GUIDELINE

DAILY IRON SUPPLEMENTATION

in infants
and children

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World Health Organization

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DAILY IRON SUPPLEMENTATION IN INFANTS AND CHILDREN

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WHO GUIDELINE[1]: DAILY IRON SUPPLEMENTATION IN INFANTS AND CHILDREN

EXECUTIVE SUMMARY

Approximately 300 million children globally had anaemia in 2011. Deficiency in iron, a mineral necessary to carry oxygen in haemoglobin, is thought to be the most common cause of anaemia. Iron deficiency can result from inadequate intake or absorption of dietary iron, increased need in periods of growth, increased losses from menstruation in adolescent girls, or infection by intestinal helminths, such as schistosomiasis or hookworm infestation, in areas endemic to these parasites.

Iron is an essential nutrient for development and cell growth in the immune and neural systems, as well as in regulation of energy metabolism and exercise. The economic costs of iron deficiency anaemia from annual physical productivity losses have been calculated to be around US$ 2.32 per capita, or 0.57% of gross domestic product in low- and middle-income countries. The WHO has consistently recommended oral iron supplementation as one of the interventions that can reduce the prevalence of anaemia.

Iron is required for the survival and virulence of many pathogens. Concerns have been expressed on a possible increased risk of malaria with iron interventions in malaria-endemic areas, particularly among iron-replete children. On the other hand, screening to identify iron deficiency in children prior to iron supplementation is not feasible in many malaria-endemic settings. Given the importance and magnitude of anaemia globally, particularly in areas where malaria transmission is intense, an assessment of all available evidence has been carried out, to examine the safety and effectiveness of iron supplementation in children, including in malaria-endemic areas.

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 adolescents' health (2016–2030) (3).* The recommendations in this guideline are intended for a wide audience, including policy-makers, their expert advisers, and technical and programme staff at organizations involved in the design, implementation and scaling-up of programmes for anaemia prevention and control, and in nutrition actions for public health.

The recommendations supersede those of previous WHO guidelines on iron supplementation in children where they pertain specifically to daily oral iron supplementation among infants and children.

Guideline development methodology

WHO developed the present evidence-informed recommendations 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 recommendations, 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.

[1] This publication is a World Health Organization (WHO) guideline. A WHO guideline is any document, whatever its title, containing WHO recommendations about health interventions, whether they be clinical, public health or policy interventions. A 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.

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 children 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. Two experts served as technical peer-reviewers of the draft guideline.

Available evidence

The available evidence comprised four systematic reviews that followed the procedures of the *Cochrane handbook for systematic reviews of interventions (6)* and assessed the effects of daily iron supplementation in infants, preschool-age and school-age children, as well as the effect of iron on the incidence and severity of malaria, including deaths in children living in malaria-endemic settings. The reviews included individually randomized and cluster-randomized controlled trials. All studies compared a group of children who received iron supplementation to a group that did not receive iron. For systematic reviews done prior to 2013, the WHO Secretariat conducted an additional search on PubMed (June 2014) prior to the meeting of the guideline development group. In addition, in August 2015, a full literature search was performed as part of the review of evidence for malaria and iron supplementation. These searches did not identify any relevant additional studies.

The overall quality of the available evidence for daily iron supplementation in children and in malaria-endemic settings varied from high to very low for the critical outcomes of anaemia, iron deficiency and iron deficiency anaemia. The quality of evidence was moderate to very low for morbidity, mortality and growth measurements. The evidence for clinical malaria as an outcome in studies conducted in malaria-endemic settings was considered of high to moderate quality.

Recommendations[1]

- Daily iron supplementation is recommended as a public health intervention in infants and young children aged 6–23 months, living in settings where anaemia is highly prevalent,[2] for preventing iron deficiency and anaemia (*strong recommendation, moderate quality of evidence*).

Table A. Suggested scheme for daily iron supplementation in infants and young children aged 6–23 months

TARGET GROUP	**Infants and young children (6–23 months of age)**
SUPPLEMENT COMPOSITION	10–12.5 mg elemental iron[a]
SUPPLEMENT FORM	Drops/syrups
FREQUENCY	Daily
DURATION	Three consecutive months in a year
SETTINGS	Where the prevalence of anaemia in infants and young children is 40% or higher[b]

[a] 10–12.5 mg of elemental iron equals 50–62.5 mg of ferrous sulfate heptahydrate, 30–37.5 mg of ferrous fumarate or 83.3–104.2 mg of ferrous gluconate.

[b] 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) *(7)*.

1 These recommendations supersede those of previous WHO guidelines on iron supplementation in children.

2 Where the prevalence of anaemia is 40% or higher in this age group. For the latest estimates, please refer to the Vitamin and Mineral Nutrition Information System (VMNIS) hosted at WHO *(7)*.

- Daily iron supplementation is recommended as a public health intervention in preschool-age children aged 24–59 months, living in settings where anaemia is highly prevalent,[2] for increasing haemoglobin concentrations and improving iron status (*strong recommendation, very low quality of evidence*).

Table B. Suggested scheme for daily iron supplementation in children aged 24–59 months

TARGET GROUP	**Preschool-age children (24–59 months of age)**
SUPPLEMENT COMPOSITION	30 mg elemental iron[a]
SUPPLEMENT FORM	Drops/syrups/tablets
FREQUENCY	Daily
DURATION	Three consecutive months in a year
SETTINGS	Where the prevalence of anaemia in infants and young children is 40% or higher[b]

[a] 30 mg of elemental iron equals 150 mg of ferrous sulfate heptahydrate, 90 mg of ferrous fumarate or 250 mg of ferrous gluconate.

[b] 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) *(7)*.

- Daily iron supplementation is recommended as a public health intervention in school-age children aged 60 months and older, living in settings where anaemia is highly prevalent,[2] for preventing iron deficiency and anaemia (*strong recommendation, high quality of evidence*).

Table C. Suggested scheme for daily iron supplementation in school-age children (5–12 years of age)

TARGET GROUP	**School-age children (5–12 years of age)**
SUPPLEMENT COMPOSITION	30–60 mg elemental iron[a]
SUPPLEMENT FORM	Tablets or capsules
FREQUENCY	Daily
DURATION	Three consecutive months in a year
SETTINGS	Where the prevalence of anaemia in infants and young children is 40% or higher[b]

[a] 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.

[b] 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) *(7)*.

- In malaria-endemic areas, the provision of iron supplementation in infants and children should be done in conjunction with public health measures to prevent, diagnose and treat malaria (*strong recommendation, high quality of evidence*).

Remarks

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

- Daily oral iron supplementation is a preventive strategy for implementation at the population level. If a child is diagnosed with anaemia, national guidelines for the treatment of anaemia should be followed.

- If the prevalence of anaemia is 20–40%, intermittent regimens of iron supplementation can be considered.

- 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.

- In malaria-endemic areas, iron supplementation does not increase the risk of clinical malaria or death when regular malaria-surveillance and treatment services are provided. Oral iron interventions should not be given to children who do not have access to malaria-prevention strategies (e.g. provision of insecticide-treated bednets and vector-control programmes), prompt diagnosis of malaria illness, and treatment with effective antimalarial drug therapy.

- The risk of clinical malaria is not more likely among iron-replete children given iron supplementation in malaria-endemic areas. There is no need to screen for anaemia prior to iron supplementation in settings where anaemia is highly prevalent.

- Since malaria infection occurs in early infancy and is especially dangerous at this age, in malaria-endemic areas, iron supplements should only be given to infants who sleep under insecticide-treated bednets, and where all episodes of malaria illness can be promptly treated with effective antimalarial drug therapy according to national guidelines.

- In the presence of comprehensive surveillance and prompt diagnosis and treatment of malaria, there was no compelling evidence of increased risk of adverse events from iron supplementation. Insufficient and inequitable health-care services are associated with an increase in risks in general.

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 infants and children, particularly in the following areas:

- the optimal dose, schedule and duration of iron supplementation; the effect of different doses and durations 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 children);

- 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. cognitive and motor development).

SCOPE AND PURPOSE

This guideline provides global, evidence-informed recommendations on daily iron supplementation in infants and children, as a public health intervention for the prevention of anaemia and iron deficiency. It also includes recommendations for iron supplementation in countries where malaria is prevalent.

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 adolescents' health (2016–2030) (3).*

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

BACKGROUND

Approximately 300 million children globally had anaemia in 2011 *(8, 9)*. The highest prevalence of anaemia is among children aged under 5 years and women *(10, 11)*. South Asia and central and west Africa continue to have the highest burden of anaemia *(9–11).*

Anaemia is characterized by a decrease in the number of red blood cells, sometimes with changed size or shape of the red blood cells, to a level that impairs the normal physiological capacity of the blood to transport oxygen to cells around the body. Anaemia is measured most reliably by a fall in haemoglobin concentration and can indicate poor nutrition and health *(12, 13).* Anaemia has been estimated to cause 68.4 million years lost to disability in 2010, or 8.8% of disability from all conditions that year *(11).*

Deficiency in iron, a mineral necessary to carry oxygen in haemoglobin, is thought to be the most common cause of anaemia *(10–14).* Iron deficiency can result from inadequate intake or absorption of dietary iron, increased need for iron in periods of growth or pregnancy, increased losses from menstruation, or infection with intestinal helminths such as schistosomiasis or hookworm infection, in areas where these infestations are endemic *(12–16).* Other important causes of anaemia include infections such as malaria, tuberculosis and HIV; other nutritional deficiencies such as of folate and vitamins B_{12}, A and C; genetic conditions and haemoglobinopathies such as sickle cell disease and thalassaemia; and chronic kidney disease *(9–11)*. Iron is an essential nutrient in development and cell growth in the immune and neural systems, as well as in regulation of energy metabolism and exercise *(17,18)*. Approximately 38–62% of anaemia is responsive to iron supplementation. In malaria-hyperendemic settings, only 6–32% of anaemia is responsive to iron supplementation *(19).*

