Review Article

Systematic review on supplementation, fortification, and food-based interventions for preventing iron deficiency anemia in low- and middle-income countries

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Background and Objectives: Prioritizing key preventive and therapeutic interventions is one of the actions to accelerate the reduction of anemia. This study aimed to examine interventions designed to prevent anemia. **Methods and Study Design:** A systematic search was conducted in PubMed, Web of Science, Scopus, and Cochrane Library. Analysis of publication bias was done using The Joanna-Briggs Institute critical appraisal tool. Data collected from articles included author, year of publication, setting and location of the study, study type, participant of the study, intervention and control given, main outcome, main findings, and risk of bias. **Results:** Three nutrition-specific interventions aimed at preventing iron deficiency anemia in low- and middle-income countries used various types and dosages of iron. While most studies showed success, some indicated a worsening trend in anemia, even with standard dosages and the same form of iron. Determining effective interventions requires consideration of factors such as other micronutrient composition, compliance rate, availability of educational intervention, and dietary backgrounds in those countries. **Conclusions:** Supplementation, fortification, and food-based interventions generally lead to higher hemoglobin levels and a lower prevalence of anemia. However, it is important to consider several factors before deciding on an approach.

Key Words: iron deficiency anemia, iron, vitamin C, supplementation, fortification

INTRODUCTION

Anemia remains a global public health problem affecting both developed and developing countries. In particular, iron deficiency anemia (IDA) is the most common type in low- and middle-income countries.[1,2] Anemia leads to decreased labor productivity in adults and poor cognitive and motor development in children, which impacts the country's economic progress. Many factors contribute to anemia, including inadequate dietary intake, low nutrient absorption, increased needs during growth and pregnancy, inflammation, and infection.[2-6] Anemia can negatively impact infant development and work productivity of women of reproductive age, including pregnant women.[5,7] Anemia during pregnancy is associated with poor pregnancy and birth outcomes, including preterm birth, low birth weight, and maternal mortality.

In 2019, anemia affected 37% of pregnant women, 30% of women aged 15 to 49 years, and 40% of children aged between 6 months and 5 years. At least 1.92 billion people worldwide were anemic in 2021, with Western and Central sub-Saharan Africa and South Asia having the highest number of cases.[8] Therefore, various efforts must be made to reduce anemia rates globally to meet the target of reducing anemia in women of childbearing age by 50% by 2025.[4,9]

The World Health Organization (WHO) recommends five action areas to accelerate the reduction of anemia, one of which is prioritizing key preventive and therapeutic interventions. Increasing consumption of certain micronutrients, particularly iron, folate, vitamin B12, vitamin A, and riboflavin, as well as other micronutrients,

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through food diversification, food fortification, and supplementation is one way to reduce the prevalence of anemia. It is estimated that for every US$1 invested in interventions aimed at reducing anemia in women, such as iron and folic acid (IFA) supplementation for both pregnant and non-pregnant women, preventive treatment for malaria in pregnancy, and iron fortification of cereals, there is an economic return of US$12.[10,11]

IFA supplementation greatly benefits iron-deficient women, and is increasingly included in various micronutrient formulations.[12,13] Several studies have shown the positive impact of iron supplementation and fortification on iron status.[14] Some studies have also reported adverse events such as increased risk of illness (e.g. diarrhea or inflammation of the gastrointestinal tract), reduced growth, or effects on child development.[15,16] Food-based approaches have the potential to be a simple and sustainable method to prevent and treat not only IDA, but also malnutrition. However, improving food quality and promoting behavior change may take a long time.[17]

Iron enhancers and inhibitors affect the success of interventions to prevent iron deficiency anemia. Therefore, it is necessary to consider which micronutrients need to be added or consumed together to increase iron absorption, such as vitamin C.[18] Health educators must also understand micronutrient content, dietary differences, cultural practices, food processing and preparation methods and economic constraints when educating the public.[17,19] This systematic review discusses several interventions aimed at preventing anemia.

METHODS

Study design and research sample

This systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and has been registered on the Prospective Register of Systematic Reviews (PROSPERO) database with registered number CRD42023479171. This review included articles published from 2018-2023, sourced from four databases: PubMed, Scopus, Web of Science, and Cochrane. The research focuses on studies about preventing anemia in pregnant women and children through the supplementation and fortification of iron and vitamin C.

Research query

We searched on the databases with the following query "children under 5" OR "children under 2" OR "pregnant*" AND "fortification" OR "supplementation" OR "vitamin C" OR "deworming" OR "digital screening" AND "anaemia" OR "anemia" OR "anaemic" OR "anemic" OR "low haemoglobin" OR "iron status".

Data collection procedures

Article was selected based on population-intervention-comparison-outcome-study design (PICOS): (1) Population: pregnant women and children under 5 in low- and middle-income countries; (2) Intervention: iron and vitamin C fortification or supplementation; (3) Comparison/control: government recommendation or active placebo; (4) Outcomes: anemia prevalence and/or incidence, hemoglobin (Hb) level, and ferritin; (5) Study design: studies must be experimental studies with RCTs or quasi-experimental studies.

The studies had to be published between 2018 and 2023 to ensure research novelty. To meet the study objective and research strategy, we included only articles that investigated the effects of iron and vitamin C supplementation, fortification, or food-based prevention of anemia in pregnant women and/or children under five. The review also considers the amount of iron content provided. Table 1 presents iron recommendations and their forms for pregnant women and children.

Conversely, studies were excluded if they were reviews, proceedings, or protocols. Studies involving subjects with comorbidities (except tuberculosis and worm infections) or conducted in high-income countries were also excluded. Additionally, articles lacking full text or not in English were excluded. The data collection process is illustrated in Figure 1.

Table 1. Iron recommendations for pregnant women and children

Subject	Recommendations
Pregnant women as part of antenatal care	30-60 mg/day of elemental iron (equivalent to 150-300 mg ferrous sulfate heptahydrate, 250-500 mg ferrous gluconate, and 90-180 mg ferrous fumarate).[20]
Pregnant women in countries where the prevalence of anemia exceeds 40%	60 mg/day of elemental iron along with 400 µg of folic acid.[21]
Children aged 6-23 months	Supplementation 10 – 12.5 mg of elemental iron (equals with 50 – 62.5 mg of ferrous sulfate heptahydrate, 30 – 37.5 mg of ferrous fumarate or 83.3 – 104.2 mg of ferrous gluconate) per day.[22]
Children aged 24 – 59 months	Supplementation 30 mg of elemental iron (equals with 150 mg of ferrous sulfate heptahydrate, 90 mg of ferrous fumarate or 250 mg of ferrous gluconate) per day.[22]
Children aged 6-23 months and 2 – 4 years	Fortification in Micronutrient Powder (MNP) 10 – 12.5 elemental iron (12.5 mg elemental iron equals to 37.5 mg ferrous fumarate or 62.5 mg ferrous sulfate).[23]
Children aged 5-12 years	Fortification in MNP 12.5 – 30 mg elemental iron.[23]

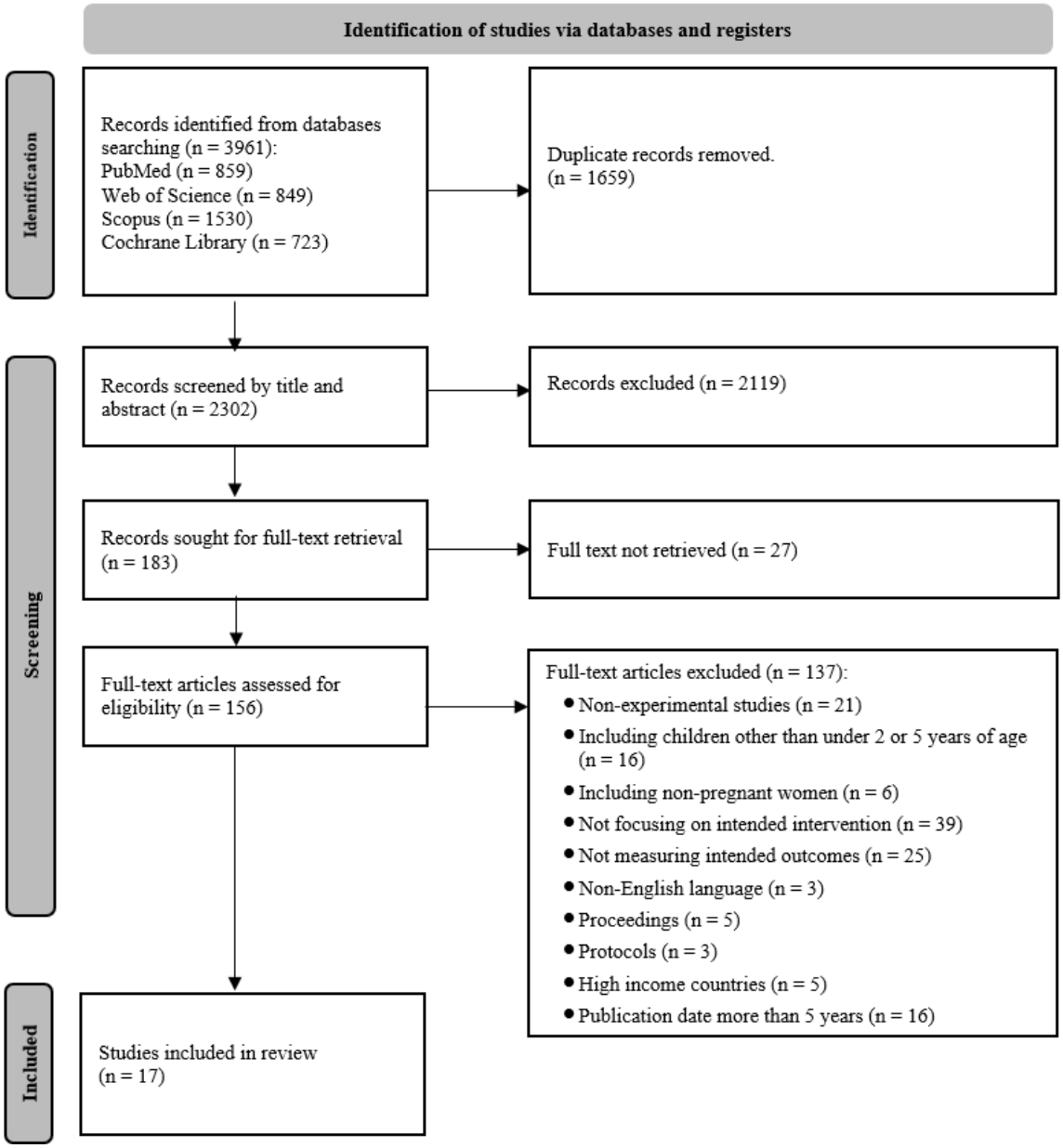


Figure 1. PRISMA systematic review flow diagram

Data extraction

Articles that meet the requirements were then extracted based on a predetermined table to obtain the following information: identity, countries, setting, study type, participant (sample size and criteria), intervention (intervention type, frequency, and duration), intervention specifics, comparison, main outcomes (outcomes and measurement), main findings, and risk of bias. SH, AS, MH, GR, YNR, and MA carried out this process separately by reading the articles' full text. The data extraction is shown in Table 2.

Data management

Article titles and abstracts were screened by SH, AS, MH, GR, YNR, and MA to determine suitability based on the predetermined inclusion criteria, and to exclude duplicate and unrelated articles. EndNote software was used to manage the articles during this process. The review process was expanded to articles with titles and abstracts that matched the inclusion criteria to view the full text of the article. The entire article selection process was shown in the PRISMA flow chart for systematic review.[24] The data that met the criteria were displayed in a matrix to identify the effects of iron or vitamin C supplementation or fortification on pregnant women and children under five.

