

**Guideline:**

**DAILY IRON SUPPLEMENTATION  
IN ADULT WOMEN  
AND ADOLESCENT GIRLS**



**World Health  
Organization**

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IN ADULT WOMEN  
AND ADOLESCENT GIRLS**

Guideline: Daily iron supplementation in adult women and adolescent girls

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## WHO GUIDELINE<sup>1</sup>: DAILY IRON SUPPLEMENTATION IN ADULT WOMEN AND ADOLESCENT GIRLS

### EXECUTIVE SUMMARY

Globally, one in three non-pregnant women, corresponding to almost 500 million women, were anaemic in 2011. Iron deficiency is thought to contribute to at least half of the global burden of anaemia. Iron deficiency occurs following prolonged negative iron balance, the major causes of which include inadequate intake (owing to insufficient bioavailable iron in the diet or decreased iron absorption), increased iron requirements (for instance, during periods of growth) and chronic blood loss (from heavy hookworm infection or menstrual bleeding). In adolescent girls, menstrual blood losses, accompanied by rapid growth with expansion of the red cell mass and increased tissue iron requirements, make them particularly vulnerable to iron deficiency compared to male counterparts. This guideline reviews the evidence and updates the recommendation for daily iron supplementation in menstruating adult women and adolescent girls.

#### *Purpose of the guideline*

This guideline aims to help Member States and their partners in their efforts to make informed decisions on the appropriate nutrition actions to achieve the [Sustainable Development Goals](#) (SDGs) (1), the global targets set in the *Comprehensive implementation plan on maternal, infant and young child nutrition* (2) and the *Global strategy for women's, children's and adolescent girls' health (2016–2030)* (3). The recommendation in this guideline is intended for a wide audience, including policy-makers, their expert advisers, and technical and programme staff at organizations involved in the design, implementation and scaling-up of programmes for anaemia prevention and control, and in nutrition actions for public health. The recommendation supersedes those of previous WHO guidelines on iron supplementation in menstruating adult women and adolescent girls.

#### *Guideline development methodology*

WHO developed the present evidence-informed recommendation using the procedures outlined in the *WHO handbook for guideline development* (4). 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 recommendation, including research priorities; and planning for (v) dissemination; (vi) implementation, equity and ethical considerations; and (vii) impact evaluation and updating of the guideline. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was followed (5), to prepare evidence profiles related to preselected topics, based on up-to-date systematic reviews.

The guideline development group consisted of content experts, methodologists and representatives of potential stakeholders and beneficiaries. One guideline group participated in a meeting concerning this guideline, held in Geneva, Switzerland, on 20–25 February 2010, where the guideline was scoped. A second guideline group participated in a meeting held in Geneva, Switzerland, on 14–18 March 2011, to discuss the safety of iron supplementation in menstruating adult women and adolescent girls living in areas of high malaria transmission, and a third meeting was convened in Geneva, Switzerland, on 23–26 June 2014, where the guideline was finalized. Three experts served as technical peer-reviewers of the draft guideline.

#### *Available evidence*

The available evidence comprised a systematic review (6) that followed the procedures of the *Cochrane*

<sup>1</sup> 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 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.

handbook for systematic reviews of interventions (7) and assessed the effects of daily iron supplementation in menstruating adult women and adolescent girls. The reviews included individually randomized and cluster-randomized controlled trials. All studies compared a group of non-pregnant adolescent girls and menstruating adult women who received daily oral iron supplementation to a group that did not receive iron. The overall quality of the available evidence for daily iron supplementation in menstruating adult women and adolescent girls was moderate for the critical outcomes of anaemia and iron deficiency. No evidence was available for the outcomes of iron deficiency anaemia and malaria-related morbidity. The WHO Secretariat conducted an additional search for evidence prior to the finalization of the guideline (November 2015), and did not identify any additional relevant studies.

### Recommendation<sup>1</sup>

Daily iron supplementation is recommended as a public health intervention in menstruating adult women and adolescent girls, living in settings where anaemia is highly prevalent ( $\geq 40\%$  anaemia prevalence),<sup>2</sup> for the prevention of anaemia and iron deficiency (*strong recommendation, moderate quality of evidence*).

### Suggested scheme for daily iron supplementation in adult women and adolescent girls

|                        |  |
|------------------------|--|
| TARGET GROUP           | Menstruating adult women and adolescent girls (non-pregnant females in the reproductive age of group)          |
| SUPPLEMENT COMPOSITION | 30–60 mg elemental iron <sup>a</sup>   |
| SUPPLEMENT FORM        | Tablets  |
| FREQUENCY              | Daily  |
| DURATION               | Three consecutive months in a year   |
| SETTINGS               | Where the prevalence of anaemia in menstruating adult women and adolescent girls is 40% or higher <sup>b</sup> |

<sup>a</sup> 30–60 mg of elemental iron equals 150–300 mg of ferrous sulfate heptahydrate, 90–180 mg of ferrous fumarate or 250–500 mg of ferrous gluconate.

<sup>b</sup> In the absence of prevalence data in this group, consider proxies for high risk of anaemia. For the most recent estimates, visit the WHO hosted Vitamin and Mineral Nutrition Information System ([VMNIS](#)) (8).

### Remarks

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

- Daily oral iron supplementation is a preventive strategy for implementation at the population level. If a menstruating woman or adolescent girl is diagnosed with anaemia, national guidelines for the treatment of anaemia should be followed.
- Daily iron supplementation should be considered in the context of other interventions containing iron (fortified foods, multiple micronutrient powders, lipid-based nutrient supplements).

<sup>1</sup> This recommendation supersedes those of previous WHO guidelines on iron supplementation in menstruating adult women and adolescent girls.

<sup>2</sup> Where the prevalence of anaemia is 40% or higher in this age group. For the latest estimates, please refer to the WHO-hosted Vitamin and Mineral Nutrition Information System ([VMNIS](#)) (8).



- The selection of the most appropriate delivery platform should be context specific, with the aim of reaching the most vulnerable populations and ensuring a timely and continuous supply of supplements.
- All women, from the moment they begin trying to conceive until 12 weeks of gestation, should take a folic acid supplement. Daily oral iron and folic acid supplementation should be part of routine antenatal care, begun as early as possible and continued throughout pregnancy. Where the prevalence of anaemia in pregnant women is high (40% or more), supplementation should continue for 3 months in the postpartum period (10, 11).

