

Guideline:

USE OF MULTIPLE MICRONUTRIENT POWDERS

FOR POINT-OF-USE FORTIFICATION OF FOODS CONSUMED BY **PREGNANT WOMEN**



World Health
Organization

GUIDELINE:

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CONSUMED BY PREGNANT WOMEN**

WHO Library Cataloguing-in-Publication Data

Guideline: use of multiple micronutrient powders for point-of-use fortification of foods consumed by pregnant women.

1.Micronutrients - administration and dosage. 2.Anaemia, Iron-Deficiency - prevention and control. 3.Pregnancy. 4.Food, Fortified. 5.Dietary Supplements. 6.Guideline. I.World Health Organization.

ISBN 978 92 4 154951 6

(NLM classification: WH 160)

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Design and layout: Elysium sàrl

Cover photo by Gerardo Zamora and Mikel Otxotorena

Printed by the WHO Document Production Services, Geneva, Switzerland

SUGGESTED CITATION

WHO. Guideline: *Use of multiple micronutrient powders for point-of-use fortification of foods consumed by pregnant women*. Geneva: World Health Organization; 2016.

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PUBLICATION HISTORY

This guideline, *Use of multiple micronutrient powders for point-of-use fortification of foods consumed by pregnant women* is an update of the 2011 WHO guideline, *Use of multiple micronutrient powders for home fortification of foods consumed by pregnant women*. The word “home” has been substituted by “point-of-use”, to reflect the variety of settings where this intervention may take place. In order to produce this current guideline, the standard guideline development process was followed, according to the *WHO handbook for guideline development*. The current guideline updates the evidence on the use of multiple micronutrient powders by pregnant women and the overall evidence supports the continuance of the 2011 recommendation. This document expands the sections on dissemination and updates the summary of evidence used for this guideline, based on the most recent systematic review on the topic.

ACKNOWLEDGEMENTS

This updated guideline was coordinated by Mr Gerardo Zamora and Dr Lisa Rogers, under the supervision of Dr Juan Pablo Peña-Rosas. Thanks are due to Dr Susan Norris and staff from the World Health Organization (WHO) Guidelines Review Committee Secretariat for their support throughout the process and to Ms Alma Alic from the Office of Compliance and Risk Management and Ethics for her support in the management of conflicts of interest procedures. Thanks are also due to the office of the Deputy Minister for the Prevention and Promotion of Health, Ministry of Health, Mexico, for their support in the preparation of one of the consultative meetings where this guideline was discussed. WHO acknowledges the technical contribution from the following individuals (in alphabetical order): Ms Mónica Flores-Urrutia, Dr Jonathan Siekmann and Dr Pattanee Winichagoon. Ms Jennifer Volonnino from the Evidence and Programme Guidance Unit, Department of Nutrition for Health and Development, provided logistic support.

WHO gratefully acknowledges the technical input of the members of the Nutrition Steering Committee and the WHO guidelines development group – nutrition actions 2013–2014, especially the chairs of the meetings, Dr Rebecca Stoltzfus and Ms Rusidah Selamat. WHO is also grateful to the staff of the Cochrane Pregnancy and Childbirth Group, for their support during the development of the systematic review used to inform this updated guideline.

Financial support

WHO thanks the Bill & Melinda Gates Foundation for providing financial support for this work. Micronutrient Initiative provides financial support to the Evidence and Programme Guidance Unit for the commissioning of systematic reviews of nutrition interventions. 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 recommendations.

WHO GUIDELINE¹: USE OF MULTIPLE MICRONUTRIENT POWDERS FOR POINT-OF-USE FORTIFICATION OF FOODS CONSUMED BY PREGNANT WOMEN

EXECUTIVE SUMMARY

Background

Pregnant women are particularly vulnerable to vitamin and mineral deficiencies because of the increase in metabolic demands to meet fetal requirements for growth and development. It is estimated that 38.2% of pregnant women (aged 15–49 years) worldwide are anaemic and that iron deficiency anaemia represents approximately 60% of these cases in non-malarious areas and 50% in malaria-endemic settings. Vitamin and mineral deficiencies in pregnancy are associated with adverse health outcomes in both the mother and her neonate.

Purpose of the guideline

Member States have requested guidance from the World Health Organization (WHO) on the effects and safety of the use of multiple micronutrient powders for point-of-use² fortification of foods consumed by pregnant women. This guideline is intended to help Member States in their efforts to make evidence-informed decisions on the appropriate nutrition actions to improve the nutritional status of pregnant women. It will also support their efforts to achieve the [Sustainable Development Goals \(2\)](#), the global targets set by the [Comprehensive implementation plan on maternal, infant and young child nutrition \(3\)](#) and the [Global strategy for women's, children's, and adolescents' health 2016–2030 \(4\)](#).

The guideline is intended for a wide audience, including governments, nongovernmental organizations, health-care workers, scientists and donors involved in the design and implementation of micronutrient programmes and antenatal care services and their integration into national and subnational public health strategies and programmes.

