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Intermittent iron supplementation in preschool and school-age children

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Contents

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WHO Guideline[1]

Intermittent iron supplementation in preschool and school-age children

Summary

It is estimated that 600 million preschool and school-age children worldwide are anaemic, and it is assumed that at least half of these cases are attributable to iron deficiency. Member States have requested guidance from the World Health Organization (WHO) on the effects and safety of intermittent iron supplementation in children as a public health intervention to improve their iron status and reduce the risk of developing iron deficiency anaemia, in support of country efforts to achieve the Millennium Development Goals.

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

The guideline development group for nutrition interventions, the Nutrition Guidance Expert Advisory Group (NUGAG), comprises content experts, methodologists, representatives of potential stakeholders and consumers. These experts participated in several WHO technical consultations concerning this guideline, held in Geneva, Switzerland, and Amman, Jordan, in 2010 and 2011. Members of the External Experts and Stakeholders Panel were identified through a public call for comments, and this panel was involved throughout the guideline development process. NUGAG members voted on the strength of the recommendation, taking into consideration: (i) desirable and undesirable effects of this 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. All NUGAG members completed a Declaration of Interests Form before each meeting.

In settings where the prevalence of anaemia in preschool or school-age children is 20% or higher, intermittent use of iron supplements is recommended as a public health intervention to improve iron status and reduce the risk of anaemia among children (strong recommendation). In comparison with a placebo or no intervention, the overall quality of the available evidence was found to be moderate for anaemia, low for haemoglobin and ferritin concentrations and very low for iron deficiency. When compared with daily supplementation, the quality of the available evidence for intermittent supplementation with regard to anaemia and haemoglobin and ferritin concentrations was found to be low and for iron deficiency it was very low.

[1] 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.

Scope and purpose

This guideline provides global, evidence-informed recommendations on the intermittent use of iron supplements for preschool and school-age children as a public health intervention to improve iron status and reduce the risk of childhood iron deficiency anaemia.

The guideline will help Member States and their partners in their efforts to make informed decisions on the appropriate nutrition actions to achieve the Millennium Development Goals, in particular, the eradication of extreme poverty and hunger (MDG 1), achievement of universal primary education (MDG 2) and reduction of child mortality (MDG 4). The 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 nutrition actions for public health.

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

Background

Iron deficiency, a common form of nutritional deficiency during childhood, results from sustained negative iron balance, which is caused by inadequate dietary intake, absorption or utilization of iron, increased iron requirements during the growth period, or blood loss due to parasitic infections such as malaria, soil-transmitted helminth infestations and schistosomiasis. In later stages of iron depletion, the haemoglobin concentration decreases, resulting in anaemia. Anaemia is characterized by a reduction in the oxygen-carrying capacity of blood, such that the physiological oxygen needs of the affected individual can no longer be met. In addition to iron deficiency, other micronutrient deficiencies (e.g. folate, vitamin B_{12} and vitamin A), chronic inflammation and inherited disorders of haemoglobin structure can all cause anaemia (*1*). Diagnosis of anaemia requires measurement of the haemoglobin concentration, while serum ferritin and serum soluble transferrin receptor levels are commonly used as indicators of iron status. A diagnosis of iron deficiency anaemia is made when there is both anaemia and iron deficiency (*2*).

Children are particularly vulnerable to iron deficiency anaemia because of their increased iron requirements in the periods of rapid growth, especially in the first 5 years of life. It is estimated that worldwide, 600 million preschool and school-age children are anaemic, and it is assumed that at least half of these cases are attributable to iron deficiency (*3*). Iron deficiency anaemia in children has been linked to increased childhood morbidity and impaired cognitive development and school performance. Both epidemiological and experimental data suggest that when these impairments occur at an early age, they may be irreversible, even after repletion of iron stores, thus reinforcing the importance of preventing this condition (*4, 5*).

Public health interventions to ameliorate micronutrient malnutrition in preschool and school-age children include the promotion of dietary diversification to include foods rich in highly absorbable vitamins and minerals, anthelminthic treatment, mass fortification of staple foods and condiments, home (point of use) fortification of foods, and provision of micronutrient supplements (*6*). The effectiveness of such interventions in these age groups is variable and not always aimed at meeting children's needs (for example, in the case of mass fortification) whereas in other cases the interventions are not feasible because of economic or behavioural constraints (*7*). Although daily iron supplementation has proven to be effective in increasing haemoglobin concentrations in children, especially in those who are anaemic (*8*), in real-world settings, the low coverage rates and insufficient tablet distribution, the prolonged duration of the intervention and the associated side-effects (e.g. gastrointestinal discomfort, constipation and staining of teeth with drops or syrups) may limit adherence to the intervention, especially in young children (*7*, *9*).