Quality assessment

The risk of bias in the articles was evaluated by GR, YNR, and MA using The Joanna Briggs Institute (JBI) critical appraisal tools for Randomized Controlled Trial (RCT) and Quasi-Experimental Studies.[25,26] Any discrepancies were addressed through discussion. Articles were classified into three categories: (1) low risk of bias (the RCT article had 10-13 "Yes" answers or 7-9 in quasi-experimental stud-

Table 2. General characteristics of studies

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Supplementation				
1. Bah et al.[27] 2019	Community-based (rural areas) in Gambia (Africa)	Three-arm, randomized, double-blind, non-inferiority trial	n = 498 Pregnant women 18-45 years between 14 and 22 weeks of gestation	Multiple micronutrient capsules including iron with hepcidin- guided screen-and- treat approach (1) 60 mg iron screen-and- treat approach. (2) 30 mg iron screen-and- treat approach Duration: 84 days; Frequency: daily
2. Addo et al.[28] 2020	Community-based (intervention group: rural areas, control group: urban areas) in Democratic Republic of Congo (Africa)	Quasi experimental study	n = 2995 Children aged 6-18 months and their mothers or caregivers in two health zones	Small-quantity lipid-based nutrient supplements (SQ LNS) for infants 6-12 months Duration: ≥3 months; Frequency: daily

Control	Main Outcomes	Main Findings	Risk of bias
(1) WHO's recommended 60 mg ferrous fumarate regimen (no screen-and- treat approach)	Hb at Outcomes: Hb at day 84, prevalence of anemia (Hb), iron deficiency (plasma ferritin, CRP), IDA (Hb, plasma ferritin, CRP). Hb measurement: Rapid (HemoCue Hb301 analyser, cobas integra)	1. The mean difference in the amount of Hb at day 84 was –2.2 g/L with the 60 mg screen-and-treat approach and –2.7 g/L with the 30 mg screen-and-treat approach. 2. Anemia prevalence: (a)WHO 60 mg ferrous fumarate: dropped from 58% to 45% (b) 60 mg iron screen-and-treat: increased from 52% to 57% (c) 30 mg iron screen-and-treat: increased from 53% to 59% 2. IDA prevalence: (a) WHO 60 mg ferrous fumarate: dropped from 39% to 17% (b) 60 mg iron screen-and-treat: dropped from 40% to 29% (c) 30 mg iron screen-and-treat: increased from 37% to 40% 3. Adherence at 3 groups: 86%	Medium
Standard infant young children feeding package	Outcomes: Anemia, iron and vitamin A deficiencies, stunting, wasting, and underweight Hb measurement: Rapid (HemoCue® 301 Hb system)	1. There was a reduction in anemia prevalence by 11.0% point (95% CI: −18.1, −3.8; $p<0.01$) an increase in Hb by mean +0.26-g/dL (95% CI: 0.04, 0.48; $p=0.02$), but no effect on anthropometry or iron or vitamin A deficiencies. Children who received ≥ 3 months of SQ LNS had higher Hb (+0.65 g/dL, $p=0.007$). 2. Hb change (a) SQ LNS: changed from 10.13 to 9.83 g/dL (-0.3 g/dL) (b) Standard package: changed from 11.31 to 10.83 g/dL (-0.48 g/dL) 3. Anemia prevalence (a) SQ LNS: changed from 64.8% to 72.2 % (+7.4%) (b) Standard package: changed from 32.1% to 48.7% (+16.6%) 4. Compliance rate 74.7%	Medium

Table 2. General characteristics of studies (cont.)

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Supplementation				
3. Bumrungpert et al.[29] 2022	Hospital-based (antenatal care clinic) in Thailand (Asia)	Simple RCT	n = 120 Pregnant women with iron deficiency (20-40 years)	Oral iron as ferrous bisglycinate (equiv. iron 24 mg) in supplement form with folinic acid and multivitamins Duration: 6 months; Frequency: daily
4. Byamugisha et al.[30] 2022	Hospital-based (antenatal clinics) in Uganda (Africa)	Randomized controlled open-label/non blinded trial	n = 952 Pregnant women who receive IFA supplementation in their second trimester up to 28 weeks	Blister packaged IFA supplementation Duration: 60 days; Frequency: daily

Control	Main Outcomes	Main Findings	Risk of bias
Oral iron as ferrous fumarate (equiv. iron 66 mg iron) + multivitamin.	Outcomes: Blood chemistry (hematological, iron status, and inflammatory status). Hb measurement: Non-rapid (laboratory analysis).	1. Ferrous bisglycinate with folinic acid as a multivitamin nutraceutical format comparatively had better absorption, tolerability, and efficacy and with a lower elemental iron dosage (equiv. iron 24 mg) than standard ferrous fumarate. 2. Hb change: (a) Ferrous bisglycinate with folinic acid. - Baseline: 10.04 ± 0.83 g/dL. - After 3 months: 12.40 ± 0.68 g/dL (mean change 2.356 ± 0.69). - After 6 months: 12.82 ± 0.66 g/dL (mean change 2.78 ± 0.822). (b) Ferrous fumarate. - Baseline: 10.17 ± 0.77 g/dL. - After 3 months: 11.78 ± 0.72 g/dL (mean change 1.61 ± 0.838). - After 6 months: 12.09 ± 0.60 g/dL (mean change 1.92 ± 0.89). 3. Compliance at intervention vs control: 97% vs 92%.	Medium
Loose packaged iron-folic acid supplementation	Outcomes: Hb level and adherence Hb measurement: Non-rapid. CBC analyzer machine model MEK-6500K	1. The mean Hb level at 4 weeks was higher in the blister than in the loose packaging arms (11.9 + 1.1 g/dL and 11.8 ± 1.3 g/dL, respectively; p=0.02), however, similar at week 8 (12.1 ± 1.2 and 12.0 ± 1.3, respectively; p=0.23). 2. Over the 8-week period blister packaging arm had a higher change in Hb level compared to loose package (0.6 ± 1.0 vs 0.2 ± 1.1; difference: 0.4 g/dL (95% CI: 0.24–0.51 g/dL); p=0.001. 3. Adherence at 8 weeks: 51.9% vs 46.8%	Medium

Table 2. General characteristics of studies (cont.)

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Supplementation				
5. Jorgensen et al.[31] 2018	Mangochi District of rural Malawi (Africa)	Randomized, controlled, outcome assessor-blinded supplementation trial	n = 1391 Mean age 25 years, gestational age <20 week.	1) 20 mg iron plus 17 micronutrients in a capsule or multi micronutrient (MMN) 2) lipid-based nutrient supplement (LNS) contain the same 18 micronutrients as the MMN + as well as four additional minerals, protein, and fat, and also provided 118 kcal of energy. Duration: from enrollment to delivery. Frequency: daily.

Control	Main Outcomes	Main Findings	Risk of bias
1) 60 mg IFA	Outcomes: Hb, iron status (zinc protoporphyrin (ZPP) and transferrin receptor (sTfR)). Hb measurement: Rapid (Hb = Hemocue 201+ system).	1. Women in the IFA group had higher Hb at 36 gestational weeks than women in the LNS group and higher iron status than women in both the LNS and MMN. 2. Hb change (a) IFA: increased from 111.3 to 112.7 g/L (b) MMN: decreased from 111.4 to 110.3 g/L (c) LNS: decreased from 111.7 to 110.0 g/L 3. Prevalence of IDA (a) IFA: cut-off 100g/L decreased from 10.7% to 10.0%; cut-off =110 g/L increased from 10.7% to 20.5% (b) MMN: cut-off 100g/L increased from 12.6% to 14.6%; cut-off =110 g/L increased from 12.6% to 28.3% (c) LNS: cut-off 100g/L increased from 12.2% to 15.7%; cut-off =110 g/L increased from 12.2% to 30.1%	Medium

Table 2. General characteristics of studies

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Supplementation				
6. Matias et al.[32] 2018	Community-based, in the poorest region of Bangladesh (Asia)	Cluster, randomized effectiveness trial	n = 4011 Pregnant women, gestational age ≤20 weeks	Lipid-based Nutrient Supplements for Pregnant and Lactating women (LNS-PL) containing 20 mg of iron Duration: during pregnancy and the first month postpartum Frequency: daily during pregnancy and every other day during the first 3 mo postpartum
7. Srivastava et al.[33] 2019	Antenatal clinic of hospital in Faridabad, India (Asia)	Single-blinded, active comparator, simple RCT	n = 204 Pregnant women aged ≥18 years with gestational age >12 weeks.	Iron supplementation in capsule formulation (100 mg iron, ferrous fumarate) Duration: 3 months; Frequency: daily

Control	Main Outcomes	Main Findings	Risk of bias
IFA containing 60 mg of iron	Outcomes: Anemia (Hb), iron status (ferritin and sTfR), iron deficiency (low ferritin or high sTfR), IDA (anemia and iron deficiency) Hb measurement: Rapid (HemoCue Hb 301 System)	1. Women in the LNS-PL group had lower ferritin (–6.2 µg/L) and higher sTfR concentrations (+0.5 mg/L), and higher risk of iron deficiency (OR=1.93) at 36 weeks of gestation but not at 6 mo postpartum. Among infants at 6 mo, there were no group differences except for a lower risk of elevated sTfR (OR=0.61) in the LNS-PL group than in the IFA group. 2. Hb change (a) LNS-PL Mother: changed from 116.2 ± 12.7 to 114.1 (36 weeks gestation) to 122.5 g/L (6mo postpartum). Child: decreased from 116.1 ± 13.0 to 106.9 g/L (6mo of age). (b) IFA Mother: changed from 116.0 ± 13.0 to 115.6 (36 weeks gestation) to 122.2 g/L (6mo postpartum). Child: changed from 115.5 ± 13.0 to 105.6 g/L (6mo of age).	Medium
Iron supplementation in tablet formulation (100 mg iron, ferrous sulfate)	Outcomes: Compliance to oral iron supplementation, change in mean Hb and serum ferritin level Hb measurement: Rapid (HemoCue Hb 301)	1. Proportion of women with good compliance (>90%) at the end of 3 months was 16% in control and 22% in the intervention arm, the difference was statistically not significant. 2. Mean change in Hb levels for the intervention arm was 0.79 (±1.21) g/dL while the control arm was 0.44 (±1.50) g/dL, which was statistically not significant (p=0.11). 3. The mean serum ferritin level decreased by 0.80 (19.2) ng/mL in the intervention arm and 1.14 (30.8) ng/mL in the control arm, among pregnant women who completed the trial. The difference between the two arms was not statistically significant (p=0.93).	Medium

Table 2. General characteristics of studies (cont.)

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Supplementation				
8. Wang et al.[34] 2022	Antenatal clinics in Dares Salaam, Tanzania (Africa)	Randomized, double-blind, Placebo-controlled trial	n= 8428 Mean age= 25 years. Gestational age= 12-27 weeks.	Multiple-micronutrient supplementation (MMS) (20mg of vitamin B-1 (thiamine), 20mg of vitamin B-2 (riboflavin), 100mg of vitamin B-3 (niacin), 25mg of vitamin B-6 (pyridoxine), 0.8mg of folic acid, 50lg of vitamin B12 (cobalamin), 500mg of vitamin C and 30mg of vitamin E) Frequency: daily

Control	Main Outcomes	Main Findings	Risk of bias
Placebo (IFA)	Outcomes: Child-growth and nutrition outcomes (weight, length, head circumference, arm-circumference, and Hb concentrations) and child-morbidity outcomes (diarrhea, cough, fever, and common cold) Hb measurement: Non rapid (laboratory analysis)	1. Prenatal MMS slightly increases weight-for-age z-scores and length-for-age z-scores during the first six months of life. 2. There's no effect of prenatal and postnatal MMS on Hb concentration. 3. Hb concentration: (a) MMS Prenatal: - At birth: 13.9 g/dL - 6 months of age: 10.1 g/dL - 12 months of age: 10.3 g/dL Postnatal: - At birth: 14.1 g/dL - 6 months of age: 10.5 g/dL - 12 months of age: 11.3 g/dL (b) IFA Prenatal - At birth: 14 g/dL - 6 months of age: 10.2 g/dL - 12 months of age: 10.2 g/dL Postnatal: - At birth: 14.1 g/dL - 6 months of age: 10.5 g/dL - 12 months of age: 11.4 g/dL	Low

Table 2. General characteristics of studies (cont.)