Guideline development methodology

WHO developed the present evidence-informed recommendation using the procedures outlined in the [WHO handbook for guideline development \(5\)](#). 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 (v) planning for dissemination implementation, impact evaluation and updating of the guideline. The Grading of Recommendations Assessment, Development and Evaluation ([GRADE](#)) methodology was followed (6), to prepare evidence profiles related to prioritized questions, based on up-to-date systematic reviews.

The guideline development group – nutrition actions 2013–2014 consisted of content experts, methodologists, and representatives of potential stakeholders and beneficiaries. The first meeting to scope the guideline was held on 18–21 February 2013, Geneva, Switzerland. The second meeting on 23–26 June 2014, Geneva, Switzerland, aimed to examine the evidence and assess the results of the systematic review. The third and final meeting on 3–6 November 2014, Cancun, Mexico, was held to finalize the formulation of the recommendation and the research priorities. External experts, as resource persons, assisted the guideline development group during the guideline development process, in presenting the evidence and contributing to the identification

¹ This publication is a 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 Point-of-use fortification with multiple micronutrient powders refers to the addition of powders containing vitamins and minerals to energy-containing foods at home or in any other place where meals are to be consumed, such as schools, nurseries and refugee camps (1).

of research priorities. All meeting participants completed a declaration of interests form before each meeting. The final guideline document was peer-reviewed by two experts.

Available evidence

The systematic review included two trials. One trial, involving 478 pregnant women, assessed micronutrient powders for point-of-use fortification of foods versus iron and folic acid supplements. The other trial, involving 470 pregnant women, assessed micronutrient powders for point-of-use fortification of foods versus the same multiple micronutrients in supplements. No trials that assessed the other comparisons were found. Both trials took place in rural settings, one in Bangladesh and the other in Mexico. Neither of the included trial settings was endemic for malaria. The overall quality of evidence was very low and there was no evidence available for the majority of critical and important outcomes. Maternal adherence to micronutrient powders was reported to be lower than adherence to iron and folic acid supplementation (risk ratio [RR]: 0.76; 95% confidence interval [CI]: 0.66 to 0.87; $n = 405$). There were no significant differences in the prevalence of maternal anaemia at term or near term between multiple micronutrient supplements and multiple micronutrient powders containing the same micronutrient (RR: 0.92; 95% CI: 0.53 to 1.59; $n = 470$, very low quality evidence).

Recommendation

- Routine use of multiple micronutrient powders during pregnancy is *not* recommended as an alternative to standard iron and folic supplementation during pregnancy for improving maternal and infant health outcomes (*strong recommendation, very low quality of evidence*).

This recommendation is based on the very limited evidence to directly assess the potential benefits or harms of the use of point-of-use fortification with multiple micronutrient powders in pregnant women for improving maternal and infant health outcomes.

Remarks

- Evidence to date shows no added value of multiple micronutrient powders over iron and folic acid supplementation in pregnant women.
- An efficient system for the routine collection of relevant data, including therapeutic adherence and measures of programme performance, is critical to ensure supplementation programmes are effective and sustained, especially for iron and folic acid supplementation (7, 8).
- Monitoring is key to identifying barriers that might be sustaining unequal access to antenatal care, including iron and folic supplementation. Sustained implementation and scale-up largely benefit from appropriate monitoring mechanisms.

The WHO Secretariat will continue to follow the research development in the area of micronutrient supplementation for pregnant women. If the guideline merits an update, or if there are concerns about the validity of the guideline, the Department of Nutrition for Health and Development will coordinate the guideline update, following the formal procedures of the [WHO handbook for guideline development](#) (5).

As the guideline nears the 10-year review period agreed by the guideline development group, 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 new evidence. WHO welcomes suggestions regarding additional questions for evaluation in the guideline when it is due for review.

WHO GUIDELINE¹: USE OF MULTIPLE MICRONUTRIENT POWDERS FOR POINT-OF-USE FORTIFICATION OF FOODS CONSUMED BY PREGNANT WOMEN

1. SCOPE AND PURPOSE

This guideline provides a global, evidence-informed recommendation on the use of multiple micronutrient powders for point-of-use fortification of foods consumed by pregnant women.

Member States have requested guidance from the World Health Organization (WHO) on the effects and safety of the use of multiple micronutrient powders for point-of-use fortification of foods consumed by pregnant women. The guideline is intended to help Member States and their partners in their efforts to make informed decisions on the appropriate nutrition actions to improve the nutritional status of pregnant women. It will also support their efforts to achieve the Sustainable Development Goals (2), in particular, ending of hunger and improving nutrition (SDG 2) and ensuring healthy lives and promoting well-being, particularly by reducing maternal and newborn mortality (SDG 3). It will also help Member States and their efforts to achieve the global targets set by the [Comprehensive implementation plan on maternal, infant and young child nutrition](#) as endorsed by the Sixty-fifth World Health Assembly (3) and the [Global Strategy for Women's, Children's, and Adolescents' Health 2016–2030](#) (4).

The guideline is intended for a wide audience, including governments, nongovernmental organizations, health-care workers, scientists and donors involved in the design and implementation of micronutrient programmes and antenatal care services and their integration into national and subnational public health strategies and programmes.

