GUIDELINE:
FORTIFICATION OF RICE WITH VITAMINS AND MINERALS AS A PUBLIC HEALTH STRATEGY

World Health Organization

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PUBLICATION HISTORY

This *Guideline: fortification of rice with vitamins and minerals as a public health strategy*, is the first evidence-informed guideline from the World Health Organization (WHO) for this intervention with this specific food vehicle – rice. The focus of this document is on the use of this intervention as a public health strategy and not on market-driven fortification of rice.[1] Given the many types of rice consumed in various countries worldwide as food vehicles for fortification, as well as an update on the process currently used in fortification of rice kernels, a separate guideline for this food vehicle was deemed necessary. In order to produce this guideline, the rigorous procedures described in the *WHO handbook for guideline development* were followed. This guideline complements the WHO/FAO (Food and Agriculture Organization of the United Nations) *Guidelines on food fortification with micronutrients* (2006) and the Pan American Health Organization publication, *Iron compounds for food fortification: guidelines for Latin America and the Caribbean 2002*. This document expands the sections on dissemination and updates the summary of evidence used for the guideline, based on the most recent systematic and narrative reviews on the topic.

ACKNOWLEDGEMENTS

This guideline was coordinated by the World Health Organization (WHO) Evidence and Programme Guidance Unit, Department of Nutrition for Health and Development. Dr Maria Nieves Garcia-Casal, Dr Juan Pablo Peña-Rosas and Dr Lisa Rogers oversaw the planning and development of this guideline. Dr Maria Nieves Garcia-Casal led the preparation of this document. WHO acknowledges the technical contributions of the following individuals (in alphabetical order): Mr Filiberto Beltran, Ms Evelyn Boy-Mena and Mr Gerardo Zamora.

We would like to express our gratitude to Dr Susan Norris from the WHO Guidelines Review Committee Secretariat, and members of the Guidelines Review Committee, for their technical support throughout the process. Thanks are also due to Ms Alma Alic and Marie-Sabine Bombin from the Department of Compliance and Risk Management and Ethics, for their support in the management of conflicts-of-interest procedures. Ms Jennifer Volonnino from the Evidence and Programme Guidance Unit, Department of Nutrition for Health and Development, provided logistic support.

Special thanks are extended to the authors of the systematic reviews used in this guideline, as well as the other commissioned literature reviews used to inform this process, for their assistance and collaboration in preparing or updating them. We appreciate the feedback provided by a large number of international stakeholders during the guideline development process.

WHO gratefully acknowledges the technical input of the members of the two WHO guideline development groups involved in this process, especially the chairs and co-chairs of the two meetings concerning this guideline, Dr Janet King (2010) and Ms Rusidah Selamat and Dr Rebecca Joyce Stoltzfus (2014). We thank the peer-reviewers for their thoughtful feedback on a preliminary version of this guideline. WHO is also grateful to the staff of the Cochrane Public Health Group for their support in developing and updating the Cochrane systematic review used to inform this guideline.

[1] 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, in order to increase sales and profitability. Fortification as a public health strategy refers to the practice of deliberately increasing the content of one or more micronutrients, i.e. vitamins and minerals (including trace elements), in a food, in order to improve the nutritional quality of the food supply and provide a public health benefit with minimal risk to health.

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We would also like to thank the Global Alliance for Improved Nutrition (GAIN) for their partial financial support in a non-normative dialogue on technical considerations for rice fortification as a public health strategy, convened in Geneva, Switzerland, 8–9 October 2012, to discuss logistic aspects related to fortification programmes, including fortification technologies and current evidence on the bioavailability of micronutrients based on processing and cooking techniques.

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

GUIDELINE:[1]
FORTIFICATION OF RICE WITH VITAMINS AND MINERALS AS A PUBLIC HEALTH STRATEGY

EXECUTIVE SUMMARY

Fortification of staple foods, when appropriately implemented, can be an efficient, simple and inexpensive strategy for supplying additional vitamins and minerals to the diets of large segments of the population. Rice is cultivated in many parts of the world, as it grows in diverse climates. Industrial fortification of rice with vitamins and minerals has been practised for many years in several countries in the World Health Organization (WHO) Eastern Mediterranean Region, Western Pacific Region and Region of the Americas, where rice is a staple consumed regularly in the preparation of many common local dishes.

Decisions about the types and amounts of nutrients to add to fortified rice are commonly based on the nutritional needs and gaps in dietary intake of the target populations; the usual level of consumption of rice; the sensory and physical effects of the fortificant on the rice kernels; the fortification processing used in the production of the fortified kernels; the availability and coverage of fortification of other staple food vehicles; the population consumption of vitamin and mineral supplements; the costs; the feasibility of implementation; and the acceptability to the consumers.

Rice kernels can be fortified with several micronutrients, such as iron, folic acid and other B-complex vitamins,[2] vitamin A and zinc – some are used for restitution of the intrinsic nutritional contents prior to milling and others are used for fortification purposes. Their bioavailability will depend, importantly, on the processing used in the production of the fortified kernels.

PURPOSE OF THE GUIDELINE

This guideline provides global, evidence-informed recommendations on the fortification of rice with micronutrients, as a strategy to improve the health status of populations.

It aims to help Member States and their partners to make informed decisions on the appropriate nutrition actions to achieve the 2030 Sustainable Development Goals[3] and the global targets set in the *Comprehensive implementation plan on maternal, infant and young child nutrition*.[4]

The recommendations in this guideline are intended for a wide audience, including policy-makers, their 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 guideline complements the WHO/FAO (Food and Agriculture Organization of the United Nations) *Guidelines on food fortification with micronutrients*[5] and the Pan American Health Organization document, *Iron compounds for food fortification: guidelines for Latin America and the Caribbean 2002*.[6]

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

[2] The 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] Sustainable Knowledge Development Platform. Sustainable Development Goals (https://sustainabledevelopment.un.org/sdgs).

[4] Comprehensive implementation plan on maternal, infant and young child nutrition. Geneva: World Health Organization; 2014 (WHO/NMH/NHD/14.1; http://apps.who.int/iris/bitstream/handle/10665/113048/WHO_NMH_NHD_14.1_eng.pdf?sequence=1).

[5] Allen L, de Benoist B, Dary O, Hurrell R, editors. Guidelines on food fortification with micronutrients. Geneva: World Health Organization and Food and Agriculture Organization of the United Nations; 2006 (http://apps.who.int/iris/bitstream/handle/10665/43412/9241594012_eng.pdf?sequence=1).

[6] Dary O, Freire W, Kim S. Iron compounds for food fortification: guidelines for Latin America and the Caribbean 2002. Nutr Rev. 2002;60(7):S50–61. doi:10.1301/002966402320285218.

SUMMARY OF THE EVIDENCE

A Cochrane systematic review on fortification of rice with vitamins and minerals for addressing micronutrient malnutrition included 16 studies (14 267 participants). The search strategy was conducted in 2012 and updated in 2017. Twelve were randomized controlled trials (5167 participants) with 10 involving children in urban and rural settings and two studies involving non-pregnant non-lactating women. Four studies were controlled before-and-after studies (9100 participants). The 16 selected studies reported fortification with iron. Of these, six studies fortified rice with iron only; in 10 studies, other micronutrients were added (iron, zinc and vitamin A, and folic acid). Five studies provided other B-complex vitamins. The control for all trials was unfortified rice. The iron content ranged from 0.2 mg to 112.8 mg/100 g uncooked rice, given for a period varying from 2 weeks to 48 months.

The review showed that the provision of rice fortified with vitamins and minerals including iron, when compared with unfortified rice, probably improves iron status by reducing the risk of iron deficiency by 35% and increasing the average concentration of haemoglobin by almost 2 g/L, but may not make a difference to the risk of anaemia in the general population of those aged over 2 years. When the fortification of rice includes vitamin A, it may reduce both iron deficiency and vitamin A deficiency. When fortification includes folic acid, fortified rice may slightly increase serum folate concentrations.

In addition to the direct and indirect evidence (vitamins and minerals delivered using food vehicles other than rice) and its overall quality, other considerations were taken into account by the guideline development group, to define the direction and strength of the recommendations. They included values and preferences of the populations related to fortification of rice in different settings; trade-off between benefits and harms; costs; and feasibility.

For developing the recommendations, the guideline development group considered the certainty of the existing evidence,[1] values and preferences, costs, baseline prevalence of anaemia and/or other nutritional deficiencies, equity, and the feasibility of implementation.

[1] The Grading of Recommendations Assessment, Development and Evaluation (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 the effect estimates across all outcomes considered critical to the recommendation. Each of the critical outcomes had a confidence rating based on certainty of evidence – high, moderate, low or very low. High-certainty evidence indicates confidence that the true effect lies close to that of the estimate of the effect. Moderate-certainty evidence indicates moderate confidence 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 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 very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of effect.

RECOMMENDATIONS

- Fortification of rice with iron is recommended as a public health strategy to improve the iron status of populations, in settings where rice is a staple food[1] (*strong recommendation*,[2] *moderate-certainty evidence*).
- Fortification of rice with vitamin A may be used as a public health strategy to improve the iron status and vitamin A nutrition of populations (*conditional recommendation*,[3] *low- certainty evidence*).
- Fortification of rice with folic acid may be used as a public health strategy to improve the folate nutritional status of populations (*conditional recommendation*,[3] *very low-certainty evidence*).

REMARKS

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

- The number and amounts of nutrients should be adapted according to the needs of the country. If other fortification programmes with other food vehicles (i.e. wheat flour, maize flour or corn meal) and other micronutrient interventions are jointly implemented effectively, these suggested fortification levels need to be adjusted downwards as necessary. A combined fortification strategy using multiple vehicles appears to be a suitably effective option for reaching all segments of the population.
- There are several methods available for the fortification of rice. The method chosen depends on the local technology available, costs and other preferences. The process of adding nutrients to rice through dusting reduces the number of nutrients consumed in settings where rice is commonly washed before cooking. In particular, washing and cooking practices among a population are important considerations in selecting a method for fortification of rice. For example, rinse-resistant methods to ensure that nutrients are retained after washing will be important if rice is commonly washed before cooking.
- Rice milling results in the loss of a significant proportion of B vitamins and minerals that are found predominately in the outer germ and bran layers. Nutrient losses during milling can be minimized by a process called parboiling, in which raw rice is soaked in water and partially steamed before drying and milling, resulting in some of the B vitamins migrating further into the grain.
- Since some of the fat- and micronutrient-rich bran layers are removed during rice milling, the restoration of thiamine, niacin, riboflavin and vitamin B_6 in the fortification profile should remain a regular practice in fortification.

1 A staple food, or simply a staple, is a food that is consumed regularly and provides an important proportion of the energy (calories) and nutrient requirements. Its preparation is variable in different contexts and is closely linked to the most available foods in each place.