Iron deficiency affects approximately two billion people worldwide; of these, about 500 million have anaemia *(20).* The economic costs of iron deficiency anaemia from annual physical productivity losses have been calculated to be around US$ 2.32 per capita, or 0.57% of gross domestic product in low- and middle-income countries *(21)*. WHO has consistently recommended iron supplementation as one of the interventions that can decrease rates of anaemia *(22, 23).*

Iron deficiency anaemia has been correlated with suboptimal mental and motor development in children *(24–33)* and women *(34)*, though some of the effects reported may be due to confounding *(35)*. Iron supplementation has been shown to improve some of the mental or motor outcomes *(18, 36–40)*, but the effects of supplementation have been inconsistent *(41–47)* and some impairment may be irreversible *(29)*. Conversely, there are concerns that iron may produce adverse effects, including increased susceptibility to infections such as malaria *(48–50)* and impaired physical growth *(51, 52).*

Anaemia in infants and children

The risks for anaemia in children start during gestation. Anaemia in the child's mother during pregnancy is associated with increased risk of low birth weight and maternal and child mortality *(53).* Children born to mothers with anaemia may be more likely to be iron deficient and anaemic early in life. This may irreversibly affect the cognitive development and physical growth of infants *(17, 23, 54, 55).*

Iron is required by infants to produce red blood cells in the first months after birth. Infants commonly use iron stored during the last months of gestation. When the infant is 4–6 months of age, the stores can become low or depleted. This is exacerbated when there are inadequate iron stores due to low birth weight and prematurity *(56);* increased requirements from rapid growth and erythropoiesis; inadequate iron from the diet, such as in cases of early introduction of cereal-based complementary food, from which iron absorption can be as low as 5% *(57)*, or with prolonged milk feeding *(10, 58)*; and blood loss due to intestinal parasitic infections *(59).*

In the preschool years, children undergo rapid growth, with an increase in red blood cells and high iron requirements *(60).* As children reach their third year, growth velocity decreases and daily iron requirements may decline. They are becoming ambulant and, if sanitation is poor, are more likely to acquire intestinal parasitic infections that cause iron deficiency *(61)*. Young children are being weaned from breastfeeding but foods being given may be inadequate for their iron needs *(53).*

Among school-age children, iron deficiency has been associated with impaired cognitive and physical development *(20, 28)*, and provision of iron showed a positive effect *(44, 62, 63)*. However, a causal relation between iron deficiency and cognitive impairment has not been confirmed *(64)*. Assurance of cognitive and physical development though optimal nutrition in school-age children could have benefits beyond school performance *(24).*

No increase in the incidence of respiratory infections has been found as a result of iron supplementation among children *(37–39, 65)*, although, in systematic review, there is evidence of a very slight increase in the risk of developing diarrhoea (at an estimated incidence rate difference of 0.05 episodes per child-year) *(65).*

Iron supplementation in malaria-endemic areas

Malaria is a leading cause of morbidity and mortality in children in sub-Saharan Africa, with most infections caused by *Plasmodium falciparum (66).* The effect of malaria on anaemia in areas of high transmission has been observed to be less after 36 months of age *(67, 68)*. At a very young age, children are somewhat less vulnerable to malaria, owing to immunity passively acquired from their mothers, as well as lower exposure to transmission *(69, 70).* Malaria infection is an important contributor to anaemia in endemic regions, through direct haemolysis of infected red blood cells, the body's immune destruction of both parasitized and uninfected red blood cells, and temporary dysfunction of the bone marrow *(71, 72).*

Iron is required for both regulation of immunity against infections and the survival and virulence of many pathogens *(17, 73).* One study reported a small decrease in the risk for mild clinical malaria in a cohort of children in Kenya *(74),* while others have shown increased risk of malaria with iron interventions *(49, 50).*

In 2006, the results of an evaluation of iron and folate supplements in a malaria-endemic area of Zanzibar (Pemba Island) were published *(48).* This study was terminated prematurely, based on a higher proportion of hospitalization or death among participants randomized to the iron and folic acid treatment group, particularly among those who were iron replete at baseline.

Previous recommendations on daily iron supplementation as a public health measure for infants and children have not differentiated between malaria-endemic or non-endemic areas. A 2007 technical consultation convened by WHO considered iron supplementation among children in malaria-endemic settings, and suggested that, in malaria-endemic areas, screening to identify iron deficiency in children aged less than 2 years, prior to treatment with iron, would need to be in place *(75).*

Concerns have been expressed about the implementation of the conclusions of this consultation in a public health setting *(76–79).* Given the importance and magnitude of anaemia globally, an assessment of all available evidence has been carried out, to examine the positive and adverse effects of daily iron supplementation in children, including in malaria-endemic areas.

OBJECTIVES

The recommendations in this guideline supersede those of previous WHO guidelines on iron supplementation in children such as *Iron deficiency anaemia: assessment, prevention, and control. A guide for programme managers (23)* and the Conclusions and recommendations of the WHO Consultation on prevention and control of iron deficiency in infants and young children in malaria-endemic areas *(80)*, as they pertain specifically to daily oral iron supplementation among infants and children.

SUMMARY OF AVAILABLE EVIDENCE

Three systematic reviews that followed the procedures of the *Cochrane handbook for systematic reviews of interventions (6)* were prepared on the use of iron supplementation among children aged 4–23 months *(81)*, 2–5 years *(46)* and 5–12 years *(82)*. A further review was done on iron supplementation in children in malaria-endemic areas, based on an update of previous systematic reviews *(79, 84).* In all the reviews, iron was administered orally (excluding parenteral administration). All reviews searched the Cochrane Central Register of Controlled Trials, Medline and Embase. Some also searched through the WHO regional databases (African Index Medicus, WHO Regional Office for Africa Health Sciences Library, Latin American and Caribbean Health Science Literature Database, Index Medicus for the South-East Asia Region, the Western Pacific Region, and the Eastern Mediterranean Region *(46, 81, 82)*, the WHO International Clinical Trials Registry Platform *(81, 83)*, the Proquest Digital Thesis *(46, 81, 82),* the Australian Digital Theses Database *(46, 81, 82),* OpenSIG*LE (46, 81)* and OpenGrey *(82)*.

The reviews that limited the analysis to specific age ranges (4–23 month*s (81),* 2–5 years *(46)* or 5–12 years *(82)*) considered studies that specifically recruited children from the specified age range but also included studies if the mean or median fell within the age range, if at least 75% of the subjects fell within the designated age range, or if the majority of the study's recruitment age range overlapped with the review's designated age range. These reviews included studies that recruited otherwise healthy children, excluding studies that recruited only children with severe anaemia, those with developmental disability, or those with conditions that affect iron metabolism. Studies were included if they administered iron daily *(81)* or at least 5 days a week *(46, 82)*. Studies were excluded if they provided iron through point-of-use (home) fortification or fortified food and condiments. Outcomes included haemoglobin concentration, anaemia prevalence, iron deficiency, iron deficiency anaemia, cognitive performance, physical growth and safety (including gastrointestinal adverse events and infections like malaria).

Daily iron supplementation in infants and children aged 6–23 months

Summary of the evidence

The evidence that informed the recommendations on daily iron supplementation in infants and children aged 6–23 months is based on a systematic review of trials involving infants and children aged 4–23 months *(81)*. The systematic review on daily iron supplementation in infants and young children aged 4–23 months included 33 trials (*n* = 42 015 children). Two of the 33 trials were cluster-randomized trials that involved 32 976 infants and young children. Excluding these two large studies would result in inclusion of 31 trials (9039 infants and young children) *(81)*.

Infants and young children aged 4–23 months who received daily iron supplementation had a lower risk for the critical outcomes of anaemia (risk ratio [RR]: 0.61; 95% confidence interval [CI]: 0.50 to 0.74; 17 trials, *n* = 4825), iron deficiency (RR: 0.30; 95% CI: 0.15 to 0.60; 9 trials, *n* = 2464) and iron deficiency anaemia (RR: 0.14; 95% CI: 0.10 to 0.22; 6 trials, *n* = 2145), compared to children receiving placebo or supplementation without iron.

There was no difference in growth measures between those receiving daily iron supplementation and those receiving placebo or supplementation without iron: stunting (RR: 1.10; 95% CI: 0.92 to 1.32; 3 trials, *n* = 1504) and wasting (RR: 1.03; 95% CI: 0.65 to 1.64; 3 trials, *n* = 1504).

The quality of evidence for the critical outcomes varied from high for iron deficiency anaemia; moderate for anaemia and stunting; and low for wasting and mortality, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology *(5, 85, 86)*. The GRADE summary of findings table for daily oral iron supplementation compared to placebo or control in infants and young children aged 6–23 months is shown in Annex 1A.

Recommendation

- Daily iron supplementation is recommended as a public health intervention in infants and young children aged 6–23 months, living in settings where anaemia is highly prevalent,[1] for preventing iron deficiency and anaemia (*strong recommendation, moderate quality of evidence*).

The suggested scheme for daily iron supplementation in infants and young children (6–23 months of age) is presented in Table A.

Table A. Suggested scheme for daily iron supplementation in infants and young children aged 6–23 months

TARGET GROUP	**Infants and young children (6–23 months of age)**
SUPPLEMENT COMPOSITION	10–12.5 mg elemental iron[a]
SUPPLEMENT FORM	Drops/syrups
FREQUENCY	Daily
DURATION	Three consecutive months in a year
SETTINGS	Where the prevalence of anaemia in infants and young children is 40% or higher[b]

[a] 10–12.5 mg of elemental iron equals 50–62.5 mg of ferrous sulfate heptahydrate, 30–37.5 mg of ferrous fumarate or 83.3–104.2 mg of ferrous gluconate.

[b] 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) *(7)*.

[1] 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) (*7*).

Rationale

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

- The outcome of iron deficiency anaemia had high-quality evidence. Heterogeneity in results was noted for the outcomes of anaemia and iron deficiency but was related to different beneficial effect sizes rather than different effects. The effect sizes of the intervention on the outcomes were large. The evidence for morbidity and developmental outcomes is weak but the recommendation does not directly address these outcomes.

