td>MODERATE*</td>
</tr>
<tr>
<td></td>
<td>The mean adverse effect (copper status as measured by serum or plasma copper level in µg/dL was 0</td>
<td>MD 9.79 lower (22.5 lower to 2.92 higher)</td>
<td>-</td>
<td>24 (1 RCT)</td>
<td>MODERATE*</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

* Downgraded 1 level for risk of bias. One of the two studies contributing data for this outcome was done among 24 healthy 7–11-year old children with asymptomatic zinc deficiency (defined as serum zinc less than 65 µg/dL).

* Downgraded 1 level for indirectness. One study was conducted among children with asymptomatic zinc deficiency and another among zinc-deficient (serum zinc ≤ 70 µg/dL) non-pregnant, non-lactating women aged 19 to 49 years.

* Downgraded 1 level for risk of bias. One study had high attrition rate and no allocation concealment and the assignment was done based on the order in which the women visited hospital for antenatal care.

* Downgraded 1 level for inconsistency. The direction of the effects was different in the two studies that provided data for this outcome.

* Downgraded 1 level for indirectness. The only study contributing data for this outcome was conducted among healthy 7–11-year old children with asymptomatic zinc deficiency (defined as serum zinc < 65 µg/dL).
### 1G. ZINC-FORTIFIED WHEAT FLOUR PLUS OTHER MICRONUTRIENTS COMPARED TO WHEAT FLOUR FORTIFIED WITH OTHER MICRONUTRIENTS WITHOUT ZINC FOR IMPROVING ZINC STATUS AND OTHER HEALTH OUTCOMES IN THE GENERAL POPULATION

**Patient or population:** general population above 2 years of age

**Setting:** any country (settings of studies providing data for this comparison: China, Peru, Senegal)

**Intervention:** zinc-fortified wheat flour plus other micronutrients

**Comparison:** wheat flour fortified with other micronutrients without zinc

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc deficiency (as defined by authors, depending on the age and gender)</td>
<td>100 per 1000</td>
<td>RR 0.17 (0.01 to 3.94)</td>
<td>30</td>
<td>💫⊝⊝⊝</td>
<td>INCLUDED STUDY: Lope de Romaña 2005</td>
</tr>
<tr>
<td>Risk with foods fortified with other micronutrients without zinc</td>
<td>17 per 1000</td>
<td></td>
<td></td>
<td></td>
<td>VERY LOW a,b,c</td>
</tr>
<tr>
<td>Risk with foods fortified with zinc plus other micronutrients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum or plasma zinc (in µmol/L)</td>
<td>The mean serum or plasma zinc (in µmol/L) was 0</td>
<td>MD 0.01 lower (1.01 lower to 0.98 higher)</td>
<td>-</td>
<td>💫⊝⊝⊝</td>
<td>INCLUDED STUDIES: Aaron 2011, Haibin 2001, Lope de Romaña 2005</td>
</tr>
<tr>
<td>Anaemia (defined as haemoglobin below WHO cut-off for age and adjusted for altitude as appropriate)</td>
<td>111 per 1000</td>
<td>RR 0.89 (0.35 to 2.28)</td>
<td>137</td>
<td>💫⊝⊝⊝</td>
<td>INCLUDED STUDIES: Haibin 2001, Lope de Romaña 2005</td>
</tr>
<tr>
<td>99 per 1000 (39 to 253)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse effect (iron status measured as serum ferritin in µg/L (Ln transformed))</td>
<td>The mean adverse effect (iron status measured as serum ferritin in µg/L (Ln transformed) was 0</td>
<td>MD 0.36 lower (1.19 lower to 0.46 higher)</td>
<td>-</td>
<td>💫⊝⊝⊝</td>
<td>INCLUDED STUDY: Lope de Romaña 2005</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: risk ratio.