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Supplementation				
9. Adu-Afarwuah et al.[35] 2019	Community-based (semi-urban areas) in Ghana (Africa)	Partially double-blind, individually RCT	n = 1057. Women ≥18 years from ≤20 week pregnancy until their children aged 6-18 months	Intervention: (1) MMN including 20-mg Fe one capsul/d during pregnancy until 6 months postpartum (2) SQ LNS, 118 kcal/d with the same micronutrient levels as in MMN daily during pregnancy until 6 months postpartum + SQ LNS for infants Duration: during pregnancy until delivery or 6 months postpartum for mothers, and from 6-18 months for infants Frequency: daily

Control	Main Outcomes	Main Findings	Risk of bias
60mg Fe+400-µgfolic acid (IFA) one capsule/d during pregnancy	Outcomes: Hb (g/L) and iron status (zinc protoporphyrin, ZPP, µmol/mol heme) Hb measurement: Rapid (HemoCue Hb301; Hemocue AG)	1. At 18 months of age, ZPP was lower in the SQ LNS group than the IFA, but not the MMN group. Further, the SQ LNS group had a lower prevalence of elevated ZPP compared to IFA and MMN combined, and marginally lower prevalence of anemia (38.7% compared with 44.9%; *p*=0.06). 2. Hb change (a) IFA - At 6 mo of age: 114 g/L - At 18 mo of age: 112 g/L (b) MMN - At 6 mo of age: 112 g/L - At 18 mo of age: 112 g/L (c) LNS - At 6 mo of age: 114 g/L - At 18 mo of age: 113 g/L 3. Anemia prevalence (a) IFA - At 6 mo of age: 33.4% - At 18 mo of age: 43.9% (b) MMN - At 6 mo of age: 38.8% - At 18 mo of age: 45.9% (c) LNS - At 6 mo of age: 33.5% - At 18 mo of age: 38.7%	Medium

Table 2. General characteristics of studies (cont.)

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Supplementation				
10. Albelbeisi et al.[36] 2020	Community setting in Gaza Strip, Palestine (Asia)	Two-arm parallel-group randomized controlled trial	n = 200 6 months-old infants	Micronutrient Powder Supplementation (MNP) + National Micronutrient Supplement (NMS) Duration: 12 months, 15 months
11. Roberts et al.[37] 2020	Community-based (villages) in Guinea-Bissau (Africa)	Cluster randomized controlled trial	n = 433 Children younger than 4 years of age	(1) NEWSUP: Supervised isocaloric servings of food supplement high in plant polyphenols and omega 3 fatty acids and protein Duration: 23 weeks, five mornings each week

Control	Main Outcomes	Main Findings	Risk of bias
NMS only	Outcomes: Change in weight, Hb concentration, and anemia Hb measurement: Non rapid (spectrophotometer)	1. Home Fortification of Foods (HFF) with MNP showed a modest change on Hb concentration and significantly reduced the rate of severe anemia 2. Hb change: (a) MNP + NMS From 11.42 ± 0.35 to 11.13 ± 0.52 to 11.24 ± 0.44 g/dL (b) NMS From 11.44 ± 0.37 to 10.92 ± 0.61 to 10.81 ± 0.59 g/dL	Low
Fortified blended food (FBF, corn soy cooked as porridge with fortified vegetable oil, sugar, and salt) Control: traditional rice breakfast (white rice cooked with water, soybean oil and salt)	Outcomes: Hb (g/dL) Hb measurement: non rapid (Sysmex KN21)	1. Children in the treatment group had increased Hb concentration compared to those in the control group (0.65 g/dL, 95%CI 0.23-1.07). 2. Hb concentration: - NEWSUP: increased from 10.2 to 10.8 g/dL (mean 10.5) - FBF: increased from 10.1 to 10.7 (mean 10.4) - Control: increased from 10.1 to 10.7 (mean 10.4)	Low

Table 2. General characteristics of studies (cont.)

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Fortification				
1. Black et al.[38] 2021	Community setting in India (Asia)	Cluster-randomized, double-masked, controlled trial	n = 22. Children 29-49 months	MNP including 13 mg iron (encapsulated ferrous fumarate), 5 mg zinc, 20 µg folic acid, 150 µg vitamin A, 20 mg vitamin C, 0.5 µg vitamin B-12, and 0.5 mg ribo-flavin Duration: 8 months; Frequency: 6 days per week
2. Garcia-Guerra et al.[39] 2022	Urban areas of southern Mexico from 54 communities assigned to a national program	Cluster randomized trial	n = 988. Children 6-12 months	(1) MNP; or (2) Micronutrient syrup Duration: 4 months, Frequency: 6 days per week.

Control	Main Outcomes	Main Findings	Risk of bias
Placebo fortification containing 0.5 mg riboflavin	Outcomes: Child development and anemia biomarker Hb measurement: Rapid (HemoCor-D)	1. MNP had greater reduction of anemia and iron deficiency compared with placebo (a) MNP Hb: changed from 10.9 ± 0.1 to 12.1 ± 0.1 g/dL Anemia prevalence: changed from 46.7% to 10.1% (b) Placebo riboflavin Hb: changed from 10.9 ± 0.1 to 11.2 ± 0.1 g/dL Anemia prevalence: changed from 49% to 35.5% Adherence: 74.5% (MNP), 73.4% (Placebo)	Low
Fortified food (FF) (fortified pap, Nutrisano) containing ener-gy, protein, carbohydrates, li-pids, and micronutrients;	Outcomes: Changes in serum zinc, ferritin, sTfR, Hb concentration and their deficiencies. Hb measurement: rapid (HemoCue B-Hb device)	1. Zinc concentration increased significantly in all groups with the largest change in the syrup group (+4.4 µmol/L; 95%CI:3.2, 5.5), followed by MNP (+2.9 µmol/L; 95%CI:2.1, 3.6) and FF (+0.9 µmol/L;95%CI:0.3, 1.6). 2. Hb concentration significantly increased (+5.5 g/L; 2.5, 8.4) Significant reduction in anemia prevalence (44.2% to 26.8%, p<0.01) only in the MNP.	Medium

Table 2. General characteristics of studies (cont.)

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Fortification				
3. Machado et al.[40] 2021	School-setting in Brazil (America)	Open in parallel, cluster-RCT	n = 169 Children 6 - 42 months	Group A: Anemia and receiving MNP (60 sachets) + 3.2 mg/kg/day of elemental iron Ferrous sulfate Group B: Non anemia and receiving MNP Duration: 15 weeks; Frequency: every lunch Monday-Friday
4. Somassè et al.[41] 2018	Community-based (villages in municipalities) in Mali (Africa)	Cluster-randomized controlled trial	n = 722 Children age 6-23 months	MNP Group education on child complementary feeding + HFF with MNP (containing vitamin A, folic acid, cholecalciferol, iodine, Se, vitamin B12, niacin, Fe, Zn, Cu, thiamin, riboflavin, vitamin C, vitamin B6, vitamin E) Duration: 3 months; Frequency: daily

Control	Main Outcomes	Main Findings	Risk of bias
Group C: Anemia and receiving 4.2 mg/kg/day of elemental iron + 50 µg folic acid Group D: Non anemia and receiving elemental iron (1.4 mg/kg/day) + 50 µg folic acid	Outcomes: Hb, serum ferritin and sTfR Hb Measurement: Non-rapid (electronic count Syesmex XE-2100)	Iron deficiency and anemia prevention was effective by MNP fortification (a) MNP - Hb: changed from 11.68 ± 0.13 to 12.90 ± 0.11 g/dL - Anemia prevalence: changed from 15.09% to 1.30% (b) Ferrous sulfate + Folic acid (FS_FA) - Hb: changed from 11.64 ± 0.14 to 12.53 ± 0.12 g/dL - Anemia prevalence: changed from 11.89% to 1.34%	Low
Group education on child complementary feeding only	Outcomes: Hb change, anemia and children weight Hb measurement: Rapid (Hemocue Hb301)	1. Intervention group (group education + HFF) provided a modest but statistically significant Hb change vs control group (0.50 vs 0.09 g/dL, p=0.023). 2. Prevalence of anemia changed: 91.3–85.8% (p=0.04) in the intervention group vs 88.1–87.5% (p=0.86) in the control group. 3. Proportion of severe anemia was reduced by 84% (from 9.8 to 1.6%) in the intervention group, but increased in the control group (from 8.5 to 10.8%).	Medium

Table 2. General characteristics of studies (cont.)

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Fortification				
5. Tchum et al.[42] 2021	Community-based (households in compounds) in Ghana (Africa)	Population-based RCT	n = 1958 Children aged 6-35 months	MNP containing 12.5 mg elemental iron (as ferrous fumarate), vitamin A (400 µg), ascorbic acid (30 mg) and zinc (5 mg), mixed with semi-solid meals Duration: 5 months; Frequency: daily

Control	Main Outcomes	Main Findings	Risk of bias
MNP without iron	Outcomes: Hb, serum ferritin, and sTfR; anemia status Hb measurement: Rapid (HemoCue Hb 201+ analyzer)	1. Intervention group had significantly higher Hb and serum ferritin levels than the placebo group. 2. STfR levels were more saturated among children from the intervention group compared to the control group. 3. Anemia status in the iron group improved compared to the placebo group. 4. Hb change (a) MNP + iron From 10.29 ± 1.26 to 9.65 ± 1.70 g/dL (b) MNP From 10.29 ± 1.27 to 9.31 ± 1.52 g/dL 5. Anemia status (a) MNP + Iron Increased from 36.84% to 55.52% (b) MNP Increased from 35.66% to 62.63%	Low

Table 2. General characteristics of studies (cont.)

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Food-based intervention				
1. Roy Choudhury et al.[43] 2021	Community-based (pre-schools in villages) in India (Asia)	Three-arm, non blinded, cluster-RCT	n = 261 Healthy children of 24-48 months	1) GG: cereal/pulse– based supplementary meal containing 500 kcal and 12–15 g protein + 25 gram of Guava (vitamin-C rich fruit) 2) BG: cereal/pulse– based supplementary meal containing 500 kcal and 12–15 g protein + 25 gram Banana (low vitamin C fruit) Duration: 140 days; Frequency: 6 days per week

Control	Main Outcomes	Main Findings	Risk of bias
CG: cereal/pulse– based supplementary meal containing 500 kcal and 12–15 g protein + 25 g Cucumber	Outcomes: Iron status (Hb, serum ferritin, sTfR) and cognitive development Hb measurement: Non rapid (cyanmethemoglobin31 methods)	1. A cereal/pulse-based meal with guava increased vitamin C content, thereby reducing Iron Deficiency (higher Hb, serum ferritin, vitamin C, and lower sTfR) and Acute Respiratory Infection-related morbidity. 2. Hb concentration (a) GG - Baseline: 10.0 ± 0.16 g/dL - Endline: 10.3 ± 0.20 g/dL - Mean change: 0.3 ± 0.11 (b) BG - Baseline: 10.4 ± 0.16 g/dL - Endline: 9.9 ± 0.20 g/dL - Mean change: -0.6 ± 0.11 (c) CG - Baseline: 10.3 ± 0.16 g/dL - Endline:10.0 ± 0.21 g/dL - Mean change: -0.4 ± 0.11	Medium

ies); (2) medium risk of bias (the RCT article had 7-9 "Yes" answers or 5-6 in quasi-experimental studies); (3) high risk of bias (the RCT article had 0-6 "Yes" answers or 0-4 in quasi-experimental studies).