- In cases where the population prevalence of anaemia is greater than 40%, the causes of anaemia are multifactorial and unlikely to be exclusively caused by iron deficiency. Even taking this into account, most children in most cases will benefit from iron supplementation in settings of high anaemia prevalence.

- Not enough data are available on long-term harm, for instance on overdose, specifically for children who are iron replete.

Daily iron supplementation in children aged 24–59 months

Summary of the evidence

The evidence that informed the recommendations on daily iron supplementation in children aged 24–59 months is based on a systematic review of trials involving children aged 2–5 years *(46)*. The systematic review on the effects of daily iron supplementation in preschool-age children aged 2–5 years included 15 trials (*n* =4212 children) *(46)*.

Only one trial reported on anaemia and none of the included trials reported on the other critical outcomes of iron deficiency or iron deficiency anaemia specifically. However, ferritin, an indicator of iron stores and a biomarker for iron deficiency, was reported in five trials. Children receiving daily iron supplementation had higher ferritin concentrations compared to children receiving placebo or supplementation without iron (mean difference [MD]: 11.64 ng/mL; 95% CI: 6.02 to 17.25; 5 trials, *n* = 944). Additionally, haemoglobin, a biomarker used to diagnose anaemia using age- and sex-specific cut-off values, was reported in nine trials. Children receiving daily iron supplementation had a higher mean haemoglobin concentration than those receiving placebo or supplementation without iron (MD: 6.97 g/L; 95% CI: 4.21 to 9.72; 9 trials, *n* = 2154).

There were no differences between children receiving daily iron supplementation and those receiving a placebo or supplementation without iron, in terms of final height (MD: –0.1 *Z*-score; 95% CI: –1.14 to 0.12; 3 trials, *n* = 634) and final weight (MD: –0.04 *Z*-score; 95% CI: –0.12 to 0.05; 2 trials, *n* = 634).

The quality of evidence for the critical outcomes was very low for anaemia and low for measures of physical growth, using GRADE methodology *(5, 85, 86)*. The GRADE summary of findings table for daily oral iron supplementation compared to placebo or control in children aged 24–59 months is shown in Annex 1B.

Recommendation

- Daily iron supplementation is recommended as a public health intervention in preschool-age children aged 24–59 months, living in settings where anaemia is highly prevalent,[1] for increasing haemoglobin concentrations and improving iron status (*strong recommendation, very low quality of evidence*).

[1] 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) *(7)*.

The suggested scheme for daily iron supplementation in preschool-age children (24–59 months of age) is presented in Table B.

Table B. Suggested scheme for daily iron supplementation in children aged 24–59 months

TARGET GROUP	**Preschool-age children (24–59 months of age)**
SUPPLEMENT COMPOSITION	30 mg elemental iron[a]
SUPPLEMENT FORM	Drops/syrups/tablets
FREQUENCY	Daily
DURATION	Three consecutive months in a year
SETTINGS	Where the prevalence of anaemia in infants and young children is 40% or higher[b]

[a] 30 mg of elemental iron equals 150 mg of ferrous sulfate heptahydrate, 90 mg of ferrous fumarate or 250 mg of ferrous gluconate.

[b] 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) *(7)*.

Rationale

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

- Only one study reported on anaemia; none of the studies reported on iron deficiency or iron deficiency anaemia. However, synthesis of evidence from studies that reported on ferritin concentrations and haemoglobin levels had high quality.
- There is no clear evidence regarding harms at proposed doses for diarrhoea and other gastrointestinal effects, liver damage, insulin resistance or iron overload.
- In well-established and well-functioning health-systems settings, the additional costs of distributing iron supplementation may be low. This may not be the case in low-resource settings. Therefore, reaching the children in need and ensuring a high coverage, taking into account the operational costs, merits consideration.

Daily iron supplementation in children aged 60 months and older

Summary of the evidence

The evidence that informed the recommendations on daily iron supplementation in children aged 60 months and older is based on a systematic review of trials involving children aged 5–12 years. The systematic review on daily iron supplementation in school-age children aged 5–12 years included 32 trials (*n* = 7089 children) *(82)*.

Children receiving daily oral iron supplements had a lower risk of the critical outcomes of anaemia (RR: 0.50; 95% CI: 0.39 to 0.64; 7 trials, *n* = 1763), iron deficiency (RR: 0.21; 95% CI: 0.07 to 0.63; 4 trials, *n* = 1020) and iron deficiency anaemia (RR: 0.12; 95% CI: 0.02 to 0.66; 2 trials, *n* = 334).

There was a small but statistically significant difference in final height between children receiving daily iron supplementation and those receiving a placebo or supplementation without iron (MD: 0.09 *Z*-score; 95% CI: 0.01 to 0.17; 5 trials, *n* = 1318) but not in final weight (MD: 0.10 *Z*-score; 95% CI: –0.03 to 0.23; 5 trials, *n* = 1318).

The quality of evidence varied between high (for the critical outcomes of anaemia, iron deficiency and iron deficiency anaemia) and low (for growth measures), using the GRADE methodology *(5, 85, 86)*. The GRADE summary of findings table for daily oral iron supplementation compared to placebo or control in children aged 60 months and older is shown in Annex 1C.

Recommendation

- Daily iron supplementation is recommended as a public health intervention in school-age children aged 60 months and older, living in settings where anaemia is highly prevalent[1], for preventing iron deficiency and anaemia (*strong recommendation, high quality of evidence*).

The suggested scheme for daily iron supplementation in school-age children (5–12 years of age) is presented in *Table C.*

Table C. Suggested scheme for daily iron supplementation in school-age children (5–12 years of age)

TARGET GROUP	**School-age children (5–12 years of age)**
SUPPLEMENT COMPOSITION	30–60 mg elemental iron[a]
SUPPLEMENT FORM	Tablets or capsules
FREQUENCY	Daily
DURATION	Three consecutive months in a year
SETTINGS	Where the prevalence of anaemia in infants and young children is 40% or higher[b]

[a] 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.

[b] 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) *(7)*.

Rationale

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

- The evidence is of high quality for priority outcomes (anaemia, iron deficiency, iron deficiency anaemia). Cognition and growth may be as important as haemoglobin and anaemia in this age group and the quality of evidence for these outcomes is moderate.

- The main challenge may be in reaching this age group. They can be reached through school-based programmes but success may then depend on the school systems and the attendance rates. Some consideration will need to be made for reaching children outside of the school system.

- No major harms were identified in this age group, though there is not enough evidence on gastrointestinal effects, potential toxic endpoints and the impact of iron overload.

Daily iron supplementation in infants and children in malaria-endemic areas

Summary of the evidence

The evidence that informed the recommendations on daily iron supplementation in infants and children in malaria-endemic areas is based on a systematic review of trials involving children living in malaria hyper- or

[1] 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) *(7)*.

holo-endemic areas *(83).* The systematic review on daily iron supplementation in children in malaria hyper- or holo-endemic areas included 39 trials (*n* = 32 759 children). The majority (*n* = 30) of the trials were individually randomized and nine trials were cluster randomized *(83)*. This is an update of previously published Cochrane reviews *(78, 84)*. The review included children aged less than 18 years, with or without anaemia at baseline. Pregnant women were excluded. The review included studies that gave oral iron through any form, including fortification of food or drink, as long as they provided at least 80% of the recommended daily allowance by age for the prevention of anaemia *(36).* Studies were included if they administered iron for any duration or interval.

There was no difference in the risk of clinical malaria between the iron-supplementation group and those receiving placebo or supplementation without iron (RR: 0.93; 95% CI: 0.87 to 1.00; 14 trials, *n* = 7168). The risk for clinical malaria among children receiving iron supplementation was lower, specifically among those younger than 2 years of age (RR: 0.89; 95% CI: 0.82 to 0.97; 5 trials), though there was no significant statistical difference between age groups (test for subgroup difference χ^2 = 3.56; *P* = 0.17). In the subgroup of children who did not have anaemia at baseline in particular, there was no difference in the risk for clinical malaria between those in the iron-supplementation or in the control group (RR: 0.97; 95% CI: 0.86 to 1.09; 5 trials, *n* = 4986).

In the studies where malaria-prevention and treatment programmes were being implemented, the risk of clinical malaria was lower for children randomized to receive iron supplementation (RR: 0.91; 95% CI: 0.84 to 0.97; 7 trials, *n* = 5586). However, in the subgroup of studies in which there was no malaria-prevention or treatment programme being implemented during the study, the risk for malaria among children receiving iron supplementation was higher (RR: 1.16; 95% CI: 1.02 to 1.31; 9 trials, *n* = 19 086; test for subgroup difference χ^2 = 15.70; *P* < 0.01).

The risk for clinical malaria among children receiving iron supplementation was lower when clinical malaria was accompanied by high-grade parasitaemia (RR: 0.90; 95% CI: 0.81 to 0.98; 6 trials). There was no difference in risk between the children receiving iron versus those receiving placebo or no treatment in terms of all-cause mortality (risk difference: 0.00; 95% CI: 0.00 to 0.01; 18 trials, *n* = 7576).

The quality of evidence was moderate for clinical malaria and high for severe malaria and all-cause mortality, using the GRADE methodology *(5, 85, 86).* The GRADE summary of findings table for daily oral iron supplementation compared to placebo or control in malaria-endemic areas is shown in Annex 1D.

Recommendation

- In malaria–endemic areas, the provision of iron supplementation in infants and children should be done in conjunction with public health measures to prevent, diagnose and treat malaria *(strong recommendation, high quality of evidence).*

Rationale

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

- The evidence that iron supplementation does not increase the risk of clinical malaria is of moderate quality, owing to publication bias (no small studies in favour of iron supplementation have been published). The quality of evidence that iron supplementation in malaria-endemic areas decreases the risk of severe malaria and does not increase the risk of death is high.

- In malaria-endemic settings with limited malaria prevention and clinical care, universal iron supplementation may be associated with an increased risk of malaria.

