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Childhood anemia and iron deficiency in sub-Saharan Africa—risk factors and prevention: a review

Short title: Childhood anemia and iron deficiency in sub-Saharan Africa

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ABSTRACT

Iron deficiency and iron deficiency anemia are public health issues recognized by the World Health Organization, especially in sub-Saharan Africa. In some countries on this continent, the prevalence of anemia exceeds 60% in the pediatric population. Iron supplementation could prevent around one third of anemia cases in children in Africa and could decrease morbidity and mortality.

A number of factors are behind this anemia, including iron deficiency caused by an inadequate diet, pica and geophagia, as well as chronic inflammation (malaria, digestive and urinary parasites, etc.). Ferritin is a good indicator of the body's iron stores, but it is not a specific reflection, with both inflammation and infection causing an increase. Ferritin could be interpreted according to C-reactive protein (CRP) or alpha-1 glycoprotein (AGP), or by adjusting the ferritin threshold to 30 µg/L.

The treatment of malaria and digestive or urinary worms, the correction of factors that stimulate inflammation, the fight against geophagia as well as more hygienic living conditions are all prerequisites for overcoming iron deficiency. A number of campaigns using iron supplements have proven to be effective, especially in schools, to fight against iron deficiency and malnutrition. Biofortification is an innovative and promising cultivation technique that increases the content of bioavailable iron in local produce such as beans. It will become a lever in the fight against iron deficiency.

Keywords: Iron deficiency; Anemia; Malaria; Hcpidin; Biofortification; Prevention

1. Introduction

Due to the morbidity and mortality associated with iron deficiency, the World Health Organization (WHO) has deemed it to be a public health issue since 2004 [1, 2]. Anemia is defined as hemoglobin levels of below 11 g/dL between 6–50 months, and below 11.5 g/dL in children aged over 5 years [1, 2]. Anemia is classed as *mild* at levels above 10 g/dL, *moderate* between 7 and 9.9 g/dL, and *severe* below 7 g/dL [1, 2]. Iron deficiency corresponds to ferritinemia of below 12 µg/L at under 5 years, or below 15 µg/L at over 5 years of age [1, 2]. Iron deficiency anemia affects cognitive and motor development and causes fatigue and low productivity [3]. Iron supplementation could increase hemoglobin levels in children by 0.8 g/dL, preventing 32% of anemia cases in pre-school children in Africa [3]. According to a meta-analysis of nearly 12,000 children aged between 28 days and 12 years living in six sub-Saharan countries, in case of anemia, an increase in hemoglobin of 1 g/dL reduces the risk of child mortality by 24%, thereby preventing around 1.8 million deaths of children aged 28 days–5 years every year [4]. Simple iron supplementation could achieve this objective [4], even though the causal link between iron deficiency and mortality is difficult to assess.

The WHO has also acknowledged the scale of iron deficiency without anemia and the fact that iron deficiency is not the sole cause of anemia [5]. Indeed, it is not easy to determine the exact cause of anemia in a population with hemoglobinopathies such as sickle cell anemia or thalassemia, affected by malaria and chronic inflammation caused by infections and at risk of malnutrition and nutritional deficiencies such as iron deficiency. However, in 2011, the WHO declared that “iron deficiency is thought to be the most common cause of anaemia globally” [1]. Ferritinemia, the presence of the iron storage protein in the blood, increases by about 30% in cases of infection or inflammation, meaning that there is a risk of underestimating the prevalence of anemia caused by iron deficiency in the case of inflammation [6]. For this

reason, the WHO recommends either interpreting ferritin according to the assay of blood C-reactive protein (CRP) or alpha-1 glycoprotein (AGP), or adjusting the ferritin threshold to 30 µg/L [7].

This literature review is intended to determine risk factors for iron deficiency and iron deficiency anemia and to provide an overview of existing methods for improving iron levels in the pediatric population in sub-Saharan Africa.

2. Prevalence of iron deficiency and iron deficiency anemia in sub-Saharan Africa

According to WHO data between 1995 and 2011, anemia from all causes affected 60.2% of African children aged 6–59 months—some 95 million children—3.3% of whom suffered from severe anemia [3] (Table 1). The countries in which anemia affected more than 60% of children aged 6–59 months are those found on the diagonal between Mauritania and Mozambique, reaching its highest in Burkina Faso (86% and 12.3% anemia below 7 g/dL), Mali (80%), Senegal (79%), Guinea and Niger (76%), Côte d’Ivoire (75%), and Sierra Leone (74%) [3] (Table 1).