This document presents the key recommendation. Further details of the evidence base supporting the recommendation are provided in Annex 1 and in the documents listed in the references.

This guideline is an update of the 2011 WHO guideline on *Use of multiple micronutrient powders for point-of-use fortification of foods consumed by pregnant women* (9). The current guideline updates the evidence on the use of multiple micronutrient powders by pregnant women, and the overall evidence supports continuation of the 2011 recommendation. This document expands the sections on dissemination and updates the summary of evidence used for this guideline based on the most recent systematic review on the topic.

2. BACKGROUND

Pregnant women are particularly vulnerable to vitamin and mineral deficiencies because of the increase in metabolic demands to meet fetal requirements for growth and development (10). Iron deficiency is the most common micronutrient deficiency and is the leading cause of anaemia in the general population. It is estimated that 38.2% of pregnant women (aged 15–49 years) worldwide are anaemic, i.e. 32 million pregnant women (11) and that iron deficiency anaemia represents approximately 60% of these cases in non-malarious areas and 50% in malaria-endemic settings (12). In addition to iron deficiency, pregnant women, particularly those living in low- and middle-income countries, are often deficient in multiple other nutrients such as folate, iodine or calcium (10, 13). The causes of the high burden of maternal micronutrient deficiencies include

¹ This publication is a 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 standard guideline is produced in response to a request for guidance in relation to a change in practice, or controversy in a single clinical or policy area, and is not expected to cover the full scope of the condition or public health problem. 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.

poor access to and consumption of foods with adequate micronutrient content, cultural practices and values discouraging women from gaining weight, extensive physical labour and recurrent infections (10).

Vitamin and mineral deficiencies in pregnancy are associated with adverse health outcomes in both the mother and her neonate. For example, iron deficiency accounts for 18% of maternal mortality (14) and is associated with premature delivery and low birth weight (15). Iodine deficiency is the principal cause of preventable brain damage in childhood (16) and leads to poor thyroid function and goitre in adults (17). Nearly two billion people have insufficient iodine intake, and even subclinical iodine deficiency during pregnancy increases the risk of miscarriage and fetal growth restriction (18). Vitamin A deficiency affects approximately 19 million pregnant women worldwide and is associated with an increased risk of complications and death during pregnancy and in the postpartum period (19, 20). Severe vitamin A deficiency in the mother can also lead to low vitamin A reserves in the baby, which can negatively affect lung development and survival in the first year of life (21, 22). Zinc deficiency during pregnancy may cause preterm birth or prolong labour (23) and is associated, for instance, with growth retardation, congenital abnormalities and retarded fetal neurological development (24). Inadequate consumption of calcium by pregnant women can lead to adverse effects in both the mother and the fetus, including gestational hypertension, osteopenia, tremor, delayed fetal growth, low birth weight and poor fetal mineralization (25). Folate deficiency may cause megaloblastic anaemia, and poor folate status in pregnancy has been associated with abruptio placentae, pre-eclampsia, spontaneous abortion, congenital heart defects, stillbirth, preterm delivery, low birth weight and serious congenital anomalies of the brain and spine, such as neural tube defects (26, 27). Other important micronutrients during pregnancy are vitamin B₁₂ and vitamin D.

Most women need additional iron to ensure sufficient iron stores to prevent iron deficiency during pregnancy (28). Direct iron supplementation in pregnant women is extensively used as a part of standard antenatal care to prevent and correct iron deficiency and anaemia during gestation. The provision of additional vitamins and minerals during gestation has been advocated on the basis of the assumption that, in pregnant women with iron deficiencies, other micronutrient deficiencies may also be present, which together could compromise both maternal and neonatal outcomes (29).

Recent interest in alternative ways of providing micronutrients to populations where supplementation has been difficult to implement, or where the target group is difficult to reach through mass fortification, has led to the development of multiple micronutrient powders (that is, a mixture of vitamins and minerals in powder form) (30). The powders are supplied as single-serving packets, the contents of which can be added to any semi-solid food immediately before consumption (31). Although the primary motivation behind the use of micronutrient powders has been to prevent and treat anaemia and iron deficiency in infants and young children aged 6–23 months (31), in some countries they are being used in other target groups, including preschool-age children, pregnant women and populations affected by an emergency.

3. SUMMARY OF EVIDENCE

Point-of-use fortification with multiple micronutrient powders refers to the addition of powders containing vitamins and minerals to energy-containing foods at home or in any other place where meals are to be consumed, such as schools, nurseries and refugee camps (1).

A systematic review¹ following the [Cochrane handbook for systematic reviews of interventions](#) (32) was conducted to assess the effects and safety of use of point-of-use fortification of foods with multiple micronutrient powders on maternal and neonatal health outcomes (1). The systematic review compared the

¹ The authors of the systematic review (1) are : Parminder S Suchdev (lead), Juan Pablo Peña-Rosas and Luz Maria De-Regil. PS Suchdev is with the Nutrition Branch, Emory University, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, United States of America. JP Peña-Rosas is with the World Health Organization, Geneva, Switzerland. LM De-Regil is with the Micronutrient Initiative, Ottawa, Canada.

provision of micronutrient powders added to semi-solid foods containing at least three micronutrients, with one of them being iron, provided to women during pregnancy, with: (i) no intervention or placebo; (ii) iron and folic acid supplements; (iii) iron-only supplements; (iv) folic acid-only supplements; and (v) the same multiple micronutrient supplements.