- The risk of clinical malaria is not more likely among iron-replete children given iron supplementation in malaria-endemic areas. The cost and logistics that would otherwise be used to screen for anaemia prior to universal iron supplementation in settings where anaemia is highly prevalent can be channelled to other priority health interventions.

Remarks

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

- Daily iron supplementation is a preventive strategy for implementation at the population level. If a child is diagnosed with anaemia, national guidelines for the treatment of anaemia should be followed.

- If the prevalence of anaemia is 20–40%, intermittent regimens of iron supplementation can be considered *(87)*.

- 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.

- In malaria-endemic areas, iron supplementation does not increase the risk of clinical malaria or death when regular malaria-surveillance and treatment services are provided. Oral iron interventions should not be given to children who do not have access to malaria-prevention strategies (e.g. provision of insecticide-treated bednets and vector-control programmes), prompt diagnosis of malaria illness, and treatment with effective antimalarial drug therapy.

- The risk of clinical malaria is not more likely among iron-replete children given iron supplementation in malaria-endemic areas. There is no need to screen for anaemia prior to iron supplementation in settings where anaemia is highly prevalent.

- In the presence of comprehensive surveillance and prompt diagnosis and treatment of malaria, there was no compelling evidence of increased risk of adverse events from iron supplementation. Insufficient and inequitable health-care services are associated with an increase in risks in general.

- Infants and children under 5 years of age are at considerably higher risk of contracting malaria *(66)*. The WHO *Global technical strategy for malaria 2016–2030* provides a technical framework to guide and support malaria-endemic countries as they work towards malaria control and elimination *(89)*.

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, antenatal and neonatal care, and improved infant and young child nutrition. 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. Antenatal programmes should 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 for children 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 areas, meriting further research on iron supplementation in infants and children, particularly in the following areas:

- the optimal dose, schedule and duration of iron supplementation; the effect of different doses and durations of iron supplementation on different severity, prevalence and 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 children);
- 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 alternative delivery mechanisms for iron supplements;
- additional long-term studies on functional outcomes (e.g. cognitive and motor development).

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 either the WHO Nutrition mailing lists *(89)*, social media, the WHO nutrition website *(89)* or the WHO e-Library of Evidence for Nutrition Actions (eLENA) *(89)*. 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 recommendations, 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 for infants and children 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 infants and children.

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 children 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 child health, which includes addressing micronutrient deficiencies.

Considering the actual experience of children and their caregivers 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 therapeutic adherence 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, gender norms may create unequal opportunities for girls and boys at any age, within and outside of school; in other settings, social perceptions around ethnicity and race intervene in how certain population groups access and use an intervention.

Furthermore, intersectoral action is fundamental in those settings where the intervention is delivered in coordination with the education sector. The education sector is an important partner in the implementation of the recommendation referring to school-age children. Appropriate coordination mechanisms and proper training of health workers and education staff is necessary for delivery of the intervention and also for collection of data needed for programme monitoring and surveillance, including information on factors related to health inequities.

Specific efforts to increase the acceptability of the intervention to children and their caregivers are also important. Greater acceptability and adoption are better achieved if they are accompanied by simple and easy-to-access information that can be understood by different population groups, in a way that is culturally appropriate and understandable.

Accessing hard-to-reach population groups is extremely important during implementation stages, as it contributes to preventing or tackling health inequities and to furthering the realization of children's rights to health. 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 development of norms, standards and guidelines to promote quality assurance and quality control is a responsibility enshrined in WHO's Constitution. Their development involves consultation with and input from regulatory authorities in the country, including its national drug quality-control laboratories *(91)*.

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 *(92)*. 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 should take into account WHO/Food and Agriculture Organization of the United Nations standards *(93)*.

Universal access to essential medicines is part of the approach of universal health coverage and is used to assess national commitment and progress towards the highest attainable standard of health. Three basic criteria contribute to promoting access to essential medicines: quality, pricing and supply. WHO's regulatory capacity guidance can assist Members States in need of support, in terms of availability, quality and safety of essential medical products, decrease of prices, and improvement of financing, health insurance and social-protection coverage mechanisms *(94).*

Ethical considerations

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

Four principles constitute the most widely accepted framework for ethics in medicine, and are used in other health-related fields: (i) respect for individual autonomy; (ii) beneficence; (iii) non-maleficence; and (iv) justice. These principles assist health workers in identifying whether an intervention is producing benefits to individuals and communities; preventing harms, also at the individual and societal levels; distributing health benefits across social groups, i.e. how much an intervention is contributing to health equity; and respecting and promoting the exercise of human rights.

The delivery of micronutrients to infants and children with micronutrient deficiency is in line with the right to health of children and with the aforementioned ethical principles. For this reason, an assessment of the ethical implications of implementing this intervention is pertinent in malaria-endemic settings, owing to the possible interactions and potential adverse effects of increased iron intake by children affected by malaria. Children who live in malaria-endemic settings should indeed receive adequate iron. However, the provision of iron supplementation should be done in conjunction with public health measures to prevent, diagnose and treat malaria. Otherwise, a nutrition programme working in isolation and not coordinated with a malaria-prevention and treatment programme may lead to unintentional harm, absence of benefit and increased health inequities.

Coordination with public health measures to prevent, diagnose and treat malaria is not just a sound implementation decision, but also an ethics-informed decision. Such coordination should comprise appropriate training for health workers in public health nutrition, so they are knowledgeable of the particular requirements of an iron-supplementation programme for infants and children that should be observed in malaria-endemic areas. Such training should also be provided to education staff co-working in the implementation of this intervention in school-age children and educational settings.

These considerations by no means imply that iron supplementation should not be provided to children in malaria-endemic settings. On the contrary, children in these settings should receive iron supplementation, inasmuch as they suffer greater vulnerability to ill-health, including malnutrition. It requires, however, that appropriate coordination between nutrition and malaria programmes is in place, so the intervention can actually produce health benefits.

Monitoring and evaluation of guideline implementation

A plan for monitoring and evaluation with appropriate indicators, including equity-oriented indicators, is encouraged at all stages *(95)*. 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 *(96)*, 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 (97)*, 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 *(7)*. 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 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) *(98)* 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 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 *(98)*, so inequities can be identified and tackled. It is particularly important to design sound implementation strategies to serve as the base for scaling up efforts. 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 6), 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 meets 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.

Two guideline development groups participated in the development of this guideline (see Annex 7). Their 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 gender mix, multiple disciplinary areas of expertise, and representation from all WHO regions. Efforts were made to include content experts, methodologists, representatives of potential stakeholders (such as managers and other health professionals involved in the health-care process), and technical staff from WHO and ministries of health from Member States. Representatives of commercial organizations may not be members of a WHO guideline group.

The final draft guideline was peer-reviewed by three content experts, who provided technical feedback. These peer-reviewers (see Annex 8) were identified through various expert panels within and outside WHO *(5, 85, 86, 101)*.

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 11). 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 recommendations 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 11.

Four systematic reviews *(46, 81, 82, 83)* were used to summarize and appraise the evidence, using the Cochrane methodology *(6)* 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, 85, 86, 101)*. 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, which also included a section for documenting their views on (i) the desirable and undesirable effects of the intervention; (ii) the quality of the available evidence; (iii) values and preferences related to the intervention in different settings; and (iv) the cost of options available to health-care workers in different settings (see Annex 2). Each member used one form, if not advised otherwise after managing any potential conflict of interests. Abstentions were not allowed. The process was improved with the availability of a predefined link to an online form prepared using survey

software. Subsequent deliberations among the members of the guideline development group were of private character. 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 guideline development group members decided that each 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 (102)* and the processes recommended in the *WHO handbook for guideline development (4)*, all experts participating in WHO meetings must declare any interest relevant to the meeting, prior to their participation. The responsible technical officer and the relevant departments reviewed the declarations-of-interest statements for all 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 interest 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 interest declared by themembers of the guideline group is summarized next.[1]

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 (MI) 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 recommendations for iron supplementation but recused herself from voting on this guideline.

[1] A conflict-of-interest analysis must be performed whenever WHO relies on the independent advice of an expert in order to take a decision or to provide recommendations to Member States or other stakeholders. The term "conflict of interest" means any interest declared by an expert that may affect, or be reasonably perceived to affect, the expert's objectivity and independence in providing advice to WHO. WHO's conflict-of-interest rules are designed to avoid potentially compromising situations that could undermine or otherwise affect the work of the expert, the committee or the activity in which the expert is involved, or WHO as a whole. Consequently, the scope of the inquiry is any interest that could reasonably be perceived to affect the functions that the expert is performing.

Dr 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 recommendations related to iron supplementation.

Dr Héctor Bourges Rodriguez declared being chair of the Board of Directors of the Danone Institute in Mexico (DIM), a non-profit organization promoting research and dissemination of scientific knowledge in nutrition, and receiving funds as chair honorarium from DIM. DIM is funded by Danone Mexico, a food company and subsidiary of The Danone Company, Inc. The main products of Danone group worldwide are dairy, bottled water and baby products. Because Danone does not manufacture products nor make claims related to anaemia or iron supplementation, it was agreed that he could participate fully in the deliberations and decision-making on this guideline.

External experts also declared their interest 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 infants and children 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.

REFERENCES

1. United Nations Department of Economic and Social Affairs. Sustainable Development Knowledge Platform. Sustainable Development Goals (https://sustainabledevelopment.un.org/topics, accessed 4 December 2015).

2. Resolution WHA65.6. Comprehensive implementation plan on maternal, infant and young child nutrition. In: Sixty-fifth World Health Assembly, Geneva, 21–26 May 2012. Resolutions and decisions, annexes. Geneva: World Health Organization; 2012:12–13 (http://www.who.int/nutrition/topics/WHA65.6_resolution_en.pdf?ua=1, accessed 4 December 2015).

3. Global strategy for women's children's and adolescents' health (2016–2030). Survive,thrive, transform. Geneva: Every Woman Every Child; 2015 (http://www.who.int/life-course/partners/global-strategy/globalstrategyreport2016-2030-lowres.pdf?ua=1, accessed 4 December 2015).