Intermittent use of oral iron supplements (i.e. once, twice or three times a week on non-consecutive days) has been proposed as an effective alternative to daily iron supplementation to prevent anaemia among children (*10, 11*). The proposed rationale behind this intervention is that intestinal cells turn over every 5–6 days and have limited iron absorptive capacity. Thus intermittent provision of iron would expose only the new epithelial cells to this nutrient, which should, in theory, improve the efficiency of absorption (*12, 13*). Intermittent supplementation also may minimize blockage of absorption of other minerals due to the high iron levels in the gut lumen and in the intestinal epithelium (*14*). This overall reduced exposure to iron is particularly relevant in malaria settings (where it has been suggested that the provision of additional iron may exacerbate the infection) as less iron may be available for the parasite's growth (*15*). Experience in different populations has shown that intermittent regimens reduce the frequency of other side-effects associated with daily iron supplementation and are also more acceptable to recipients, thus increasing compliance with supplementation programmes (*16*).

Summary of evidence

A Cochrane systematic review (*17*) was conducted to assess the effects and safety of intermittent iron supplementation alone or in combination with other micronutrients inchildren under 12 years of age with regard to health and nutrition outcomes. The review compared the provision of iron supplements on an intermittent basis versus no intervention or placebo, and versus daily use of iron supplements, among children living in a variety of settings, including malaria-endemic areas.

The outcomes considered to be critical for decision-making by the Nutrition Guidance Expert Advisory Group (NUGAG) were anaemia, haemoglobin concentration, iron status and mortality. The potential modifying effects of the baseline anaemia prevalence, total iron dose per week, the intermittent regimen scheme, duration of the intervention, supplement formulation and sex were also assessed.

The review included 33 randomized controlled trials involving 13 144 children from 20 countries in Latin America, Africa and Asia where anaemia prevalence was moderate to high. Most of the trials used ferrous sulfate as the iron source, with doses ranging from 7.5 mg to 200 mg of elemental iron per week. In five studies, iron was given in combination with folic acid, in doses that ranged from 100 µg (0.1 mg) to 500 µg (0.5 mg) per week.

Compared with placebo or no intervention, intermittent iron supplementation (alone or in combination with other nutrients) in children younger than 12 years of age significantly increased the concentration of haemoglobin (mean difference (MD) 5.20 g/l, 95% confidence interval (CI) 2.51–7.88, 19 studies) and ferritin (MD 14.17 µg/l, 95% CI 3.53–24.81, five studies), and reduced the risk of presenting anaemia at the end of the intervention (relative risk (RR) 0.51, 95% CI 0.37–0.72, 10 studies).

On the other hand, compared with children receiving daily iron supplements, those receiving iron supplements intermittently were more likely to be anaemic at the end of the intervention (RR 1.23, 95% CI 1.04–1.47, six studies) but the mean difference in the haemoglobin and ferritin concentrations between the two groups was not significant (MD –0.60, g/l 95% CI –1.54 to 0.35, 19 studies, and –4.19 µg/l, 95% CI –9.42 to 1.05, 10 studies, respectively). Adherence tended to be higher among children receiving intermittent supplementation compared with those receiving daily supplementation, although this result was not statistically significant.

The micronutrient composition of the supplements (iron alone, iron plus folic acid, or iron plus other micronutrients) did not impact on the above findings, although most of the evidence was derived from trials using supplements containing only iron. In addition, the intervention seemed efficacious in settings with different baseline prevalence of anaemia, in both sexes, across trials lasting either less or more than 3 months and with all intermittent regimens.

No deaths were reported in the trials. Although limited data were available on outcomes related to morbidity, neurocognitive outcomes, other indicators of vitamin and mineral status, and side-effects, no evidence was found of increased morbidity or side-effects, including in malaria-endemic settings.

In comparison with a placebo or no intervention, the overall quality of the available evidence was found to be moderate for anaemia, low for haemoglobin and ferritin concentrations and very low for iron deficiency. When compared with daily supplementation, the quality of the available evidence for intermittent supplementation with regard to anaemia and haemoglobin and ferritin concentrations was found to be low and for iron deficiency it was very low (Annex 1).