### *Research priorities*

Discussions between the members of the WHO guideline development group and the external review group highlighted the limited evidence available in some knowledge areas, meriting further research on iron supplementation in menstruating adult women and adolescent girls, particularly in the following areas:

- the optimal dose, schedule and duration of iron supplementation; the effect of different doses and duration of iron supplementation on different severity, prevalence or causes of anaemia in all WHO regions;
- additional data on the safety of iron supplementation (liver damage; iron overload after continuing the supplementation programme for a number of years; iron supplementation given in conjunction with other interventions; insulin resistance; effects on non-anaemic or non-iron-deficient women and adolescent girls);
- the effect of adding other micronutrients to the iron supplement on haemoglobin concentrations and the prevalence of anaemia;
- implementation research on effective behaviour-change strategies for sustained adherence and innovative delivery mechanisms for iron supplements;
- additional long-term studies on functional outcomes (e.g. exercise performance and productivity);
- cost, cost–benefit and feasibility analysis of the distribution of iron supplementation to be taken daily or intermittently among menstruating adult women and adolescent girls.

## WHO GUIDELINE<sup>1</sup>: DAILY IRON SUPPLEMENTATION IN ADULT WOMEN AND ADOLESCENT GIRLS

### SCOPE AND PURPOSE

This guideline provides a global, evidence-informed recommendation on daily iron supplementation in menstruating adult women and adolescent girls, as a public health intervention for the prevention of anaemia and iron deficiency.

The guideline aims to help Member States and their partners in their efforts to make informed decisions on the appropriate nutrition actions to achieve the Sustainable Development Goals (SDGs) (1), in particular, Goal 2: End hunger, achieve food security and improved nutrition and promote sustainable agriculture. It will also support Member States in their efforts to achieve the global targets set in the *Comprehensive implementation plan on maternal, infant and young child nutrition*, as endorsed by the Sixty-fifth World Health Assembly in 2012, in resolution WHA65.6 (2), and the *Global strategy for women's, children's, and adolescent girls' health (2016–2030)* (3).

The recommendation in this guideline is intended for a wide audience, including policy-makers, their expert advisers, and technical and programme staff at government institutions and organizations involved in the design, implementation and scaling-up of programmes for anaemia prevention and control, and in 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. This document presents the key recommendation and a summary of the supporting evidence.

### BACKGROUND

Globally, one in three non-pregnant women, corresponding to almost 500 million women, were anaemic in 2011 (12). Iron deficiency is thought to contribute to at least half of the global burden of anaemia, though this proportion can vary widely and is very context specific. Iron deficiency occurs following prolonged negative iron balance, the major causes of which include inadequate intake (owing to insufficient bioavailable iron in the diet or decreased iron absorption), increased iron requirements (for instance, during periods of growth) and chronic blood loss (from heavy hookworm infection or menstrual bleeding) (13).

From the time that girls enter menarche until menopause, women are at high risk of iron deficiency, owing to menstrual blood losses. In adolescent girls, menstrual blood losses, accompanied by rapid growth with expansion of the red cell mass and increased tissue iron requirements, make them particularly vulnerable to iron deficiency compared to their male counterparts (14).

Public health interventions that improve iron status in populations include nutrition counselling that promotes diet diversity and food combinations that improve iron absorption; fortification of staple or routinely consumed foods with iron; point-of-use fortification with multiple micronutrients including iron; treatment of preventable causes of iron losses such as hookworm infestation; and iron supplementation.

In 2001, WHO recommended preventive supplementation of 60 mg/day iron for three months for non-pregnant women of reproductive age in settings where the prevalence of anaemia is above 40% (13). This guideline reviews the evidence and updates the recommendation for daily iron supplementation in menstruating adult women and adolescent girls.

<sup>1</sup> 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 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.

## OBJECTIVES

The recommendation in this guideline supersedes those of previous WHO guidelines on iron supplementation, such as *Iron deficiency anaemia: assessment, prevention, and control. A guide for programme managers* (13), where they pertain specifically to daily oral iron supplementation among menstruating adult women and adolescent girls (non-pregnant females in the reproductive age group). This guideline complements the WHO *Guideline: intermittent iron and folic acid supplementation in menstruating women* (9), which is applicable to settings where the prevalence of anaemia among non-pregnant women of reproductive age is 20% or higher.

## SUMMARY OF AVAILABLE EVIDENCE

The evidence that informed the recommendation on daily iron supplementation in menstruating adult women and adolescent girls is based on a systematic review of women and adolescent girls beyond menarche and prior to menopause who were not pregnant or lactating and did not have any condition that impedes the presence of menstrual periods (6). The systematic review also included studies for which results for girls and women aged between 12 and 50 years (plausible age range for menstruation) could be extracted separately, or in which more than half of the participants fulfilled this criterion. The review excluded studies on populations with conditions affecting iron metabolism, intestinal malabsorption conditions, ongoing excessive blood loss (including ongoing blood donations), inflammatory bowel disease, cancer, chronic congestive cardiac failure, chronic renal failure, chronic liver failure or chronic infectious disease, or hospitalized or ill patients.

The review included randomized controlled trials comparing daily iron supplementation (with or without a co-intervention such as folic acid or vitamin C) to placebo or supplementation without iron. Daily supplementation was defined as receiving iron for at least 5 days in a week.

The systematic review searched the Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, Embase (Ovid), CINAHL (EBSCOHost), Conference Proceedings Citation Index – Science (CPCI-S), Science Citation Index (SCI), POPLINE, IMSEAR, LILACS, IMERM, African Index Medicus, and the following databases for grey literature: WorldCat, DART-Europe E-theses Portal, Australasian Digital Theses Program, Theses Canada Portal, and ProQuest-Dissertations and Theses. The search for evidence was done in September 2014.

The review included 62 trials involving 7523 women and adolescent girls (3951 in the intervention arm and 3572 in the control arm). These studies were conducted in 24 countries with representation from low-, middle- and high-income countries. The sample size ranged between 10 and 1390 participants. Overall, the sample size tended to be small; 96% of the studies included fewer than 400 women and adolescent girls.

Menstruating women and adolescent girls who received daily iron supplementation had a lower risk for the critical outcomes of anaemia (risk ratio [RR]: 0.34; 95% confidence interval [CI]: 0.20 to 0.57; 9 trials,  $n = 2905$ ) and iron deficiency (RR: 0.61; 95% CI: 0.47 to 0.77; 6 trials,  $n = 1033$ ) compared to menstruating women and adolescent girls receiving placebo or supplementation without iron. No trials reported on the outcome of iron deficiency anaemia.