4. WHO Handbook for guideline development, 2nd ed. Geneva: World Health Organization; 2014 (http://www.who.int/kms/handbook_2nd_ed.pdf, accessed 4 December 2015).

5. GRADE Working Group (http://www.gradeworkinggroup.org/, accessed 4 December 2015).

6. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 (updated March 2011). London: The Cochrane Collaboration; 2011 (http://community.cochrane.org/handbook, accessed 4 December 2015).

7. World Health Organization. Vitamin and Mineral Nutrition Information System (VMNIS). Micronutrients database (http://www.who.int/vmnis/en/, accessed 4 December 2015).

8. The global prevalence of anaemia in 2011. Geneva: World Health Organization; 2015 (http://www.who.int/nutrition/publications/micronutrients/global_prevalence_anaemia_2011/en/, accessed 4 December 2015).

9. Stevens GA, Finucane MM, De-Regil LM, Paciorek CJ, Flaxman SR, Branca F et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995–2011: a systematic analysis of population-representative data. Lancet Glob Health. 2013;1(1):e16–25. doi:10.1016/S2214-109X(13)70001-9.

10. De Benoist B, McLean E, Egli I, Cogswell M, editors. Worldwide prevalence of anaemia 1993–2005. WHO global database on anaemia. Geneva: World Health Organization; 2008 (http://apps.who.int/iris/bitstream/10665/43894/1/9789241596657_eng.pdf, accessed 4 December 2015).

11. Kassebaum NJ, Jasrasaria R, Naghavi M, Wulf SK, Johns N, Lozano R et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood. 2014;123(5):615–24. doi:10.1182/blood-2013-06-508325.

12. Assessing the iron status of populations: a report of a joint World Health Organization/Centers for Disease Control technical consultation on the assessment of iron status at the population level, 2nd ed including literature reviews. Geneva: World Health Organization; 2008 (http://apps.who.int/iris/bitstream/10665/75368/1/9789241596107_eng.pdf?ua=1&ua=1, accessed 4 December 2015).

13. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva: World Health Organization; 2011 (http://www.who.int/vmnis/indicators/haemoglobin/en/, accessed 4 December 2015).

14. Serum ferritin concentrations for the assessment of iron status and iron deficiency in populations. Geneva: World Health Organization; 2011 (http://www.who.int/vmnis/indicators/serum_ferritin.pdf, accessed 4 December 2015).

15. Tolentino K, Friedman JF. An update on anemia in less developed countries. Am J Trop Med Hyg. 2007;77(1):44–51.

16. Stoltzfus RJ, Dreyfuss ML, Chwaya HM, Albonico M. Hookworm control as a strategy to prevent iron deficiency. Nutr Rev. 1997;55(6):223–32.

17. Beard JL. Iron biology in immune function, muscle metabolism and neuronal functioning. J Nutr. 2001;131(2s-2):568S–579S; discussion 580S.

18. Iannotti LL, Tielsch JM, Black MM, Black RE. Iron supplementation in early childhood: health benefits and risks. Am J Clin Nutr. 2006;84(6):261–76.

19. Gera T, Sachdev HP, Nestel P, Sachdev SS. Effect of iron supplementation on haemoglobin response in children: systematic review of randomised controlled trials. J Pediatr Gastroenterol Nutr. 2007;44(4):468–86.

20. Stoltzfus RJ, Mullany L, Black RE. Iron deficiency anaemia. In: Ezzati M, Lopez AD, Rodgers A, Murray CJL, editors. Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors. Geneva: World Health Organization; 2004:163–209 (http://apps.who.int/iris/bitstream/10665/42792/1/9241580348_eng_Volume1.pdf, accessed 4 December 2015).

21. Horton S, Ross J. The economics of iron deficiency. Food Policy. 2003;28(1):51–75.

22. Essential nutrition actions: improving maternal, newborn, infant and young child health and nutrition. Geneva: World Health Organization; 2013 (http://apps.who.int/iris/bitstream/10665/84409/1/9789241505550_eng.pdf, accessed 4 December 2015).

23. Iron deficiency anaemia: assessment, prevention and control: a guide for programme managers. Geneva: World Health Organization; 2001 (http://apps.who.int/iris/bitstream/10665/66914/1/WHO_NHD_01.3.pdf?ua=1, accessed 4 December 2015).

24. Bryan J, Osendarp S, Hughes D, Calvaresi E, Baghurst K, van Klinken JW. Nutrients for cognitive development in school-aged children. Nutr Rev. 2004;62(8):295–306.

25. Fanjiang G, Kleinman RE. Nutrition and performance in children. Curr Opin Clin Nutr Metab Care. 2007;10(3):342–7.

26. Grantham-McGregor SM, Walker SP, Chang S. Nutritional deficiencies and later behavioural development. Proc Nutr Soc. 2000;59(1):47–54.

27. Kretchmer N, Beard JL, Carlson S. The role of nutrition in the development of normal cognition. Am J Clin Nutr. 1996;63(6):997s–1001s.

28. Tamura T, Goldenberg RL, Hou J, Johnston KE, Cliver SP, Ramey SL et al. Cord serum ferritin concentrations and mental and psychomotor development of children at five years of age. J Pediatr. 2002;140(2):165–70.

29. Lozoff B. Iron deficiency and child development. Food Nutr Bull. 2007;28(4 Suppl.):S560–71.

30. Greisen G. Mild anaemia in African school children: effect on running performance and an intervention trial. Acta Paediatr Scand. 1986;75(4):662–7.

31. Gera T, Sachdev HP, Nestel P. Effect of iron supplementation on physical performance in children and adolescents: systematic review of randomized controlled trials. Indian Pediatr. 2007;44(1):15–24.

32. Gewa CA, Weiss RE, Bwibo NO, Whaley S, Sigman M, Murphy SP et al. Dietary micronutrients are associated with higher cognitive function gains among primary school children in rural Kenya. Br J Nutr. 2009;101(9):1378–87. doi:10.1017/S0007114508066804.

33. Aukett MA, Parks YA, Scott PH, Wharton BA. Treatment with iron increases weight gain and psychomotor development. Arch Dis Child. 1986;61(9):849–57.

34. Beard JL, Murray Kolb LE, Perez E, Berg A, Tomlinson M, Irlam J et al. Iron status alters cognitive and behavioral functoining in women during reproductive years. In: Report of the 2003 International Nutritional Anemia Consultative Group Symposium.

Integrating programs to move iron deficiency and anemia control forward. 6 February 2003. Washington DC: INACG; 2003:40 (http://www.ilsi.org/ResearchFoundation/Publications/INACGfinal.pdf, accessed 4 December 2015).

35. Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. J Nutr. 2001;131(2s-2):649S–666S; discussion 666S-668S.

36. Stoltzfus RJ, Dreyfus ML, WHO. Guidelines for the use of iron supplements to prevent and treat iron deficiency anemia. Washington DC: ILSI Press; 1998.

37. de Silva A, Atukorala S, Weerasinghe I, Ahluwalia N. Iron supplementation improves iron status and reduces morbidity in children with or without upper respiratory tract infections: a randomized controlled study in Colombo, Sri Lanka. Am J Clin Nutr. 2003;77(1):234–41.

38. Mitra AK, Akramuzzaman SM, Fuchs GJ, Rahman MM, Mahalanabis D. Long-term oral supplementation with iron is not harmful for young children in a poor community of Bangladesh. J Nutr. 1997;127(8):1451–5.

39. Richard SA, Zavaleta N, Caulfield LE, Black RE, Witzig RS, Shankar AH. Zinc and iron supplementation and malaria, diarrhea, and respiratory infections in children in the Peruvian Amazon. Am J Trop Med Hyg. 2006;75(1):126–32.

40. Tielsch JM, Khatry SK, Stoltzfus RJ, Katz J, LeClerq SC, Adhikari R et al. Effect of routine prophylactic supplementation with iron and folic acid on preschool child mortality in southern Nepal: community-based, cluster-randomised, placebo-controlled trial. Lancet. 2006;367(9505):144–52.

41. Black MM. Micronutrient deficiencies and cognitive functioning. J Nutr. 2003;133(11 Suppl. 2):3927s–3931s.

42. Bhandari N, Bahl R, Taneja S. Effect of micronutrient supplementation on linear growth of children. Br J Nutr. 2001; 85(Suppl. 2):S131–7.

43. Ramakrishnan U, Aburto N, McCabe G, Martorell R. Multimicronutrient interventions but not vitamin a or iron interventions alone improve child growth: results of 3 meta-analyses. J Nutr. 2004;134(10):2592–602.

44. Sachdev H, Gera T, Nestel P. Effect of iron supplementation on mental and motor development in children: systematic review of randomised controlled trials. Public Health Nutr. 2005;8(2):117–32.

45. Sachdev H, Gera T, Nestel P. Effect of iron supplementation on physical growth in children: systematic review of randomised controlled trials. Public Health Nutr. 2006;9(7):904–20.

46. Thompson J, Biggs BA, Pasricha SR. Effects of daily iron supplementation in 2- to 5-year-old children: systematic review and meta-analysis. Pediatrics. 2013;131(4):739–53. doi:10.1542/peds.2012-2256.

47. Wang B, Zhan S, Gong T, Lee L. Iron therapy for improving psychomotor development and cognitive function in children under the age of three with iron deficiency anaemia. Cochrane Database Syst Rev. 2013;(6):CD001444. doi:10.1002/14651858.CD001444.pub2.

48. Sazawal S, Black RE, Ramsan M, Chwaya HM, Stoltzfus RJ, Dutta A et al. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. Lancet. 2006;367(9505):133–43.

49. Oppenheimer SJ. Iron and its relation to immunity and infectious disease. J Nutr. 2001;131(2s-2):616S–633S; discussion 633S–635S.

50. Oppenheimer SJ, Gibson FD, Macfarlane SB, Moody JB, Harrison C, Spencer A et al. Iron supplementation increases prevalence and effects of malaria: report on clinical studies in Papua New Guinea. Trans R Soc Trop Med Hyg. 1986;80(4):603–12.