The prevalence of anemia is higher in populations at risk of inflammation (Sierra Leone, Côte d’Ivoire, Mozambique, Liberia, Cameroon) linked to infections (malaria, parasitosis, including schistosomiasis) and hygiene conditions [8]. Due to the many compounding factors, and in particular infections and general inflammation, accurate epidemiological data on the prevalence of iron deficiency are difficult to obtain. At an equivalent proportion of anemia in a pre-school pediatric population, iron deficiency is only present in 5% of anemic children in Sierra Leone, 16% in Côte d’Ivoire and 24% in Mozambique [8] (Table 1). In Southern Rwanda, one child in three is anemic, and 18% suffer from iron deficiency, especially children aged under 2 years [9] (Table 1). In Kenya, 51% of anemic children also have iron deficiency, with a prevalence of anemia by iron deficiency of 11–13% [8, 10] (Table 1). In

Ghana, 63% of children are anemic, 68% have an iron deficiency and 46% have iron deficiency anemia [11] (Table 1). In Zimbabwe, in a geographical area unaffected by malaria and where hookworm is not endemic, 26% of infants aged 3–60 months have an iron deficiency [12] (Table 1).

3. Iron deficiency and anemia risk factors

3.1 Iron dietary deficiency

Malnutrition is widespread in Africa, influenced by geographical location, humidity and the rainy season, high exposure to the sun, altitude and latitude as well as soil and crop quality [5]. According to UNICEF, in 2016 at least one in three African children aged under 5 years was malnourished, with a higher prevalence in Niger, the Central African Republic, Congo, Zambia, Mozambique, Madagascar, and Eritrea [13]. One of the main causes of iron deficiency is inadequate intake. Iron deficiency and iron deficiency anemia are correlated with childhood malnutrition [14–16].

Africa is the continent where the consumption of meat is the lowest in the world [17]. Apart from economic and natural factors, urbanization, religion, and culture are parameters that influence meat consumption [17]. In Africa, and in Tanzania in particular where most of the population is rural, the main foodstuffs consumed by infants aged 6–23 months, other than breast milk, include corn-based products, onions and tomatoes, sunflower oil, peanuts, beans, rice, and baobab powder. During the dry season, animal products were almost completely absent from the diet, with the exception of small dried fish [18]. In rural Kenya, half of the infants aged 7 months were consuming only maize porridge as the main complementary food [19]. Only 9% of these Kenyan infants consumed meat [19].

While calorie consumption was generally satisfactory (144–306% of recommended daily amounts [RDA]), inadequate intakes were found for vitamin A, calcium, zinc, and iron. With

regard to iron, consumption was 23% of RDA at 6–8 months, 29% RDA at 9–11 months and 58% RDA at 12–23 months [18]. Most studies calculate iron intake without distinguishing hem iron and non-hem iron. In terms of absorbed iron [20], the RDA of the previous study [18] were probably even lower.

3.2 Richness of soils and crops

The iron content of the soil affects the amount of iron found in crops and drinking water. A very low prevalence of iron deficiency is observed in Sierra Leone, despite it being one of the world's poorest countries. This is probably due to the ferrallitic soils that contain high levels of free iron, which may leak into drinking water [21]. However, the efficiency of free iron absorption from water is unknown.

In the Amhara region of Ethiopia, fewer than 2% of children consume meat [22]. And yet only 9.1% of children have iron deficiency, with a prevalence of anemia by iron deficiency of 5.3% [22] (Table 1). The hypotheses to explain this are that the country's cereals are richer than usual in iron due to the quality of the soil and that fermented foodstuffs reduce phytic acid in some cereals [22]. Phytic acid is a potential inhibitor of non-hem iron absorption [23]. Acidic soils also limit iron absorption by plants [5].

3.3 Socioeconomic status

Controversially, there are data on the link between socioeconomic status and iron deficiency anemia. The social status of the mother is linked to higher consumption of iron-rich products by their children [24]. The prevalence of anemia is higher in children of mothers with little education [21], but there is no significant association between social class of the subjects and iron deficiency [25].

3.4 Maternal nutritional status

Malnutrition in mothers is an important risk factor for iron deficiency anemia in children [15] (Table 1). Maternal iron deficiency increases vulnerability to iron deficiency anemia in infancy through an intergenerational transfer of poor iron status from mother to child [6, 15]. Iron deficiency erythropoiesis at mid-pregnancy is associated with prematurity [26]. There is a strong positive correlation for the micronutrient status, in particular ferritin level, between lactating mothers and children [27] (Table 1).

3.5 Prolonged breastfeeding

Breast milk is low in iron (0.35 mg/L), but the iron bioavailability is very high (50%) [20]. Iron requirements are low during the first 6 months of life, since infants consume iron stored during the last trimester of pregnancy and iron issued from physiological hemolysis during the first weeks of life [20]. When breastfeeding is prolonged over 6 months, iron provided from breast milk is not sufficient to meet the child's needs [20].