2 A strong recommendation is one for which the guideline development group is confident that the desirable effects of adherence outweigh the undesirable effects. Implications of a strong recommendation are that most people in these settings would desire the recommended fortification of rice with iron and only a small proportion would not. For policy-makers, a strong recommendation indicates that the recommendation can be adopted as policy in most situations.

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

- The prevalence of depletion and deficiency of vitamin B_{12} is high in all age groups, reaching 50% in some countries. The inclusion of vitamin B_{12} is recommended when staples are fortified with folic acid, to avoid the masking effect of folic acid on vitamin B_{12} deficiency.
- Fortification of rice with iron has been a challenge, since most of the bioavailable iron powders used in food fortification are coloured, which produces changes in the aspect of fortified kernels compared to unfortified ones. Ferric pyrophosphate been the choice for rice fortification because it is a white powder, although its bioavailability is low.[1] In human absorption studies, the addition of enhancing compounds such as citric acid/trisodium citrate mixtures has been linked to an increase in iron absorption from ferric pyrophosphate.[2]
- Mandatory rice-fortification programmes can only be effective if they are properly implemented and legislation enforced.
- 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 of consumption patterns and evaluation of micronutrient status in the population can inform adjustment of fortification levels over time.
- Rice fortification on a national scale requires a large, cost-effective and sustainable supply of fortified kernels.
- In malaria-endemic areas, the provision of iron through rice fortification as a public health strategy should be done in conjunction with public health measures to prevent, diagnose and treat malaria.
- Behaviour-change communication strategies may be necessary for overcoming barriers and creating and maintaining demand for fortified rice.

RESEARCH PRIORITIES

During discussions in the WHO technical meeting on rice fortification, the WHO guideline development groups and the external review group highlighted the limited evidence available in some knowledge areas, meriting further research on the fortification of rice, particularly in the following areas:

- the bioavailability of different iron compounds for use in food fortification, including mixtures of different compounds and the development of bioavailable iron compounds that do not change the colour of the rice grain;
- the effects of different phytate contents on the absorption of iron from the premix formulation;
- the efficacy and effectiveness of rice fortification with nutrients other than iron in country/ programme settings, and for different age and sex groups;

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1 Moretti D, Zimmermann MB, Wegmüller R, Walczyk T, Zeder C, Hurrell RF. Iron status and food matrix strongly affect the relative bioavailability of ferric pyrophosphate in humans. Am J Clin Nutr. 2006;83(3):632–8. doi:10.1093/ajcn.83.3.632.

2 Hackl L, Cercamondi C, Zeder C, Wild D, Adelmann H, Zimmermann M et al. Cofortification of ferric pyrophosphate and citric acid/trisodium citrate into extruded rice grains doubles iron bioavailability through in situ generation of soluble ferric pyrophosphate citrate complexes. Am J Clin Nutr. 2016;103(5):1252–9. doi:10.3945/ajcn.115.128173.

- determination of appropriate levels and combinations of nutrients and their interactions, the stability of micronutrient compounds, and their physical properties and acceptability to consumers;
- the stability of different micronutrients and compounds in different cooking processes that are context specific;
- the relative bioavailability among different chemical forms of various micronutrients that can be used in rice fortification, including nutrient–nutrient interactions;
- the acceptability of changes, if any, in organoleptic characteristics with different micronutrient combinations for different fortified-rice preparations and cooking methods;
- the most appropriate delivery platforms for reaching the intended target population;
- the effectiveness of different methods for fortification of rice in different contexts;
- validated assays for measuring the vitamin and mineral content in fortified rice.

GUIDELINE DEVELOPMENT METHODOLOGY

WHO developed the present evidence-informed recommendations using the procedures outlined in the *WHO handbook for guideline development*.[1] The steps in this process included: (i) identification of priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations, including research priorities; and planning for (v) dissemination; (vi) 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 synthesis of the evidence.

The guideline development groups consisted of content experts, methodologists and representatives of potential stakeholders and beneficiaries. For developing this guideline, one guideline group participated in a meeting held in Geneva, Switzerland on 22–25 February 2010, where the guideline was scoped. A second guideline group participated in a meeting held in Cancun, Mexico, on 3–6 November 2014, to discuss the evidence and finalize the recommendations. Additionally, WHO convened a non-normative dialogue with stakeholders, to discuss technical considerations for rice fortification in public health, on 9 and 10 October 2012, in Geneva, Switzerland. The objective of this dialogue was to review the industrial and regulatory technical considerations in rice fortification, as well as the considerations for implementing it as a public health strategy and assuring equitable access and universal coverage. External experts, as resource persons, assisted the guideline development group during the guideline development process, in presenting the evidence and identifying research priorities. Four technical experts were invited to peer-review the draft guideline.

[1] WHO handbook for guideline development, second edition. Geneva: World Health Organization; 2014 (http://apps.who.int/medicinedocs/documents/s22083en/s22083en.pdf).

PLANS FOR UPDATING THE GUIDELINE

The WHO steering group will continue to follow research developments in the area of rice fortification, particularly for areas in which the evidence was limited and its certainty 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 for Health and Development, in collaboration with other WHO departments or programmes, will coordinate the guideline update, following the formal procedures of the *WHO handbook for guideline development*.[1]

As the guideline nears the 10-year review period, the Department of Nutrition for Health and Development at the WHO headquarters in Geneva, Switzerland, along with its internal partners, will be responsible for conducting a search for appropriate new evidence.

1 WHO handbook for guideline development, second edition. Geneva: World Health Organization; 2014 (http://apps.who.int/medicinedocs/documents/s22083en/s22083en.pdf).

GUIDELINE:[1]
FORTIFICATION OF RICE WITH VITAMINS AND MINERALS AS A PUBLIC HEALTH STRATEGY

SCOPE AND PURPOSE

This guideline provides global, evidence-informed recommendations on the fortification of rice with micronutrients, as a strategy to improve the health status of populations.

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

The recommendations in this guideline are intended for a wide audience, including policy-makers, their expert advisers, 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

Cereals are the major source of food for direct human consumption. Wheat, maize and rice represent the most important cereal crops, accounting for 94% of the total cereal consumption worldwide *(4)*. Because of its wide local consumption, acceptability, reach and quantum of consumption, rice (*Oryza sativa*) far exceeds the requirements of a staple food vehicle that can be considered for fortification purposes at a population-level intervention.

According to the *Codex Alimentarius,* rice is defined as "whole and broken kernels obtained from the species *Oryza sativa* L" *(5)*. There are approximately 22 species of the genus *Oryza,* of which 20 are wild. Two species of rice are important for human consumption: *Oryza sativa*, cultivated in Asia, North and South America, the European Union, the Middle East and Africa, and *Oryza glaberrima*, confined to Africa, where it is fast being replaced by *Oryza sativa (6)*.

Paddy rice is the end-product of the harvesting and threshing of rice grains. The paddy rice is made up of an outer husk layer, germ and bran layers, and the endosperm. Various levels of milling can remove the outermost husk layer to yield brown rice kernels, or further remove the bran and germ layers to yield white rice kernels. On average, paddy rice produces 25% husk, 10% bran and germ, and 65% white rice *(7, 8)*.

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

In an average diet, 30% of calories come from rice and this can increase to more than 70% in some low-income countries, which makes rice a potentially good vehicle for delivering micronutrients to a very large number of people. From the 740 955 973 tonnes of rice produced in 2014, 90% were produced and consumed in Asia *(9)*.

Rice is a rich source of macro- and micronutrients in its unmilled form. During rice milling, the fat as well as the micronutrient-rich bran layers are removed to produce the commonly consumed starch-rich white rice, removing 75–90% of the B-group vitamins thiamine, niacin and vitamin B_6,[1] and vitamin E *(10)*.

In many cases, procedures for fortification of rice and flours (wheat and maize) 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 *(11)*. It is now recognized that there is much more variability in processing fortified rice, and that the principles that apply to fortification of wheat flour may not necessarily apply to fortification of rice *(12)*.

The technologies currently available for fortification of rice with vitamins and minerals are listed next.

- *Hot extrusion*: dough made of rice flour, vitamin/mineral mix, and water is passed through a single- or twin-screw extruder that cuts it into grain-like structures that resemble rice grains. Hot extrusion involves relatively high temperatures (70–110 °C), obtained by preconditioning and/or heat transfer through steam-heated barrel jackets. It results in fully or partially precooked simulated rice-like grains that have a similar appearance (sheen and transparency) to unfortified rice kernels *(13)*.
- *Cold extrusion*: the only thermal energy used comes from the heat generated during the process itself; thus, this is primarily a low-temperature (below 70 °C) forming process, resulting in grains that are uncooked, opaque and easier to differentiate from unfortified rice kernels. The rice premix thus developed is blended with natural polished rice at a ratio of about 1:200, to produce fortified rice *(13)*.
- *Coating*: high concentrations of micronutrients are added to a fraction of the rice and subsequently coat the rice kernels with water-resistant edible coatings; the coated kernels are then mixed with unfortified rice in a ratio ranging from 1:50 to 1:200. The major problems encountered with coating technologies are related to colour, taste and a loss of micronutrients during washing, as well as during cooking. High variability is reported among technologies for coating and in many of them, consumers are easily able to distinguish the fortified kernels, which will most likely be discarded during rice cleaning *(13, 14)*.
- *Dusting*: the polished rice grains are blended with the powder form of the vitamin/mineral premix. The vitamin/mineral mix sticks to the grain surface because of electrostatic forces. Nutrients are removed through washing and therefore a remark about not washing before cooking should be included in package *(10, 15)*.

[1] 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.

The temperatures used during the extrusion process have been recently refined to include other categories and temperature ranges that are slightly different from the above-mentioned definitions: hot extrusion (80–110 °C); warm extrusion (60–80 °C) and cold extrusion (30–50 °C) *(16)*. In general, the extruded or coated fortified rice kernels are then blended with unfortified rice in a ratio ranging from 1:50 to 1:200 *(16)*.

There are other technological processes that can increase the nutritional content of rice.

- *Parboiling* refers to soaking, steaming and drying the rice kernels before removing the bran, thus increasing the content of thiamine, niacin and vitamin B_6 in the endosperm by three-fold, owing to their migration from the bran into the endosperm, without changes in iron or zinc contents *(17)*.
- *Germination*: the steps involved in preparing germinated brown rice include soaking high-quality brown rice for 20 h in water at temperatures of 30–40 °C, then washing and cooking. The product is packaged either dry (at a moisture level of 15%) or wet (at a moisture level of 30%). The soaking process improves the rice texture and also increases the availability of nutrients, such as vitamins B_6, B_{12} and E, lysine, magnesium, fibre, inositol, potassium, zinc and magnesium. This process also heightens bioavailable forms of protein and fibre *(18)*.