Recommendation

Intermittent iron supplementation is recommended as a public health intervention in preschool and school-age children to improve iron status and reduce the risk of anaemia (*strong recommendation*)[1].

The suggested schemes for intermittent iron supplementation in preschool and school-age children are presented in Table 1.

Table 1

Suggested schemes for intermittent iron supplementation in preschool and school-age children

Target group	Preschool-age children (24–59 months)	School-age children (5–12 years)
Supplement composition	25 mg of elemental iron[a]	45 mg of elemental iron[b]
Supplement form	Drops/syrups	Tablets/capsules
Frequency	One supplement per week	
Duration and time interval between periods of supplementation	3 months of supplementation followed by 3 months of no supplementation after which the provision of supplements should restart If feasible, intermittent supplements could be given throughout the school or calendar year	
Settings	Where the prevalence of anaemia in preschool or school-age children is 20% or higher	

[a] 25 mg of elemental iron equals 75 mg of ferrous fumarate, 125 mg of ferrous sulfate heptahydrate or 210 mg of ferrous gluconate.
[b] 45 mg of elemental iron equals 135 mg of ferrous fumarate, 225 mg of ferrous sulfate heptahydrate or 375 mg of ferrous gluconate.

[1] A strong recommendation is one for which the guideline development group is confident that the desirable effects of adherence outweigh the undesirable effects. This can be either in favour of or against an intervention. Implications of a strong recommendation for patients are that most people in their situation would desire the recommended course of action and only a small proportion would not. Implications for clinicians are that most patients should receive the recommended course of action, and adherence to this recommendation is a reasonable measure of good-quality care. With regard to policy-makers, a strong recommendation means that it can be adapted as a policy in most situations.

Remarks

- In malaria-endemic areas, the provision of iron supplements should be implemented in conjunction with adequate measures to prevent, diagnose and treat malaria (*18, 19*).
- Intermittent iron supplementation is a preventive strategy for implementation at population level. If a child is diagnosed with anaemia in a clinical setting, he or she should be treated with daily iron supplementation until the haemoglobin concentration rises to normal (*20*). He or she can then be switched to an intermittent regimen to prevent the recurrence of anaemia.
- As there is limited evidence for the effective dose of folic acid or other vitamins and minerals for intermittent supplementation, it is suggested providing two times the recommended nutrient intake in these age groups without exceeding the daily upper limit (*21*). Thus children 24–59 months of age may be given a dose of 300 µg (0.3 mg) of folic acid once a week, whereas older children may be given 400 µg (0.4 mg).
- Where infection with hookworm is endemic (prevalence 20% or greater) it may be more effective to combine iron supplementation with anthelminthic treatment in children above the age of 5 years. Universal anthelminthic treatment, irrespective of infection status, is recommended at least annually in these areas (*20*, *22*).
- The provision of iron supplements on an intermittent basis may be integrated into school or community programmes to reach the target populations. These programmes should ensure that the daily nutritional needs of preschool or school-age children are met and not exceeded, through the evaluation of nutritional status and intake, as well as consideration of existing anaemia and micronutrient deficiency control measures (such as provision of vitamin A supplements, fortified foods and anthelminthic therapy).
- The intermittent provision of supplements may include a behaviour communication change strategy that promotes the awareness and correct use of this product along with other practices such as hand washing with soap, prompt attention to fever in malaria settings, and measures to manage diarrhoea, particularly among younger children (*23*).
- The establishment of a quality assurance process is important to ensure that supplements are manufactured, packaged and stored in a controlled and uncontaminated environment (*24*).
- The selection of the most appropriate delivery platform should be context-specific, with the aim of ensuring that the most vulnerable members of the populations are reached. For example, if the education system is selected as delivery channel, efforts should be made to reach children who do not attend school.
- Oral supplements are available as drops or syrups for preschool-age children, and tablets or capsules for school-age children. Liquid preparations for oral use are usually supplied as solutions, emulsions or suspensions containing one or more of the active ingredients in a suitable vehicle. All these preparations are supplied either in the finished form or, with the exception of oral emulsions,

may need to be prepared just before use by dissolving or dispersing the granules or powder in the vehicle as stated on the label. Tablets (soluble tablets, effervescent tablets, dissolvable tablets for use in the mouth and modified-release tablets) are solid dosage forms containing one or more active ingredients. They are manufactured by single or multiple compression (in certain cases they are moulded) and may be uncoated or coated. Capsules are solid dosage forms with hard or soft shells, which are available in a variety of shapes and sizes, and contain a single dose of one or more of the active ingredients (*25*).