**GRADE Working Group grades of evidence**

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
- **Moderate certainty:** 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 certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
- **Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

a. Downgraded 1 level for imprecision and inconsistency. The confidence intervals are wide and the direction varies in the included studies.
b. Downgraded 1 level for indirectness. One study contributing data was conducted among stunted, moderately anaemic children aged 3–4 years, residing in a poor community on the periphery of Lima, Peru, and who were considered as at high risk for zinc deficiency.
c. Downgraded 1 level for imprecision. The confidence interval is very broad and data is coming from only one study among stunted, moderately anaemic children aged 3–4 years, residing in a poor community on the periphery of Lima, Peru, and who were considered as at high risk for zinc deficiency.
d. Downgraded 1 level for limitations in the study design or execution (risk of bias). In one study they were divided into five groups based on the order in which they visited hospital for antenatal care with no sequence generation.
1H. WHEAT FLOUR FORTIFIED WITH VITAMIN A COMPARED TO THE SAME FLOUR, UNFORTIFIED, FOR VITAMIN A DEFICIENCY

**Patient or population:** general population above 2 years of age

**Setting:** any country (setting of the study providing data for this comparison: Philippines)

**Intervention:** wheat flour fortified with vitamin A only

**Comparison:** same unfortified wheat flour (no micronutrients added)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Risk with same unfortified staple foods</th>
<th>Risk with wheat flour fortified with vitamin A</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum/plasma retinol (μmol/L)</td>
<td>The mean serum/plasma retinol (μmol/L) was 0</td>
<td>MD 0.01 higher (0.04 lower to 0.06 higher)</td>
<td>-</td>
<td>835 (1 study)</td>
<td>⬤⬤⬤⊝</td>
<td>LOW</td>
</tr>
<tr>
<td>Inadequate liver vitamin A stores (ratio of 3,4-dehydroretinol to retinol &lt;0.06)</td>
<td>286 per 1000</td>
<td>151 per 1000 (80 to 291)</td>
<td>RR 0.53 (0.28 to 1.02)</td>
<td>149 (1 study)</td>
<td>⬤⬤⬤⊝</td>
<td>LOW</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: risk ratio.

**GRADE Working Group grades of evidence**

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
- **Moderate certainty:** 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 certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
- **Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

* Downgraded 1 level for indirectness and 1 level for imprecision (wide confidence intervals consistent with the possibility of either a decrease or increase in the outcome).

The study was conducted in children aged 6–13 years from four schools in neighbouring villages in St Tomas, Batangas located ~60 km south of Manila, Philippines.
11. WHEAT FLOUR FORTIFIED WITH VITAMIN A PLUS OTHER MICRONUTRIENTS COMPARED TO SAME UNFORTIFIED WHEAT FLOUR FOR VITAMIN A DEFICIENCY

**Patient or population:** general population above 2 years of age  
**Setting:** any country (setting of study providing data for this comparison: Bangladesh)  
**Intervention:** wheat flour fortified with vitamin A plus other micronutrients  
**Comparison:** same unfortified wheat flour (no micronutrients added)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Serum/plasma retinol (μmol/L) | Risk with same unfortified staple foods: The mean serum/plasma retinol (μmol/L) was 0  
Risk with wheat flour fortified with vitamin A: MD 0.12 higher (0.05 higher to 0.19 higher) | - | 182 (1 study) | ⬤⬤⬤⊝ MODERATE* | Included study: Rahman 2015 (C) |
| Subclinical vitamin A deficiency (serum/plasma retinol 0.70 μmol/L or less) | 221 per 1000  
66 per 1000 (29 to 152) | RR 0.30 (0.13 to 0.69) | 182 (1 study) | ⬤⬤⬤⊝ MODERATE* | Included study: Rahman 2015 (C) |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

(C): denotes cluster RCT; CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence  
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect  
**Moderate certainty:** 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 certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect  
**Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

* Downgraded 1 level for indirectness. The only study that provided data for this outcome was conducted among children aged 6–15 years (vitamin A deficiency 13.6%) from the Mirsarai sub-district study site in the south-east Bangladesh.


### EFFECTS AND SAFETY OF RICE FORTIFICATION WITH MICRONUTRIENTS AS A PUBLIC HEALTH INTERVENTION

1. Could mass fortification of wheat flour with iron improve health outcomes?  
- If so, what iron compound(s) should be used and in what amounts?

#### POPULATION:
- General population
- Subpopulations
  - By group: young children (6–23 months; 24–59 months), school-age children (5–12 years), pregnant women, women of reproductive age (15–49 years)
  - By range of wheat flour consumption patterns: <75 g/day, 75–149 g/day, 150–300 g/day, >300 g/day
  - By overall intake of dietary enhancers or inhibitors
  - By fermentation practices: fermented versus non-fermented
  - By malaria transmission (four categories: (i) no transmission or elimination achieved, (ii) susceptibility to epidemic malaria, (iii) year-round transmission with marked seasonal fluctuations, (iv) year-round transmission; together with consideration of *Plasmodium falciparum* and/or *P. vivax*)
  - By use of concurrent antimalarial measures
  - 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%)
  - By population prevalence of hemoglobinopathies
  - By populations receiving iron supplementation versus no supplementation
  - By populations with fortification (mandatory or otherwise) of other products with iron versus no fortification
  - By prevalence of hookworm and presence or absence of a deworming programme