51. Idjradinata P, Watkins WE, Pollitt E. Adverse effect of iron supplementation on weight gain of iron-replete young children. Lancet. 1994. 343(8908):1252–4.

52. Soofi S, Cousens S, Iqbal SP, Akhund T, Khan J, Ahmed I et al., Effect of provision of daily zinc and iron with several micronutrients on growth and morbidity among young children in Pakistan: a cluster-randomised trial. Lancet. 2013;382(9886):29–40. doi:10.1016/S0140-6736(13)60437-7.

53. International Nutritional Anemia Consultative Group (INACG). Guidelines for the eradication of iron deficiency anaemia. A report of the International Nutritional Anaemia Consultative Group. Washington DC: The Nutrition Foundation; 1977.

54. Beard JL. Why iron deficiency is important in infant development. J Nutr. 2008;138(12):2534–6.

55. Lozoff B, Brittenham GM, Viteri FE, Wolf AW, Urrutia JJ. The effects of short-term oral iron therapy on developmental deficits in iron-deficient anemic infants. J Pediatr. 1982;100(3):351–7.

56. Chaparro CM. Setting the stage for child health and development: prevention of iron deficiency in early infancy. J Nutr. 2008;138(12):2529–33.

57. Vitamin and mineral requirements in human nutrition, 2nd ed. Geneva: World Health Organization and Food and Agriculture Organization of the United Nations; 2004 (http://apps.who.int/iris/bitstream/10665/42716/1/9241546123.pdf?ua=1, accessed 4 December 2015).

58. Pasricha S-R, Shet AS, Black JF, Sudarshan H, Prashanth NS, Biggs BA et al. Vitamin B-12, folate, iron, and vitamin A concentrations in rural Indian children are associated with continued breastfeeding, complementary diet, and maternal nutrition. Am J Clin Nutr. 2011;94(5): 1358–70. doi:10.3945/ajcn.111.018580.

59. Stoltzfus RJ, Chway HM, Montresor A, Tielsch JM, Jape JK, Albonico M et al. Low dose daily iron supplementation improves iron status and appetite but not anemia, whereas quarterly anthelminthic treatment improves growth, appetite and anemia in Zanzibari preschool children. J Nutr. 2004;134(2):348–56.

60. Wharton BA. Iron deficiency in children: detection and prevention. Br J Haematol. 1999;106(2):270–80.

61. Hotez PJ, Brooker S, Bethony JM, Bottazzi ME, Loukas A, Xiao S. Hookworm infection. N Engl J Med. 2004;351(8):799–807.

62. Falkingham M, Abdelhamid A, Curtis P, Fairweather-Tait S, Dye L, Hooper L. The effects of oral iron supplementation on cognition in older children and adults: a systematic review and meta-analysis. Nutr J. 2010;9:4. doi:10.1186/1475-2891-9-4.

63. Seshadri S, Gopaldas T. Impact of iron supplementation on cognitive functions in preschool and school-aged children: the Indian experience. Am J Clin Nutr. 1989;50(3):675–86.

64. McCann JC, Ames BN. An overview of evidence for a causal relation between iron deficiency during development and deficits in cognitive or behavioral function. Am J Clin Nutr. 2007;85(4):931–45.

65. Gera T, Sanchev HPS. Effect of iron supplementation on incidence of infectious illness in children. BMJ. 2002;325(7373):1142–51.

66. World malaria report 2014. Geneva: World Health Organization; 2014 (http://www.who.int/malaria/publications/world_malaria_report_2014/wmr-2014-no-profiles.pdf, accessed 4 December 2014).

67. Korenromp EL, Armstrong-Schellenberg JR, Williams BG, Nahlen BL, Snow RW. Impact of malaria control on childhood anaemia in Africa – a quantitative review. Trop Med Int Health. 2004;9(10):1050–65.

68. Schellenberg D, Menendez C, Kahigwa E, Font F, Galindo C, Acosta C et al. African children with malaria in an area of intense *Plasmodium falciparum* transmission: features on admission to the hospital and risk factors for death. Am J Trop Med Hyg. 1999;61(3):431–8.

69. Riley EM, Wagner GE, Akanmori BD, Koram KA et al. Do maternally acquired antibodies protect infants from malaria infection? Parasite Immunol. 2001;23(2):51–9.

70. Sitali L, Chipeta J, Miller JM, Moonga HB, Kumar N, Moss WJ et al. Patterns of mixed Plasmodium species infections among children six years and under in selected malaria hyper-endemic communities of Zambia: population-based survey observations. BMC Infect Dis. 2015;15:204. doi:10.1186/s12879-015-0935-7.

71. Menendez C, Fleming AF, Alonso PL. Malaria-related anaemia. Parasitol Today. 2000;16(11):469–76.

72. Ekvall H. Malaria and anemia. Curr Opin Hematol. 2003;10(2):108–14.

73. Kochan I. The role of iron in bacterial infections, with special consideration of host-tubercle bacillus interaction. Curr Top Microbiol Immunol. 1973;60:1–30.

74. Nyakeriga AM, Troye-Blomberg M, Dorfman JR, Alexander ND, Bäck R, Kortok M et al. Iron deficiency and malaria among children living on the coast of Kenya. J Infect Dis. 2004;190(3):439–47.

75. Report of the World Health Organization Technical Consultation on Prevention and Control of Iron Deficiency in Infants and Young Children in Malaria-Endemic Areas, Lyon, France, 12–14 June 2006. Food Nutr Bull. 2007;28(4 Suppl.):S489–631.

76. Prentice AM, Cox SE. Iron and malaria interactions: research needs from basic science to global policy. Adv Nutr. Journal. 2012;3(4):583–91. doi:10.3945/an.111.001230.

77. Stoltzfus RJ. Iron and malaria interactions: programmatic ways forward. Adv Nutr. 2012;3(4):579–82. doi:10.3945/an.111.000885.

78. Suchdev PS, Leeds IL, McFarland DA, Flores R. Is it time to change guidelines for iron supplementation in malarial areas? J Nutr. 2010;140(4):875–6. doi:10.3945/jn.109.118638.

79. Ojukwu JU, Okebe JU, Yahav D, Paul M. Oral iron supplementation for preventing or treating anaemia among children in malaria-endemic areas. Cochrane Database Syst Rev. 2009;(3):CD006589. doi:10.1002/14651858.CD006589.pub2.

80. World Health Organization Secretariat on behalf of the participants of the Consultation. Lyon, France 12–14 June 2006. Conclusions and recommendations of the WHO consultation on prevention and control of iron deficiency in infants and young children in malaria-endemic areas. Food Nutr Bull. 2007;28(4 Suppl.):S621–S627.

81. Pasricha SR, Hayes E, Kalumba K, Biggs BA. Effect of daily iron supplementation on health in children aged 4–23 months: a systematic review and meta-analysis of randomised controlled trials. Lancet Glob Health. 2013;1(2):e77–86. doi:10.1016/S2214-109X(13)70046-9.

82. Low M, Farrell A, Biggs BA, Pasricha SR. Effects of daily iron supplementation in primary-school-aged children: systematic review and meta-analysis of randomized controlled trials. CMAJ. 2013;185(17):E791–802. doi:10.1503/cmaj.130628.

83. Neuberger A, Okebe J, Yahav D, Paul M.Oral iron supplements for children inmalaria-endemic areas. Cochrane Database Syst Rev. 2016;(2):CD006589. doi: 10.1002/14651858.CD006589.pub4.

84. Okebe JU, Yahav D, Shbita R, Paul M. Oral iron supplements for children in malaria-endemic areas. Cochrane Database Syst Rev. 2011(10):CD006589. doi:10.1002/14651858.CD006589.pub3.

85. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al., GRADE Worknig Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6. doi:10.1136/bmj.39489.470347.AD.

86. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383–94. doi:10.1016/j.jclinepi.2010.04.026.

87. Guideline: intermittent iron supplementation in preschool and school-age children. Geneva: World Health Organization; 2011 (http://apps.who.int/iris/bitstream/10665/44648/1/9789241502009_eng.pdf, accessed 4 December 2015).

88. Global technical strategy for malaria 2016–2030. Geneva: World Health Organization; 2015 (http://www.who.int/malaria/publications/atoz/9789241564991/en/, accessed 4 December 2015).

89. World Health Organization. Nutrition (http://www.who.int/nutrition/en/, accessed 4 December 2015).

90. World Health Organization, e-Library of Evidence for Nutrition Actions (eLENA) Guideline development process (http://www.who.int/elena/about/guidelines_process/en/, accessed 4 December 2015).

91. The WHO Expert Committee on Specification for Pharmaceutical Preparations. Quality assurance of pharmaceuticals: meeting a major public health challenge. Geneva: World Health Organization; 2014 (http://www.who.int/medicines/publications/brochure_pharma.pdf, accessed 4 December 2015).

92. World Health Organization. Essential medicines and health products (http://www.who.int/medicines/services/essmedicines_def/en/, accessed 4 December 2015).

93. World Health Organization (WHO) and Food and Agriculture Organization of the United Nations (FAO). Codex Alimentarius: Guidelines for vitamin and mineral food supplements. Geneva: World Health Organization and the Food and Agriculture Organization; 2005 (CAC/GL 55; http://www.codexalimentarius.org/standards/list-of-standards/en/?provide=standards&orderField=fullReference&sort=asc&num1=CAC/GL, accessed 4 December 2015).

94. Continuity and change. Implementing the third WHO Medicines Strategy 2008–2013. Geneva: World Health Organization; 2010 (WHO/EMP/2010.2; http://apps.who.int/medicinedocs/documents/s16880e/s16880e.pdf, accessed 4 December 2015).

95. Evaluation of the Good Governance for Medicines programme (2004–2012). Brief summary of findings. Geneva: World Health Organization; 2013 (WHO/EMP/MPC/2013.1; http://apps.who.int/medicinedocs/documents/s20188en/s20188en.pdf, accessed 4 December 2015).

96. Centers for Disease Control and Prevention (CDC). Division of Nutrition, Physical Activity, and Obesity. International Micronutrient Malnutrition Prevention and Control (IMMPaCt) (http://www.cdc.gov/immpact/, accessed 4 December 2015).