Dissemination, adaptation and implementation

Dissemination

The current guideline will be disseminated through electronic media such as slide presentations, CD-ROMs and the World Wide Web, either through the WHO Micronutrients and United Nations Standing Committee on Nutrition (SCN) mailing lists or the WHO nutrition web site. The Department of Nutrition for Health and Development has developed the WHO electronic Library of Evidence for Nutrition Actions (eLENA). This library aims to compile and display 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.

Adaptation and implementation

As this is a global guideline it should be adapted to the context of each Member State. Prior to implementation, an iron supplementation programme should have well-defined objectives that take into account available resources, existing policies, suitable delivery platforms and suppliers, communication channels and potential stakeholders. Supplementation programmes should start with a pilot and scaled up as experience and evidence grow and resources allow. Ideally, an iron supplementation programme should be implemented as part of an integrated strategy to control nutritional deficiencies.

To ensure that WHO global guidelines and other evidence-informed recommendations for micronutrient interventions are better implemented in low- and middle-income countries, the Department of Nutrition for Health and Development works with the WHO Evidence-Informed Policy Network (EVIPNet) programme. EVIPNet promotes partnerships at country level between policy-makers, researchers and civil society to facilitate policy development and implementation through use of the best available evidence.

Monitoring and evaluation of guideline implementation

A plan for monitoring and evaluation with appropriate indicators is encouraged at all stages. The impact of this guideline can be evaluated within countries (i.e. monitoring and evaluation of the programmes implemented at scale) and across countries (i.e. the adoption and adaptation of the guideline globally). The WHO Department of Nutrition for Health and Development, Micronutrients Unit, jointly with the 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 to depict the plausible relationships between inputs and expected MDGs by applying the micronutrient programme evaluation theory. Member States can adjust this model and use it in combination with appropriate indicators, for designing, implementing, monitoring and evaluating the successful scaling-up of nutrition actions (*26*).

For evaluation at global level, the WHO Department of Nutrition for Health and Development is developing 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 nutrition actions.

Implications for future research

Discussion with NUGAG members and stakeholders highlighted the limited evidence in some areas, meriting further research on intermittent iron supplementation in preschool and school-age children, in particular, in the following areas:

- the most effective and safe dose of folic acid that can be provided intermittently;
- provision of multiple micronutrients on an intermittent basis and their effects on other indicators of vitamin and mineral status, such as retinol and zinc;
- efficacy of intermittent iron regimens with regard to neurocognitive and developmental outcomes and growth (attempts should be made to use comparable measures across studies when possible);
- efficacy of intermittent supplementation in the treatment of anaemia, iron deficiency and iron deficiency anaemia, as well as the best therapeutic regimen (dose, frequency, duration);
- cost-effectiveness of intermittent compared with daily iron supplementation, taking into account more than just the cost differential of the supplements themselves;
- whether this intervention requires continuous or periodic implementation over the year, taking into account both biological and programmatic feasibility.

In addition, future studies are encouraged to comprehensively document the effects of intermittent supplementation on anaemia, iron deficiency, haemoglobin and ferritin concentrations and other indicators of iron status and inflammation. Reporting of side-effects in greater detail according to recommended definitions is highly desirable to better understand the factors influencing adherence. A more systematic and comparable reporting system addressing the relevance of direct and continued supervision is also needed.

Guideline development process

This guideline was developed in accordance with WHO evidence-informed guideline development procedures, as outlined in the *WHO handbook for guideline development* (*27*).

Advisory groups

A WHO Steering Committee for Nutrition Guidelines Development, led by the Department of Nutrition for Health and Development and the Department of Research Policy and Cooperation, was established in 2009 with representatives from all WHO departments with an interest in the provision of scientific nutrition advice including Child and Adolescent Health and Development, Reproductive Health and Research, and the Global Malaria Programme. The Steering Committee guided the development of this guideline and provided overall supervision of the guideline development process (Annex 2). Two additional groups were formed: an advisory guideline group and an External Experts and Stakeholders Panel.