Six countries have mandatory fortification of rice with at least iron and folic acid (Costa Rica, Nicaragua, Panama, Papua New Guinea, Philippines and United States of America [USA]). In 2016, the status of fortification was: Costa Rica 100% implementation, Papua New Guinea 80%, USA 70%, Philippines 1%, while in Panama and Nicaragua the implementation rate varied. Another six countries have non-mandatory, market-based fortification programmes (Brazil, Peru, Colombia, Indonesia, Mali and Myanmar) *(19)*.

Decisions about which nutrients to add, and the appropriate amounts to add to rice, should be based on the nutritional needs and gaps in dietary intake of the target populations; the usual level of consumption of fortifiable rice; the sensory and physical effects of the fortificant on the rice kernels; the fortification process used in the production of the fortified kernels; the availability and coverage of fortification of other staple food vehicles; the population consumption of vitamin and mineral supplements; the costs; the feasibility of implementation; and the acceptability to consumers *(20–23)*.

The supply chain for rice in a given country is an intricate network of public and private entities that links farmers, rice millers, rice collectors and traders, wholesale traders, 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 prices of paddy, according to their individual governmental policies *(24)*.

Countries can integrate food fortification as part of their national efforts to address malnutrition in all its forms, specifically micronutrient deficiencies and insufficiencies. The choice and concentration of nutrients for rice fortification should be considered in the context of the strategy, including consideration of the vitamin and mineral nutritional needs and the estimated dietary intake gaps of the target populations; the usual level of consumption of rice; the sensory and physical effects of the fortificant on the rice kernel and on the blended rice; the fortification of other food vehicles; population consumption of vitamin and mineral supplements; the costs; the feasibility of implementation; and the acceptability of the fortified rice to the consumers *(21)*.

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 people who mainly consume locally produced, unprocessed rice are less likely to benefit from an industrial, large-scale, rice-fortification programme.

OBJECTIVES

This guideline provides information on the health impact of the fortification of rice with micronutrients.

It complements the WHO/FAO (Food and Agriculture Organization of the United Nations) *Guidelines on food fortification with micronutrients* *(21)* and the Pan American Health Organization document, *Iron compounds for food fortification: guidelines for Latin America and the Caribbean 2002* *(25)*.

SUMMARY OF THE EVIDENCE

EFFECTS OF RICE FORTIFICATION WITH VITAMINS AND MINERALS (IRON, VITAMIN A, ZINC OR FOLIC ACID) ON MICRONUTRIENT STATUS AND HEALTH-RELATED OUTCOMES IN THE GENERAL POPULATION

A Cochrane systematic review was commissioned to inform this guideline on the effect of rice fortification on micronutrient status *(26)*. The search was initially done in 2012 and updated in July 2017. 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) (see **Annexes 1–3**).

The systematic review included 16 studies (14 267 participants) *(27–42)* and identified three ongoing studies. Twelve included studies were randomized controlled trials (5167 participants) and four were controlled before-and-after studies (9100 participants). Four studies were conducted in India, three in Thailand, two in Philippines, two in Brazil, and one each in Burundi, Cambodia, Indonesia, Mexico and USA. Two trials involved non-pregnant and non-lactating women and 10 involved preschool or school-age children. One study reported that it was conducted in a malaria-endemic area, while four studies were reported to be from non-endemic areas for malaria. The other 11 studies did not report on endemicity for malaria. All 16 studies reported fortification with iron. Of these, six studies fortified rice with iron only; in 10 studies, other micronutrients were added (iron, zinc and vitamin A, and folic acid). Five studies provided other B-complex vitamins. The control for all trials was unfortified rice. Elemental iron content ranged from 0.2 mg to 112.8 mg/100 g uncooked rice, given for a period varying from 2 weeks to 48 months. One randomized controlled trial had a high risk of bias. All controlled before-and-after studies had a high risk or unclear risk in most domains.

Regarding the fortification method for the 16 included studies, eight used a hot-extrusion process, three reported a cold-extrusion process and one included two arms with hot extrusion and one arm with warm extrusion. Two studies reported using coating methods and two did not report the method.

Fortification of rice with iron (alone or in combination with other micronutrients) may make little or no difference to the risk of anaemia (risk ratio [RR] 0.85, 95% confidence interval [CI] 0.69 to 1.04; 7 studies, 3938 participants; *low-certainty evidence*), but probably reduces the risk of iron deficiency (RR 0.65, 95% CI 0.51 to 0.82; 9 studies, 3420 participants, *moderate-certainty evidence*) and probably increases mean haemoglobin concentration (mean difference [MD] 1.77 g/L, 95% CI 0.37 g/L to 3.17 g/L; 11 studies, 4186 participants; *moderate-certainty evidence*).

Fortification of rice with vitamin A (in combination with other micronutrients) probably makes little or no difference to the risk of anaemia (RR 0.88, 95% CI 0.75 to 1.04; 3 studies, 2423 participants, *moderate-certainty evidence),* may reduce iron deficiency (RR 0.70, 95% CI 0.52 to 0.95; 5 studies, 2792 participants, *low-certainty evidence*) and may increase mean haemoglobin concentration (MD 2.35 g/L, 95% CI 0.26 g/L to 4.44 g/L; 5 studies, 2602 participants; *low-certainty evidence*). Rice fortified with vitamin A may reduce vitamin A deficiency (RR 0.55, 95% CI 0.33 to 0.92; 5 studies, 2407 participants; *low-certainty evidence*).

Fortification of rice with zinc (in combination with other micronutrients) may make little or no difference to the risk of anaemia (RR 0.99, 95% CI 0.89 to 1.11; 3 studies, 3236 participants, *moderate-certainty evidence*) or to iron deficiency (RR 0.73, 95% CI 0.45 to 1.17; 3 studies, 620 participants; *low-certainty evidence*), and may slightly increase mean haemoglobin concentration (MD 1.69 g/L, 95% CI 0.89 g/L to 2.49 g/L; 3 studies, 925 participants; *low-certainty evidence*).

Fortification of rice with folic acid (in combination with other micronutrients) may make little or no difference to the risk of anaemia (RR 0.98, 95% CI 0.88 to 1.08; 4 studies, 3494 participants; *moderate-certainty evidence*) or to iron deficiency (RR 0.84, 95% CI 0.66 to 1.07; 2 studies, 2165 participants; *very-low certainty evidence*) or mean haemoglobin concentration (MD 1.14 g/L, 95% CI –0.83 g/L to 3.10 g/L; 4 studies, 3139 participants; *very-low certainty evidence*). It may increase the serum folate concentration (MD 4.30 nmol/L, 95% CI 2.00 nmol/L to 6.60 nmol/L; one study, 215 participants; *very-low certainty evidence*). There were no included studies reporting on congenital anomalies (neural tube defect, cleft lip, cleft palate, congenital cardiovascular defects and others).

One study reported that fortification of rice with iron alone or in combination with other micronutrients increased hookworm infection (RR 1.78, 95% CI 1.18 to 2.70; 1 study, 785 participants; *low-certainty evidence).*

The review concluded that fortification of rice with iron alone or in combination with other micronutrients probably improves iron status, by reducing the risk of iron deficiency by 35% and by increasing mean haemoglobin concentrations by almost 2 g/L, but may make little or no difference to the risk of anaemia in the general population of those aged over 2 years. In addition to iron, fortification of rice with vitamin A or zinc or folic acid and other micronutrients may make little or no difference to the risk of anaemia or iron deficiency. Fortification of rice with zinc and other micronutrients may slightly increase mean haemoglobin concentrations. Fortification of rice with vitamin A and other micronutrients may reduce vitamin A deficiency. A single included study reported an increase in serum folate concentrations.

There is limited evidence on any adverse effects of rice fortification. Two studies reported on three adverse effects. There were no significant differences in reported diarrhoea or abdominal pain when consuming fortified rice. One randomized controlled trial indicated that participants taking rice fortified with iron and other micronutrients were more likely to have hookworm infection. There were no included studies reporting the effects of rice fortified with folic acid on congenital anomalies.

The quality of the direct evidence for the critical outcomes was moderate and low, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology *(43, 44)*. The GRADE summary of findings tables for the fortification of rice are shown in **Annex 1A–D**. In addition to the direct and indirect evidence (fortification delivered using food vehicles other than rice) and its overall quality, other considerations were taken into account by the guideline development group, to define the direction and strength of the recommendations. They included values and preferences of the populations related to fortification of rice in different settings; trade-off between benefits and harms; and costs and feasibility (see **Annex 3**).

Three types of iron compounds were used in the studies included in the systematic review *(26)*: ferric phosphate tetrahydrate (one study), ferrous sulfate (one study) and ferric pyrophosphate (nine studies). Ferric pyrophosphate is used to fortify rice, owing to its white colour that does not produce major changes in the appearance of the fortified kernel, although its bioavailability is low and varies with particle size *(45)*. Two studies used a micronized ferric pyrophosphate that had a particle size of 0.3 µm and was encapsulated. One study reported a particle size of 3.1 µm. Five studies described the iron used as micronized ground ferric pyrophosphate and three of these specified the particle size as 2.5 µm. One study described the iron compound as ferric pyrophosphate, without any reference to micronization or particle size, and one study did not specify the iron compound used. The amount of iron added to fortify rice also varied widely: from 0.2 mg to 112.8 mg elemental iron per 100 g rice. **Table 1** presents the iron added per 100 g of uncooked rice in each of the included studies.