RESULTS

Characteristics of studies

This study retrieved 3961, with 859 from PubMed, 849 from Web of Science, 1530 from Scopus, and 723 from Cochrane Library. After deletion of the duplicates in EndNote, 2302 articles were screened by title and abstract, which resulted in 183 articles screened for full-text review. The 156 articles were assessed according to the inclusion and exclusion criteria. Finally, 17 studies were eligible for inclusion in this review. A detailed description of the selected articles is reported in Table 2.

All studies included were conducted across low- and middle-income countries. Three studies were conducted in India, two in Ghana, and one study each in Gambia, Thailand, Uganda, Malawi, Bangladesh, Tanzania, Republic of Congo, Palestine, Mexico, Brazil, Mali, and Guinea-Bissau. This systematic review included sixteen RCTs and one quasi-experimental study. A total of six studies had pregnant women as their subjects, nine had children under five as their subjects, and two observed pregnant women and continued to track their children until they reached the age of 6-18 months as its subject.[27-43]

Three types of interventions were identified based on the approaches: supplementation intervention in eleven studies, fortification intervention in five studies, and food-based intervention in one study. Meanwhile, no experimental research was found that discussed preventive interventions for anemia using screening. The quality assessment of the articles using JBI critical appraisal tools (Table 3) revealed that seven studies had a low risk of bias and ten had a medium risk of bias.[27-43]

Outcomes measurement

Among all seventeen studies, there were various identified outcomes. Identified biochemical markers of iron status outcomes include Hb level, serum ferritin level, serum transferrin level, and soluble transferrin receptor level. Other observed outcomes were the prevalence of anemia and compliance with the intervention.[27-30,33,36,38,39]

Supplementation intervention

A total of eleven studies examined the effect of supplementation intervention. The types of supplementations provided for pregnant women include IFA, MMN and LNS. The iron in these supplements comes in several forms, including ferrous sulfate, ferrous fumarate, and ferrous bisglycinate.

Srivastava et al. conducted a study comparing the effects of an IFA fumarate capsule and an IFA sulfate tablet, both containing 100 mg elemental iron and 500 µg folic acid. Pregnant women receiving daily IFA fumarate capsules for three months had a greater change in Hb than those who received IFA sulfate tablets (0.79 vs 0.44 mg/dL, respectively) (Figure 2). The proportion of women with good compliance (>90%) at the end of 3 months was 16.8% in the IFA sulfate group and 22.0% in the IFA fumarate group.[33]

A study by Byamugisha et al. compared IFA with two types of packaging: blister and loose. The proportion of women with 100% adherence was higher in the blister package group compared with the loose package group. After two months, pregnant women who received daily IFA in blister packaging showed a higher change in Hb than those who received IFA in loose packaging (0.6 vs 0.2 g/dL, respectively) (Figure 2).[30]

Matias et al. compared the effect of daily LNS-PL containing 20 mg of iron to daily IFA containing 60 mg of iron and 400 µg of folic acid in pregnant women. Both groups had a decrease in Hb, but the decrease was smaller in pregnant women who received IFA.[32] A study by Jorgensen et al. compared the effects of MMN, LNS, and IFA on Hb levels in pregnant women. IFA contained 60 mg of elemental iron and folic acid, while MMN and LNS contained 20 mg of elemental iron and 17 other micronutrients. The results showed that after 5 months of intervention, the groups receiving MMN and LNS had a decrease in Hb, while the group given IFA had a slight increase in Hb (0.14 g/dL) (Figure 2).[31]

A study by Bumrungpert et al. compared iron supplementation in the form of ferrous fumarate (containing 66 mg elemental iron and multivitamin) vs ferrous bisglycinate (containing 24 mg elemental iron with folinic acid and multivitamins) for pregnant women. After 6 months of intervention, the ferrous bisglycinate group showed a higher change in Hb compared with the ferrous fumarate group (2.78 vs 1.92 g/dL) (Figure 2).[29]

Bah et al. conducted experimental research on pregnant women aged 14-22 weeks. The intervention involved administering multiple micronutrient capsules daily for 12 weeks, provided in three ways: (1) according to WHO standards (60 mg ferrous fumarate); (2) using a 60 mg iron hepcidin-guided screen-and-treat approach; and (3) using a 30 mg iron hepcidin-guided screen-and-treat approach. The results showed that after 12 weeks of intervention, a reduction in anemia prevalence occurred only in the group receiving the WHO standard intervention (from 58% to 45%). Additionally, a decrease in the prevalence of IDA was observed in the WHO standard intervention group (from 39% to 17%) and in the 60 mg iron screen-and-treat approach group (from 40% to 29%).[27]

The study of Adu-Afarwuah et al. compared Hb and iron status of children born to women enrolled in the International Lipid-based Nutrient Supplements (iLiNS) Project. Supplementation provided to pregnant women was IFA, MMN, or SQ LNS during pregnancy until six months postpartum. From 6-18 months of age, infants born to women in the IFA and MMN groups didn't receive any micronutrient supplementation. Meanwhile, women in the LNS group were asked to consume SQ LNS designed for infants. At 6 and 18 months of age, the Hb concentration of infants was measured. The results showed that in the IFA group, the Hb concentration decreased from 11.4 g/dL at six months of age to 11.2 g/dL at 18 months of age. In the LNS group, the Hb concentration also decreased from 11.4 g/dL at 6 months of age to 11.3 at 18 months of age. While in the MMN group, the

Table 3. Critical appraisal summary using the JBI approach

	Bah et al.[27]	Bumrungpert et al.[29]	Byamugisha et al.[30]	Jorgensen et al.[31]	Matias et al.[32]	Srivastava et al.[33]	Wang et al.[34]	Adu-Afarwuah et al.[35]	Albelbeisi et al.[36]
Was true randomization used for assignment of participants to treatment groups?	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was allocation to treatment groups concealed?	✓	?	✓	✓	✓	✓	✓	✓	✓
Were treatment groups similar at the baseline?	✓	✓	✓	X	✓	✓	✓	✓	✓
Were participants blind to treatment assignment?	✓	✓	X	X	X	?	✓	X	X
Were those delivering treatment blind to treatment assignment?	✓	?	?	X	?	?	✓	X	?
Were outcomes assessors blind to treatment assignment?	X	✓	?	✓	✓	?	✓	X	?
Were treatment groups treated identically other than the intervention of interest?	X	✓	?	✓	✓	?	✓	X	✓
Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	✓	X	✓	✓	✓	✓	?	✓	✓

	Roberts et al.[37]	Black et al.[38]	Garcia-Guerra et al.[39]	Machado et al.[40]	Somasse et al.[41]	Tchumet al.[42]	Roy Choudhury et al.[43]	Addo et al.[28†]
Was true randomization used for assignment of participants to treatment groups?	✓	✓	?	✓	✓	✓	✓	
Was allocation to treatment groups concealed?	✓	✓	X	X	X	✓	X	
Were treatment groups similar at the baseline?	✓	✓	✓	✓	✓	✓	✓	✓
Were participants blind to treatment assignment?	✓	✓	X	X	X	✓	X	
Were those delivering treatment blind to treatment assignment?	✓	✓	X	X	X	✓	X	
Were outcomes assessors blind to treatment assignment?	✓	?	✓	✓	X	?	✓	
Were treatment groups treated identically other than the intervention of interest?	✓	✓	✓	✓	X	✓	✓	
Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	X	✓	?	✓	✓	✓	?	?

†Quasi-Experimental Studies; ‡Critical Appraisal Using JBI for Quasi-Experimental Studies.

Table 3. Critical appraisal summary using the JBI approach (cont.)

	Bah et al.[27]	Bumrungpert et al.[29]	Byamugisha et al.[30]	Jorgensen et al.[31]	Matias et al.[32]	Srivastava et al.[33]	Wang et al.[34]	Adu-Afarwuah et al.[35]	Albelbeisi et al.[36]
Were participants analyzed in the groups to which they were randomized?	X	✓	✓	X	✓	?	✓	✓	✓
Were outcomes measured in the same way for treatment groups?	✓	✓	✓	✓	✓	?	✓	✓	✓
Were outcomes measured in a reliable way?	?	?	✓	✓	✓	✓	✓	✓	✓
Was appropriate statistical analysis used?	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	?	✓	✓	✓	✓	✓	?	✓	✓
Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?‡									
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?‡									

	Roberts et al.[37]	Black et al.[38]	Garcia-Guerra et al.[39]	Machado et al.[40]	Somasse et al.[41]	Tchumet al.[42]	Roy Choudhury et al.[43]	Addo et al.[28†]
Were participants analyzed in the groups to which they were randomized?	✓	✓	✓	✓	✓	✓	✓	
Were outcomes measured in the same way for treatment groups?	✓	✓	✓	✓	✓	✓	✓	✓
Were outcomes measured in a reliable way?	✓	✓	✓	✓	✓	✓	✓	✓
Was appropriate statistical analysis used?	✓	✓	✓	✓	✓	✓	✓	✓
Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	✓	✓	✓	✓	✓	✓	✓	
Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?‡								✓
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?‡								✓

†Quasi-Experimental Studies; ‡Critical Appraisal Using JBI for Quasi-Experimental Studies.

Table 3. Critical appraisal summary using the JBI approach (cont.)

	Bah et al.[27]	Bumrungpert et al.[29]	Byamugisha et al.[30]	Jorgensen et al.[31]	Matias et al.[32]	Srivastava et al.[33]	Wang et al.[34]	Adu-Afarwuah et al.[35]	Albelbeisi et al.[36]
Was there a control group?‡									
Were there multiple measurements of the outcome both pre and post the intervention/exposure?‡									

	Roberts et al.[37]	Black et al.[38]	Garcia-Guerra et al.[39]	Machado et al.[40]	Somasse et al.[41]	Tchumet al.[42]	Roy Choudhury et al.[43]	Addo et al.[28†]
Was there a control group?‡								✓
Were there multiple measurements of the outcome both pre and post the intervention/exposure?‡								✓

†Quasi-Experimental Studies; ‡Critical Appraisal Using JBI for Quasi-Experimental Studies.

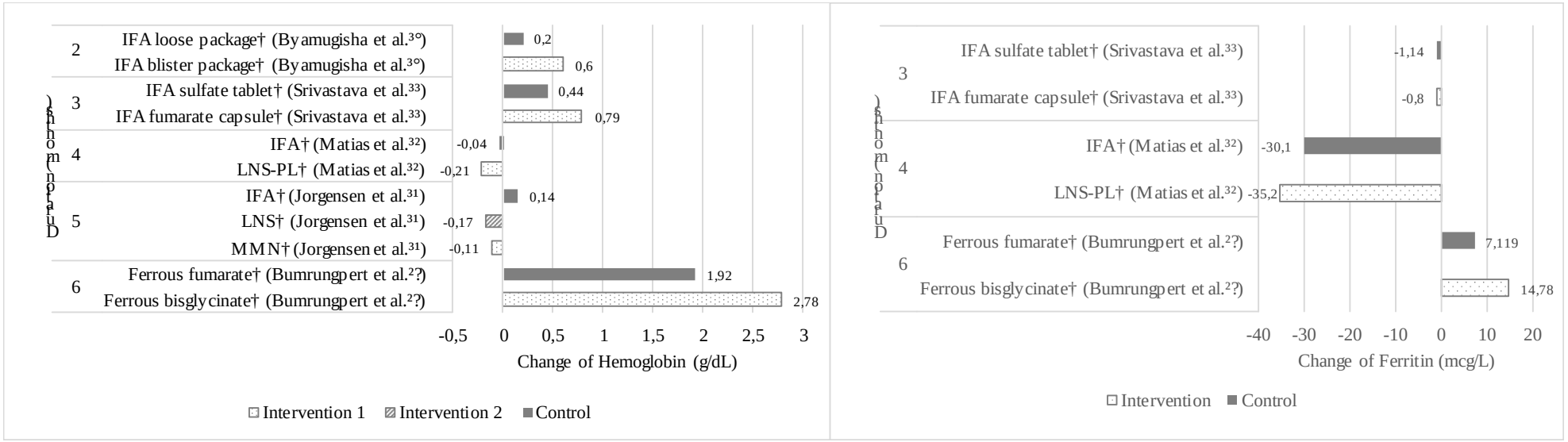


Figure 2. Change of hemoglobin and ferritin in pregnant women. †supplementation

Hb concentration remained at 11.2 g/dL at both 6 and 18 months of age. Meanwhile, at 6 to 18 months of age, the IFA, MMN, and LNS groups showed an increase in anemia prevalence of 10.5%, 7.1%, and 5.2%, respectively. In the IDA indicator, the IFA and MMN groups showed an increase in IDA prevalence of 5.4% and 1.8%, respectively, while the LNS group showed a decrease of 1.6%.[35]