97. World Health Organization. eCatalogue of indicators for micronutrient programmes (https://extranet.who.int/indcat/, accessed 4 December 2015).

98. World Health Organization. Global database on the Implementation of Nutrition Action (GINA) (http://www.who.int/nutrition/gina/en/, accessed 4 December 2015).

99. Handbook on health inequality monitoring: with a special focus on low- and middle-income countries. Geneva: World Health Organization; 2013 (http://apps.who.int/iris/bitstream/10665/85345/1/9789241548632_eng.pdf, accessed 4 December 2015).

100. United Nations System Standing Committee on Nutrition (SCN) (http://www.unscn.org, accessed 4 December 2015).

101. National Collaborating Centre for Methods and Tools. Critically appraising practice guidelines: The AGREE II instrument (updated 1 November, 2013). Hamilton: McMaster University; 2011 (http://www.nccmt.ca/registry/view/eng/100.html, accessed 4 December 2015).

102. Basic documents, 48th ed. Geneva: World Health Organization; 2014 (http://apps.who.int/gb/bd/, accessed 4 December 2015).

ANNEX 1. GRADE SUMMARY OF FINDINGS TABLES

A. Daily iron supplementation in infants and young children aged 6–23 months

Daily oral iron supplementation compared to placebo or control in infants and young children aged 6–23 months

Patient or population: infants and young children aged 6–23 months
Intervention: daily oral iron supplementation
Comparison: placebo or control
Setting: all settings (including malaria-endemic areas)

Outcomes	Relative effect* (95% CI)	Number of Pparticipants (studies)	Quality of the evidence (GRADE)	Comments
Anaemia (haemoglobin below a cut-off value determined by the trialists)	**RR 0.61** (0.50 to 0.74)	4825 (17 RCTs)	⨁⨁⨁⨀ MODERATE [1]	
Iron deficiency (as measured by trialists by using indicators of iron status such as ferritin or transferrin)	**RR 0.30** (0.15 to 0.60)	2464 (9 RCTs)	⨁⨁⨁⨀ MODERATE [2]	
Iron deficiency anaemia (defined by the presence of anaemia plus iron deficiency, diagnosed with an indicator of iron status selected by trialists)	**RR 0.14** (0.10 to 0.22)	2145 (6 RCTs)	⨁⨁⨁⨁ HIGH [3]	
Growth measures (stunting)	**RR 1.10** (0.92 to 1.32)	1504 (3 RCTs)	⨁⨁⨁⨀ MODERATE [4]	
Growth measures (wasting)	**RR 1.03** (0.65 to 1.64)	1504 (3 RCTs)	⨁⨁⨀⨀ LOW [5]	
Mortality (all cause, acute respiratory infections, diarrhoea, malaria)	**Rate ratio 1.10** (0.91 to 1.34)	(3 RCTs)	⨁⨁⨀⨀ LOW [6]	Reported as rate ratio using generic inverse variance method.

*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

1. There was no serious risk of bias among the studies that included this outcome. There was significant heterogeneity in the analysis. Thus, the quality of evidence was downgraded owing to inconsistency.
2. There was no serious risk of bias among the studies that included this outcome. There was significant heterogeneity in the analysis. Thus, the quality of evidence was downgraded owing to inconsistency. 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).
3. There was no serious risk of bias among the studies that included this outcome. The magnitude of effect was very large, with the RR less than 0.2 (the quality of evidence was not upgraded for this).
4. The effect size has a wide confidence interval that range from large benefit to small harm. The quality of evidence for this outcome was downgraded for imprecision.
5. The effect size has a wide confidence interval that range from large benefit to large harm. There was low total number of events. The quality of evidence for this outcome was downgraded for very serious concerns on imprecision.
6. The effect size has a wide confidence interval that range from small benefit to large harm. Only two studies reported on this outcome with a few total number of events. The quality of evidence for this outcome was downgraded for serious concerns on imprecision and possible publication bias.

For details of studies included in the review, see reference *(81)*.

B. Daily iron supplementation in children aged 24–59 months

Daily oral iron supplementation compared to placebo or control in children aged 24–59 months

Patient or population: children aged 24–59 months
Intervention: daily oral iron supplementation
Comparison: placebo or control
Setting: all settings (including malaria-endemic areas)

Outcomes	Relative effect* (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
Anaemia (haemoglobin below a cut-off value determined by the trialists)	**RR 0.98** (0.88 to 1.08)	359 (1 RCT)	⨁⊖⊖⊖ VERY LOW [1]	
Iron deficiency (as measured by trialists by using indicators of iron status such as ferritin or transferrin)	Not estimable	None of the studies reported on this outcome.		
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.		
Growth measures (height *Z*-score)	The mean growth measures (height *Z*-score) in the intervention group was **0.01 *Z*-score lower** (1.14 lower to 0.12 higher)	634 (3 RCTs)	⨁⨁⊖⊖ LOW [2]	
Growth measures (weight *Z*-score)	The mean growth measures (weight *Z*-score) in the intervention group was **0.04 *Z*-score lower** (0.12 lower to 0.05 higher)	634 (3 RCTs)	⨁⨁⊖⊖ LOW [3]	
Mortality	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

1. Only one cross-over design study reported on this outcome. The quality of evidence was downgraded for serious risk of bias (incomplete outcome data and selective reporting), indirectness (the age of the participants ranged from 12 to 48 months) and suspected publication bias.
2. The studies synthesized for this outcome had uncertain random sequence generation and allocation concealment. The quality of evidence was downgraded for serious risk of bias and strongly suspected publication bias.
3. The studies synthesized for this outcome had uncertain random sequence generation and allocation concealment. The quality of evidence was downgraded for serious risk of bias and strongly suspected publication bias.

For details of studies included in the review, see reference *(46)*.

C. Daily iron supplementation in children aged 60 months and older

Daily oral iron supplementation compared to placebo or control in children aged 60 months and older

Patient or population: children aged 60 months and older
Intervention: daily oral iron supplementation
Comparison: placebo or control
Setting: all settings (including malaria-endemic areas)

Outcomes	Relative effect* (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
Anaemia (haemoglobin below a cut-off value determined by the trialists)	**RR 0.50** (0.39 to 0.64)	1763 (7 RCTs)	⨁⨁⨁⨀ MODERATE[1]	
Iron deficiency (as measured by trialists by using indicators of iron status such as ferritin or transferrin)	**RR 0.21** (0.07 to 0.63)	1020 (5 RCTs)	⨁⨁⨀⨀ LOW[2]	
Iron deficiency anaemia (defined by the presence of anaemia plus iron deficiency, diagnosed with an indicator of iron status selected by trialists)	**RR 0.12** (0.02 to 0.66)	334 (2 RCTs)	⨁⨁⨁⨀ MODERATE[3]	
Growth measures (height *Z*-score)	The mean growth measures (height *Z*-score) in the intervention group was **0.09 *Z*-score higher** (0.01 higher to 0.17 higher)	1318 (5 RCTs)	⨁⨁⨁⨀ MODERATE[4]	
Growth measures (weight *Z*-score)	The mean growth measures (weight *Z*-score) in the intervention group was **0.1 *Z*-score higher** (0.03 lower to 0.23 higher)	1318 (5 RCTs)	⨁⨁⨀⨀ LOW [5]	
Mortality (all cause, acute respiratory infections, diarrhoea, malaria)	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

1. There was no serious risk of bias among the studies that included this outcome. There was significant heterogeneity in the analysis. Thus, the quality of evidence was downgraded owing to inconsistency. 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).
2. There was no serious risk of bias among the studies that included this outcome. There was significant heterogeneity in the analysis. There were no small studies with negative results. Thus, the quality of evidence was downgraded owing to inconsistency and strongly suspected publication bias. The magnitude of effect was large, with the RR is between 0.5 and 0.2 (the quality of evidence was not upgraded for this).
3. Only two studies reported on this outcome with a low total number of events. Neither study had serious risk of bias. The quality of evidence was downgraded for strongly suspected publication bias. The magnitude of effect was very large, with the RR less than 0.2 (the quality of evidence was not upgraded for this).
4. Most of the studies had risk of bias (unknown random sequence generation or allocation concealment or selective reporting).
5. Most of the studies had risk of bias (unknown random sequence generation or allocation concealment or selective reporting). There was significant heterogeneity in studies. The quality of evidence was thus downgraded for serious risk of bias and inconsistency.

For details of studies included in the review, see reference *(82)*.

D. Daily iron supplementation in infants and children in malaria-endemic areas

Daily oral iron supplementation compared to placebo or control in infants and children in malaria-endemic settings

Patient or population: infants and children (aged 6 months to 18 years)
Intervention: iron supplementation1
Comparison: placebo or control
Setting: malaria-endemic areas

Outcomes		Relative effect* (95% CI)	Number of articipants (studies)	Quality of the evidence (GRADE)	Comments
Clinical malaria (fever >37.5 °C and any parasitaemia), all		**RR 0.93** (0.87 to 1.00)	7168 (14 RCTs)	⨁⨁⨁⨀ MODERATE[2]	
Clinical malaria by age:[3]	6–23 months	**RR 0.89** (0.82 to 0.97)	3720 (5 RCTs)		
	24–59 months	**RR 0.97** (0.75 to 1.26)	1415 (3 RCTs)		
	60 months or older	**RR 1.04** (0.91 to 1.20)	2033 (6 RCTs)		
Clinical malaria by baseline anaemia:[4]	Anaemic at baseline	**RR 0.92** (0.84 to 1.00)	2112 (9 RCTs)		
	Non-anaemic at baseline	**RR 0.97** (0.86 to 1.09)	4986 (5 RCTs)		
Clinical malaria by availability of malaria-prevention and treatment programme:[5]	Yes (malaria-prevention and treatment programme available)	**RR 0.91** (0.84 to 0.97)	5586 (7 RCTs)		
	No (malaria-prevention and treatment programme not available or unclear)	**RR 1.16** (1.02 to 1.31)	19 086 (9 RCTs)		
Severe malaria (clinical malaria with high-grade parasitaemia)		**RR 0.90** (0.81 to 0.98)	3421 (6 RCTs)	⨁⨁⨁⨁ HIGH	
All-cause mortality		**Risk difference 0.00** (0.00 to 0.01)	7576 (18 RCTs)	⨁⨁⨁⨀ MODERATE[6]	

*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

1. Both arms might include antimalarial treatment as long as both arms receive the same antimalarial treatment.
2. The quality of evidence was downgraded for possible publication bias. There were no small positive studies in favour of iron.
3. Test for subgroup difference for clinical malaria by age: $\chi^2 = 3.56$; $P = 0.17$
4. Test for subgroup difference for clinical malaria by baseline anaemia: $\chi^2 = 0.61$; $P = 0.43$
5. Test for subgroup difference for clinical malaria by availability of malaria prevention and treatment programme: $\chi^2 = 15.70$; $P<0.01$
6. The quality of evidence was downgrade for possible publication bias.