There were 48 studies that reported on haemoglobin concentration. The large number of studies and participants for this outcome allowed for evaluation of subgroup differences. Haemoglobin levels were significantly higher among those given iron supplementation compared to those given placebo or supplementation without iron (mean difference [MD]: 5.61 g/L; 95% CI: 4.44 to 6.79; 48 trials,  $n = 6390$ ). There was no evidence of difference in the effect of iron supplementation compared to placebo or supplementation without iron on haemoglobin by dose (<30 mg, 31–60 mg, 61–100 mg, >100 mg; test for subgroup difference  $\chi^2 = 1.32$ ;  $P = 0.72$ ) or duration (<1 month, 1–3 months, >3 months; test for subgroup difference  $\chi^2 = 4.12$ ;  $P = 0.13$ ).

Only one study specifically reported being performed in a malaria-endemic area (15). One of the two villages

in Northern Thailand where this study was performed was endemic to malaria (10% of the population had a positive blood smear). However, malaria-related morbidities were not reported in this study.

Results from six trials on “any side effect” did not show a statistically significant difference in the risk of side effects between the iron-supplementation group and those receiving placebo or supplementation without iron (RR: 2.11; 95% CI: 0.87 to 5.11; 6 trials,  $n = 534$ ; very low quality evidence). There was an increased risk of any gastrointestinal side-effects (RR: 1.99; 95% CI: 1.26 to 3.12; 5 trials,  $n = 521$ ; low quality evidence). Side-effects were not pre-specified as critical guideline outcomes and these data are not shown in the Grading of Recommendations Assessment Development and Evaluation ([GRADE](#)) summary of findings table.

The quality of evidence for the critical outcomes is moderate for anaemia and iron deficiency, using the GRADE methodology (5, 16, 17); there was no evidence for the outcome of iron deficiency anaemia. The GRADE summary of findings table for daily oral iron supplementation compared to placebo or control in menstruating adult women and adolescent girls is shown in Annex 1.

## RECOMMENDATION

Daily iron supplementation is recommended as a public health intervention in menstruating adult women and adolescent girls, living in settings where anaemia is highly prevalent,<sup>1</sup> for the prevention of anaemia and iron deficiency (*strong recommendation, moderate quality of evidence*).

The suggested scheme for daily iron supplementation in menstruating adult women and adolescent girls is presented in Table 1.

*Table 1. Suggested scheme for daily iron supplementation in adult women and adolescent girls*

|                        |  |
|------------------------|--|
| TARGET GROUP           | Menstruating adult women and adolescent girls (non-pregnant females in the reproductive age group)             |
| SUPPLEMENT COMPOSITION | 30–60 mg elemental iron <sup>a</sup>   |
| SUPPLEMENT FORM        | Tablets  |
| FREQUENCY              | Daily  |
| DURATION               | Three consecutive months in a year   |
| SETTINGS               | Where the prevalence of anaemia in menstruating adult women and adolescent girls is 40% or higher <sup>b</sup> |

<sup>a</sup> 30–60 mg of elemental iron equals 150–300 mg of ferrous sulfate heptahydrate, 90–180 mg of ferrous fumarate or 250–500 mg of ferrous gluconate.

<sup>b</sup> In the absence of prevalence data in this group, consider proxies for high risk of anaemia. For the most recent estimates, visit the WHO-hosted Vitamin and Mineral Nutrition Information System ([VMNIS](#)) (8).

## RATIONALE

The guideline development group took into consideration the following factors during the deliberations:

- Anaemia and iron deficiency had moderate quality of evidence. None of the studies reported on iron deficiency anaemia. However, synthesis of evidence from studies that reported on

<sup>1</sup> Where the prevalence of anaemia is 40% or higher in this age group. For the latest estimates, please refer to the WHO-hosted Vitamin and Mineral Nutrition Information System ([VMNIS](#)) (8).

haemoglobin concentration had high quality. The effect sizes of the intervention on the outcomes with data were large. There was no evidence presented for malaria-related morbidity.

- Adherence may be a concern if the intervention is perceived as non-essential. Barriers to adherence may need to be addressed (for instance, with behaviour-change communication if the intervention is not perceived as necessary among the beneficiaries). Among the studies that measured compliance, between 65% and 98% of the tablets were consumed, with no difference between the iron supplementation and control arms.
- Costs will largely be determined by operational challenges rather than the cost of the supplement itself. Distribution of daily iron supplementation in this population, particularly in settings where health-care interventions do not specifically target menstruating adult women and adolescent girls, may entail operational challenges. The resources and investments needed should be considered in designing programmes to reach this population.

## REMARKS

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

- Daily oral iron supplementation is a preventive strategy for implementation at the population level. If a menstruating woman is diagnosed with anaemia, national guidelines for the treatment of anaemia should be followed.
- The prevalence of anaemia should be considered when determining the dose, duration and frequency of iron supplementation among menstruating adult women and adolescent girls. If the prevalence of anaemia is less than 40%, other guidelines are available for consideration. For instance, for anaemia prevalence of 20–40%, intermittent regimens of iron supplementation may be an option (9).
- Daily iron supplementation should be considered in the context of other interventions containing iron (fortified foods, multiple micronutrient powders, lipid-based nutrient supplements).
- The selection of the most appropriate delivery platform should be context specific, with the aim of reaching the most vulnerable populations and ensuring a timely and continuous supply of supplements.
- All women, from the moment they begin trying to conceive until 12 weeks of gestation, should take a folic acid supplement. Daily oral iron and folic acid supplementation should be part of routine antenatal care, begun as early as possible and continued throughout pregnancy. Where the prevalence of anaemia in pregnant women is high (40% or more), supplementation should continue for 3 months in the postpartum period (10, 11).

Iron supplementation is the customary intervention that comes to mind to address anaemia but it should ideally form only a part of a comprehensive, integrated programme for anaemia reduction and addressing women's health across the life-course. Interventions for decreasing iron deficiency or iron deficiency anaemia should include nutrition counselling that promotes diet diversity and food combinations that improve iron absorption; malaria-control programmes, including intermittent preventive treatment of malaria in pregnancy and in children, as well as use of insecticide-treated bednets; control of parasitic infections; and improvement in sanitation. Once, a woman is pregnant, antenatal programmes help promote adequate gestational weight gain and other complementary measures for monitoring, prevention and control of anaemia, such as screening

for anaemia, deworming treatment and a referral system for the management of cases of severe anaemia. Delayed umbilical cord clamping is effective in preventing iron deficiency in infants and young children. Other options include fortification of staple foods and provision of micronutrient powders, including iron.