The Nutrition Guidance Expert Advisory Group, NUGAG, was also established in 2009 (Annex 3). NUGAG consists of four subgroups: (i) Micronutrients, (ii) Diet and Health, (iii) Nutrition in Life course and Undernutrition, and (iv) Monitoring and Evaluation. Its role is to advise WHO on the choice of important outcomes for decision-making and in the interpretation of the evidence. The group includes experts from various WHO expert advisory panels and those identified through open calls for specialists, taking into consideration a balanced gender mix, multiple disciplinary areas of expertise and representation from all WHO regions. Efforts were made to include content experts, methodologists, representatives of potential stakeholders (such as managers and other health professionals involved in the health-care process) and consumers. Representatives of commercial organizations may not be members of a WHO guideline group.

The External Experts and Stakeholders Panel was consulted on the scope of the guideline, the questions addressed, and the choice of important outcomes for decision-making, as well as with regard to review of the completed draft guideline (Annex 4). This was done through the WHO Micronutrients and SCN mailing lists that together include over 5500 subscribers, and through the WHO nutrition web site.

Scope of the guideline, evidence appraisal and decision-making

An initial set of questions (and the components of the questions) to be addressed in the guideline was the critical starting point for formulating the recommendation. The questions were drafted by technical staff at the Micronutrients 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 (Annex 5). The questions were discussed and reviewed by the WHO Steering Committee for Nutrition Guidelines Development, and feedback was received from 48 stakeholders.

The first NUGAG meeting was held on 22–26 February 2010 in Geneva, Switzerland, to finalize the scope of the questions and rank the critical outcomes and populations of interest. The NUGAG – Micronutrients Subgroup discussed the relevance of the questions and modified them as needed. The guideline group members 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 iron supplements in children 24–59 months of age and those 60 months and older, along with the outcomes that were identified as critical and important for decision-making are listed using the PICO format in Annex 5.

WHO staff, in collaboration with researchers from other institutions, summarized and appraised the evidence by using the Cochrane methodology for randomized controlled trials.[1] For identifying unpublished studies or trials still in progress, a standard procedure was followed to contact more than 10 international organizations working on micronutrients interventions. In addition, the International Clinical Trials Registry Platform (ICTRP), hosted at WHO, was systematically searched for any trials still in progress. No language restrictions were applied to the search. Evidence summaries were prepared according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the overall quality of the evidence (*28*). GRADE considers the study design; the limitations of the studies in terms of their conduct and analysis; the consistency of the results across the available studies; the directness (or applicability and external validity) of the evidence with respect to the populations, interventions and settings where the proposed intervention may be used; and the precision of the summary estimate of the effect.

Both the systematic reviews and the GRADE evidence profiles for each of the critical outcomes were used for drafting this guideline. The draft recommendation was discussed by the WHO Nutrition Guidance Steering Committee and NUGAG at a second NUGAG consultation, held on 15–18 November 2010, in Amman, Jordan, and the third consultation, held on 14–16 March 2011 in Geneva, Switzerland, where NUGAG members also voted on the strength of the recommendation, taking into account: (i) desirable and undesirable effects of this 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 (Annex 6). Consensus was defined as agreement by simple majority of guideline group members. WHO staff present at the meeting as well as other external

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

technical experts involved in the collection and grading of the evidence were not allowed to vote. There were no strong disagreements among the guideline group members.

A public call for comments on the final draft guideline was then released. All interested stakeholders became members of the External Experts and Stakeholders Panel but were only allowed to comment on the draft guideline after submitting a signed Declaration of Interests Form. Feedback was received from 15 stakeholders. WHO staff then finalized the guideline and submitted it for clearance by WHO before publication.

Management of conflicts of interest

According to the rules in the WHO *Basic documents* (*29*), all experts participating in WHO meetings must declare any interest relevant to the meeting prior to their participation. The conflicts 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. 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)* (*30*). The potential conflicts of interest declared by members of the guideline group are summarized below.

- 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 the DIM may generally relate to nutrition and are funded by Danone Mexico, a food producer.

- Dr Norm Campbell at the first meeting declared owning stock in Viterra, a wheat pool for farmers that neither manufactures products nor has activities related to this guideline. In 2011, Dr Campbell declared no longer owning stocks in this company. He serves as a Pan American Health Organization (PAHO) consultant and has been an adviser to Health Canada and Blood Pressure Canada, both of which are government agencies.