The population of interest was pregnant women (any trimester and parity); HIV-positive women or pregnant women with any other pathology were excluded. The maternal outcomes were: (i) maternal anaemia at term or near term, (haemoglobin concentration less than 110 g/L at 34 weeks' gestation or more); (ii) maternal iron deficiency at term or near term, as defined by authors of the trials, based on any indicator of iron status at 34 weeks' gestation or more; (iii) all-cause maternal mortality, i.e. death while pregnant or within 42 days of termination of pregnancy; and (iv) any adverse effects. Infant outcomes were: (i) serum ferritin concentration ($\mu\text{g/L}$) within the first 3 months; (ii) stillbirths (as defined by trial authors); (iii) haemoglobin concentration within the first three months (g/L); (iv) neonatal death (death occurring in days 0 to 28 of life); (v) stunting at any time within the first 6 months (-2 Z-score or lower); (vi) small-for-gestational-age (birth weight less than 10% of weight in reference population); (vii) early initiation of breastfeeding (put to breast within 1 h of birth); and (viii) exclusive breastfeeding (infants fed exclusively with breast milk). For populations in malaria-endemic areas, the following outcomes were reported: malaria incidence, malaria severity and placental malaria (see Annex 8).

The systematic review only included two trials (33–37), the second of which included published and unpublished data (34–37).^{1,2} One trial, involving 478 pregnant women, assessed micronutrient powders for point-of-use fortification of foods versus iron and folic acid supplements. The other trial, involving 470 pregnant women, assessed micronutrient powders for point-of-use fortification of foods versus same multiple micronutrients in supplements. No trials that assessed the other comparisons were found. Both trials took place in rural settings, one in Bangladesh and the other in Mexico. Neither of the included trial settings was endemic for malaria. The overall quality of evidence was very low (owing to methodological limitations) and there was no evidence available for the majority of critical and important outcomes.

The trial involving 478 pregnant women did not report on any of the critical outcomes. However, maternal adherence to micronutrient powders was reported to be lower than adherence to iron and folic acid supplementation (risk ratio [RR]: 0.76; 95% confidence interval [CI]: 0.66 to 0.87; $n = 405$).

The trial involving 470 pregnant women reported only one of the critical outcomes: maternal anaemia at term or near term. The comparison between multiple micronutrient supplements and multiple micronutrient powders containing the same micronutrient showed no clear difference in the prevalence of maternal anaemia at term or near term (RR: 0.92; 95% CI: 0.53 to 1.59; $n = 470$, very low quality evidence).

4. RECOMMENDATION

- Routine use of multiple micronutrient powders during pregnancy is *not* recommended as an alternative to standard iron and folic supplementation during pregnancy for improving maternal and infant health outcomes (*strong recommendation, very low quality of evidence*).

¹ The first trial is: Choudhury N, Aimone A, Hyder SM, Zlotkin SH. Relative efficacy of micronutrient powders versus iron-folic acid tablets in controlling anemia in women in the second trimester of pregnancy. *Food Nutr Bull.* 2012;33(2):142–9.

² The second trial included published and unpublished data: Colchero A, Neufeld LM. Cost estimations of different types of micronutrient supplements for children and pregnant women. *FASEB J.* 2008;22:Abstract No:678.21. Hernández Cabrera A, García Guerra A, Domínguez CP, García Feregrino R, Neufeld LM. Effect of three supplements with identical micronutrient content on anemia in pregnant Mexican women. *FASEB J.* 2008;22:Abstract No:677.8. Neufeld L. Efficacy of 3 nutritional supplements to improve diverse outcomes in children under 2 years of age and pregnant women. *ClinicalTrials.gov*. (<https://clinicaltrials.gov/ct2/show/NCT00531674>, accessed 1 March 2016). Young SL, Blanco I, Hernandez-Cordero S, Peltó GH, Neufeld LM. Organoleptic properties, ease of use, and perceived health effects are determinants of acceptability of micronutrient supplements among poor Mexican women. *J Nutr.* 2010;140(3):605–11.

This recommendation is based on the very limited evidence to directly assess the potential benefits or harms of the use of point-of-use fortification with multiple micronutrient powders in pregnant women for improving maternal and infant health outcomes.

5. REMARKS

This section presents the remarks of the guideline development group with respect to the implementation of the recommendation. The remarks, or points of good practice, are intended to assist in the implementation of this recommendation in the context of antenatal care and other delivery platforms for multiple micronutrient powders during pregnancy.

- Evidence to date shows no added value of multiple micronutrient powders over iron and folic acid supplementation in pregnant women.
- An efficient system for the routine collection of relevant data, including therapeutic adherence and measures of programme performance, is critical to ensure programmes are effective and sustained, especially iron and folic acid supplementation (7, 8).
- Monitoring is key to identifying barriers that might be sustaining unequal access to antenatal care, including iron and folic acid supplementation. Sustained implementation and scale-up largely benefit from appropriate monitoring mechanisms, as well as sustained behaviour-change interventions.