A similar study was conducted by Wang et al. This study provided MMS as an intervention or placebo as a control to pregnant women from 12-27 weeks of gestation until 6 weeks postpartum. At 6 weeks to 18 months postpartum, participants were randomized again to receive MMS or placebo. From birth to less than 18 months of age, the Hb concentration of the children was measured. Prenatal led to a decrease in Hb at 6 months but a slight increase by 12 months. Meanwhile, postnatal MMS resulted in a slightly greater increase in Hb at 12 months compared to prenatal MMS.[34]

Several studies gave standard NMS combined with MNP or SQ LNS for children in the intervention group.[28,36] Some studies also used supplementation as an intervention in the control groups. The types used include NMS only, multi-micronutrient syrup, and IFA supplementation.[28,36,39,40]

Addo et al. compared the use of SQ LNS with IFA in children aged 6–12 months. The control group received standard care, including IFA supplementation, antimalarial medication, and counseling, while the intervention group received an enhanced program with three additional components: daily SQ LNS, a nutrition education campaign, and reinforcement of the community health worker's role. After ≥3 months, results showed a decrease in Hb and an increase in the prevalence of anemia in both groups. However, there was an increase in ferritin levels and a decrease in the prevalence of iron deficiency (serum ferritin ≤12 µg/L) in both groups after the intervention.[28]

The study by Albelbeisi et al. compared the effectiveness of MNP + NMS with NMS only in 6-month-old children. The NMS was a component of the national nutrition supplementation program in the Gaza Strip and included 2 mg/kg/day of iron sulfate administered as 2 drops annually for children aged 6 months and older. The program also provided one capsule containing 200-600 µg of vitamin A every 6 months, and two drops of 10 µg of vitamin D daily for 30 days every 3 months for children aged 9 months and older. In contrast, the MNP was a multi-micronutrient powder containing 400 µg of vitamin A, 30 mg of vitamin C, 5 µg of vitamin D, 90 µg of folic acid, 10 mg of iron, and other micronutrients including vitamin B1, B2, B6, B12, vitamin E, niacin, zinc, copper, selenium, and iodine. The intervention group received 3 sachets of MNP every week for 12 months. Results showed that both groups experienced a decrease in average Hb levels at the end of the study. However, the decrease was smaller in the MNP + NMS group compared to the NMS-only group (Figure 3). The MNP + NMS group was able to maintain its average Hb level within normal limits (11.92 g/dL), whereas the NMS-only group observed a drop in Hb below normal (10.92 g/dL) (Figure 3).[36]

Fortification intervention

A total of five studies examined the effects of fortification intervention on children. Studies by Black et al., Garcia-Guerra et al., Machado et al., and Somassè et al. showed Hb gain in groups with MNP intervention.[38-41] These studies also reported a decrease in the prevalence of anemia in the groups that used MNP as an intervention. Meanwhile, a study of Tchum et al. showed that MNP intervention using either iron or no iron reduce Hb concentration. However, the reduction in the iron group was slightly lower than in the non-iron group. [42]

The highest increase in Hb was observed in the study by Black et al. which reported a 1.2 g/dL increase within eight months following MNP intervention containing iron (encapsulated ferrous fumarate), zinc, folic acid, vitamin A, vitamin C, vitamin B12, and riboflavin (Figure 3).[38] The study by Black et al. also found that the MNP intervention resulted in the greatest reduction in anemia prevalence, with a decrease of 36% (Figure 4).[38] In the study by Machado et al. the MNP intervention, which contained retinol acetate, cholecalciferol, alpha-tocopherol acetate, ascorbic acid, thiamine nitrate, riboflavin, pyridoxine hydrochloride, niacinamide, cyanocobalamin, folic acid, encapsulated ferrous fumarate, zinc gluconate, copper gluconate, sodium selenite, and potassium iodide, showed a considerable increase in Hb of 0.86 g/dL within four months.[40] Further, studies by Garcia-Guerra et al., Machado et al., and Black et al. revealed success in achieving normal Hb levels (reference value = 11 g/dL) at the end of the study with interventions using MNP, micronutrient syrup, ferrous sulfate folic acid, and placebo riboflavin.[38-40] The highest Hb value was found in the fortification using ferrous sulfate folic acid in the study of Machado et al.[40] (Figure 3).

Furthermore, regarding ferritin values as an indicator of IDA, studies by Garcia-Guerra et al., Machado et al., Tchum et al., and Black et al. showed an increase in ferritin levels in groups with MNP intervention (Figure 3).[38-40,42] Furthermore, the greatest change in ferritin was observed with MNP fortification in the study by Tchum et al., reaching 102.75 µg/L.[42]

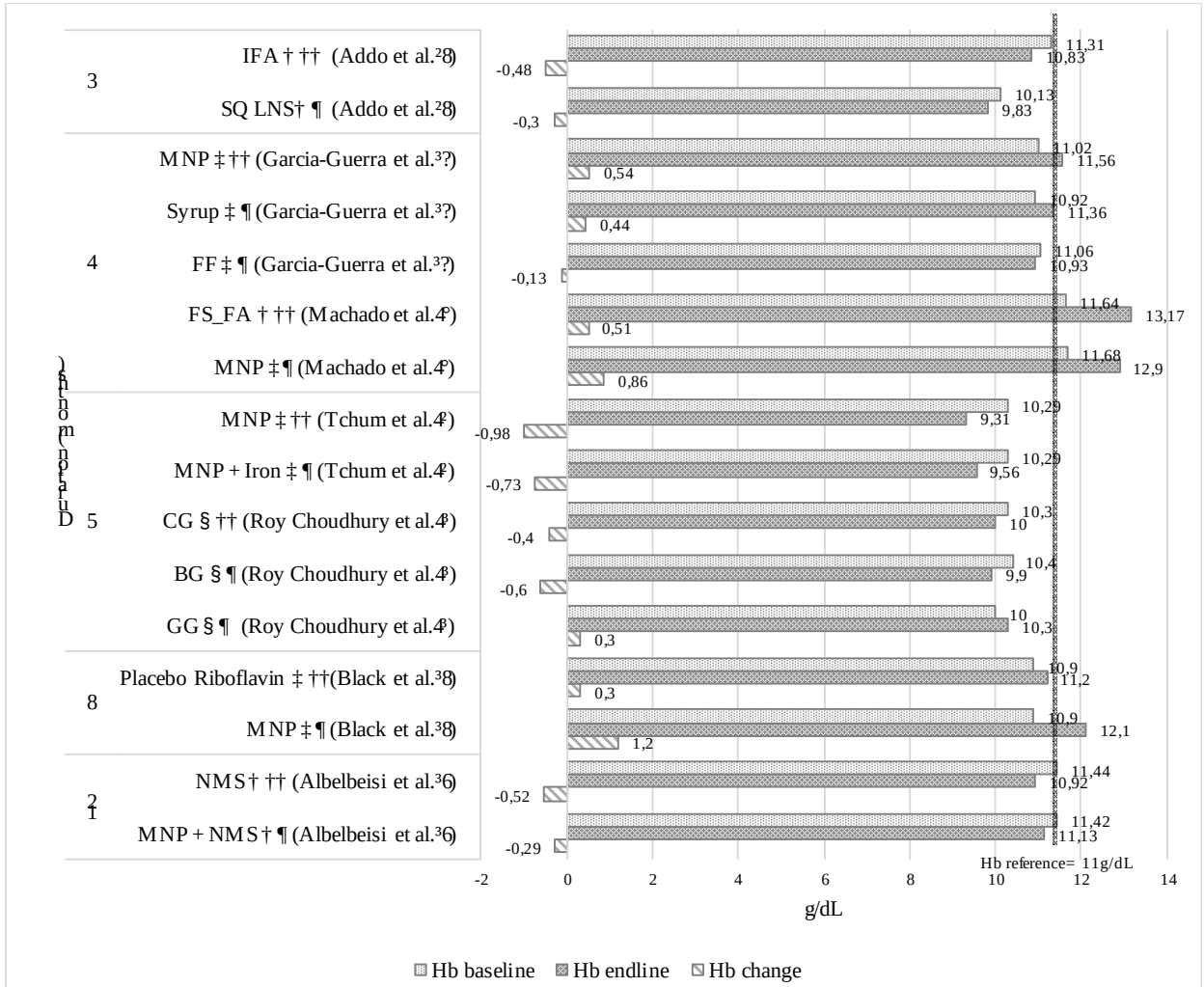
Food-based intervention

One study examined the effect of food-based intervention. The intervention provided included vitamin C-rich fruit along with a cereal and pulse-based Supplementary Nutrition Program (SNP) meal. Roy Choudhury, et al.[43] showed that a cereal and pulse-based SNP meal with guava increased Hb levels and serum ferritin after 140 days of intervention.

DISCUSSION

The WHO suggests that there are effective interventions to prevent and treat IDA. These interventions focus on addressing causal and risk factors by increasing consumption of specific micronutrients such as iron, folate, vitamin B12, vitamin A, and riboflavin as well as other micronutrients that can be obtained from food diversification, fortification, and supplementation.[2]

The studies reviewed used three types of iron: ferrous sulfate, ferrous fumarate, and ferrous bis-glycinate. Among these, ferrous bis-glycinate is noted for its high



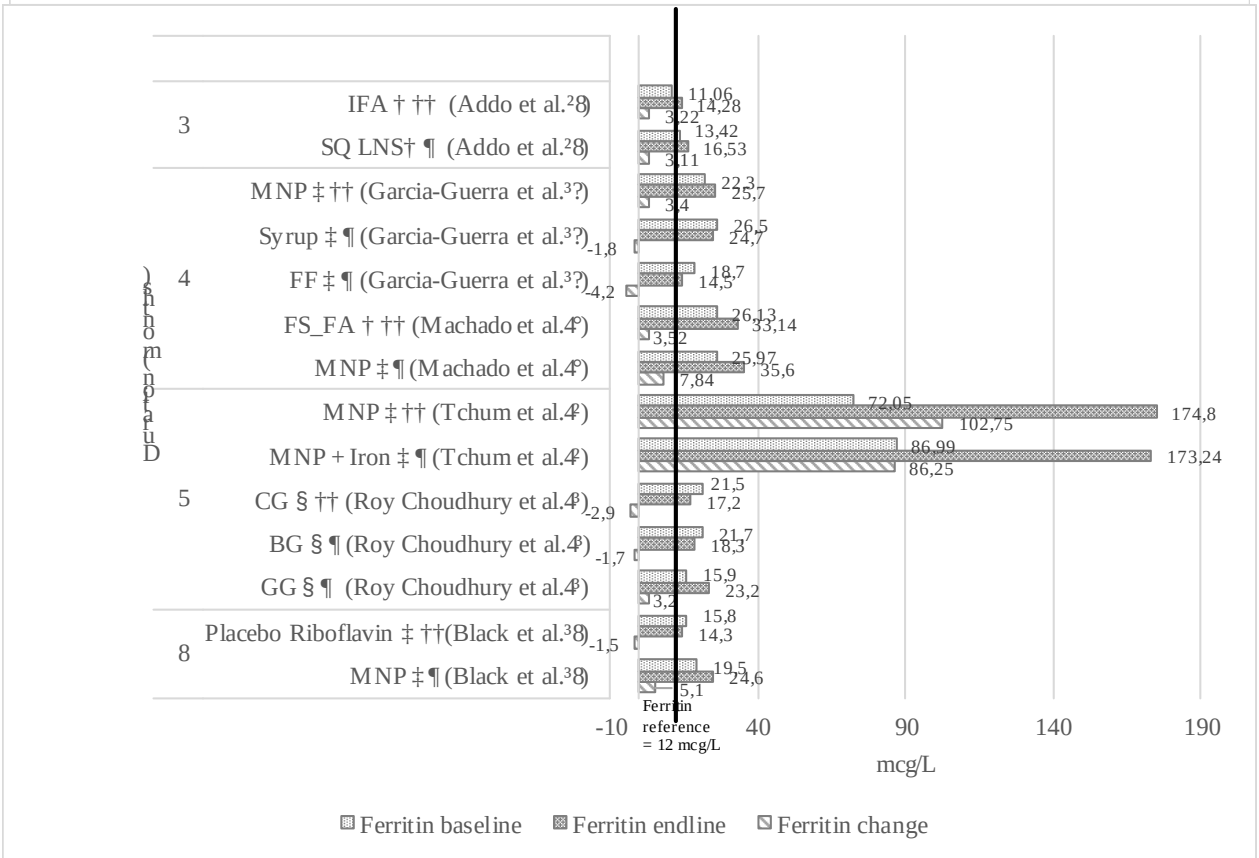


Figure 3. Change of hemoglobin and ferritin in children.
†supplementation; ‡fortification; §food-based; ¶intervention; ††control