TABLE 1. Fortification profile per 100 g of uncooked fortified rice in included studies

Study (author, date)	Elemental iron (mg)	Vitamin A (mg)	Zinc (mg)	Folic acid (µg)	Vitamin B_1 (thiamine) (mg)	Vitamin B_2 (riboflavin) (mg)	Vitamin B_3 (niacin) (mg)	Vitamin B_6 (pyridoxine) (mg)	Vitamin B_{12} (cobalamin) (mg)
Angeles-Agdeppa et al., 2008 *(27)*	6.25	—	—	—	—	—	—	—	—
Della Lucia et al., 2017 *(28)*	8.4	—	4.2	144	0.72	—	—	—	—
Gershoff et al., 1977 *(29)*	0.2	0.815	—	—	0.087	0.04	—	—	—
Hardinsyah et al., 2016 *(30)*	10.8	0.283	5.2	145	—	—	—	—	3.2
Hotz et al., 2008 *(31)*	26.6	—	—	—	—	—	—	—	—
Hussain et al., 2014 *(32)*	4	—	—	—	—	—	—	—	—
	—	1.2 (as beta-carotene)	—	—	—	—	—	—	—
	—	0.18	—	—	—	—	—	—	—
	4	0.18	—	—	—	—	—	—	—
	4	1.2 (as beta-carotene)	—	—	—	—	—	—	—
Losso et al., 2017 *(33)*	18	—	—	—	—	—	—	—	—
Moretti et al., 2006 *(34)*	20	—	—	—	—	—	—	—	—
Nogueira Arcanjo et al., 2013 *(35)*	112.8	—	—	—	—	—	—	—	—
Parker et al., 2015 *(36)*	11.9	—	5.7	400	—	—	—	—	—
Perignon et al., 2016 *(37)*	10.67	—	3.04	170	1.06	—	—	—	—
	7.55	0.642	2.02	280	1.43	—	12.57	—	3.8
	7.46	0.288	3.68	140	0.69	—	7.98	0.92	1.26
Pinkaew et al., 2013 *(38)*	20	2.1	18	—	—	—	—	—	—
Pinkaew et al., 2014 *(39)*	20	2.1	18	—	—	—	—	—	—
Radhika et al., 2011 *(40)*	15	—	—	—	—	—	—	—	—
Salcedo et al., 1950 *(41)*	2.86	—	—	—	0.44	—	0.33	—	—
Thankachan et al., 2012 *(42)*	12.5	0.5	3	75	0.38	—	5	0.38	0.75
	6.25	0.5	3	75	0.38	—	5	0.38	0.75

NUTRIENT STABILITY IN FORTIFIED RICE

The review *(26)* also addressed nutrient stability, depending on fortification processes and cooking practices and procedures. One study quantified the losses of five different micronutrients (vitamin A, iron, zinc, folic acid and vitamin B_{12}) in fortified rice that was produced using three different techniques (hot extrusion, cold extrusion and coating) during cooking, and five different cooking methods (absorption method with or without soaking, washing before cooking, cooking in excess water, and frying rice before cooking). The overall retention of iron, zinc, folic acid and vitamin B_{12} was between 75% and 100% and was unaffected by the cooking method, while the retention of vitamin A was significantly affected by the cooking method, with retention ranging from 0% (excess water) to 80% (soaking). All production techniques for fortified kernels yielded similar results, showing that coating was not inferior to extrusion techniques *(46)*. However, rice fortified by the same fortification methods (hot extrusion, cold extrusion, and coating) and stored in two different environments (25 ± 5 °C at a humidity of 60% and 40 ± 5 °C at a humidity of 75%) for up to 1 year, showed that under mild conditions (25 °C and humidity of 60%), losses off vitamin A ranged from 20% for cold extrusion to 30% for hot extruded rice and 77% for coated kernels. At higher temperatures and humidity, losses of vitamin A were 40–50% for extruded kernels and 93% for coated kernels after 6 months *(47)*.

Vitamin A is one of the nutrient contents most affected by the fortification procedure, storage and cooking. Fortified rice obtained by mixing artificial rice grains containing 10 mg iron, 5 mg zinc and 225 µg retinyl palmitate/g, with unfortified rice in a 1:200 mixing ratio, showed that retinyl palmitate losses were 5.3% during extrusion, 28.5% during storage and 9.8% during cooking. Further storage and light exposure increased retinyl palmitate losses, but these were not related to iron or zinc content *(47)*.

The stability of folic acid in rice obtained by hot extrusion and also containing ferric pyrophosphate and titanium oxide (as food whitener) was maintained under high temperature and humidity (40 °C, 60% relative humidity). Folic acid was generally stable, with the best sample retaining 95% and more than 75% of folic acid after 3 and 9 months of storage, respectively *(48)*. Another study showed that the stability of thiamine and folic acid varied according to the cooking method (microwaved, stir-fried, boiled + stir-fried, and from a food service) and the stability of folic acid was higher in relation to thiamine, irrespective of the cooking method employed. Retention varied between 50% and 65% for thiamine and between 76% and 96% for folic acid. Stir-frying and cooking in a microwave oven presented the highest stability for folic acid and thiamine, respectively *(49)*.

For developing the recommendations, the guideline development group considered the quality of the existing evidence, values and preferences, costs, baseline prevalence of anaemia and/or other nutritional deficiencies, equity and the feasibility of implementation. The summary of the considerations for determining the strength of the recommendations is presented in **Annex 3**.

RECOMMENDATIONS

- Fortification of rice with iron is recommended as a public health strategy to improve the iron status of populations, in settings where rice is a staple food[1] (*strong recommendation,*[2] *moderate-certainty evidence*).
- Fortification of rice with vitamin A may be used as a public health strategy to improve the iron status and vitamin A nutrition of populations (*conditional recommendation,*[3] *low- certainty evidence*).
- Fortification of rice with folic acid may be used as a public health strategy to improve the folate nutritional status of populations (*conditional recommendation,*[3] *very low-certainty evidence*).

REMARKS

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

- The number and amounts of nutrients should be adapted according to the needs of the country. If other fortification programmes with other food vehicles (i.e. wheat flour, maize flour or corn meal) and other micronutrient interventions are jointly implemented effectively, these suggested fortification levels need to be adjusted downwards as necessary. A combined fortification strategy using multiple vehicles appears to be a suitably effective option for reaching all segments of the population.
- There are several methods available for the fortification of rice. The method chosen depends on the local technology available, costs and other preferences. The process of adding nutrients to rice through dusting, reduces the number of nutrients consumed in settings where rice is commonly washed before cooking *(10).* In particular, washing and cooking practices among a population are important considerations in selecting a method for fortification of rice method. For example, rinse-resistant methods to ensure that nutrients are retained after washing will be important if rice is commonly washed before cooking.
- Rice milling results in the loss of a significant proportion of B vitamins and minerals that are found predominately in the outer germ and bran layers. Nutrient losses during milling can be minimized by a process called parboiling, in which raw rice is soaked in water and partially steamed before drying and milling, resulting in some of the B vitamins migrating further into the grain *(50).*

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1 A staple food, or simply a staple, is a food that is consumed regularly and provides an important proportion of the energy (calories) and nutrient requirements. Its preparation is variable in different contexts and is closely linked to the most available foods in each place.

2 A strong recommendation is one for which the guideline development group is confident that the desirable effects of adherence outweigh the undesirable effects. Implications of a strong recommendation are that most people in these settings would desire the recommended fortification of rice with iron and only a small proportion would not. For policy-makers, a strong recommendation indicates that the recommendation can be adopted as policy in most situations.

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

- Since some of the fat- and micronutrient-rich bran layers are removed during rice milling, the restoration of thiamine, niacin, riboflavin and vitamin B_6 in the fortification profile should remain a regular practice in fortification.
- The prevalence of depletion and deficiency of vitamin B_{12} is high in all age groups, reaching 50% in some countries *(51, 52)*. The inclusion of vitamin B_{12} is recommended when staples are fortified with folic acid, to avoid the masking effect of folic acid on vitamin B_{12} deficiency *(52, 53)*.
- Fortification of rice with iron has been a challenge, since most of the bioavailable iron powders used in food fortification are coloured, which produces changes in the aspect of fortified kernels compared to unfortified ones. Ferric pyrophosphate been the choice for rice fortification because it is a white powder, although its bioavailability is low *(45)*. In human absorption studies, the addition of enhancing compounds such as citric acid/trisodium citrate mixtures has shown an increase in iron absorption from ferric pyrophosphate *(54)*.
- Mandatory rice-fortification programmes can only be effective if they are properly implemented and legislation enforced.
- 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 of consumption patterns and evaluation of micronutrient status in the population can inform adjustment of fortification levels over time.
- Rice fortification on a national scale requires a large, cost-effective and sustainable supply of fortified kernels.
- In malaria-endemic areas, the provision of iron through rice fortification as a public health strategy should be done in conjunction with public health measures to prevent, diagnose and treat malaria.
- Behaviour-change communication strategies may be necessary for overcoming barriers and creating and maintaining demand for fortified rice.

RESEARCH PRIORITIES

During discussions in the WHO technical meeting on rice fortification, the WHO guideline development groups and the external review group highlighted the limited evidence available in some knowledge areas, meriting further research on the fortification of rice, particularly in the following areas:

- the bioavailability of different iron compounds for use in food fortification, including mixtures of different compounds and the development of bioavailable iron compounds that do not change the colour of the rice grain;
- the effects of different phytate contents on the absorption of iron from the premix formulation;
- the efficacy and effectiveness of rice fortification with nutrients other than iron in country/programme settings, and for different age and sex groups;

- determination of appropriate levels and combinations of nutrients and their interactions, the stability of micronutrient compounds, and their physical properties and acceptability to consumers;
- the stability of different micronutrients and compounds in different cooking processes that are context specific;
- the relative bioavailability among different chemical forms of various micronutrients that can be used in rice fortification, including nutrient–nutrient interactions;
- the acceptability of changes, if any, in organoleptic characteristics with different micronutrient combinations for different fortified-rice preparations and cooking methods;
- the most appropriate delivery platforms for reaching the intended target population;
- the effectiveness of different methods for fortification of rice in different contexts;
- validated assays for measuring the vitamin and mineral content in fortified rice.

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 list *(55)* social media, the WHO nutrition website *(56)* or the WHO e-Library of Evidence for Nutrition Actions (eLENA) *(57)*. 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.

This guideline will be disseminated via the *Bulletin of the World Health Organization (58),* in the public health round-up section. In addition, it will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, universities, other United Nations agencies and nongovernmental organizations. Derivative products that are useful for end-users, such as summaries and collation of recommendations related to food fortification, may be developed.

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

EQUITY, HUMAN RIGHTS AND IMPLEMENTATION CONSIDERATIONS

This guideline provides Member States with evidence-informed recommendations on the effects and safety of fortifying rice with micronutrients, as a strategy to improve the health status of populations, specifically for the reduction of anaemia and the improvement of iron status. The 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.[1] Currently, fortification of rice with micronutrients is already taking place in several Member States, and up to six countries have developed mandatory legislation *(22)*. 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 rice 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 *(59)*.

Sound data on dietary intake and a robust baseline or database on the prevalence of micronutrient deficiencies across the population are the optimal foundations 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) *(60)*. 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* *(61)* and the WHO *Health Equity Assessment Toolkit (HEAT)* *(62)*. These resources will assist Member States in the assessment of within-country health inequalities and can inform Member States adopting this guideline in the process of adaptation.

An analysis is recommended during pre-implementation stages, regarding capacities for rice production and industrialization, the nutrients needed and consumption of rice. 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 premixes. It is also recommended to carefully identify pathways and required distribution channels to inprove access and benefit hard-to-reach

[1] Equity in health refers to the absence of unjust differences in health, which are avoidable by reasonable action *(58)*. 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.

population groups. Policy-makers and 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 rice should be promoted, irrespective of geographical, cultural or economic factors, including factors that arise as a result of the implementation of the programme, which must be corrected (e.g. poor planning of distribution channels; limited access to roads for small producers; culturally irrelevant messages; weak monitoring standards). In the context of staple foods like rice, even slight changes in geographical placement, culturally adapted communication strategies, and variations in the price of the food could affect accessibility. For example, small land-holding famers often mill their rice free of cost at the local village mill in exchange for rice bran. These households may not benefit from medium- or large-scale fortification of rice *(13)*. Concurrent measures may be designed within multisectoral efforts, in order to avoid inequities in access to and availability of iron-containing fortified foods (e.g. awareness-raising campaigns; food subsidies; cash-transfer programmes; direct distribution of culturally appropriate fortified foods; and the coordinated use of other interventions distributing micronutrients, such as point-of-use fortification or supplementation).