6. IMPLICATIONS FOR FUTURE RESEARCH

Discussions within the WHO guideline development group – nutrition actions 2013–2014 highlighted the limited available evidence on point-of-use fortification of foods with multiple micronutrient powders to reduce vitamin and mineral deficiencies in pregnant women, and the need for well-conducted randomized controlled trials to evaluate this intervention. In particular, future research should consider:

- Population-relevant health outcomes, including side-effects of this intervention, in pregnant women and neonates;
- Factors such as accessibility, acceptability and feasibility of and adherence to micronutrient interventions. It is necessary to further explore barriers to effective iron and folic acid supplementation in pregnant women from the user and the supply sides. It is also necessary to research the appropriate packaging of the product.

7. DISSEMINATION AND PROGRAMME IMPLICATIONS

The current guideline will be disseminated through electronic media such as slide presentations and the World Wide Web, either through the WHO Nutrition or the United Nations Standing Committee on Nutrition (SCN) mailing lists (38), social media, the [WHO nutrition web site](#) (39) or the WHO e-Library of Evidence for Nutrition Actions (eLENA) (40). eLENA compiles and displays WHO guidelines related to nutrition, along with complementary documents such as systematic reviews and other evidence that informed the guidelines; biological and behavioural rationales; and additional resources produced by Member States and global partners. In addition, the guideline will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, universities, other United Nations agencies and nongovernmental organizations. It will also be published in the [WHO Reproductive Health Library](#) (41).

Particular attention will be given to improving access to these guidelines for stakeholders that may face barriers in accessing information (e.g. distance barriers, language barriers, lack of up-to-date training), or to those that play a crucial role in antenatal care. The recommendation of this guideline states that delivering multiple

micronutrient powders is not an alternative to iron and folic acid supplementation during pregnancy. Therefore, health-care workers should be informed and, if possible, trained on what the recommended intervention is and what to do when faced with queries or demands relating to the use of multiple micronutrient powders for point-of-use fortification of foods consumed by pregnant women as an alternative to the recommended standard of care. An assessment of the barriers that may impede access to this guideline by health workers, and of training needs to understand the content of the guideline, is encouraged. Further dissemination of the current guidelines (7, 8) recommending iron and folic acid supplementation is also encouraged.

Additionally, this guideline and the information contained therein should be accessible to nongovernmental organizations and development agencies working on the implementation of nutrition interventions, especially those related to the prevention and control of anaemia in women, including pregnant women, as they usually work in close coordination with national authorities.

8. 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](#) (5).

Advisory groups

The WHO Steering Committee for Nutrition Guidelines Development (see Annex 3), led by the Department of Nutrition for Health and Development, was established in 2009 with representatives from all WHO departments with an interest in the provision of scientific nutrition advice, including the Department of Maternal, Neonatal, Child and Adolescent Health and Development and the Department of Reproductive Health and Research. The WHO Steering Committee for Nutrition Guidelines Development meets twice yearly and both guided and provided overall supervision of the guideline development process.

The guideline development group, called guideline development group – nutrition actions, was established for the biennium 2013–2014 (see Annex 4). Its role was to advise WHO on the choice of important outcomes for decision-making and in the interpretation of the evidence and formulation of the recommendation. The group included experts from various [WHO expert advisory panels](#) (42) and those identified through open calls for specialists, taking into consideration a balanced mix of sex, 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 ministries of health from Member States. Representatives of commercial organizations are not allowed to be members of a WHO guideline development group.

An external group of resource experts was also formed (see Annex 6) in order to assist the guideline development group – nutrition actions 2013–2014 in the assessment of the evidence, the identification of research priorities and programme considerations. Members of the external group of resource experts do not participate in or vote for final formulation of the recommendation.

The guideline development group – nutrition actions 2013–2014 agreed on a recommendation in the meeting held on 3–6 November 2014 in Cancun, Mexico. The WHO Secretariat prepared the guideline document containing the recommendation and the other sections, which reflect the discussions of the guideline development group.

The final draft guideline was peer-reviewed by three experts who provided technical feedback. These peer-reviewers were identified through various expert panels within and outside WHO (see Annex 7). Peer-reviewers received a finalized version of the guideline and were requested to comment or suggest changes restricted to errors of fact, clarifications, or considerations related to implementation, adaptation and the conditions in which the recommendation apply. If guideline users and readers wish to assess the methodological rigour for

developing this global guideline, the Appraisal of Guidelines, Research and Evaluation II ([AGREE II](#)) Instrument can be used for this purpose (43).

Scope of the guideline

An initial set of questions (and the components of the questions) to be addressed in the guidelines was the critical starting point for formulating the recommendation. The questions were drafted by technical staff at the Evidence and Programme Guidance Unit, Department of Nutrition for Health and Development, based on policy and programme guidance needs of Member States and their partners. The population, intervention, control, outcomes (PICO) format was used (see Annex 8). The questions were discussed and reviewed by the WHO Steering Committee for Nutrition Guidelines Development.