## RESEARCH PRIORITIES

Discussions between the members of the WHO guideline development group and the external review group highlighted the limited evidence available in some knowledge areas, meriting further research on iron supplementation in menstruating adult women and adolescent girls, particularly in the following areas:

- the optimal dose, schedule and duration of iron supplementation; the effect of different doses and duration of iron supplementation on different severity, prevalence or causes of anaemia in all WHO regions;
- additional data on the safety of iron supplementation (liver damage; iron overload after continuing the supplementation programme for a number of years; iron supplementation given in conjunction with other interventions; insulin resistance; effects in non-anaemic or non-iron-deficient menstruating adult women and adolescent girls);
- the effect of adding other micronutrients to the iron supplement on haemoglobin concentrations and the prevalence of anaemia;
- implementation research on effective behaviour-change strategies for sustained adherence and innovative delivery mechanisms for iron supplements;
- additional long-term studies on functional outcomes (e.g. exercise performance and productivity)
- cost, cost–benefit and feasibility analysis of the distribution of iron supplementation to be taken daily or intermittently among menstruating adult women and adolescent girls.

## DISSEMINATION, IMPLEMENTATION AND ETHICAL CONSIDERATIONS

### *Dissemination*

The current guideline will be disseminated through electronic media, such as slide presentations and the World Wide Web, through the WHO Nutrition mailing lists, social media, the WHO nutrition website (18) or the WHO e-Library of Evidence for Nutrition Actions ([eLENA](#)) (19). eLENA compiles and displays WHO guidelines related to nutrition, along with complementary documents such as systematic reviews and other evidence that informed the guidelines; biological and behavioural rationales; and additional resources produced by Member States and global partners. In addition, the guideline will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, universities, other United Nations agencies and nongovernmental organizations. Derivative products such as summaries and collation of recommendations related to iron supplementation will be developed for a more tailored product that is useful for end-users.

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 who play a crucial role in the implementation of the guideline recommendation, for example, policy-makers and decision-makers at subnational level that disseminate the contents of the guideline, and health workers and education staff that contribute to the delivery of the intervention. Disseminated information may emphasize the benefits of iron supplementation in menstruating adult women and adolescent girls in populations or regions presenting an important risk of anaemia and iron deficiency. In addition, these guidelines and the information contained therein should be

accessible to the nongovernmental organizations working in coordination with national authorities on the implementation of nutrition interventions, especially those related to the prevention and control of anaemia. in menstruating adult women and adolescent girls.

### *Implementation*

As this is a global guideline, it should be adapted to the context of each Member State. Prior to implementation, a public health programme that includes the provision of iron supplements to menstruating adult women and adolescent girls should have well-defined objectives that take into account available resources, existing policies, suitable delivery platforms and suppliers, communication channels, and potential stakeholders. Ideally, iron supplementation should be implemented as part of an integrated programme on adolescent and reproductive health, which includes addressing micronutrient deficiencies.

Considering the experiences of menstruating adult women and adolescent girls with the intervention is also a relevant implementation consideration: ongoing assessment of the accessibility and acceptability of the intervention can inform programme design and development, in order to increase adherence to supplementation and better assess the impact of the programme. This is particularly relevant in settings where the prevailing social norms and determinants may set unequal conditions and opportunities for different groups. For instance, in some settings, social perceptions around ethnicity and race intervene in how certain population groups access and use an intervention.

Supplementation programmes in menstruating adult women and adolescent girls need to be carefully designed, based on locally available evidence and experience. These can include data that can inform the implementation strategies on procurement and supply-chain issues, optimal distribution channels, behaviour-change communication and specific strategies to identify and reach the most vulnerable adult women and adolescent girls. These are particularly important in the absence of a well-functioning health-care system that reaches this population.

Accessing hard-to-reach population groups is extremely important during implementation stages, as it contributes to preventing or tackling health inequities. Appropriate surveillance and monitoring systems can thus provide information on the impact of the disseminated guidelines and their implementation (including information on the adequacy of funding and the effectiveness of the supply chain and distribution channels).

### *Regulatory considerations*

The WHO Essential Medicines List (EML) compiles medicines that satisfy the priority health-care needs of populations and are selected with due regard to disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness (20). Hence, the WHO EML is used by countries for the development of their own national essential medicines lists. The quality criteria for vitamins and minerals included in the WHO EML take into account Food and Agriculture Organization of the United Nations/WHO standards (21).

### *Monitoring and evaluation of guideline uptake and adaptation*

A plan for monitoring and evaluation with appropriate indicators, including equity-oriented indicators, is encouraged at all stages (22). 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. adoption and adaptation of the guideline globally). The WHO Department of Nutrition for Health and Development, Evidence and Programme Guidance Unit, jointly with the United States Centers for Disease Control and Prevention (CDC) International Micronutrient Malnutrition Prevention and Control (IMMPaCt) programme, and with input from international partners, has developed a generic logic model for micronutrient interventions in public health (23), to depict the plausible relationships between inputs and expected SDGs, by applying the micronutrient programme evaluation theory. Member States can adjust the



model and use it in combination with appropriate indicators, for designing, implementing, monitoring and evaluating the successful escalation of nutrition actions in public health programmes. Additionally, the WHO/CDC *eCatalogue of indicators for micronutrient programmes* (24), which utilizes the logic model, has been developed as 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. Indicators for iron supplementation are currently being developed and, once complete, will provide a list of potential indicators with standard definitions that can be selected, downloaded and adapted to a local programme context. The eCatalogue will serve as a repository of indicators to monitor and evaluate micronutrient interventions. While it does not provide guidance for designing or implementing a monitoring or evaluation system in public health, some key indicators may include useful references for that purpose.

Since 1991, WHO has hosted the [VMNIS micronutrients database](#) (8). Part of WHO's mandate is to assess the micronutrient status of populations, monitor and evaluate the impact of strategies for the prevention and control of micronutrient malnutrition, and track related trends over time. The Evidence and Programme Guidance Unit of the Department of Nutrition for Health and Development manages the VMNIS micronutrient database, through a network of regional and country offices, and in close collaboration with national health authorities.

For evaluation at the global level, the WHO Department of Nutrition for Health and Development has developed a web-based WHO Global Targets Tracking Tool 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, 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 Action ([GINA](#)) (25) 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.