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

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

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1 "Fidelity" is an implementation outcome variable, which indicates the degree to which an intervention is or was implemented as it was designed in an original policy, plan or protocol. A full description of different implementation outcomes (e.g. acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost, coverage and sustainability) can be found in reference *(63)*.

The programme should have well-defined objectives that take into account available resources, existing policies, suitable delivery platforms and suppliers, communication channels and potential stakeholders. Ideally, a programme for the fortification of rice should be implemented as part of a coordinated and comprehensive programme aiming to address micronutrient deficiencies. A coordinated and comprehensive fortification programme may include several food items. The selection of the foods to be fortified and the levels of nutrients to be added to those different foods must be carried out in a coordinated manner. Some countries offer suitable case-studies, such as Costa Rica, where the national fortification programme includes a basket of foods: wheat flour, maize flour, rice, milk, sugar and salt. The levels of nutrients added to these foods are determined in a coordinated manner *(65)*. While the present guideline does not offer suggested levels of nutrients for fortifying rice, a table detailing all the nutrients and concentrations used in the studies that were used for the meta-analysis in the systematic review on rice fortification *(26)* is included (see **Table 1**). National programmes considering the adoption of rice fortification should take into account any coexisting mass-fortification programmes and determine the levels of micronutrients for fortification accordingly.

Programmes fortifying rice with iron should be coordinated with antenatal care programmes that supply iron and folic acid supplements to pregnant women. Likewise, when a malaria-prevention and treatment programme is in place, the coexistence of a public health programme distributing iron is feasible, provided that coordinating measures between both programmes are formulated and observed, as has been pointed out by recent WHO guidelines *(66, 67)*.

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

REGULATORY CONSIDERATIONS

A general legislation framework, and technical specifications that are included in standards and regulations, could be placed at different levels of the rice-fortification programme. Regulations and standards might include recommended nutrients, fortification target levels, minimum and/or maximum levels, and chemical forms of nutrients in the fortified foods; labelling, claims and advertising; and regulatory monitoring, sampling procedures and enforcement measures to assure compliance. Other specifications might include physical, microbiological and contaminants limits *(66)*. Several standards of the *Codex Alimentarius* provide general guidance regarding addition of essential nutrients; labelling and claims; composition; and quality and food safety factors in rice that may be helpful to regulators *(68, 69)*.

Recommended nutrients should be adapted according to the needs of the country. A wide variety of iron compounds are currently used as food fortificants. Regulations and standards for rice fortification can either include a list of all the permitted iron-fortificant compounds based on bioavailability and safety, or it can permit the use of specific compounds. Ferric pyrophosphate has been the fortificant of choice for rice fortification because it is a white powder, although its bioavailability is low *(45)*. Absorption studies in humans, adding citric acid/trisodium citrate mixtures to ferric pyrophosphate before extrusion, showed an increase in iron absorption from ferric pyrophosphate, comparable to the absorption from ferrous fumarate or sulfate *(54)*. Purity criteria for these compounds will also need to be stipulated, with reference to texts such as the *Food Chemicals Codex (70)*. The legal minimum and maximum levels of total iron can be expressed, in order to account for significant differences in the relative bioavailability of iron from the added fortificant *(21)*.

A well-designed regulatory monitoring system is an essential component, to ensure that nutrient quality and safety standards are set in 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 that include the role of national authorities in establishing procedures, methodologies and reporting requirements to evaluate the fortification programme; allocation of responsibilities between the different actors; and a monitoring mechanism *(21)*.

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 *(71)*.

Regulatory monitoring encompasses all monitoring activities conducted at the production level, as well as monitoring at customs warehouses and at retail stores, by concerned 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 *(21, 72)*.

Competent authorities should determine whether the addition of micronutrients to rice should be mandatory or voluntary. This decision may be based on the severity and extent of public health need *(66)*. Input from all involved sectors when developing the regulation and standard, including producers, public institutions, academia, research organizations and consumer protection groups, will help to ensure a realistic approach.

Governments should also consider regulations about trade. Mandatory fortification may impose trade restrictions on imported products, either because they are unfortified or because they have been fortified differently. On the other hand, countries with similar needs may benefit from a common agreement on fortification policy and regulation that could be regionally adopted. Further information can be found in Chapter 11 of the WHO/FAO *Guidelines on food fortification with micronutrients* *(21)*.

ETHICAL CONSIDERATIONS

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

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

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

An additional ethical consideration could arise with regard to the provision of iron through rice fortification to groups in the population that are not affected by iron deficiency, triggering questions on how to avoid causing harm. Mass fortification of food 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 rice that includes iron as one of the added nutrients must be carefully designed so the levels of iron are within appropriate limits. Thus, technical expertise and proper training are necessities for all staff involved in the food programme. Likewise, coordination is fundamental between different food-fortification initiatives taking place in the same setting and between public health programmes distributing micronutrients to the same populations.

Another concern that may arise is the potential effects of iron-fortified foods on individuals suffering from thalassaemia. Since resemblance between thalassaemia and iron deficiency can confuse the diagnosis of either disorder *(75)*, appropriate clinical procedures and services should be designed to identify and treat individuals suffering from this condition. Usually, these individuals are advised to refrain from taking standard iron supplements, and have been treated with regular blood transfusions. Iron overload in individuals suffering from thalassaemia comes from both their diet and the blood transfusions. Therefore, these individuals take iron chelators to remove excessive iron from their bodies. 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, so both patients with thalassaemia and the clinical staff treating them are provided with all the information they require to enable them to adapt their diet to reduce iron absorption and plan for the quality care they need *(76)*.

Another challenge that may arise when adopting fortification of rice with iron is its relationship with corn–soy blends (CSBs), which are the main form of fortified blended foods (FBFs). CSBs are designed to provide protein and to prevent and address micronutrient deficiencies *(77)*. They are mixed with water and cooked as porridge and are often used in food aid throughout the world, especially in emergency situations and settings *(78)*. The composition[1] of CSB usually includes iron *(77)*. Therefore, in settings where CSBs are distributed to affected populations, careful coordination must be observed if fortified rice becomes available or is distributed, in order to avoid any potential risk of excessive intake, which is, nevertheless, likely to be within tolerable levels. Further, a human-rights-based approach to development suggests that the involvement of potential beneficiaries in nutrition interventions in emergency settings has been associated with improvements in their nutritional status *(79)*.

Sound implementation of this guideline, as informed by these considerations, can contribute to systematic detection of facilitators and barriers to achieving the programme goals, and to better design of any scaling-up strategy *(80)*.

MONITORING AND EVALUATION OF GUIDELINE IMPLEMENTATION

A plan for monitoring and evaluation with appropriate indicators, including equity-oriented indicators, is encouraged at all stages *(66)*. The impact of this guideline can be evaluated within countries (i.e. monitoring and evaluation of the programmes implemented at national or regional scale) and across countries (i.e. the adoption and adaptation of the guideline globally). The WHO Department of Nutrition for Health and Development and the United States Centers for Disease Control and Prevention (CDC) have developed a logic model for micronutrient interventions *(81)*, to depict the plausible relationships between inputs and expected Sustainable Development Goals (SDGs) *(1)*, especially SDG 2 and SDG 3, by applying the micronutrient-programme evaluation theory.

Member States can adjust the model presented in **Annex 4** 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 (82)*, which utilizes this logic model, can be customized for programmes of fortification of rice with vitamins and minerals in public health. This eCatalogue is a user-friendly and non-comprehensive web resource for those actively engaged in providing technical assistance in monitoring, evaluation and surveillance of public health programmes implementing micronutrient interventions. It provides potential indicators, with standard definitions that can be selected, downloaded and adapted to a local programme context.

Since 1991, WHO has hosted the Micronutrients Database as part of the Vitamin and Mineral Nutrition Information System (VMNIS) *(83)*. Part of WHO's mandate is to assess the micronutrient status of populations, monitor and evaluate the impact of strategies for the prevention and control of micronutrient malnutrition, and track related trends over time. The Evidence and Programme Guidance Unit of the Department of Nutrition for Health and Development manages the VMNIS Micronutrient Database through a network of regional and country offices, and in close collaboration with national health authorities.

[1] The following is the usual nutritional value for FBFs, including CSB, as per information from the World Food Programme *(77)*: energy, minimum 380 kcal; protein, minimum 18%; fat, minimum 6%; micronutrients, vitamins A, B_2, B_6, B_{12}, C, D, E, K, calcium, folic acid plus zinc, iron, niacin, pantothenic acid, potassium and thiamine.

For evaluation at the global level, the WHO Department of Nutrition for Health and Development has developed a web-based WHO Global targets tracking tool *(84)* 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 *(85)*, 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) *(86)* 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* *(87)*.

ADVISORY GROUPS

A WHO steering committee (see **Annex 5**), led by the Department of Nutrition for Health and Development, was established with representatives from relevant WHO departments with an interest in the provision of scientific advice on nutrition. The steering committee guided and provided overall supervision of the development process for this guideline. Three additional groups were formed: two guideline development groups and an external review group.

The WHO guideline development group – micronutrients, was established for the biennium 2010–2011 (see **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, established for the biennium 2013–2014 (see **Annex 6B**) reviewed the evidence and held deliberations on the interpretation of the evidence and the recommendations. WHO guideline development groups include experts from various WHO expert advisory panels *(88)* and those identified through open calls for specialists, taking into consideration a balanced gender mix, multiple disciplinary areas of expertise and representation from all WHO regions. Efforts were made to include content experts, methodologists, representatives of potential stakeholders (such as managers and other health professionals involved in the health-care process) and technical staff from WHO and ministries of health from Member States. Representatives of commercial organizations may not be members of a WHO guideline group. External technical experts in food fortification and review authors participated only in the open meetings and recused themselves during the deliberations (see **Annex 7).**

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

SCOPE OF THE GUIDELINE, EVIDENCE APPRAISAL AND DECISION-MAKING

An initial set of questions (and the components of the questions) to be addressed in the guideline was the critical starting point for formulating the recommendations. The questions were drafted by technical staff at the Evidence and Programme Guidance Unit, Department of Nutrition for Health and Development, based on the policy and programme guidance needs of Member States and their partners. The population, intervention, control, outcomes (PICO) format was used (see **Annex 2**). The questions were discussed and reviewed by the WHO steering committee and the guideline development group – micronutrients 2010–2011, and were modified as needed. The guideline 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**.