A meeting of the guideline development group – nutrition actions 2013–2014 was held on 18–21 February 2013, in Geneva, Switzerland, to scope the guideline and rank the critical outcomes and populations of interest for the recommendation on the use of multiple micronutrient powders for point-of-use fortification of foods consumed by pregnant women. The guideline development group discussed the relevance of the questions and modified them as needed. The 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 the use of multiple micronutrient powders in pregnant women, along with the outcomes that were identified as critical and important for decision-making, are listed in PICO format in Annex 8.

A second meeting of the guideline development group – nutrition actions 2013–2014 was held on 23–26 June 2014, in Geneva, Switzerland, to review programmatic experiences, a presentation on the preliminary results of the systematic review and implementation research needs.

A third meeting of the guideline development group – nutrition actions 2013–2014 was held on 3–6 November 2014, in Cancun, Mexico. In this meeting, the members of the guideline development group were able to agree on the recommendation and its remarks, as well as on research priorities.

Evidence appraisal and decision-making

A systematic review (1) was used to summarize and appraise the evidence using the [Cochrane handbook for systematic reviews of interventions](#) (32) for randomized controlled trials and observational studies. This systematic review matched the PICO questions appropriately. Evidence profiles were prepared according to the Grading of Recommendations Assessment, Development and Evaluation ([GRADE](#)) approach to assess the overall quality of the evidence (6, 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 systematic review (1) and the GRADE evidence profiles for each of the critical outcomes were used for drafting this guideline. The draft recommendation was discussed by the WHO Steering Committee for Nutrition Guidelines Development and with the guideline development group, at a consultation held on 3–6 November 2014 in Cancun, Mexico.

The procedures for decision-making are established at the beginning of the meetings, including a minimal set of rules for agreement and decision-making documentation. The guideline development group members secretly noted the direction and strength of the recommendation, using a form designed for this purpose, which also included a section for documenting their views on (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 of options available to health-care workers in different settings (see Annex 2). These aspects were discussed openly in the meeting, followed by notation of each member's primary considerations in these areas on individual forms. Each member used one form, if not advised otherwise after managing any potential conflict of interests. Abstentions were not allowed. The process was improved with the availability of a predefined link to an online form prepared using survey software. Subsequent deliberations among the members of the guideline development group were of private character, i.e. only members of the guideline development group were allowed to be present during these deliberations and the external resource people had to leave the room. The WHO Secretariat collected the forms 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 voting took place. If no unanimous agreement was reached, a two-thirds vote of the guideline development group members present was required for the approval of the proposed recommendation (secondary decision rule). Divergent opinions could be recorded in the guideline. The results from voting forms are kept on file by WHO for 5 years. Although there was no unanimous consensus, more than 70% of the voting members of the guideline development group members decided it was a strong recommendation.

WHO staff present at the meeting, as well as other external technical experts involved in the collection and grading of the evidence, were not allowed to participate in the decision-making process. Two co-chairs with expertise in managing group processes and interpreting evidence were nominated at the opening of the consultation, and the nomination was approved by the guideline development group. 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.

9. MANAGEMENT OF CONFLICTS OF INTEREST

According to the rules in the WHO [Basic documents](#) (45) and the processes recommended in the *WHO handbook for guideline development* (5), all experts participating in WHO meetings must declare any interest relevant to the meeting prior to their participation. The declarations-of-interest statements for all guideline group members were reviewed by the responsible technical officer and the relevant departments before finalization of the group composition and invitation to attend a guideline group meeting. All guideline group members and participants of the guideline development meetings submitted a declaration-of-interests form, along with their curriculum vitae, before each meeting. Participants of the guideline development group meetings participated in their individual capacity and not as institutional representatives. In addition, they verbally declared potential conflicts of interest at the beginning of each meeting. The procedures for management of conflicts of interests strictly followed WHO Guidelines for declaration of interests (WHO experts) (46). The potential conflicts of interest declared by members of the guideline group are summarized next.¹

Dr Mary Chea is employed by the National Maternal and Child Health Centre, Ministry of Health of Cambodia. Dr Chea declared having carried out research and work on projects related to multiple micronutrient powders. First, she has carried out operational research for the Good Food for Children Project, which compared infant and young child feeding (IYCF) education and Sprinkles™ for infants and young children in poor settings in Svay Rieng District, Svay Rieng Province, Cambodia. Second, she has coordinated, managed and implemented the Good Food for Children Study (Sprinkles™ Project) for the whole project period (2007–2010). It was agreed that she could participate fully in the deliberations and decision-making on this recommendation.

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 Luz Maria De-Regil declared that her present employer is an international nongovernmental organization devoted to the improvement of micronutrient status among infants, children and women. These activities are primarily financed by the government of Canada. The Micronutrient Initiative (MI) is a leading organization working exclusively to eliminate vitamin and mineral deficiencies in the world's most vulnerable populations, including work on and support of multiple micronutrient powders. Dr De-Regil declared that she is a co-author of systematic reviews on: (a) point-of-use fortification of foods with micronutrient powders containing iron in children of preschool and school age; (b) multiple micronutrient powders for point-of-use fortification of foods in pregnant women; and (c) point-of-use fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age. Dr De-Regil also declared that she was involved in the preparation of the guideline on point-of-use fortification with multiple micronutrient powders as a former member of WHO staff. Dr De-Regil was allowed to be a member of the guideline development group and could participate in the deliberations related to recommendations on the use of multiple micronutrient powders for point-of-use fortification of foods consumed by pregnant women, but recused herself from voting on this recommendation.