#### INTERVENTION:
- Wheat flour fortified with iron alone versus wheat flour fortified with iron plus other micronutrients
- Subgroup analyses
  - By type of iron compound: elemental iron powders versus ferrous sulfate versus other iron compound versus a mix of iron compounds
  - By amount of iron added to the flour, and by the wheat flour consumption group
  - Mandatory or otherwise regulated versus market-driven (voluntary) fortification of wheat flour with iron
  - By type of flour extraction: ≤80% extraction versus >80% extraction

#### CONTROL:
- Same wheat flour without added iron, or no intervention
### OUTCOMES
(in order of relevance, according to guideline development group voting):

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Iron status (as defined by trialists)</td>
</tr>
<tr>
<td>2.</td>
<td>Iron deficiency</td>
</tr>
<tr>
<td>3.</td>
<td>Iron deficiency anaemia</td>
</tr>
<tr>
<td>4.</td>
<td>Anaemia</td>
</tr>
</tbody>
</table>
| 5. | Adverse effects  
   a. Iron overload |
| 6. | Intake of dietary iron (mg/day) |
| 7. | Cognitive development *(for children only)* |
| 8. | Motor skill development *(for children only)* |
| 9. | Cognitive and work performance *(for adults only)* |
| 10. | Malaria  
   a. Incidence  
   b. Severity |
| 11. | Other infections  
   a. Sepsis |
| 12. | Birth/pregnancy outcomes  
   a. Birth weight (<1500 g versus <2500 g versus ≥2500 g)  
   b. Gestational age (<34 weeks versus <37 weeks versus ≥37 weeks)  
   c. Maternal mortality |

### SETTING:
- All countries
2. Could mass fortification of wheat flour with folic acid improve health outcomes?
- If so, what amounts should be used?

<table>
<thead>
<tr>
<th>POPULATION:</th>
<th>INTERVENTION:</th>
<th>CONTROL:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• General population</td>
<td>• Wheat flour fortified with folic acid alone versus folic acid with iron versus wheat flour fortified with folic acid plus other micronutrients</td>
<td>• Same wheat flour without added folic acid, or no intervention</td>
</tr>
<tr>
<td>• Subpopulations</td>
<td>• Subgroup analysis</td>
<td></td>
</tr>
<tr>
<td>- By group: young children (6–23 months; 24–59 months), school-age children and adolescents (5–14 years), women of reproductive age (15–49 years), pregnant women, adult males (≥19 years), older adults (≥50 years)</td>
<td>- By amount of folic acid added to the flour, and by the wheat flour consumption groups</td>
<td></td>
</tr>
<tr>
<td>- By range of wheat flour consumption patterns: &lt;75 g/day, 75–149 g/day, 150–300 g/day, &gt;300 g/day</td>
<td>- Mandatory or otherwise regulated versus market-driven (voluntary) fortification of wheat flour with folic acid</td>
<td></td>
</tr>
<tr>
<td>- By malaria transmission (four categories: (i) no transmission or elimination achieved, (ii) susceptibility to epidemic malaria, (iii) year-round transmission with marked seasonal fluctuations, (iv) year-round transmission; with consideration of <em>P. falciparum</em> and/or <em>P. vivax</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- By use of concurrent antimalarial measures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- By populations receiving supplements containing folic acid versus no folic acid supplementation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- By population prevalence of MTHFR polymorphisms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- By populations with fortification (mandatory or otherwise) of other products with folic acid versus no fortification</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### OUTCOMES (in order of relevance, according to guideline development group voting):

1. Neural tube defects
2. Other birth defects
3. Folate status (as measured by serum or red cell folate) in women of reproductive age and older adults (≥50 years)
4. Cancer
   a. Any
   b. Colorectal
5. Any adverse effects
6. Vitamin B<sub>12</sub> deficiency (as defined by trialists)
7. Intake of dietary folate (µg/day)
8. Serum homocysteine concentrations (µmol/l)
9. Anaemia
10. Efficacy of drugs
    a. Sulfadoxine-pyrimethamine
    b. Cotrimoxazole
11. Malaria
    a. Incidence
    b. Severity
12. Birth/pregnancy outcomes
    a. Birth weight (<1500 g versus <2500 g vs ≥2500 g)
    b. Gestational age (<34 weeks versus <37 weeks versus ≥37 weeks)
    c. Maternal mortality