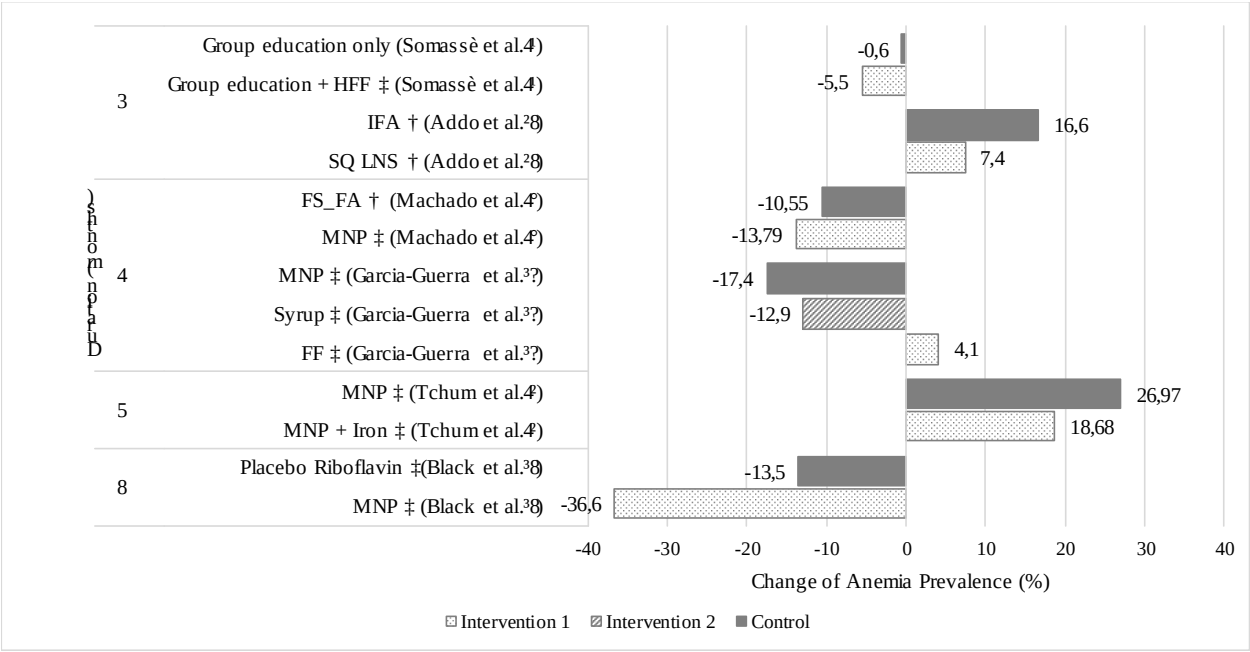


Figure 4. Change of anemia prevalence in children. †supplementation; ‡fortification

efficacy.[29] Ferrous bis-glycinate has lower gastrointestinal side effects and higher bioavailability compared to conventional iron salts like ferrous sulfate and ferrous fumarate. Additionally, its absorption is not affected by phytate.[44,45] However, ferrous bisglycinate is the most expensive type of iron salt when compared to ferrous fumarate.[44]

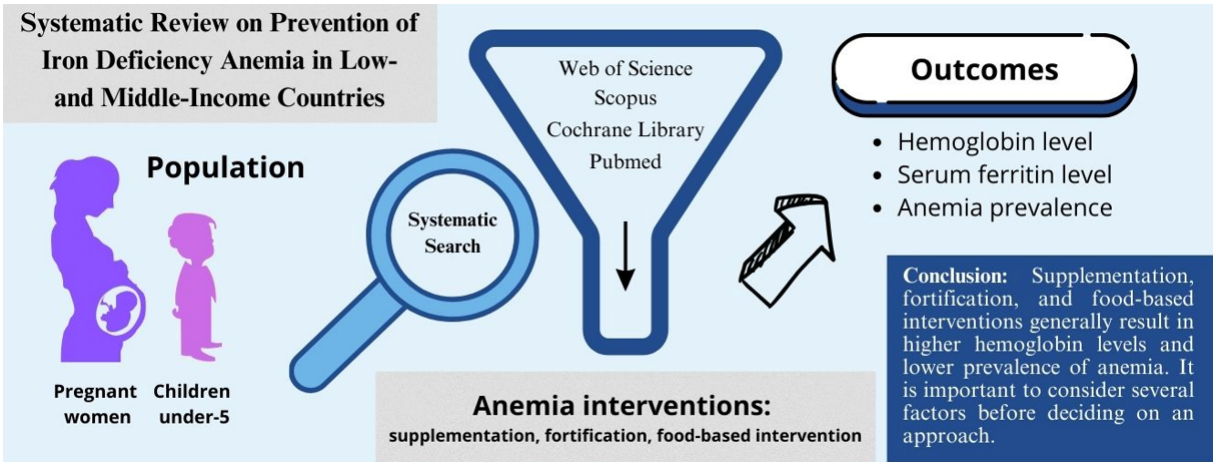
Ferrous fumarate is the most cost-effective type of iron salt. It has equivalent efficacy to ferrous bisglycinate in increasing Hb levels and is known to produce a more significant increase in ferritin. However, side effects are more common with ferrous fumarate, which should be considered when using it as an anemia-prevention intervention for pregnant women and children.[44]

The studies reviewed used different doses. All intervention groups that used standard IFA showed better outcomes than the comparison groups. In research conducted by Bumrungpert and colleagues in 2022, the intervention group received ferrous bisglycinate with 24 mg of iron, while the control group received ferrous fumarate with 66 mg of iron. Contrary to expectations, the group receiving the lower dose of ferrous bisglycinate showed an increase in Hb.[29] This may be attributed to the advantages of ferrous bisglycinate, as previously explained.

In children, the dose of iron given depended on the child's age. In this review, the doses used vary but remain within the recommended range for both iron supplementation and fortification in MNP. Another study also demonstrated that fortification with 10 mg of iron in MNP significantly improved Hb values and reduced the prevalence of anemia.[46]

However, in this systematic review, only some interventions were effective in raising Hb levels or decreasing the prevalence of anemia. Based on these results, it is crucial to consider several factors to determine the most effective intervention for addressing IDA.

First, the presence of substances that inhibit or enhance iron absorption in the supplementation or fortification composition should be considered. Most multivitamin formulations contain insufficient iron to treat anemia and may include other minerals that inhibit iron absorption.[47] Most studies involving children provide MNP with added



Graphical abstract.

zinc for growth-related benefits. However, iron and zinc have antagonistic interactions; zinc competes with iron for the same receptor sites on intestinal mucosal cells, potentially inhibiting iron absorption.[48] Additionally, calcium can also interfere with iron absorption by regulating enterocyte iron transporter proteins, which further reduces iron bioavailability.[18]

On the other hand, there are iron absorption enhancers such as vitamin C and protein.[18] Some studies in this review used multi-micronutrient supplements or powders containing around 30-50 mg of vitamin C. Ascorbic acid, or vitamin C, is known to increase the absorption of iron, particularly non-heme iron, and enhance the mobilization of iron from storage.[17,49] Vitamin C can create a more acidic environment in the stomach and prevent oxidation of ferrous iron to ferric iron.[50,51] A study by Lauryn et al. showed a greater increase in Hb levels in women who received 65 mg of iron along with 75 mg of vitamin C compared to those who received iron alone.[52]

Second, compliance is crucial for the effectiveness of the provided intervention. Compliance rates in the articles reviewed ranged from 16.8% to 97%.[27-30,33,38] Adherence to the given intervention is influenced by various factors, including side effects, forgetfulness, boredom, an education level, socioeconomic status, ethnicity, occupation, parity, improper storage, low motivation and lack of awareness, dietary habits, and improper method of taking supplements.[20,30,53-56] The side effects of taking iron supplements often manifest as gastrointestinal disorders, which typically occur when the dose of ferrous iron reaches 180-200 mg per day.[45] Therefore, the iron dose should be reduced if gastrointestinal disorders occur.[20]

Third, educational interventions contribute significantly to the effectiveness of intervention programs. The study by Somassè et al. showed that HFF combined with group education led to increased Hb levels and reduced anemia prevalence.[41] This finding aligns with the study of Beinner and Lamounier, which indicated that education led to behavior change and greater awareness of the importance of combating iron-deficiency anemia.[57] Their study also showed that iron fortification of drinking water, combined with education, improved Hb concentrations and reduced the prevalence of iron deficiency and anemia. Besides fortification, education is also known to affect the effectiveness of supplementation programs. Shet et al. stated that children receiving supplements along with parental education or counseling from health workers showed an increase in Hb levels and better adherence to supplement consumption compared to the group that only received standard care.[58] This suggests that maternal or caregiver education and counseling can enhance awareness of a child's anemia, thereby optimizing adherence to and effectiveness of iron treatment for anemia.[59]

Fourth, the dietary background of the population plays a crucial role. Dietary patterns are a significant factor in the etiology of IDA. Therefore, interventions to address anemia should consider the dietary background of the target group. None of the 17 articles reviewed specifically examined the subjects' dietary background during the intervention, though some studies noted the potential role of diet in the success of the intervention. For example, Albelbeisi et al. found a decrease in Hb after a 12-month intervention with ferrous fumarate fortification in MNP + NMS.[36] The study explained that infants and children are often introduced to cereal and plant-based fortified foods, which are typically low in energy and may lack micronutrients with high bioavailability due to the presence of phytates.[36]

The WHO recommends fortifying maize flour, cornmeal, wheat flour, and rice with vitamins and minerals such as iodine, iron, vitamin A, and folic acid.[60] Additionally, milk and its products can be used as a food vehicle for iron fortification to help combat anemia. A review study by Vohra et al. found that iron fortification in milk and milk products can improve iron status in all ages.[61] This will help in reducing the prevalence of anemia. Sazawal et al. provided milk fortified with zinc, iron, selenium, copper, vitamin A, vitamin C, and vitamin E to children 1-4 years old. After 1 year of intervention, the result showed that children who received the fortified milk had an 88% lower risk of IDA.[62] El Menchawy et al. studied schoolchildren by providing iron fortified milk.[63] This intervention resulted in a 27% reduction in iron deficiency prevalence. However, the number of studies examining iron-fortified milk has been limited in the past five years, so none were included in this review. Therefore, to review the effectiveness of iron-fortified milk in preventing anemia, it is recommended to extend the range of publication years in the inclusion criteria for future studies.