Dr Rukhsana Haider is employed by the Training and Assistance for Health and Nutrition (TAHN) Foundation, Dhaka, Bangladesh. Dr Haider declared that, at the time of the meeting, she was a member of the Technical Advisory Group for Helen Keller International's Assessment and Research on Child Feeding (ARCH) Project. It was agreed that she could participate fully in the deliberations and decision-making on this recommendation.

Dr Maria Elena del Socorro Jefferts is employed by United States Centers for Disease Control and Prevention (CDC). She declared that she was a co-investigator on a CDC-funded study on the effectiveness of micronutrient powders in Kenya and is lead author and co-author of several publications on this topic, including being co-author and editor of a special *Sight and Life* supplement on micronutrient powders published in 2013. She also declared that she participated in a United Nations Children's Fund (UNICEF)/CDC workshop on scaling up micronutrient-powder interventions for children aged 6–23 months. She also declared that she was the coordinator and writer of a monitoring manual for home fortification interventions, including micronutrient powders, for the Home Fortification Technical Advisory Group (HF-TAG); that she was an investigator on the first global assessment of home fortification interventions and the lead author of the corresponding report and of a related journal article, both published in 2013; and that she is a co-author of a Cochrane systematic review of micronutrient powders intervention in children aged 6–23 months and 2–12 years. She was allowed to participate in the deliberations on recommendations related to multiple micronutrient powders but she recused herself from decision-making (voting) on the recommendations related to the use of multiple micronutrient powders for point-of-use fortification of foods.

Dr Lynette Neufeld declared that her current employer has received funding in the past 4 years for research and programming related to micronutrient powders, but that she is not leading any of these initiatives. She also declared that, in her previous position with a different employer, she was involved in research studies related to micronutrient powders. She declared her membership on the Steering Committee of HF-TAG. She was allowed to participate in the deliberations on recommendations related to multiple micronutrient powders but she recused herself from decision-making (voting) on the recommendations relating to the use of multiple micronutrient powders for point-of-use fortification of foods.

All other members completed and signed a written declaration of interests before the meeting and made a verbal declaration of their interest during the meeting. It was considered that these interests were not relevant for this guideline on the use of multiple micronutrient powders for point-of-use fortification of foods consumed by pregnant women. External experts also declared their interest but did not participate in the deliberations or decision-making process.

10. PLANS FOR UPDATING THE GUIDELINE

The WHO Secretariat will continue to follow the research development in the area of micronutrient supplementation for pregnant women. If the guideline merits an update, or if there are concerns about the validity of the guideline, the Department of Nutrition for Health and Development will coordinate the guideline update, following the formal procedures of the [WHO handbook for guideline development](#) (5).

As the guideline nears the 10-year review period agreed by the guideline development group, 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 new evidence. WHO welcomes suggestions regarding additional questions for evaluation in the guideline when it is due for review.

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ANNEX 1. GRADE SUMMARY OF FINDINGS TABLES

a. Micronutrient powders for point-of-use fortification of foods versus iron and folic acid supplements

Micronutrient powders for point-of-use fortification of foods versus iron and folic acid supplements

Patient or population: women during pregnancy

Settings: all settings

Intervention: micronutrients powders for point-of-use fortification of foods versus iron and folic acid supplements

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
Maternal anaemia at term or near term (haemoglobin [Hb] less than 110 g/L at 34 weeks' gestation or more)	No data	0	No data	
Maternal iron deficiency at term or near term (as defined by authors of the trials, based on any indicator of iron status at 34 weeks' gestation or more)	No data	0	No data	
All-cause maternal mortality (death while pregnant or within 42 days of termination of pregnancy)	No data	0	No data	
Adverse effects (any)	No data	0	No data	
Low birth weight (birth weight less than 2500 g)	No data	0	No data	
Preterm births (births before 37 weeks of gestation)	No data	0	No data	

CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence:

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

b. Micronutrient powders for point-of-use fortification of foods versus the same multiple micronutrients in supplements

Micronutrient powders for point-of-use fortification of foods versus same multiple micronutrients in supplements

Patient or population: women during pregnancy

Settings: all settings

Intervention: micronutrients powders for point-of-use fortification of foods versus micronutrients in supplements

Outcomes	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Maternal anaemia at term or near term (haemoglobin [Hb] less than 110 g/L at 34 weeks' gestation or more)	0.92 (0.53 to 1.59)	470	⊕⊖⊖⊖ VERY LOW ¹	
Maternal iron deficiency at term or near term (as defined by authors of the trials, based on any indicator of iron status at 34 weeks' gestation or more)	No data	0	No data	
All-cause maternal mortality (death while pregnant or within 42 days of termination of pregnancy)	No data	0	No data	
Adverse effects (any)	No data	0	No data	
Low birth weight (birth weight less than 2500 g)	No data	0	No data	
Preterm births (births before 37 weeks of gestation)	No data	0	No data	

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence:

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ The quality of evidence has been downgraded for serious risk of bias (unclear method of randomization, no blinding, and high loss to follow-up) and imprecision (wide confidence interval spanning both large benefit and harm).