### SETTING:

- All countries
3. Could mass fortification of wheat flour with zinc improve health outcomes?  
- If so, what zinc compound(s) should be used and in what amounts?

| POPULATION: | • General population  
• Subpopulations  
  - By group: young children (6–23 months; 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 wheat flour consumption patterns: <75 g/day, 75–149 g/day, 150–300 g/day, >300 g/day  
  - By overall intake of dietary enhancers or inhibitors  
  - By fermentation practices: fermented versus non-fermented  
  - By risk of zinc deficiency in the population (as defined by inadequate zinc intakes or a high prevalence of zinc deficiency)  
  - By nutritional status: stunted or wasted versus non-stunted or non-wasted children  
  - By populations receiving zinc supplementation versus no supplementation  
  - By populations with fortification (mandatory or otherwise) of other products with zinc versus no fortification |
|---|---|

| INTERVENTION: | • Wheat flour fortified with zinc alone versus wheat flour fortified with zinc plus other micronutrients  
• Subgroup analyses  
  - By type of zinc compound: zinc oxide versus zinc sulfate versus others  
  - By amount of zinc added to the flour and by the wheat flour consumption groups  
  - By type of flour extraction: ≤80% extraction versus >80% extraction  
  - Mandatory or otherwise regulated versus market-driven (voluntary) fortification of wheat flour with zinc |
|---|---|

<table>
<thead>
<tr>
<th>CONTROL:</th>
<th>• Same wheat flour without added zinc, or no intervention</th>
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| OUTCOMES (in order of relevance, according to guideline development group voting): | 1. Zinc deficiency  
2. Zinc status (as measured by plasma zinc)  
3. Any adverse effects  
  a. Iron status (possibly resulting from reduced iron absorption?)  
  b. Copper status  
  c. Vomiting  
4. Intake of dietary zinc (mg/day)  
5. Growth (as defined by stunting, wasting, or underweight)  
6. Morbidity  
  a. All-cause  
  b. Diarrhoea  
  c. Pneumonia  
7. Anaemia  
8. Cognitive development (for children only)  
9. Motor skill development (for children only)  
10. Cognitive and work performance (for adults only) |
|---|---|

| SETTING: | • All countries |
### ANNEX 3. SUMMARY OF GUIDELINE DEVELOPMENT GROUP CONSIDERATIONS TO DETERMINE THE STRENGTH OF THE RECOMMENDATIONS

#### CERTAINTY OF EVIDENCE:
- The certainty of the evidence was moderate, low (for most of the included studies), and very low.
- Two of the recommendations were considered strong and one was considered as moderate, although the certainty of the evidence was low or very low for the priority critical outcomes.
- In most of the included studies, the certainty of the evidence was low or very low because of experimental design, especially the type of study, imprecision, inconsistency, or publication bias.
- There was a lack of good quality evidence from the systematic reviews in response to iron status, iron deficiency or iron deficiency anaemia. Only a few studies at the country level showed the public health impact of fortification of wheat flour: a significant difference in reduction of neural tube defects and increase in haemoglobin concentrations.
- Findings indicated significant losses in B vitamins (B1, B2, B3, B6, B9 and B12) during manufacturing, distribution and cooking.
- Vitamins A and D3 are recent additions to fortification premixes for wheat and have not been well studied.

#### VALUES AND PREFERENCES:
- It is essential to consider consumer acceptability and consumers should be made aware of the potential benefits and costs. It is important that the fortificants do not change the characteristics of the flour or the products made with the wheat flour.
- The group considered that wheat flour fortification is a well-accepted intervention, although recognized the existence of sectors that are opposed to the addition of anything to foods.
- Values and preferences vary about whether a general population strategy is better than a more targeted strategy.
- Values about the importance of iron deficiency at the population level, and folate status during pregnancy, vary among settings.
- Overall benefits are uncertain since costs are involved and it is uncertain whether the public sector is willing to absorb the costs.
- Fortification requires less behaviour change than other interventions, which improves acceptability and feasibility.

#### TRADE-OFF BETWEEN BENEFITS AND HARMs:
- Benefits of fortification clearly outweigh harms.
- The evidence for undesirable effects was uncertain for iron, folic acid, zinc and vitamin A, since studies were limited in number and quality and some studies showed inconsistent results.
- The group considered the potential benefits of preventing anaemia and neural tube defects to be greater than any potential harms, for which there is no evidence.