An efficient system for the routine collection of relevant data, including relevant determinants of health, therapeutic adherence, and measures of programme performance, is critical to ensure supplementation programmes are effective and sustained, and drivers to the achievement of the right to health for all population groups. Monitoring differences across groups in terms of accessibility, availability, acceptability and the quality of the interventions contributes to the design of better public health programmes. The creation of indicators for monitoring can be informed by the approaches of social determinants of health (26), so inequities can be identified and tackled. Appropriate monitoring requires suitable data, so efforts to collect and organize information on the implementation are also fundamental.

## **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* (4).

### **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. The WHO Steering Committee for Nutrition Guidelines Development met twice yearly and both guided and provided overall supervision of the guideline development process. Two additional groups were formed: a guideline development group and an external review group.



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One guideline development group participated in the development of this guideline (see Annex 4). Its role was to advise WHO on the choice of important outcomes for decision-making and on interpretation of the evidence. The WHO guideline development group – nutrition actions includes experts from various WHO expert advisory panels 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 ministries of health from Member States. Representatives of commercial organizations may not be members of a WHO guideline group.

The final draft guideline was peer-reviewed by three content experts, who provided technical feedback. These peer-reviewers (see Annex 7) were identified through various expert panels within and outside WHO (5, 18, 27).

### *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 formed 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 the 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 and the guideline development group – nutrition actions, and were modified as needed.

A meeting of the guideline development group – nutrition actions was held on 14–16 March 2010, in Geneva, Switzerland, to finalize the scope of the questions and rank the outcomes and populations of interest for the recommendation on iron supplementation. 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 this intervention, along with the outcomes that were identified as critical for decision-making, are listed in PICO format in Annex 8.

A systematic review (6) was used to summarize and appraise the evidence using the Cochrane methodology (7) for randomized controlled trials and observational studies. Evidence summaries were prepared according to the (GRADE) approach to assess the overall quality of the evidence (5, 16, 17). GRADE considers the study design; the limitations of the studies in terms of their conduct and analysis; the consistency of the results across the available studies; the directness (or applicability and external validity) of the evidence with respect to the populations, interventions and settings where the proposed intervention may be used; and the precision of the summary estimate of the effect.

Both the systematic review and the GRADE 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 in consultations with the WHO guideline development group – nutrition actions, held on 14–18 March 2011 and 23–26 June 2014 in Geneva, Switzerland.

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. At least two thirds of the guideline development group should be present for an initial discussion of the evidence and proposed recommendation and remarks. The members of the guideline development group secretly noted the direction and strength of the recommendation, using a form designed for this purpose, that 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). 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. 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 was required for 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 up to 5 years. Although there was no unanimous consensus, more than 80% of the voting members of the guideline development group decided that the recommendation was strong.

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 guideline development group approved the 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* (28) and the processes recommended in the WHO *handbook for guideline development* (4), all experts participating in WHO meetings must declare any interests relevant to the meeting, prior to their participation. The responsible technical officer and the relevant departments reviewed the declarations-of-interests statements for all guideline development group members before finalization of the group composition and invitation to attend a guideline development group meeting. All members of the guideline development group, and participants of the guideline development meetings, submitted a declaration-of-interests form, along with their curriculum vitae, before each meeting. Participants of the guideline development group meetings participated in their individual capacity and not as institutional representatives. In addition, they verbally declared potential conflicts of interests at the beginning of each meeting. The procedures for management of competing interests strictly followed the WHO guidelines for declaration of interests. The management of the perceived or real conflicts of interests declared by the members of the guideline group is summarized next.<sup>1</sup>

**Dr Beverley-Ann Biggs** declared that the University of Melbourne received funding from the National Health and Medical Research Council and Australian Research Council for research on intermittent iron and folic acid supplementation in pregnancy, conducted in collaboration with the Research and Training Center for Community Development, the Key Centre for Women's Health and the Murdoch Children's Research Institute. It was agreed that she could participate fully in the deliberations and decision-making on this guideline.

**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 is a leading organization working exclusively to eliminate vitamin and mineral deficiencies in the world's most vulnerable populations. It was decided that Dr De-Regil could be a member of the guideline development group and would disclose her interests and the interests of her organization in the relevant guidelines related to micronutrient interventions. She participated in the deliberations related to the recommendation for iron supplementation but recused herself from voting on this guideline.

<sup>1</sup> 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.

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**Dr Lynnette Neufeld** declared that her current employer has received funding in the past 4 years for research and programming related to iron supplementation. At the moment she is not leading any of these initiatives. In a prior position she held with MI, she commissioned research related to iron supplementation. It was decided that Dr Neufeld could be a member of the guideline development group and had to disclose her and her organization's interests in the relevant guidelines related to micronutrient interventions. She could participate in the deliberations but she recused herself from the decision-making (voting) on the recommendation related to iron supplementation.

**Dr Héctor Bourges Rodriguez** declared being chair of the executive board 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. Some of the activities of DIM may generally relate to nutrition and are funded by Danone Mexico, a food producer. It was agreed that he could participate fully in the deliberations and decision-making on this guideline.

All other members made a verbal declaration of their interests and it was considered that they were not relevant for this guideline on iron supplementation in adult women and adolescent girls. External resource persons 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 the research development in the area of oral iron supplementation in menstruating adult women and adolescent girls in malaria-endemic and non-malaria endemic settings, particularly for questions in which 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 will coordinate the guideline update, following the formal procedures of the *WHO handbook for guideline development* (4).

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.

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## ANNEX 1. GRADE SUMMARY OF FINDINGS TABLE

## Daily oral iron supplementation compared to placebo or control in menstruating adult women and adolescent girls

Patient or population: menstruating adult women and adolescent girls (non-pregnant females in the reproductive age group)

Intervention: daily oral iron supplementation

Comparison: placebo or control<sup>1</sup>

Setting: all settings (including malaria-endemic areas)

| Outcomes  | Relative effect*<br>(95% CI)     | Number of participants<br>(studies)           | Quality of the<br>evidence<br>(GRADE) | Comments |
|---|----------------------------------|---|---------------------------------------|----------|
| Anaemia (haemoglobin below a cut-off value determined by the trialists)   | <b>RR 0.34</b><br>(0.20 to 0.57) | 2905<br>(9 RCTs)                              | ⊕ ⊕ ⊕ ⊖<br>MODERATE <sup>2</sup>      |          |
| Iron deficiency (as measured by trialists by using indicators of iron status such as ferritin or transferrin)                                       | <b>RR 0.61</b><br>(0.47 to 0.77) | 1033<br>(6 RCTs)                              | ⊕ ⊕ ⊕ ⊖<br>MODERATE <sup>3</sup>      |          |
| Iron deficiency anaemia (defined by the presence of anaemia plus iron deficiency, diagnosed with an indicator of iron status selected by trialists) | Not estimable                    | None of the studies reported on this outcome. |                                       |          |
| Morbidity (malaria incidence and severity)  | Not estimable                    | None of the studies reported on this outcome. |                                       |          |

\*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).  
**CI:** confidence interval; **RCT:** randomized controlled trial; **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

<sup>1</sup>. Studies in which iron supplements were given along with cointerventions such as other nutrients (e.g. zinc, vitamin A), deworming, education or other approaches were included in the analysis but only if the cointerventions were the same in both the intervention and comparison groups.