On 9–10 October 2012, WHO, in collaboration with the Global Alliance for Improved Nutrition, convened a non-normative dialogue in Geneva, Switzerland, on "Technical considerations for rice fortification in public health", to provide input to the guideline development process and discuss technical considerations for the fortification processes for rice. The technical consultation brought together about 50 technical experts, researchers, producers, policy-makers, programme implementers and representatives from the private sector and civil society, to collate opinions on the technology, feasibility, economic impact and legislation related to fortification of rice for the improvement of micronutrient status. The results of this meeting and the aspects covered during the meeting, the discussions and group conclusions were published in a volume of the *Annals of the New York Academy of Sciences* *(89)*.

To inform this guideline, WHO commissioned a Cochrane systematic review of the evidence, to determine the benefits and harms of fortification of rice with vitamins and minerals (iron, vitamin A, zinc or folic acid) on micronutrient status and health-related outcomes in the general population *(26)*, following the Cochrane methodology for systematic reviews of interventions *(90)*.[1] For identification of unpublished studies or studies still in progress, a standard procedure was followed to contact more than 10 international organizations working on micronutrient interventions. In addition, the clinicaltrials.gov registry (USA) *(91)* and the International Clinical Trials Registry Platform (ICTRP) *(92)*, 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 Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, to assess the overall certainty of the evidence *(43, 44)*. 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 PRISMA graph from the systematic review and the GRADE summary of findings tables for each of the critical outcomes were used for drafting this guideline (see **Annex 1A–E**). The draft recommendation was discussed by the WHO steering committee and the guideline development group – nutrition actions 2013–2014, at a consultation, held on 3–6 November 2014 in Cancun, Mexico, where

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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 (http://www.cochrane.org/). The *Cochrane handbook for systematic reviews of interventions* *(90)* describes in detail the process of preparing and maintaining Cochrane systematic reviews on the effects of health-care interventions.

the members of the guideline development group received and filled out an online consensus-building form prepared using survey software (QuestionPro® Inc., San Francisco, USA). On this form, members could indicate their positions on the recommendation, and the judgements on harms and benefits. They also noted the strength of the recommendation, taking into account: (i) the desirable and undesirable effects of the intervention; (ii) the quality of the available evidence; (iii) values and preferences related to the intervention in different settings; and (iv) the cost and feasibility of the intervention in different settings (see **Annex 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 of private character. The WHO Secretariat (see **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 other external technical experts 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 nomination. Members of the WHO Secretariat were available at all times, to help guide the overall meeting process, but did not vote and did not have veto power.

MANAGEMENT OF COMPETING INTERESTS

According to the rules in the WHO *Basic documents* *(93)* and the processes recommended in the *WHO handbook for guideline development* *(87),* all experts participating in WHO meetings must declare any interest relevant to the meeting, prior to their participation. The responsible technical officer and the relevant departments reviewed the declarations-of-interest statements for all members of the guideline development groups, before finalization of the group composition and invitation to attend a guideline development group meeting. All members of the guideline development groups, and participants of the guideline development meetings, submitted a declaration-of-interests form, along with their curriculum vitae before each meeting, as required by the Office of Compliance, Risk Management and Ethics and WHO policy. Participants of these meetings took part in their individual capacity and not as institutional representatives. In addition, they verbally declared potential conflicts of interest at the beginning of each meeting. The procedures for management of competing interests strictly followed the WHO *Guidelines for declaration of interests (WHO experts)* *(94)*. The management of the perceived or real conflicts of interest declared by the members of the guideline development groups that are relevant to this guideline is summarized next.[1] The other members of the guideline development groups declared no significant conflicts of interest.

[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.

Dr Hector Bourges Rodriquez 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 rice, it was agreed that he could participate fully in the deliberations and decision-making process on the recommendations for this guideline.

Dr Luz Maria De-Regil works for an international nongovernmental agency, Nutrition International (formerly Micronutrient Initiative), which supports food-fortification programmes. She also co-authored the systematic review related to rice fortification, which was discussed in the guideline development group meeting. She participated in the deliberations of the evidence used to inform the recommendations on the fortification of rice but recused herself from the deliberations and decision-making process on the recommendations for this guideline.

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

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

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

PLANS FOR UPDATING THE GUIDELINE

The WHO Secretariat will continue to follow research developments in the area of rice fortification, particularly for areas in which the evidence was limited and the quality 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 for Health and Development, in collaboration with other WHO departments or programmes, will coordinate the guideline update, following the formal procedures of the *WHO handbook for guideline development* *(87)*.

As the guideline nears the 10-year review period, the Department of Nutrition for Health and Development at the WHO headquarters in Geneva, Switzerland, along with its internal partners, will be responsible for conducting a search for appropriate new evidence.

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ANNEX 1. GRADE SUMMARY OF FINDINGS TABLES

A. RICE FORTIFIED WITH IRON ALONE OR IN COMBINATION WITH OTHER MICRONUTRIENTS COMPARED TO UNFORTIFIED RICE (NO MICRONUTRIENTS ADDED) FOR ADDRESSING MICRONUTRIENT MALNUTRITION

Patient or population: general population older than 2 years of age (including pregnant women) from any country
Setting: all
Intervention: rice fortified with iron alone or in combination with other micronutrients
Comparison: unfortified rice (no micronutrients added)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with unfortified rice (no micronutrients added)	Risk with rice fortified with iron alone or in combination with other micronutrients				
Anaemia (defined as haemoglobin [Hb] below the WHO cut-off value, adjusted for altitude as appropriate)	316 per 1000	**268 per 1000** (218 to 328)	**RR 0.85** (0.69 to 1.04)	3938 (7 studies)	⊕⊕⊖⊖ LOW [1]	Included studies: Angeles-Agdeppa et al., 2008 *(27)*; Hardinsyah et al., 2016 *(30)*; Hotz et al., 2008 *(31)*; Parker et al., 2015 *(36)*; Perignon et al., 2016 *(37)*; Radhika et al., 2011 *(40)*; Thankachan et al., 2012 *(42)*
Iron deficiency (as defined by trialists, based on a biomarker of iron status)	200 per 1000	**130 per 1000** (102 to 164)	**RR 0.65** (0.51 to 0.82)	3420 (9 studies)	⊕⊕⊕⊖ MODERATE [2]	Included studies: Angeles-Agdeppa et al., 2008 *(27)*; Hardinsyah et al., 2016 *(30)*; Hotz et al., 2008 *(31)*; Hussain et al., 2014 *(32)*; Moretti et al., 2006 *(34)*; Perignon et al., 2016 *(37)*; Pinkaew et al., 2013 *(38)*; Radhika et al., 2011 *(40)*; Thankachan et al., 2012 *(42)*
Haemoglobin concentration (g/L)	The mean haemoglobin concentration (g/L) in the intervention group was 1.77 more (0.37 more to 3.17 more)		—	4186 (11 studies)	⊕⊕⊕⊖ MODERATE [2]	Included studies: Angeles-Agdeppa et al., 2008 *(27)*; Hardinsyah et al., 2016 *(30)*; Hotz et al., 2008 *(31)*; Hussain et al., 2014 *(32)*; Losso et al., 2017 *(33)*; Moretti et al., 2006 *(34)*; Parker et al., 2015 *(36)*; Perignon et al., 2016 *(37)*; Pinkaew et al., 2013 *(38)*; Radhika et al., 2011 *(40)*; Thankachan et al., 2012 *(42)*
Any adverse effects (hookworm infection risk)	119 per 1000	**211 per 1000** (140 to 320)	**RR 1.78** (1.18 to 2.70)	785 (1 study)	⊕⊕⊖⊖ LOW [3]	Included study: Perignon et al., 2016 *(37)*

CI: confidence interval; **RR:** risk ratio; **WHO:** World Health Organization.
***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High 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.

[1] The baseline characteristics were not similar in all groups and the method of randomization was unclear in half of the studies.
[2] Most studies, except one, were conducted in children. In two studies, the children were moderately anaemic or the prevalence of anaemia was high in the study setting. There were inconsistencies among the studies.
[3] Only one study assessed this adverse effect of hookworm infection in an endemic setting for soil-transmitted helminth infections among children.

B. RICE FORTIFIED WITH VITAMIN A ALONE OR IN COMBINATION WITH OTHER MICRONUTRIENTS COMPARED TO UNFORTIFIED RICE (NO MICRONUTRIENTS ADDED) FOR ADDRESSING MICRONUTRIENT MALNUTRITION

Patient or population: general population older than 2 years of age (including pregnant women) from any country
Setting: all
Intervention: rice fortified with vitamin A alone or in combination with other micronutrients
Comparison: unfortified rice (no micronutrients added)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with unfortified rice (no micronutrients added)	Risk with rice fortified with iron alone or in combination with other micronutrients				
Anaemia (defined as haemoglobin below the WHO cut-off value, adjusted for altitude as appropriate)	223 per 1000	**196 per 1000** (167 to 232)	**RR 0.88** (0.75 to 1.04)	2423 (3 studies)	⊕⊕⊕⊖ MODERATE [1]	Included studies: Hardinsyah et al., 2016 *(30)*; Perignon et al., 2016 *(37)*; Thankachan et al., 2012 *(42)*
Iron deficiency (as defined by trialists, based on a biomarker of iron status)	161 per 1000	**113 per 1000** (84 to 153)	**RR 0.70** (0.52 to 0.95)	2792 (5 studies)	⊕⊕⊖⊖ LOW [2, 3]	Included studies: Hardinsyah et al., 2016 *(30)*; Hussain et al., 2014 *(32)*; Perignon et al., 2016 *(37)*; Pinkaew et al., 2013 *(38)*; Thankachan et al., 2012 *(42)*
Haemoglobin concentration (g/L)	The mean haemoglobin concentration (g/L) in the intervention group was 2.35 more (0.26 more to 4.44 more)		—	2602 (5 studies)	⊕⊕⊖⊖ LOW [3, 4, 5]	Included studies: Hardinsyah et al., 2016 *(30)*; Hussain et al., 2014 *(32)*; Perignon et al., 2016 *(37)*; Pinkaew et al., 2013 *(38)*; Thankachan et al., 2012 *(42)*
Vitamin A deficiency (as defined by trialists, by using a biomarker)	146 per 1000	**80 per 1000** (48 to 134)	**RR 0.55** (0.33 to 0.92)	2407 (5 studies)	⊕⊕⊖⊖ LOW [4, 5]	Included studies: Hardinsyaet al., 2016 *(30)*; Hussain et al., 2014 *(32)*; Perignon et al., 2016 *(37)*; Pinkaew et al., 2013 *(38)*; Thankachan et al., 2012 *(42)*
Any adverse effects (hookworm infection risk)	119 per 1000	**211 per 1000** (140 to 320)	**RR 1.78** (1.18 to 2.70)	785 (1 study)	⊕⊕⊖⊖ LOW [6]	Included study: Perignon et al., 2016 *(37)*

CI: confidence interval; **RR:** risk ratio; **WHO:** World Health Organization.
***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High 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.