ANNEX 2. SUMMARY OF THE CONSIDERATIONS OF THE MEMBERS OF THE GUIDELINE DEVELOPMENT GROUP FOR DETERMINING THE STRENGTH OF THE RECOMMENDATION FOR USE OF MULTIPLE MICRONUTRIENT POWDERS FOR POINT-OF-USE FORTIFICATION OF FOODS CONSUMED BY PREGNANT WOMEN

QUALITY OF EVIDENCE:	<p>There is not sufficient evidence available to assess this intervention.</p> <p>The number of trials and participants is low.</p> <p>The scarce available evidence did not show that the intervention would benefit both mother and neonate.</p>
VALUES AND PREFERENCES:	<p>The absence of evidence limits the ability to judge the possible value of this intervention.</p> <p>The adherence is quite low according to the available, limited evidence. The scarce available evidence suggests that acceptability and maternal satisfaction were higher with iron and folic acid tablets than with multiple micronutrient powders, thus affecting therapeutic adherence.</p>
TRADE-OFF BETWEEN BENEFITS AND HARMS:	<p>There is uncertainty regarding the benefits and harms of this intervention.</p> <p>Although no harms are documented, there seems to be no added value when compared to the current iron and folic acid supplementation.</p>
COSTS AND FEASIBILITY:	<p>The use of micronutrient powders is feasible in theory, but perhaps more costly than iron supplementation.</p> <p>There are no data available to make an estimation on cost-effectiveness. Since iron and folic acid supplementation is less costly per unit than supplementation using multiple micronutrient powders, programme costs would probably depend on the scale of the programme using multiple micronutrient powders.</p>

ANNEX 3. WHO STEERING COMMITTEE FOR NUTRITION GUIDELINES DEVELOPMENT

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ANNEX 4. WHO GUIDELINE DEVELOPMENT GROUP – NUTRITION ACTIONS 2013–2014

(Note: The areas of expertise of each guideline group member are given in italics)

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ANNEX 8. QUESTIONS IN POPULATION, INTERVENTION, CONTROL, OUTCOMES (PICO) FORMAT

Effects and safety of multiple micronutrient powders for pregnant women

a. Should multiple micronutrient powders be used in pregnant women to improve health outcomes?

b. If so, at what dose, frequency and duration?

POPULATION:	<p>Pregnant women (any trimester and parity)</p> <p>Subpopulations:</p> <p><i>Critical</i></p> <ul style="list-style-type: none"> – By anaemia status: anaemia (defined as haemoglobin values <100 g/L) versus non-anaemia versus mixed/not reported – By iron status: iron deficient (as defined by ferritin, transferritin receptor, and/or zinc protoporphyrin cut-off values) versus non-iron deficient versus mixed/not reported – By malaria risk in the trial: malaria-free versus some risk (by use of concurrent antimalarial measures)
INTERVENTION:	<p>Point-of use fortification with micronutrient powders containing iron and folic acid</p> <p>Subgroup analyses:</p> <p><i>Critical</i></p> <ul style="list-style-type: none"> – By iron content of product: 30–59 mg versus ≥60 mg – By frequency: daily versus weekly versus flexible – By duration of intervention: <ul style="list-style-type: none"> – During pregnancy alone: less than 3 months versus 3 or more months – During pregnancy and the early postpartum period (0–3 months): less than 3 months versus 3 or more months
CONTROL:	<ul style="list-style-type: none"> – No provision of multiple micronutrient powders, or placebo – Iron and folic acid supplements
OUTCOMES:	<p>Maternal</p> <p><i>Critical</i></p> <ul style="list-style-type: none"> – Haemoglobin values at term of pregnancy – Anaemia at term of pregnancy – Iron deficiency anaemia at term of pregnancy – All-cause morbidity – Morbidity from preeclampsia/hypertension – Morbidity from haemorrhage – Adverse effects: diarrhoea <p><i>For malaria-endemic areas only</i></p> <ul style="list-style-type: none"> – Malaria incidence and severity (parasitaemia with or without symptoms) – Placental malaria <p>Neonates and infants</p> <p><i>Critical</i></p> <ul style="list-style-type: none"> – Gestational age <32 weeks versus 32–36 weeks versus ≥37 weeks) – Gestational weeks – Low birth weight (<1500 g versus 1500–2499 g versus ≥2500 g) – Birth weight (g) – Stillbirths – Iron status – Haemoglobin concentrations
SETTING:	<ul style="list-style-type: none"> – All settings

Guideline:

USE OF MULTIPLE MICRONUTRIENT POWDERS

FOR POINT-OF-USE FORTIFICATION OF FOODS CONSUMED BY PREGNANT WOMEN

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**World Health
Organization**

ISBN 978 92 4 154951 6



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