<sup>2</sup>. There was no serious risk of bias among the studies that included this outcome. The quality of evidence was downgraded owing to possible publication bias (missing small studies negative studies). The magnitude of effect was large, with the RR is between 0.5 and 0.2 (the quality of evidence was not upgraded for the large effect size seen).

<sup>3</sup>. There was no serious risk of bias among the studies that included this outcome. The quality of evidence was downgraded owing to possible publication bias (missing small negative studies).

For details of studies included in the review, see reference (6).

## ANNEX 2. SUMMARY OF THE CONSIDERATIONS OF THE MEMBERS OF THE GUIDELINE DEVELOPMENT GROUP FOR DETERMINING THE STRENGTH OF THE RECOMMENDATION FOR DAILY ORAL IRON SUPPLEMENTATION IN MENSTRUATING ADULT WOMEN AND ADOLESCENT GIRLS

|                                       |   |
|---------------------------------------|---|
| QUALITY OF EVIDENCE:                  | Anaemia and iron deficiency had moderate-quality evidence. The effect sizes of the intervention on these outcomes were large. The quality of the evidence for the effect on haemoglobin is high though there is currently no evidence on the outcome of iron deficiency anaemia. Although the evidence of either loose or hard stools is of high quality, the quality of the evidence for adverse effects or gastrointestinal effects in general is low or very low.                          |
| VALUES AND PREFERENCES:               | Adherence may be a concern. If the intervention is perceived as non-essential, there may be little demand for it.<br><br>Where access to health facilities is limited, as in many rural areas, the problem may be more prevalent. Inequities in access may thus negatively affect successful implementation.  |
| TRADE-OFF BETWEEN BENEFITS AND HARMS: | Benefits include improved haemoglobin and lower risk of anaemia or iron deficiency, which have functional consequences such as improved exercise performance. Potential harms include gastrointestinal effects, but evidence is of low quality. There is increased risk of either diarrhoea or constipation, with high quality of evidence.<br><br>Not enough data are available on adverse events, or long-term harm, for instance on overdose, specifically for those who are iron replete. |
| COSTS AND FEASIBILITY:                | The cost will largely be determined by the operational challenges rather than the cost of the supplementation itself. The difficulty will lie in attempting to set up vertical programmes, which can prove very costly. Health services that do not have preventive health care in menstruating adult women and adolescent girls may be more likely to find this intervention infeasible.   |

### ANNEX 3. WHO STEERING COMMITTEE FOR NUTRITION GUIDELINES DEVELOPMENT

**Dr Najeab Mohamed Al Shorbaji**

Director, Department of Knowledge Management and Sharing  
World Health Organization  
Avenue Appia 20, 1211 Geneva 27  
Switzerland

**Dr Douglas Bettcher**

Director, Department of Prevention of Noncommunicable Diseases  
World Health Organization  
Avenue Appia 20, 1211 Geneva 27,  
Switzerland

**Dr Ties Boerma**

Director, Department of Health System Policies and Workforce  
World Health Organization  
Avenue Appia 20, 1211 Geneva 27  
Switzerland

**Dr Francesco Branca**

Director, Department of Nutrition for Health and Development  
World Health Organization  
Avenue Appia, 20, 1211 Geneva 27  
Switzerland

**Dr Richard Brennan**

Director, Department of Emergency Risk Management and Humanitarian Response  
World Health Organization  
Avenue Appia 20, 1211 Geneva 27  
Switzerland

**Dr Gottfried Otto Hirschall**

Director, Department of HIV/AIDS  
World Health Organization  
Avenue Appia 20, 1211 Geneva 27  
Switzerland

**Dr Knut Lonnroth**

Medical Officer, Global TB Programme  
World Health Organization  
Avenue Appia 20, 1211 Geneva 27  
Switzerland

**Dr Elizabeth Mason**

Director, Director of Maternal, Newborn, Child and Adolescent Health  
World Health Organization  
Avenue Appia 20, 1211 Geneva 27  
Switzerland

**Dr Kazuaki Miyagishima**

Director, Department of Food Safety, Zoonoses and Foodborne Diseases  
World Health Organization  
Avenue Appia 20, 1211 Geneva 27  
Switzerland

**Dr Maria Purificacion Neira**

Director, Department of Public Health, Environmental and Social Determinants of Health  
World Health Organization  
Avenue Appia 20, 1211 Geneva 27  
Switzerland

**Dr Jean-Marie Okwo-Bele**

Director, Department of Immunization, Vaccines and Biologicals  
World Health Organization  
Avenue Appia 20, 1211 Geneva 27  
Switzerland

**Professor John Charles Reeder**

Director, Special Programme for Research and Training in Tropical Diseases  
World Health Organization  
Avenue Appia 20, 1211 Geneva 27  
Switzerland

**Dr Isabelle Romieu**

Section Head, Nutritional Epidemiology Group  
International Agency for Research on Cancer  
150, cours Albert Thomas  
69372 Lyon Cedex 08  
France

**Dr Nadia Slimani**

Group Head, Nutritional Epidemiology Group  
International Agency for Research on Cancer  
150, cours Albert Thomas  
69372 Lyon Cedex 08  
France

**Dr Marleen Temmerman**

Director, Department of Reproductive Health and Research  
World Health Organization  
Avenue Appia 20, 1211 Geneva 27  
Switzerland



## ANNEX 4. WHO GUIDELINE DEVELOPMENT GROUP

### **Ms Deena Alasfoor**

Directorate of Training and Education  
Ministry of Health  
Oman  
*Health programme management, food legislations, surveillance in primary health care*

### **Dr Beverley-Ann Biggs**

Head, International and Immigrant Health Group  
Department of Medicine  
University of Melbourne  
Australia  
*Micronutrients supplementation, clinical infectious diseases*

### **Dr Norma Campbell**

Professor  
Departments of Medicine  
Community Health Sciences and Physiology and Pharmacology  
University of Calgary  
Canada  
*Physiology and pharmacology, hypertension prevention and control*