1 The two studies contributing data for this outcome were conducted in children.
2 One study was conducted in children with zinc deficiency (serum zinc lower than 9.9 µmol/L) at baseline.
3 Three studies contributing data to this outcome also provided iron and zinc in the vitamin A-fortified rice intervention group.
4 The studies contributing data for this outcome were all conducted in children.
5 The direction of the effects was variable among the studies.
6 Only one study assessed this adverse effect of hookworm infection in an endemic setting for soil-transmitted helminth infections among children.

C. RICE FORTIFIED WITH ZINC ALONE OR IN COMBINATION WITH OTHER MICRONUTRIENTS COMPARED TO UNFORTIFIED RICE (NO MICRONUTRIENTS ADDED) FOR ADDRESSING MICRONUTRIENT MALNUTRITION

Patient or population: general population older than 2 years of age (including pregnant women) from any country
Setting: all
Intervention: rice fortified with zinc alone or in combination with other micronutrients
Comparison: unfortified rice (no micronutrients added)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with unfortified rice (no micronutrients added)	Risk with rice fortified with iron alone or in combination with other micronutrients				
Anaemia (defined as haemoglobin below the WHO cut-off value, adjusted for altitude as appropriate)	309 per 1000	**306 per 1000** (275 to 343)	RR 0.99 (0.89 to 1.11)	3236 (3 studies)	⊕⊕⊕⊖ MODERATE [1]	Included studies: Hardinsyah et al., 2016 *(30)*; Parker et al., 2015 *(36)*; Perignon et al., 2016 *(37)*
Iron deficiency (as defined by trialists, based on a biomarker of iron status)	191 per 1000	**139 per 1000** (86 to 223)	RR 0.73 (0.45 to 1.17)	620 (3 studies)	⊕⊕⊖⊖ LOW [1, 2]	Included studies: Hardinsyah et al., 2016 *(30)*; Pinkaew et al., 2014 (*39*); Thankachan et al., 2012 *(42)*
Haemoglobin concentration (g/L)	The mean haemoglobin concentration (g/L) in the intervention group was 1.69 more (0.89 more to 2.49 more)		—	925 (3 studies)	⊕⊕⊖⊖ LOW [1, 2]	Included studies: Hardinsyah et al., 2016 *(30)*; Perignon et al., 2016 *(37)*; Pinkaew et al., 2013 *(38)*
Any adverse effects (hookworm infection risk)	119 per 1000	**211 per 1000** (140 to 320)	RR 1.78 (1.18 to 2.70)	785 (1 study)	⊕⊕⊖⊖ LOW [3]	Included study: Perignon et al., 2016 *(37)*

CI: confidence interval; **RR:** risk ratio; **WHO:** World Health Organization.
***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High 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.

1 The two studies contributing data for this outcome were conducted in children.
2 The two studies contributing data for this outcome also provided iron, zinc and vitamin A in the zinc-fortified rice intervention group.
3 Only one study assessed this adverse effect of hookworm infection in an endemic setting for soil-transmitted helminth infections among children.

D. RICE FORTIFIED WITH FOLIC ACID ALONE OR IN COMBINATION WITH OTHER MICRONUTRIENTS COMPARED TO UNFORTIFIED RICE (NO MICRONUTRIENTS ADDED) FOR ADDRESSING MICRONUTRIENT MALNUTRITION

Patient or population: general population older than 2 years of age (including pregnant women) from any country
Setting: all
Intervention: rice fortified with folic acid alone or in combination with other micronutrients
Comparison: unfortified rice (no micronutrients added)

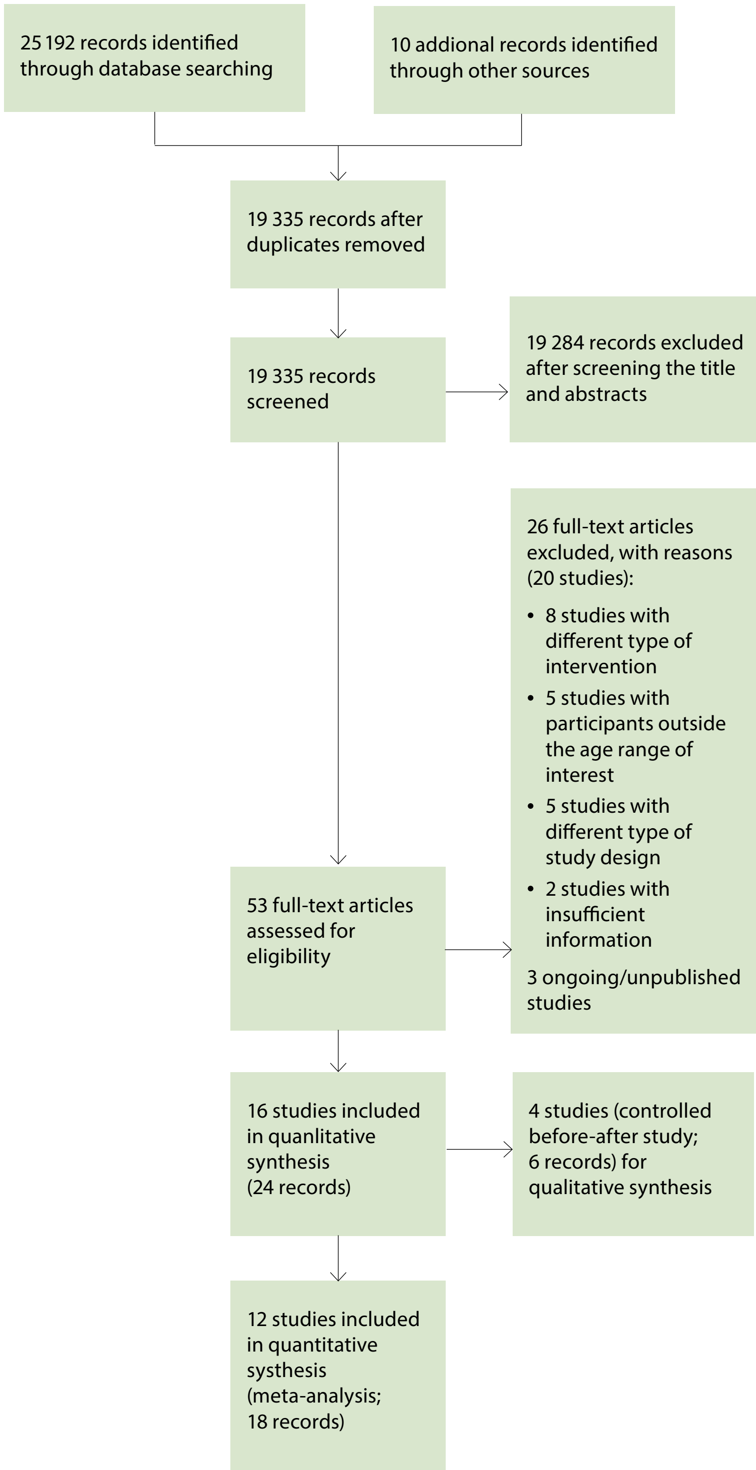
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with unfortified rice (no micronutrients added)	Risk with rice fortified with iron alone or in combination with other micronutrients				
Anaemia (defined as haemoglobin below the WHO cut-off value, adjusted for altitude as appropriate)	321 per 1000	**315 per 1000** (283 to 347)	**RR 0.98** (0.88 to 1.08)	3494 (4 studies)	⊕⊕⊕⊖ MODERATE [1]	Included studies: Hardinsyah et al., 2016 *(30)*; Parker et al., 2015 *(36)*; Perignon et al., 2016 *(37)*; Thankachan et al., 2012 *(42)*
Haemoglobin concentration (g/L)	The mean haemoglobin concentration (g/L) in the intervention group was 0.88 more (0.34 fewer to 2.1 more)		—	3139 (4 studies)	⊕⊖⊖⊖ VERY LOW [1,2,3]	Included studies: Hardinsyah et al., 2016 *(30)*; Parker et al., 2015 *(36)*; Perignon et al., 2016 *(37)*; Thankachan et al., 2012 *(42)*
Congenital anomalies (neural tube defect, cleft lip, cleft palate, congenital cardiovascular defects and others as defined by trialists)	not pooled	not pooled	not pooled	(0 studies)	—	
Serum or plasma folate (nmol/L)	The mean serum or plasma folate (nmol/L) in the intervention group was 4.3 more (2 more to 6.6 more)		—	215 (1 study)	⊕⊖⊖⊖ VERY LOW [4,5]	Included study: Hardinsyah et al., 2016 *(30)*
Any adverse effects (hookworm infection risk)	119 per 1000	**211 per 1000** (140 to 320)	**RR 1.78** (1.18 to 2.70)	785 (1 study)	⊕⊕⊖⊖ LOW [6]	Included study: Perignon et al., 2016 *(37)*

CI: confidence interval; **RR:** risk ratio; **WHO:** World Health Organization.
***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High 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.

1 The studies contributing data for this outcome were all in children.
2 The direction of the effects is not similar in all three studies contributing data for this outcome.
3 The three studies contributing data for this outcome also provided iron and zinc in the folic acid-fortified rice intervention group. One study also provided vitamin A.
4 Only one study contributed data for this outcome in this comparison.
5 Wide confidence intervals.
6 Only one study assessed this adverse effect of hookworm infection in an endemic setting for soil-transmitted helminth infections among children.

E. PRISMA STUDY FLOW DIAGRAM



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

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

1. Effects and safety of rice fortification with iron in public health

a. Could mass fortification of rice with iron and other vitamins and minerals improve health outcomes?

b. If so, what iron compound(s) should be used and in what amounts?

POPULATION:	• General population • Subgroups: – By population prevalence of anaemia in women and children aged 6–59 months (<20% versus 20–39% versus ≥40%) – By amount of iron added per quantity of rice consumed – By malaria transmission (four categories: no transmission or elimination achieved, susceptibility to epidemic malaria, year round transmission with marked seasonal fluctuations, year-round transmission; with consideration of *P. falciparum* and/or *P. vivax*) – By type of iron compound added: ferric pyrophosphate versus other – By type of method used to fortify rice: extrusion (cold, hot) versus coating versus dusting – By rice-preparation process used by consumer
INTERVENTION:	• Rice (or products made of rice) fortified with iron alone • Rice (or products made of rice) fortified with iron plus other micronutrients
CONTROL:	• Unfortified rice or no intervention • Rice fortified with other vitamins or minerals but not iron
OUTCOMES:	*Critical* 1. Anaemia (defined as haemoglobin below the World Health Organization cut-off value, adjusted for elevation above sea level, as appropriate) 2. Iron-deficiency anaemia 3. Iron deficiency 4. Haemoglobin concentration (g/L) 5. Cognitive development (for children only) 6. Any adverse effects
SETTING:	• Countries where rice is the staple food and micronutrient deficiency is prevalent or likely

2. Effects and safety of rice fortification with vitamin A in public health

a. Could mass fortification of rice with vitamin A and other vitamins and minerals improve health outcomes?

b. If so, what compound(s) should be used and in what amounts?