For details of studies included in the review, see reference (*83*).

ANNEX 2. SUMMARY OF THE CONSIDERATIONS OF THE MEMBERS OF THE GUIDELINE DEVELOPMENT GROUP FOR DETERMINING THE STRENGTH OF THE RECOMMENDATION FOR DAILY IRON SUPPLEMENTATION IN CHILDREN AGED 6–23 MONTHS

QUALITY OF EVIDENCE:	Iron deficiency anaemia had high-quality evidence. The recommendation addresses the outcomes targeted for improvement and for these outcomes the evidence is high, based on several randomized controlled trials. Heterogeneity was noted but was related to different beneficial effect sizes rather than different effects. The effect sizes of the intervention on the outcomes were large. The evidence for morbidity and developmental outcomes is weak but the recommendation does not directly address these outcomes.
VALUES AND PREFERENCES:	In cases where the population prevalence of anaemia is greater than 40%, the causes of anaemia are multifactorial and unlikely to be exclusively caused by iron deficiency. Even taking this into account, most children in most cases will benefit from intermittent iron supplementation or daily supplementation. Iron-replete children might not gain from the intervention. Acceptability might be an issue given associated side-effects (gastrointestinal) and compliance may be difficult. 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, which have functional consequences. Potential harms include diarrhoea, but evidence is low or very low or not thoroughly evaluated for potential harms. Not enough data are available on long-term harm, for instance on overdose, specifically for children who are iron replete.
COSTS AND FEASIBILITY:	Cost information was not presented but the cost of iron supplements is generally minor compared to the cost of the delivery platform and the need for strong behaviour change and monitoring. Supplements are generally cheaper lipid-based nutrient supplements.

ANNEX 3. SUMMARY OF THE CONSIDERATIONS OF THE MEMBERS OF THE GUIDELINE DEVELOPMENT GROUP FOR DETERMINING THE STRENGTH OF THE RECOMMENDATION FOR DAILY IRON SUPPLEMENTATION IN CHILDREN AGED 24–59 MONTHS

QUALITY OF EVIDENCE:	The evidence provided is based on studies from different time periods, with small sample sizes and where allocation concealment and random selection were not always evident. Studies varied in terms of dose and duration of treatment. Only one study reported on anaemia; none of the studies reported on iron deficiency or iron deficiency anaemia. Studies that reported on ferritin and haemoglobin had high or moderate quality.
VALUES AND PREFERENCES:	It is important to consider the ability to reach children in need, a child's acceptance of supplementation, family adherence and health-systems issues in the implementation.
TRADE-OFF BETWEEN BENEFITS AND HARMS:	The intervention improves haemoglobin and ferritin concentrations and prevents anaemia. There is no clear evidence regarding harms at proposed doses for diarrhoea and other gastrointestinal effects, liver damage, insulin resistance or iron overload
COSTS AND FEASIBILITY:	In well-established and well-functioning health-systems settings, the costs may be low. This may not be the case in low-resource settings. Therefore, reaching the children in need and ensuring a high coverage merits consideration. The drug cost might be acceptable, but operational costs need to be accounted for, in order to ensure a continuous supply, proper supervision and optimal monitoring, as the target group is very large.

ANNEX 4. SUMMARY OF THE CONSIDERATIONS OF THE MEMBERS OF THE GUIDELINE DEVELOPMENT GROUP FOR DETERMINING THE STRENGTH OF THE RECOMMENDATION FOR DAILY IRON SUPPLEMENTATION IN CHILDREN AGED 60 MONTHS AND OLDER

QUALITY OF EVIDENCE:	The evidence is of high quality for priority outcomes (anaemia, iron deficiency, iron deficiency anaemia). Cognition and growth may be as important as haemoglobin and anaemia in this age group and the quality of evidence for these outcomes is moderate.
VALUES AND PREFERENCES:	The main challenge may be in reaching this age group. Lack of awareness on the importance of prevention and treatment of anaemia may reduce acceptability and compliance.
TRADE-OFF BETWEEN BENEFITS AND HARMS:	The intervention improves anaemia, iron deficiency anaemia and iron deficiency. No major harms were identified in this age group, though there is not enough evidence on gastrointestinal effects, potential toxic endpoints and the impact of iron overload.
COSTS AND FEASIBILITY:	Schools may be an appropriate delivery platform for this age group and thus should be considered. The school infrastructure is usually conducive for implementing this intervention. However, success may then depend on the school systems and the attendance rates. Some consideration might need to be made for children outside of school.

ANNEX 5. SUMMARY OF THE CONSIDERATIONS OF THE MEMBERS OF THE GUIDELINE DEVELOPMENT GROUP FOR DETERMINING THE STRENGTH OF THE RECOMMENDATION FOR DAILY IRON SUPPLEMENTATION IN MALARIA– ENDEMIC AREAS

QUALITY OF EVIDENCE:	The quality of evidence that iron supplementation does not increase the risk of clinical malaria is moderate overall. It was noted that the questions for which the quality of evidence was low or very low may not necessarily be of high priority, for various reasons. Research questions that may be considered as high priority were discussed and listed in this guideline.
VALUES AND PREFERENCES:	Since malaria infection occurs in early infancy and is especially dangerous at this age, in malaria-endemic areas, iron supplements should only be given to infants who sleep under insecticide-treated bednets, and where all episodes of malaria illness can be promptly treated with effective antimalarial drug therapy according to national guidelines.
TRADE-OFF BETWEEN BENEFITS AND HARMS:	In malaria-endemic areas, where there is limited malaria prevention and clinical care, universal iron supplementation may be associated with an increased risk of malaria. Control of infectious diseases and malaria with insecticide-treated bednets and vector control, and treatment of malaria episodes with effective antimalarial therapy, are critical components of health care and should be instituted, together with promotion of exclusive breastfeeding up to the age of 6 months, followed by high-quality complementary feeding.
COSTS AND FEASIBILITY:	In the presence of comprehensive surveillance and prompt diagnosis and treatment of malaria, there was no compelling evidence of increased risk of adverse events from iron supplementation. Insufficient and inequitable health-care services are associated with an increase in risks in general.

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ANNEX 11. QUESTIONS IN POPULATION, INTERVENTION, CONTROL, OUTCOMES (PICO) FORMAT

A. Effects and safety of daily iron supplementation in infants and young children aged 6–23 months

Could iron supplements given to infants and young children aged 6–23 months improve health outcomes? If so, (a) at what dose, frequency and duration of the intervention? (b) in which settings?

POPULATION:	Children aged 6–23 months Subpopulations: – By early exposure to iron: infants who regularly received an iron supplement within the first 6 months of life versus no iron – By feeding practices: exclusively breastfed versus iron-fortified formula versus mixed (breast milk plus iron-fortified formula with or without complementary food, multiple micronutrient powders) – 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 infant's anaemia status: anaemic versus non-anaemic
INTERVENTION:	Iron supplementation Subgroup analyses: – By dose: 2 mg/kg/day versus other – By frequency: daily versus weekly versus flexible – By duration: 3 months or less versus >3 months – By additional nutrient: in combination with other micronutrients or not – By targeting: universal versus prescribed
CONTROL:	No iron supplementation Placebo Same supplement without iron
OUTCOMES:	Short-term outcomes (age 6–23 months) – 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

B. Effects and safety of daily iron supplementation in children aged 24–59 months

Could iron supplements given to children aged 24–59 months improve health outcomes? If so, (a) at what dose, frequency and duration of the intervention? (b) in which settings?

POPULATION:	Children aged 24–59 months Subpopulations: – 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: >40% versus 40% or less
INTERVENTION:	Iron supplementation Subgroup analyses: – By dose: 2 mg/kg/day versus other – By frequency: daily versus weekly versus flexible – By duration: 3 months or less versus >3 months – By additional nutrient: in combination with other micronutrients or not – By targeting: universal versus prescribed
CONTROL:	No iron supplementation Placebo Same supplement without iron
OUTCOMES:	Short-term outcomes (age 24–59 months) – 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

C. Effects and safety of daily iron supplementation in children aged 60 months and older

Could iron supplements given to children aged 60 months and older improve health outcomes? If so, (a) at what dose, frequency and duration of the intervention? (b) in which settings?

POPULATION:	Children aged 60 months and older Subpopulations: – By previous exposure to iron: infants 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: >40% versus 40% or less – By individual's anaemia status: anaemic versus non anaemic
INTERVENTION:	Iron supplementation Subgroup analyses: – By dose: 2 mg/kg/day versus other – By frequency: daily versus weekly versus flexible – By duration: 3 months or less versus > 3 months – By additional nutrient: in combination with other micronutrients or not – By targeting: universal versus prescribed
CONTROL:	No iron supplementation Placebo Same supplement without iron
OUTCOMES:	Short-term outcomes (age 6–18 years) – Anaemia – Iron deficiency anaemia – Iron deficiency – Morbidity – Malaria incidence and severity (parasitaemia with or without symptoms) – Mortality – All cause – Acute respiratory infections – Diarrhoea – Malaria
SETTING:	All countries

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