### **Dr Mary Chea**

Deputy Manager of National Nutrition Programme  
National Maternal and Child Health Centre  
Ministry of Health  
Cambodia  
*Programme implementation, midwifery*

### **Dr Maria Elena del Socorro Jefferds**

Behavioural Scientist, Division of Nutrition, Physical Activity and Obesity  
Centers for Disease Control and Prevention  
United States of America  
*Behaviour science, programme evaluation*

### **Dr Luz Maria De-Regil**

Director, Research and Evaluation and Chief Technical Adviser  
Micronutrient Initiative  
Canada  
*Epidemiology, systematic reviews, programme implementation*

### **Dr Heba El Laithy**

Professor of Statistics and Head of Statistical Departments at Faculty of Economics  
Cairo University  
Egypt  
*Statistics, economics*

### **Dr Rafael Flores-Ayala**

Team lead, International Micronutrient Malnutrition Prevention and Control Programme  
Centers for Disease Control and Prevention  
United States of America  
*Nutrition and human capital formation, nutrition and growth, impact of micronutrient interventions*

### **Professor Davina Gheri**

Senior Principal Research Scientist  
National Health and Medical Research Council  
Australia  
*Policy-making, systematic reviews, evidence*

### **Professor Malik Goonewardene**

Senior Professor and Head of Department  
Department of Obstetrics and Gynaecology  
University of Ruhuna  
Sri Lanka  
*Obstetrics and gynaecology, clinical practice*

### **Dr Rukhsana Haider**

Chairperson  
Training and Assistance for Health and Nutrition Foundation  
Bangladesh  
*Breastfeeding, capacity-building on counselling and nutrition*

### **Dr Junsheng Huo**

Professor  
National Institute for Nutrition and Food Safety  
Chinese Centre for Disease Control and Prevention  
China  
*Food fortification, food science and technology, standards and legislation*

### **Dr Janet C King**

Children's Hospital Oakland Research Institute  
United States of America  
*Micronutrients, maternal and child nutrition, dietary requirements*

### **Dr Patrick Wilfried Kolsteren**

Head of Laboratory  
Department of Food Safety and Food Quality  
Ghent University  
Belgium  
*Public health, food safety, laboratory methods*

**Dr Marzia Lazzerini**

Director  
Department of Paediatrics and Unit of Research on Health  
Services and International Health  
Institute for Maternal and Child Health  
Italy  
Paediatrics, malnutrition, infectious diseases, methods

**Dr Guansheng Ma**

Professor, Deputy Director  
National Institute for Nutrition and Food Safety  
Chinese Center for Disease Control and Prevention  
China  
Food safety, public health, programme management

**Professor Malcolm E Molyneux**

Senior Scientist  
Malawi-Liverpool Wellcome Trust Clinical Research  
Programme  
Malawi  
Malaria, international tropical diseases research and  
practice

**Dr Mahdi Ramsan Mohamed**

Chief of Party  
RTI International  
United Republic of Tanzania  
Malaria

**Dr Lynnette Neufeld**

Director, Monitoring, Learning and Research  
Global Alliance for Improved Nutrition  
Switzerland  
Micronutrients, programmes, epidemiology

**Professor Orish Ebere Orisakwe**

Professor of Pharmacology and Toxicology  
Department of Experimental Pharmacology and Toxicology  
University of Port Harcourt  
Nigeria  
Pharmacology, food safety, toxicology

**Dr Mical Paul**

Associate Professor  
Technion-Israel Institute of Technology  
Israel  
Infectious diseases, HIV

**Engineer Wisam Qarqash**

Jordan Health Communication Partnership  
Johns Hopkins University  
Bloomberg School of Public Health  
Jordan  
Design, implementation and evaluation of health  
communications and programmes

**Professor Dalip Ragoobirsingh**

Professor Dalip Ragoobirsingh  
Director, Diabetes Education Programme  
University of West Indies  
Jamaica  
Diabetes

**Dr Daniel J Raiten**

Program Officer  
Office of Prevention Research and International Programs  
Center for Research for Mothers and Children  
United States of America  
Micronutrients, programmes, infant feeding

**Dr Héctor Bourges Rodríguez**

Director, Nutrition  
Instituto Nacional de Ciencias Medicas y Nutricion  
Salvador Zubiran  
Mexico  
Nutritional biochemistry and metabolism research, food  
programmes, policy, and regulations

**Professor HPS Sachdev**

Senior Consultant Paediatrics and Clinical Epidemiology  
Sitaram Bhartia Institute of Science and Research  
India  
Paediatrics, systematic reviews

**Ms Rusidah Selamat**

Deputy Director (Operations) of Nutrition Division  
Ministry of Health  
Malaysia  
Public health nutrition

**Dr Rebecca Joyce Stoltzfus**

Professor and Director  
Program in International Nutrition, Program in Global  
Health  
Division of Nutritional Sciences  
Cornell University  
United States of America  
International nutrition and public health, iron and vitamin  
A nutrition, programme research

**Dr Kalid Asrat Tasew**

Consultant Paediatrician  
St Paul Hospital Millennium Medical College  
Ethiopia  
Paediatrics

**Dr Carol Tom**

Regional Food Fortification Advisor  
A2Z Project  
East, Central and Southern African Health Community  
United Republic of Tanzania  
Food fortification technical regulations and standards,  
policy harmonization

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**Dr Igor Veljkovic**

Health and Nutrition Officer

United Nations Children's Fund (UNICEF) Office in Skopje

The former Yugoslav Republic of Macedonia

*Programme implementation*

**Dr Maged Younes**

Independent international expert on global public health

Italy

*Food safety, public health, programme management*

## ANNEX 5. EXTERNAL RESOURCE PERSONS

**Dr Nancy Aburto**

Nutrition Adviser  
United Nations World Food Programme  
Italy

**Dr Guillermo Carroli**

Director  
Centro Rosarino de Estudios Perinatales  
Argentina

**Ms Nita Dalmiya**

Nutrition Specialist, Micronutrients  
United Nations Children's Fund  
United States of America

**Dr Maria Cecilia Dedios Sanguinetti**

Independent consultant, Evaluation  
United States of America

**Dr Kathryn Dewey**

Professor, Department of Nutrition  
Director, Program in International and Community  
Nutrition  
University of California  
United States of America