#### EQUITY AND HUMAN RIGHTS:
- The group considered how the ability to choose fortified flour is affected by a person’s location (urban versus rural), educational attainment, and level of agency in making food choices.
- The group concluded that effective interventions to improve nutrition in disadvantaged populations could help to reduce health inequalities.
- In general, effective nutrition interventions are more likely to decrease health inequities only if they are accompanied by concurrent interventions that address the root cause of the problem.
- Current programmes may not favour increased equity, although the group considered that making such interventions mandatory could increase equity.
COSTS AND FEASIBILITY:

Costs
• The presumed benefits are worth the cost.
• In comparison with other nutrition interventions, the cost of fortification is negligible for governments and might be affordable for the end users.
• The group recognized the need for investment at industrial and government levels to implement and maintain fortification programmes.
• The long-term sustainability of fortification programmes is assured when consumers are willing and able to bear the additional cost of fortified foods.

Feasibility
• Fortification could be feasible in settings where wheat is a staple. Wheat flour fortification with at least iron has been practised for many years around the world and is a feasible intervention where implemented by millers and monitored by governments.
• In contexts of extended poverty and lack of opportunities, guaranteeing access to fortified wheat flour requires addressing the drivers of exclusion and poverty, which are socially determined and thus modifiable.
• Education is important to enhance stakeholder value, and for this reason any intervention needs to be promoted and have an education component.
ANNEX 4. LOGIC MODEL FOR FORTIFICATION OF MAIZE FLOUR AND CORN MEAL WITH VITAMINS AND MINERALS IN PUBLIC HEALTH

**Policies, production, delivery, quality, and behaviour-change communication**

**Access and coverage**
- Fortification of maize flour and corn meal is permitted in country
- Coverage of fortified maize flour and corn meal

**Outputs**
- Knowledge and appropriate use
- Target population knows, demands, accepts and uses fortified maize flour and corn meal
- Target population uses fortified maize flour and corn meal
- Impact on intake, status and function in target population

**Inputs**
- Increased intake of folic acid, iron and other micronutrients
- Improved haemoglobin concentrations, as well as red-blood-cell folate concentrations and other biomarkers of nutrition
- Improved productivity, development, and performance
- Fortification of other food vehicles
- Other interventions providing additional micronutrients
- Nutrition-sensitive actions

**Outcomes**
- Decreased anaemia, iron deficiency in women and children
- Decreased incidence of births with neural tube defects
- Sustainable Development Goals 2 and 3
  - End hunger and ensure access by all people, in particular the poor and people in vulnerable situations, including infants, to safe, nutritious and sufficient food all year round
  - End all forms of malnutrition, including achieving, by 2025, the internationally agreed targets on stunting and wasting in children under 5 years of age, and address the nutritional needs of adolescent girls, pregnant and lactating women and older persons
- End preventable deaths of neonates and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births and under-5 mortality to at least as low as 25 per 1000 live births

**Policies**
- Development, update and implementation of:
  - Food-fortification policy
  - Maize flour or corn-meal standards with addition of micronutrients
  - Product registration procedures for fortified maize flour and corn-meal premix and compounds used in fortification

**Production and supply**
- Standard operating procedures for production, packaging and monitoring of fortified maize flour
- Development and implementation of provisions, production, procurement and training strategies

**Delivery**
- Strengthening of delivery system
- Development and implementation of strategy for management, training and maintaining motivation among providers and distributors

**Quality**
- Standard operating procedures in place as described in ISO/IEC 17020 for inspections of domestic maize mills, border points of imports, and markets
- Development and implementation of external and internal quality-control systems for maize flour

**Behaviour-change communication**
- Engagement of stakeholders and advocacy
- Development and integration of maize-flour fortification in strategy for information, education and communication to support acceptability
- Implementation of marketing strategies

**Sustainable Development Goals**
- 2 and 3
  - End hunger and ensure access by all people, in particular the poor and people in vulnerable situations, including infants, to safe, nutritious and sufficient food all year round
  - End all forms of malnutrition, including achieving, by 2025, the internationally agreed targets on stunting and wasting in children under 5 years of age, and address the nutritional needs of adolescent girls, pregnant and lactating women and older persons
- End preventable deaths of neonates and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births and under-5 mortality to at least as low as 25 per 1000 live births

**Source:** Reference (68).
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