POPULATION:	• General population • Subgroups: – By age: infants and children aged 6–59 months, school-age children (5–12 years), and women of reproductive age (15–49 years of age) – By population prevalence of anaemia in women and children (<20% versus 20–39% versus ≥40%) – By amount of vitamin A added per quantity of rice consumed – By type of method used to fortify rice: extrusion (cold, hot) versus coating versus dusting – By rice-preparation process used by consumer
INTERVENTION:	• Rice (or products made of rice) fortified with vitamin A alone • Rice (or products made of rice) fortified with vitamin A plus other micronutrients
CONTROL:	• Unfortified rice or no intervention • Rice fortified with other vitamins or minerals but not vitamin A
OUTCOMES:	*Critical* 1. Anaemia (defined as haemoglobin below the World Health Organization cut-off value, adjusted for elevation above sea level, as appropriate) 2. Iron deficiency (as defined by trialists, based on a biomarker of iron status) 3. Haemoglobin concentration (g/L) 4. Vitamin A deficiency (as defined by trialists, by using a biomarker) 5. Any adverse effects
SETTING:	• Countries where rice is the staple food and micronutrient deficiency is prevalent or likely

3. Effects and safety of rice fortification with zinc in public health

a. Could mass fortification of rice with zinc and other vitamins and minerals improve health outcomes?

b. If so, what compound(s) should be used and in what amounts?

POPULATION:	• General population • Subgroups: – By age: infants and children aged 6–59 months, school-age children (5–12 years), and women of reproductive age (15–49 years) – By population prevalence of anaemia in women and children (<20% versus 20–39% versus ≥40%) – By amount of zinc added per quantity of rice consumed – By type of method used to fortify rice: extrusion (cold, hot) versus coating versus dusting – By rice-preparation process used by consumer
INTERVENTION:	• Rice (or products made of) fortified with zinc alone • Rice (or products made of) fortified with zinc plus other micronutrients
CONTROL:	• Unfortified rice or no intervention • Rice fortified with other vitamins or minerals but not zinc
OUTCOMES:	*Critical* 1. Anaemia (defined as haemoglobin below the World Health Organization cut-off value, adjusted for elevation above sea level, as appropriate) 2. Iron deficiency (as defined by trialists, based on a biomarker of iron status) 3. Haemoglobin concentration (g/L) 4. Any adverse effects
SETTING:	• Countries where rice is the staple food and micronutrient deficiency is prevalent or likely

4. Effects and safety of rice fortification with folic acid in public health

a. Could mass fortification of rice with folic acid and other vitamins and minerals improve health outcomes?

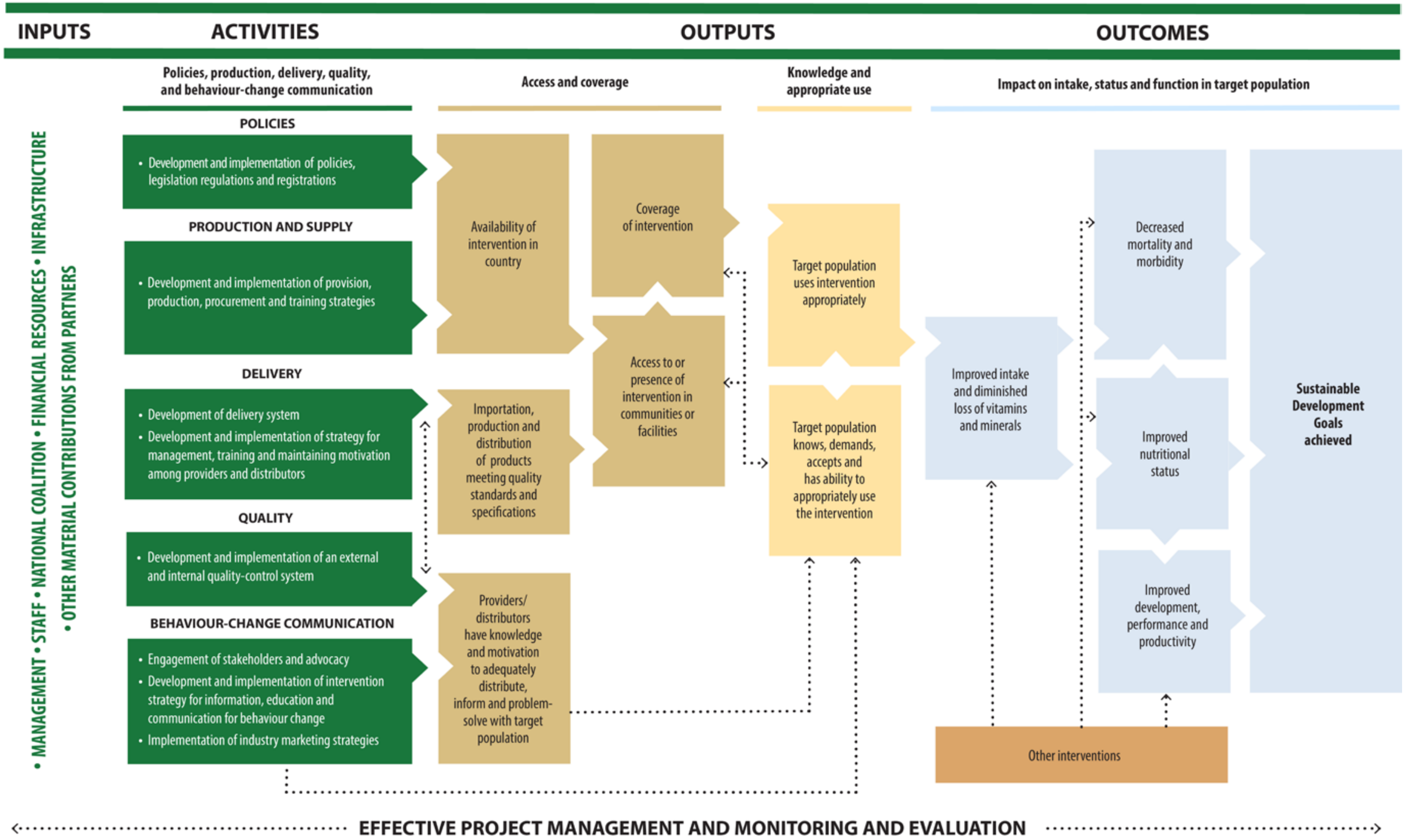
b. If so, what compound(s) should be used and in what amounts?

POPULATION:	• General population • Subgroups: – By age: infants and children aged 6–59 months, school-age children (5–12 years), women of reproductive age (15–49 years) – By population prevalence of anaemia in women and children (<20% versus 20–39% versus ≥40%) – By amount of folic acid added per quantity of rice consumed – By malaria transmission (four categories: no transmission or elimination achieved, susceptibility to epidemic malaria, year-round transmission with marked seasonal fluctuations, year-round transmission; with consideration of *P. falciparum* and/or *P. vivax*) – By type of method used to fortify rice: extrusion (cold, hot) versus coating versus dusting – By rice-preparation process used by consumer
INTERVENTION:	• Rice (or products made of) fortified with folic acid alone • Rice (or products made of) fortified with folic acid plus other micronutrients
CONTROL:	• Unfortified rice or no intervention • Rice fortified with other vitamins or minerals but not folic acid
OUTCOMES:	*Critical* 1. Anaemia (defined as haemoglobin below the World Health Organization cut-off value, adjusted for altitude as appropriate) 2. Haemoglobin concentration (g/L) 3. Congenital anomalies (neural tube defect, cleft lip, cleft palate, congenital cardiovascular defects and others, as defined by trialists) 4. Serum or plasma folate (nmol/L) 5. Any adverse effects
SETTING:	• Countries where rice is the staple food and micronutrient deficiency is prevalent or likely

ANNEX 3. SUMMARY OF THE CONSIDERATIONS OF THE MEMBERS OF THE GUIDELINE DEVELOPMENT GROUP – NUTRITION ACTIONS 2013–2014 FOR DETERMINING THE STRENGTH OF THE RECOMMENDATIONS

QUALITY OF EVIDENCE:	• The quality of direct evidence on rice fortification was moderate and low. • There was reduced risk of iron deficiency, an increase in haemoglobin concentration and no effect on anaemia risk when rice was fortified with iron. • There was reduced risk of iron and vitamin A deficiencies when the fortification of rice included vitamin A. • When fortification includes folic acid, fortified rice may slightly increase serum folate concentrations, with no effect on anaemia. • There was no effect of fortification of rice with multiple micronutrients on the risk of zinc deficiency.
VALUES AND PREFERENCES:	• The consumption of rice as a staple food varies in different settings. • Values and preferences vary about whether a general population strategy is better or a more targeted strategy. • Values about the importance of iron deficiency at the population level vary amongst settings. • Values about the importance of folate status during pregnancy vary amongst settings • Benefits are uncertain since costs are involved. Will the public sector be willing to absorb the costs?
TRADE-OFF BETWEEN BENEFITS AND HARMS:	• Benefits clearly outweigh harms. • Benefits on iron and vitamin A status. • Limited evidence on folic acid and zinc. • The studies did not show harmful effects of the fortification process on diarrhoea and gastrointestinal consequences. One study reported increases in hookworm infection. • The limited evidence shows that folic acid fortification increases serum folic acid concentrations. • Apparent harms relate to cost and providing micronutrients that may not be needed. A baseline prevalence of micronutrient deficiencies and existing programmatic data are important for implementation.
COSTS AND FEASIBILITY:	**Costs** • The presumed benefits are worth the cost. • Fortification of rice is an expensive intervention, owing to the production of fortified kernels. • The actual total costs of rice fortification are not easily captured by one conclusive number that applies globally. • Different cost elements are normally borne by different stakeholders, making the implementation of rice-fortification programmes a feasible option to reach vulnerable populations with inadequate access to affordable nutrition solutions. **Feasibility** • The capacity of industrial technology varies in different parts of the globe. • Could be feasible if the cost of fortified kernels decreased. • More research is needed to strengthen the evidence.

ANNEX 4. WORLD HEALTH ORGANIZATION/UNITED STATES CENTERS FOR DISEASE CONTROL AND PREVENTION LOGIC MODEL FOR MICRONUTRIENT INTERVENTIONS IN PUBLIC HEALTH



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

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