Finally, it is essential to consider community iron consumption patterns before implementing supplementation or fortification. Public consumption surveys often focus on macronutrients rather than micronutrients, so data on IDA are often based on assumptions. Currently, community-level data on iron consumption are limited and are typically gathered by university researchers. For example, systematic review by Helmyati et al. showed that the coverage of the IFA supplementation program in five provinces in Indonesia was still below 50%, with acceptance rates ranging from 0% to 25.2% according to the standard.[64] This situation is one of the reasons why anemia is still a problem in Indonesia. Therefore, in 2023, the Indonesian government introduced anemia screening regulations as part of primary health care services for adolescent girls aged 12 to 15 who have not been screened, as well as for brides-to-be.[65]

Anemia screening is essential for both children and pregnant women. For pregnant women, early identification of iron deficiency before anemia develops is crucial to correct the condition promptly and prevent potential long-term effects on fetal development.[66] Since the majority of anemia cases are attributable to iron deficiency, screening for IDA in children should be considered. Nowadays, several non-invasive and easy-to-use instruments for anemia screening have been developed.[59,67]

Unfortunately, in certain areas, there is insufficient evidence on the benefits and harms of universal routine screening for both children and pregnant women.[68] This has led to varying recommendations regarding anemia screening, as anemia may not be a public health issue in certain areas worldwide. Organizations such as the PrevInfad workgroup, the United Kingdom National Screen-

ing Committee, and the United States Preventive Services Task Force do not recommend universal screening. Instead, PrevInfad and the United States Preventive Services Task Force advocate for targeted screening in specific high-risk populations, such as children born prematurely, those with low birth weight, individuals living in low- and middle-income countries with poor sanitation facilities, and those with risky consumption patterns.[69]

Anemia screening aims to determine IDA status, which can be measured using indicators such as Hb, mean corpuscular volume (MCV), mean corpuscular Hb (MCH), and mean corpuscular Hb concentration (MCHC). While Hb indicators can assess IDA status in high-prevalence populations, Hb alone is not a specific biomarker due to its sensitivity to vitamin B12 or folic acid deficiencies, genetic disorders, and other chronic diseases. Therefore, Hb measurements should be combined with other biomarkers for greater specificity. Serum transferrin receptor and serum ferritin together represent about 85% of the body's iron, so combining Hb and serum ferritin measurements can enhance both sensitivity and specificity in assessing iron deficiency severity.[70]

The strengths of this systematic review include a comprehensive search strategy, adherence to PRISMA guidelines for reporting, and the use of JBI as a critical appraisal tool. Another key strength is the inclusion of two crucial at-risk groups: pregnant women and children. The review effectively captures a broad range of outcomes, including Hb levels, anemia prevalence, serum ferritin levels, and birth outcomes in interventions for pregnant women.

Conclusions

This review discusses three types of interventions for preventing anemia: supplementation, fortification, and food-based approaches. These generally increase hemoglobin (Hb) levels and reduce anemia prevalence. However, determining the appropriate intervention involves more than just considering the type of iron and the dose used. This review suggests that the effectiveness of intervention programs can be enhanced by incorporating iron absorption enhancers, such as animal protein and vitamin C, and by ensuring better compliance, appropriate dietary considerations, and educational interventions. Future studies should consider these factors to optimize Hb improvement.

The findings of this review must be interpreted carefully due to several limitations. The review is limited to English-language studies, which may exclude potentially relevant research published in other languages. Additionally, the heterogeneity of interventions and outcome measurements prevented meta-analyses, resulting in all studies being given equal weight in the narrative synthesis. Limitations in the research area include limited data on food-based interventions and the role of screening in preventing anemia. Most studies on anemia screening were cross-sectional and did not meet the inclusion criteria. Furthermore, not all studies reported the dietary background of the population, leaving the impact of diet on intervention effectiveness unclear.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors report no conflict of interest.

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REFERENCES

1. World Health Organization. The global prevalence of anaemia in 2011. Geneva: World Health Organization; 2015.
2. World Health Organization. Accelerating anaemia reduction: a comprehensive framework for action. Geneva: World Health Organization; 2023.
3. Di Renzo GC, Spano F, Giardina I, Brillo E, Clerici G, Roura LC. Iron deficiency anemia in pregnancy. Womens Health. 2015;11:891-900. doi:10.2217/whe.15.35.
4. World Health Organization. Global nutrition targets 2025: anaemia policy brief. Report No. WHO/NMH/NHD/14.4, 8. Geneva: World Health Organization; 2014.
5. World Health Organization. Anaemia in women and children. WHO Global Anaemia estimates, 2021 Edition. 2021. [cited 2023/12/17]; Available from: https://www.who.int/data/gho/data/themes/topics/anaemia_in_women_and_children.
6. Marcus H, Schauer C, Zlotkin S. Effect of Anemia on Work Productivity in Both Labor- and Nonlabor-Intensive Occupations: A Systematic Narrative Synthesis. Food Nutr Bull. 2021;42:289-308. doi:10.1177/03795721211006658.
7. McCann S, Perapoch AM, Moore SE. The Role of Iron in Brain Development: A Systematic Review. Nutrients. 2020;12. doi:10.3390/nu12072001.
8. GBD 2021 Anaemia Collaborators. Prevalence, years lived with disability, and trends in anaemia burden by severity and cause, 1990-2021: findings from the Global Burden of Disease Study 2021. The Lancet. Haematology. 2023;10:e713-e734. doi:10.1016/s2352-3026(23)00160-6.
9. World Health Organization. Sixty-fifth World Health Assembly. Report No. WHA65/2012/REC/1. Geneva: World Health Organization; 2012.
10. Shekar M, Kakietek J, Eberwein JD, Walters D. An Investment Framework for Nutrition: Reaching the Global Targets for Stunting, Anemia, Breastfeeding, and Wasting. Washington DC: The World Bank; 2017.
11. World Health Organization. Anaemia. 2023/5/1 [cited 2023/12/17]; Available from: https://www.who.int/news-room/fact-sheets/detail/anaemia#:~:text=Treatment%20and%20prevention&text=Changes%20in%20diet%20can%20help,health%2Dcare%20provider%20recommends%20them.
12. Mwangi MN, Prentice AM, Verhoef H. Safety and benefits of antenatal oral iron supplementation in low-income countries: a review. Br J Haematol. 2017;177:884-95. doi:10.1111/bjh.14584.
13. Haider BA, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. Cochrane Database Syst Rev. 2017;4:CD004905. doi:10.1002/14651858.CD004905.pub5.
14. Man Y, Xu T, Adhikari B, Zhou C, Wang Y, Wang B. Iron supplementation and iron-fortified foods: a review. Crit Rev Food Sci Nutr. 2022;62:4504-25. doi:10.1080/10408398.2021.1876623.
15. Paganini D, Zimmermann MB. The effects of iron fortification and supplementation on the gut microbiome and diarrhea in infants and children: a review. Am J Clin Nutr. 2017; 106: 1688S-93S. doi:10.3945/ajcn.117.156067.

16. Lonnerdal B. Excess iron intake as a factor in growth, infections, and development of infants and young children. Am J Clin Nutr. 2017;106:1681S-7S. doi:10.3945/ajcn.117.156042.
17. World Health Organization. Nutritional anaemias: tools for effective prevention and control. Geneva: World Health Organization; 2017.
18. Piskin E, Cianciosi D, Gulec S, Tomas M, Capanoglu E. Iron Absorption: Factors, Limitations, and Improvement Methods. ACS Omega. 2022;7:20441-56. doi:10.1021/acsomega.2c01833.
19. Sharifirad G, Golshiri P, Shahnazi H, Shakouri S, Hassanzadeh A. PRECEDE educational model for controlling iron-deficiency anaemia in Talesh, Iran. J Pak Med Assoc. 2011;61: 862-5.
20. Paliwahdana TS, Goonewardene IMR, Motha MBC, Williams HSA. Iron deficiency anaemia in pregnancy: diagnosis, prevention and treatment. Sri Lanka J. Obstet. Gyn. 2014;36:61-5. doi: 10.4038/sljog.v36i3.7713.
21. World Health Organization. Guideline: Daily Iron and Folic Acid Supplementation in Pregnant Women. Geneva: World Health Organization; 2012.
22. World Health Organization. Guideline Daily Iron Supplementation in infants and children. Geneva: World Health Organization; 2016.
23. World Health Organization. WHO guideline: use of multiple micronutrient powders for point-of-use fortification of foods consumed by infants and young children aged 6–23 months and children aged 2–12 years. Geneva: World Health Organization; 2016.
24. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372. doi: 10.1136/bmj.n71.
25. Barker TH, Stone JC, Sears K, Klugar M, Tufanaru C, Leonardi-Bee J, Aromataris E, Munn Z. The revised JBI critical appraisal tool for the assessment of risk of bias for randomized controlled trials. JBI evidence synthesis. 2023;21:494-506. doi:10.11124/jbies-22-00430.
26. JBI. Checklist For Quasi-Experimental Studies (Non-Randomized Experimental Studies). Critical Appraisal tools for use in JBI Systematic Reviews. 2020. [cited 2023/11/20]; Available from: https://jbi.global/critical-appraisal-tools.
27. Bah A, Muhammad AK, Wegmuller R, Verhoef H, Goheen MM, Sanyang S, et al. Hepcidin-guided screen-and-treat interventions against iron-deficiency anaemia in pregnancy: a randomised controlled trial in The Gambia. Lancet Glob Health. 2019;7:e1564-e74. doi:10.1016/S2214-109X(19)30393-6.
28. Addo OY, Locks LM, Jefferds ME, Nanama S, Albert B, Sandalinas F, et al. Combined infant and young child feeding with small-quantity lipid-based nutrient supplementation is associated with a reduction in anemia but no changes in anthropometric status of young children from Katanga Province of the Democratic Republic of Congo: a quasi-experimental effectiveness study. Am J Clin Nutr. 2020;112:683-94. doi:10.1093/ajcn/nqaa170.
29. Bumrungpert A, Pavadhgul P, Piromsawasdi T, Mozafari MR. Efficacy and Safety of Ferrous Bisglycinate and Folinic Acid in the Control of Iron Deficiency in Pregnant Women: A Randomized, Controlled Trial. Nutrients. 2022;14. doi:10.3390/nu14030452.
30. Byamugisha J, Adero N, Kiwanuka TS, Nalwadda CK, Ntuyo P, Namagembe I, et al. The effect of blister packaging Iron and Folate on adherence to medication and hemoglobin levels among pregnant women at National Referral Hospital antenatal clinics in a low to middle income country: a Randomised Controlled Trial (The IFAd Trial). BMC Pregnancy Childbirth. 2022;22:179. doi:10.1186/s12884-022-04507-3.
31. Jorgensen JM, Ashorn P, Ashorn U, Baldiviez LM, Gondwe A, Maleta K, Nkhoma M, Dewey KG. Effects of lipid-based nutrient supplements or multiple micronutrient supplements compared with iron and folic acid supplements during pregnancy on maternal haemoglobin and iron status. Matern Child Nutr. 2018;14:e12640. doi:10.1111/mcn.12640.
32. Matia,s SL, Mridha MK, Young RT, Hussain S, Dewey KG. Daily Maternal Lipid-Based Nutrient Supplementation with 20 mg Iron, Compared with Iron and Folic Acid with 60 mg Iron, Resulted in Lower Iron Status in Late Pregnancy but Not at 6 Months Postpartum in Either the Mothers or Their Infants in Bangladesh. J Nutr. 2018;148:1615-24. doi:10.1093/jn/nxy161.
33. Srivastava R, Kant S, Singh AK, Saxena R, Yadav K, Pandav CS. Effect of iron and folic acid tablet versus capsule formulation on treatment compliance and iron status among pregnant women: A randomized controlled trial. J Family Med Prim Care. 2019;8:378-84. doi:10.4103/jfmpc.jfmpc_339_18.
34. Wang D, Natchu UCM, Darling AM, Noor RA, Hertzmark E, Urassa W, Fawzi WW. Effects of prenatal and postnatal maternal multiple micronutrient supplementation on child growth and morbidity in Tanzania: a double-blind, randomized-controlled trial. Int J Epidemiol. 2022;51:1761-74. doi:10.1093/ije/dyab117.
35. Adu-Afarwuah S, Young RT, Lartey A, Okronipa H, Ashorn P, Ashorn U, Oaks BM, Arimond M, Dewey KG. Maternal and Infant Supplementation with Small-Quantity Lipid-Based Nutrient Supplements Increases Infants' Iron Status at 18 Months of Age in a Semiurban Setting in Ghana: A Secondary Outcome Analysis of the iLiNS-DYAD Randomized Controlled Trial. J Nutr. 2019;149:149-58. doi:10.1093/jn/nxy225.
36. Albelbeisi A, Shariff ZM, Mun CY, Rahman HA, Abed Y. Multiple micronutrient supplementation improves growth and reduces the risk of anemia among infants in Gaza Strip, Palestine: a prospective randomized community trial. Nutr J. 2020;19. doi:10.1186/s12937-020-00652-7.
37. Roberts SB, Franceschini MA, Silver RE, Taylor SF, de Sa AB, Có R, Sonco A, et al. Effects of food supplementation on cognitive function, cerebral blood flow, and nutritional status in young children at risk of undernutrition: randomized controlled trial. BMJ..2020;370: m2397. doi:10.1136/bmj.m2397.
38. Black MM, Fernandez-Rao S, Nair KM, Balakrishna N, Tilton N, Radhakrishna KV, et al. A Randomized Multiple Micronutrient Powder Point-of-Use Fortification Trial Implemented in Indian Preschools Increases Expressive Language and Reduces Anemia and Iron Deficiency. J Nutr. 2021;151:2029-42. doi:10.1093/jn/nxab066.
39. García-Guerra A, Rivera JA, Neufeld LM, Quezada-Sánchez AD, Dominguez Islas C, Fernández-Gaxiola AC, Bonvecchio Arenas A. Consumption of Micronutrient Powder, Syrup or Fortified Food Significantly Improves Zinc and Iron Status in Young Mexican Children: A Cluster Randomized Trial. Nutrients. 2022;14. doi:10.3390/nu14112231.
40. Machado MMA, Lopes MP, Schincaglia RM, da Costa PSS, Coelho ASG, Hadler MCCM. Effect of Fortification with Multiple Micronutrient Powder on the Prevention and Treatment of Iron Deficiency and Anaemia in Brazilian Children: A Randomized Clinical Trial. Nutrients. 2021;13. doi:10.3390/nu13072160.