- Dr Emorn Wasantwisut declared serving as a technical/scientific adviser to the International Life Sciences Institute (ILSI)/South East Asia's Food and Nutrients in Health and Disease Cluster and as a reviewer of technical documents and speaker for Mead Johnson Nutritionals. Her research unit received funds for research support from Sight and Life and the International Atomic Energy Agency (IAEA) for the use of stable isotopes to define interactions of vitamin A and iron.

- Dr Beverly Biggs declared that the University of Melbourne received funding from the National Health and Medical Research Council (NHMRC) and Australian Research Council (ARC) for research on weekly iron and folic acid supplementation in pregnancy, which was conducted in collaboration with the Research and Training Center for Community Development (RTCCD), the Key Centre for Women's Health and the Murdoch Childrens Research Institute.

Plans for updating the guideline

This guideline will be reviewed in 2015. If new information is available at that time, a guideline review group will be convened to evaluate the new evidence and revise the recommendation if needed. The Department of Nutrition for Health and Development at the WHO headquarters in Geneva, along with its internal partners will be responsible for coordinating the guideline update following formal *WHO handbook for guideline development* procedures (*27*). 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

Intermittent use of iron supplements versus placebo or no intervention in children 2 months –12 years of age

Patient or population: Children under 12 years of age
Settings: Community settings
Intervention: Intermittent supplementation with iron alone or with other micronutrients
Comparison: Placebo or no intervention

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)*	Comments
Anaemia (haemoglobin below a cut-off defined by the trialists, taking into account the age and altitude)	**RR 0.51** (0.37–0.72)	1824 (10 studies)	⊕⊕⊕⊖ **moderate**[1]	
Haemoglobin (g/l)	**MD 5.20** (2.51–7.88)	3032 (19 studies)	⊕⊕⊖⊖ **low**[2,3]	
Iron deficiency	**RR 0.24** (0.06–0.91)	431 (3 studies)	⊕⊖⊖⊖ **very low**[2,3,4]	
Iron deficiency anaemia	Not estimable	0 (0 studies)	See comment	None of the trials reported on this outcome
Ferritin (µg/l)	**MD 14.17** (3.53–24.81)	550 (5 studies)	⊕⊕⊖⊖ **low**[2,3]	
All-cause mortality	Not estimable	0 (0 studies)	See comment	None of the trials reported on this outcome

CI, confidence interval; RR, risk ratio; MD, mean difference.
*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 have moderate confidence 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 the effect.
[1] There was high statistical heterogeneity. Given the large and consistent effect (RR 0.51; 95% CI 0.37–0.72), the authors have refrained from downgrading even though three of 10 studies were at high risk of bias.
[2] High statistical heterogeneity but results were consistent.
[3] Some studies lacked blinding and clear methods of allocation.
[4] Wide confidence intervals.

Note: For cluster-randomized trials, the analyses only include the estimated effective sample size, after adjusting the data to account for the clustering effect.

For details of studies included in the review, see reference (*17*).

Intermittent versus daily use of iron supplements in children under 12 years of age

Patient or population: Children under 12 years of age
Settings: Community settings
Intervention: Intermittent supplementation with iron alone or with other micronutrients
Comparison: Daily supplementation with iron alone or with other micronutrients

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)*	Comments
Anaemia (haemoglobin below a cut-off defined by the trialists, taking into account the age and altitude)	**RR 1.23** (1.04–1.47)	980 (6 studies)	⨁⨁⨀⨀ **low**[1,2]	
Haemoglobin (g/l)	**MD –0.60** (-1.54, 0.35)	2834 (19 studies)	⨁⨁⨀⨀ **low**[1,3]	
Iron deficiency	**RR 4.00** (1.23–13.05)	76 (1 study)	⨁⨀⨀⨀ **very low**[4]	Only one study reported on this outcome
Iron deficiency anaemia	Not estimable	0 (0 studies)	See comment	None of the trials reported on this outcome
Ferritin (µg/l)	**MD –4.19** (–9.42 to 1.05)	902 (10 studies)	⨁⨁⨀⨀ **low**[1,3]	
All-cause mortality	Not estimable	0 (0 studies)	See comment	None of the trials reported on this outcome

CI, confidence interval; RR, risk ratio; MD, mean difference.
*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 have moderate confidence 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 the effect.
[1] Some studies lacked blinding and clear methods of randomization and allocation.
[2] Wide confidence intervals.
[3] High heterogeneity but results were mostly consistent.
[4] Only one trial with unclear methods to generate the random sequence and conceal the allocation. Wide confidence intervals.