**Ms Mary-Anne Land**

Research Associate  
The George Institute for Global Health  
Australia

**Dr Sant-Rayn Pasricha**

MRC Human Immunology Unit  
Weatherall Institute of Molecular Medicine  
University of Oxford  
John Radcliffe Hospital  
United Kingdom of Great Britain and Northern Ireland

**Dr Usha Ramakrishnan**

Program Director, Doctoral Program in Nutrition and  
Health Sciences  
Department of Global Health  
Rollins School of Public Health  
Emory University  
United States of America

## ANNEX 6. WHO SECRETARIAT

### **Ms Sanjhavi Agarwal**

Intern, Evidence and Programme Guidance  
Department of Nutrition for Health and Development

### **Ms Maryam Bigdeli**

Technical Officer  
Alliance for Health Policy and Systems Research

### **Dr Carmen Casanovas**

Technical Officer, Evidence and Programme Guidance  
Department of Nutrition for Health and Development

### **Dr Laragh Gollogly**

Editor, WHO Press  
Department of Knowledge Management and Sharing

### **Dr Maria de las Nieves Garcia-Casal**

Consultant, Micronutrients  
Department of Nutrition for Health and Development

### **Dr Eyerusalem Kebede Negussie**

Medical Officer, HIV Treatment and Care  
Department of HIV/AIDS

### **Dr Suzanna McDonald (rapporteur)**

Consultant, Immunology, Evidence and Programme Guidance  
Department of Nutrition for Health and Development

### **Ms Daniela Meneses (rapporteur)**

Intern, Evidence and Programme Guidance  
Department of Nutrition for Health and Development

### **Dr Juan Pablo Peña-Rosas**

Coordinator, Evidence and Programme Guidance  
Department of Nutrition for Health and Development

### **Dr Pura Rayco-Solon**

Epidemiologist (infectious disease and nutrition), Evidence and Programme Guidance  
Department of Nutrition for Health and Development

### **Dr Lisa Rogers**

Technical Officer, Evidence and Programme Guidance  
Department of Nutrition for Health and Development

### **Dr Nigel Rollins**

Medical Officer, Research and Development  
Department of Maternal, Newborn, Child and Adolescent Health

### **Ms Victoria Saint**

Technical Officer, Social Determinants of Health  
Department of Public Health, Environmental and Social Determinants of Health

### **Dr Eugenio Villar Montesinos**

Coordinator, Social Determinants of Health  
Department of Public Health, Environmental and Social Determinants of Health

### **Ms Zita Weise Prinzo**

Technical Officer, Evidence and Programme Guidance  
Department of Nutrition for Health and Development

### **Mr Gerardo Zamora**

Technical Officer (implementation research and equity), Evidence and Programme Guidance  
Department of Nutrition for Health and Development  
WHO regional offices

## *WHO regional offices Regional Office for Africa*

### **Dr Mercy Chikoko**

Acting Regional Adviser for Nutrition  
WHO Regional Office for Africa  
Cit  du Djou , PO Box 06 Brazzaville,  
Congo

## *Regional Office for the Americas/Pan American Health Organization*

### **Dr Chessa Lutter**

Regional Adviser, Child and Adolescent Health  
Pan American Health Organization  
525 23rd Street, NW, Washington DC 20037  
United States of America

## *Regional Office for South-East Asia*

### **Dr Kunal Bagchi**

Regional Adviser – Nutrition and Food Safety  
Healthy Ageing  
WHO Regional Office for South-East Asia  
World Health House  
Indraprastha Estate, Mahatama Gandhi Road  
New Delhi 110002  
India

## ANNEX 7. PEER-REVIEWERS

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**Ms Solange Durao**  
Senior Scientist

South Africa Cochrane Collaboration Centre  
South Africa

**Dr Tran Khanh Van**  
Vice Head of Nutrition  
National Institute of Nutrition  
Vietnam

**Ms Terrie Wefwafwa**  
Chief Executive Officer  
Karibuni Kenya (Consultancy)  
Kenya

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

### *Effects and safety of iron supplementation in menstruating adult women and adolescent girls*

Could iron supplements given to menstruating adult women and adolescent girls improve health outcomes?  
If so, (a) at what dose, frequency and duration of the intervention? (b) in which settings?

|               |  |
|---------------|--|
| POPULATION:   | Menstruating adult women and adolescent girls<br>Subpopulations: <ul style="list-style-type: none"><li>– By malaria (no transmission or elimination achieved, susceptibility to epidemic malaria, year-round transmission with marked seasonal fluctuations, year-round transmission; with consideration of <i>Plasmodium falciparum</i> and/or <i>Plasmodium vivax</i>)</li><li>– By use of concurrent antimalarial measures introduced in the study: yes versus no</li><li>– By antimalarial measures implemented by the health system: yes versus no</li><li>– By woman's anaemia status: anaemic versus non-anaemic</li><li>– By woman's iron status: iron deficient versus iron replete</li></ul> |
| INTERVENTION: | Iron supplementation<br>Subgroup analyses: <ul style="list-style-type: none"><li>– By iron dose: 30 mg versus 60 mg versus other</li><li>– By frequency: daily versus weekly versus twice weekly versus other</li><li>– By duration: 3 months or less versus &gt;3 months</li><li>– By additional nutrient: iron versus iron plus folic acid versus iron plus other micronutrients</li></ul>   |
| CONTROL:      | No iron supplementation<br>Placebo<br>Same supplement without iron   |
| OUTCOMES:     | Short-term outcomes <ul style="list-style-type: none"><li>– Anaemia</li><li>– Iron deficiency anaemia</li><li>– Iron deficiency</li><li>– Morbidity<ul style="list-style-type: none"><li>– Malaria incidence and severity (parasitaemia with or without symptoms)</li></ul></li></ul>  |
| SETTING:      | All countries  |

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**FOR MORE INFORMATION, PLEASE CONTACT:**

**Department of Nutrition for Health and Development**

World Health Organization  
Avenue Appia 20,  
CH-1211 Geneva 27,  
Switzerland

Fax: +41 22 791 4156  
E-mail: [nutrition@who.int](mailto:nutrition@who.int)  
[www.who.int/nutrition](http://www.who.int/nutrition)



## Guideline:

# DAILY IRON SUPPLEMENTATION IN ADULT WOMEN AND ADOLESCENT GIRLS

For more information, please contact:

Department of Nutrition for Health and Development  
World Health Organization  
Avenue Appia 20,  
CH-1211 Geneva 27,  
Switzerland

Fax: +41 22 791 4156  
E-mail: [nutrition@who.int](mailto:nutrition@who.int)  
[www.who.int/nutrition](http://www.who.int/nutrition)