41. Somassè YE, Dramaix M, Traoré B, Ngabonziza I, Touré O, Konaté M, Diallo M, Donnen P. The WHO recommendation of home fortification of foods with multiple-micronutrient powders in children under 2 years of age and its effectiveness on anaemia and weight: a pragmatic cluster-randomized controlled trial. Public Health Nutr. 2018;21:1350-8. doi:10.1017/S1368980017003858.
42. Tchum SK, Arthur FK, Adu B, Sakyi SA, Abubakar LA, Atibilla D, et al. Impact of iron fortification on anaemia and iron deficiency among pre-school children living in Rural Ghana. PLoS One. 2021;16:e0246362. doi:10.1371/journal.pone.0246362.
43. Roy Choudhury D, Nair Krishnapillai M, Nagalla B, Vijaya Kankipati R, Ghosh S, Buwade J, Fernandez-Rao S. Guava with an institutional supplementary meal improves iron status of preschoolers: a cluster-randomized controlled trial. Ann N Y Acad Sci. 2021;1492:82-95. doi:10.1111/nyas.14556.
44. Patil SS, Khanwelkar CC, Patil SK, Thorat VM, Jadhav SA, Sontakke AV. Comparison of efficacy, tolerability, and cost of newer with conventional oral iron preparation. Al Ameen J Med Sci. 2013;6:29-33.
45. Milman N, Jonsson L, Dyre P, Pedersen PL, Larsen LG. Ferrous bisglycinate 25 mg iron is as effective as ferrous sulfate 50 mg iron in the prophylaxis of iron deficiency and anemia during pregnancy in a randomized trial. J Perinat Med. 2014;42:197-206. doi:10.1515/jpm-2013-0153.
46. Arcanjo FPN, da Costa Rocha TC, Arcanjo CPC, Santos PR. Micronutrient Fortification at Child-Care Centers Reduces Anemia in Young Children. J Diet Suppl. 2019;16:689-98. doi:10.1080/19390211.2018.1474987.
47. O'Toole F, Sheane R, Reynaud N, McAuliffe FM, Walsh JM. Screening and treatment of iron deficiency anemia in pregnancy: A review and appraisal of current international guidelines. Int J Gynaecol Obstet. 2023. doi:10.1002/ijgo.15270.
48. Zlotkin S, Arthur P, Schauer C, Antwi KY, Yeung G, Piekarz A. Home-fortification with iron and zinc sprinkles or iron sprinkles alone successfully treats anemia in infants and young children. J Nutr. 2003;133:1075-80. doi:10.1093/jn/133.4.1075.
49. Fishman SM, Christian P, West KP. The role of vitamins in the prevention and control of anaemia. Public Health Nutr. 2000;3:125-50. doi:10.1017/s1368980000000173.
50. Rocha Dda S, Capanema FD, Netto MP, de Almeida CA, Franceschini Sdo C, Lamounier JA. Effectiveness of fortification of drinking water with iron and vitamin C in the reduction of anemia and improvement of nutritional status in children attending day-care centers in Belo Horizonte, Brazil. Food Nutr Bull. 2011;32:340-6. doi:10.1177/156482651103200405.
51. Li N, Zhao G, Wu W, Zhang M, Liu W, Chen Q. The Efficacy and Safety of Vitamin C for Iron Supplementation in Adult Patients With Iron Deficiency Anemia: A Randomized Clinical Trial. JAMA Netw Open. 2020;3:e2023644. doi:10.1001/jamanetworkopen.2020.23644.
52. Lauryn J, Joprang FS, Kurniadi A, Leonardo L, Rinaldi FX, Erlina E, Singgih GG. Effectivity of Iron Supplementation With and Without Vitamin C for Increasing Hemoglobin Levels Among Women Aged 16-21 Years Old. Sriwijaya J Med. 2022;5:18-24. doi:10.32539/SJM.v5i1.125.
53. Fouelifack FY, Sama JD, Sone CE. Assessment of adherence to iron supplementation among pregnant women in the Yaounde gynaeco-obstetric and paediatric hospital. Pan Afr Med J. 2019;34:211. doi:10.11604/pamj.2019.34.211.16446.
54. Triharini M, Nursalam, Sulistyono A, Adriani M, Armini NKA, Nastiti AA. Adherence to iron supplementation amongst pregnant mothers in Surabaya, Indonesia: Perceived benefits, barriers and family support. Int J Nurs Sci. 2018;5:243-8. doi:10.1016/j.ijnss.2018.07.002.
55. Siabani S, Siabani S, Siabani H, Moeini Arya M, Rezaei F, Babakhani M. Determinants of Compliance With Iron and Folate Supplementation Among Pregnant Women in West Iran: A Population Based Cross-Sectional Study. J Family Reprod Health. 2018;12:197-203.
56. Gonzalez-Casanova I, Nguyen PH, Young MF, Harding KB, Reinhart G, Nguyen H, et al. Predictors of adherence to micronutrient supplementation before and during pregnancy in Vietnam. BMC public health. 2017;17:452. doi:10.1186/s12889-017-4379-4.
57. Beinner MA, Lamounier JA. Recent experience with fortification of foods and beverages with iron for the control of iron-deficiency anemia in Brazilian children. Food Nutr Bull. 2003;24:268–74. doi:10.1177/156482650302400304.
58. Shet AS, Zwarenstein M, Rao A, Jebaraj P, Arumugam K, Atkins S, Mascarenhas M, Klar N, Galanti MR. Effect of a Community Health Worker-Delivered Parental Education and Counseling Intervention on Anemia Cure Rates in Rural Indian Children: A Pragmatic Cluster Randomized Clinical Trial. JAMA Pediatr. 2019;173:826-34. doi:10.1001/jamapediatrics.2019.2087.
59. Hsu DP, French AJ, Madson SL, Palmer JM, Gidvani-Diaz V. Evaluation of a Noninvasive Hemoglobin Measurement
60. Device to Screen for Anemia in Infancy. Matern Child Health J. 2016;20:827-32. doi:10.1007/s10995-015-1913-9.
61. World Health Organization. Food Fortification. 2021/9/13 [cited 2024/1/24]; Available from: https://www.who.int/health-topics/food-fortification#tab=tab_1.
62. Vohra K, Mittal M, Verma A, Keshri A, Dhasmana A, Khandelwal R, et al. Effect of Iron Fortified Milk and Milk Products on Anemia Status among the Population – A Review. Indian J Nutr. 2021;8:226.
63. Sazawal S, Dhingra U, Dhingra P, Hiremath G, Sarkar A, Dutta A, Menon VP, Black RE. Micronutrient fortified milk improves iron status, anemia and growth among children 1-4 years: a double masked, randomized, controlled trial. PLoS One. 2010;5:e12167.
64. El Menchawy I, El Hamdouchi A, El Kari K, Saeid N, Zahrou FE, Benajiba N, El Harchaoui I, El Mzibri M, El Haloui N, Aguenaou H. Efficacy of Multiple Micronutrients Fortified Milk Consumption on Iron Nutritional Status in Moroccan Schoolchildren. Journal of nutrition and metabolism 2015;2015:690954. doi:10.1155/2015/690954.
65. Helmyati S, Syarifa CA, Rizana NA, Sitorus NL, Pratiwi D. Acceptance of Iron Supplementation Program among Adolescent Girls in Indonesia: A Literature Review: Penerimaan Program Tablet Tambah Darah pada Remaja Putri di Indonesia: Studi Literatur. Amerta Nutrition. 2024;7:50-61. doi:10.20473/amnt.v7i3SP.2023.50-61.
66. Decree of the Minister of Health of the Republic of Indonesia Number HK.01.07/MENKES/2015/2023 concerning Technical Instructions for the Integration of Primary Health Services, Stat. HK.01.07/MENKES/2015/2023.
67. Mintopoulos V, Tannenbaum E, Malinowski AK, Shehata N, Walker M. Identification and treatment of iron-deficiency anemia in pregnancy and postpartum: A systematic review and quality appraisal of guidelines using AGREE II. Int J Gynaecol Obstet. 2024;164:460-75. doi:10.1002/ijgo.14978.
68. Ughasoro MD, Madu AJ, Kela-Eke IC, Akubuilo U. Parental Perception of Childhood Anaemia and Efficiency

of Instrument Assisted Pallor Detection among Mothers in Southeast Nigeria: A Field Validation Study. Int. J. Pediatr. 2019;2019:7242607. doi:10.1155/2019/7242607.
69. Freeman AM, Rai M, Morando DW. Anemia Screening. StatPearls Publishing; 2024.
70. Jullien S. Screening of iron deficiency anaemia in early childhood. BMC pediatrics. 2021;21:337. doi:10.1186/s12887-021-02725-w.
71. Helmyati S, Hasanah FC, Putri F, Sundjaya T, Dilantika C. Biochemistry Indicators for the Identification of Iron Deficiency Anemia in Indonesia: A Literature Review: Tinjauan Literatur: Indikator Biokimia untuk Identifikasi Anemia Defisiensi Zat Besi di Indonesia. Amerta Nutr. 2024;7:62-70. doi:10.20473/amnt.v7i3SP.2023.62-70.