Note: For cluster-randomized trials, the analyses only include the estimated effective sample size, after adjusting the data to account for the clustering effect.

For details of studies included in the review, see reference (*17*).

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Annex 5 Questions in Population, Intervention, Control, Outcomes (PICO) format

1. Effects and safety of iron supplementation in children 24–59 months of age

a. Should iron supplements be given to children 24–59 months of age to improve health outcomes?
b. If so, at what dose, frequency and duration of the intervention, and in which settings?

Population: Children 24–59 months of age
- Subpopulation:

Critical
- By previous exposure to iron: infants who regularly received an iron supplement within the first 23 months of life versus no iron
- By malaria (no transmission or elimination achieved, susceptibility to epidemic malaria, year-round transmission with marked seasonal fluctuations, year-round transmission with consideration of *Plasmodium falciparum* and/or *Plasmodium vivax*)
- By use of concurrent antimalarial measures introduced in the study: yes versus no
- By antimalarial measures implemented by the health system: yes versus no
- By anaemia status of population: more than 40% versus 40% or less

Intervention: Iron supplementation
- Subgroup analysis:

Critical
- By dose: 2 mg/kg/day versus other
- By frequency: daily versus weekly versus flexible
- By duration: 3 months or less versus more than 3 months
- By nutrient: in combination with other micronutrients or not
- By targeting: universal versus prescribed

Control:
- No iron supplementation
- Placebo
- Same supplement without iron

Outcomes: *Critical*
- Anaemia
- Iron deficiency anaemia
- Iron deficiency
- Morbidity
  - Malaria incidence and severity (parasitaemia with or without symptoms)
- Growth measures: underweight, stunting status, head circumference
- Mortality
  - All-cause
  - Malaria

Setting: All countries

2. Effects and safety of iron supplementation in children 60 months of age and older

a. Should iron supplements be given to children 60 months of age and older to improve health outcomes?
b. If so, at what dose, frequency and duration of the intervention, and in which settings?

Population: Children 60 months of age and older
• Subpopulation:
Critical
- By previous exposure to iron: children who regularly received an iron supplement within the first 59 months of life versus no iron
- By malaria (no transmission or elimination achieved, susceptibility to epidemic malaria, year-round transmission with marked seasonal fluctuations, year-round transmission with consideration of *Plasmodium falciparum* and/or *Plasmodium vivax*)
- By use of concurrent antimalarial measures introduced in the study: yes versus no
- By antimalarial measures implemented by the health system: yes versus no
- By anaemia status of population: more than 40% versus 40% or less
- By individual's status of anaemia: anaemic versus non-anaemic

Intervention: Iron supplementation
• Subgroup analysis:
Critical
- By dose: 2 mg/kg/day versus other
- By frequency: daily versus weekly versus flexible
- By duration: 3 months or less versus more than 3 months
- By nutrient: in combination with other micronutrients or not
- By targeting: universal versus prescribed

Control:
- No iron supplementation
- Placebo
- Same supplement without iron

Outcomes: *Critical*
- Anaemia
- Iron deficiency anaemia
- Iron deficiency
- Morbidity
  – Malaria incidence and severity (parasitaemia with or without symptoms)
- Growth measures: underweight, stunting status, head circumference
- Mortality
  – All-cause
  – Acute respiratory infections
  – Diarrhoea
  – Malaria

Setting: All countries

Annex 6 Summary of NUGAG members' considerations for determining the strength of the recommendation

Quality of evidence:	• The quality of the evidence was considered sufficient to support a recommendation in all settings, including areas of malaria transmission • High value was placed on the successful implementation of pilot programmes in both children and menstruating women in some countries
Values and preferences:	• Intermittent use of iron supplements can increase adherence as it might be easier for children and their caregivers to follow the intervention with less inconvenience • The regular and less frequent provision of iron supplements could be a good preventive measure in public health programmes where daily iron supplementation regimens are non-existent or are not being successfully implemented at scale
Trade-off between benefits and harm:	• Improved iron status may have long-term benefits and is likely to have a benefit on quality of life and development • Clear benefits outweigh any potential minimal harms
Cost and feasibility:	• This intervention is perceived as less costly compared with daily iron supplementation • Implementation of intermittent supplementation may be particularly feasible in facilities such as schools, because supplements can be given throughout the school calendar year, reaching the target population with good acceptability. However, it is important that this intervention also reaches those children who are outside the school system • This intervention should be considered in the context of all other options to improve iron nutrition

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