In rural Kenya, Uyoga et al. demonstrated a positive correlation between the duration of exclusive breastfeeding and hemoglobin ($r=0.187$, $p<0.05$), and a negative correlation with the soluble transferrin receptor, but without any difference on the level of ferritin or hemoglobinemia compared with non-exclusively breastfed infants at 8 months of age [19] (Table 1).

In Ibadan, the third largest city in Nigeria, iron deficiency after 6 months of life was more frequent in infants that were exclusively breastfed than in those that were not [25] (Table 1).

These data suggest that prolonged breastfeeding is a risk factor for iron deficiency in developing countries.

3.6 Geophagia

Pica, nutritional problems caused by the ingestion of non-nutritive and inedible substances, which includes geophagia, is a problem in Africa, albeit probably an underestimated one since it is not often sought in studies and can be masked by the population [28]. Ferritin is lower in those suffering from geophagia, and anemia is more common in children suffering from geophagia [29, 30] (Table 1). In Kenya, 73% of children eat soil (28 g per day) [30]. Similarly in Zambia, 74% of children ingest 25 g of soil or stones every day [29].

Geophagic children are more frequently diagnosed with *Ascaris lumbricoides* and *Trichuris trichiura* [29,30]. Geophagia and intestinal parasites independently cause iron deficiency [30] (Table 1).

Geophagia is not linked to poor socioeconomic conditions [30, 31], but habits are passed on through families to their youngest members [28, 29]. There are a number of causes of geophagia: dyspepsia, cultural usage of stones and soil as tranquilizers, as well as micronutrient needs. It is difficult to determine whether nutritional deficiencies are the cause or effect of geophagia [5]. Insofar as iron supplementation has no effect on the development of geophagia [29], it suggests that iron deficiency is not solely responsible for pica.

3.7 Genetic variations enhancing iron absorption

Hepcidin is the key hormone in the negative control of iron absorption. It is produced in the liver and stimulates the internalization of ferroportin on the basement membrane of enterocytes, thereby limiting the transfer of iron from enterocytes to plasma, and thus its intestinal absorption [32].

Transmembrane protease serine 6, coded by the gene *TMPRSS6*, inhibits production of hepcidin in the liver. A biallelic mutation of this gene causes an autosomal recessive disorder known as IRIDA, iron-refractory iron deficiency anemia, which is refractory to enteral-route iron supplementation due to uninhibited hepcidin production. Some variants of the *TMPRSS6*

gene promote iron deficiency in certain ethnic groups, namely, Caucasians and Europeans [33]. There is very little research into these variants in Africa. However, the allele variant TMPRSS6 736(V), found in 18% of Rwandan children in homo- or heterozygous forms, may be responsible for the country's higher prevalence of anemia [9] (Table 1).

It is also possible that other variants could have the opposite effect and reduce the risk of iron deficiency despite a diet low in hem iron.

Hepcidin limits iron absorption by ferroportin. Some variants of ferroportin increase the expression of ferroportin by inhibiting the action of hepcidin, thereby increasing intestinal absorption of iron [34]. In populations that consume few meat products, Darwinian selection has worked to increase the bioavailability of non-hem iron. The Q248H variant of the ferroportin gene (SLC40A01) is found in 2.2% of the adult population in Sao Tomé and Príncipe, 3.5% in Angola, 17.2% in Botswana [34], and 20.3% of children in Zimbabwe [12]. This genetic variant is significantly more common in Africans born in Africa than in African Americans [35] and is not found at all in Caucasians [36]. Although under normal circumstances ferritinemia does not differ between individuals with the heterozygous or homozygous Q248H allele and patients without the mutations [35, 36], in cases of inflammation, ferritin is significantly higher in heterozygous or homozygous children than in those without the mutations (74 µg/L vs. 24 µg/L; $p = 0.0016$) [12] (Table 1). This means that it is possible that individuals bearing this variant have better absorption of non-hem iron.

Lastly, when there is a shortage of hepcidin, as is the case when the HFE gene mutates into the homozygous state (most common mutation: p.C282Y), the body finds itself overloaded with iron (hemochromatosis), as digestive iron absorption is uninhibited. This disorder is mostly found in Northern Europe and is symptomatic from the age of 30–40 years. The p.H63D variant of the HFE gene is found in both the heterozygous and homozygous state in

some populations in North Africa, the Middle East and Asia. Young adults with this variant are less susceptible to iron deficiency than the population without the mutation [37].

3.8 Malaria

The African countries most affected by malaria are Nigeria and the Democratic Republic of Congo, which alone account for more than one third of global cases (25% and 11%, respectively) [2]. Infection with malaria only serves to increase the prevalence of existing anemia, from 61% to 79% in sub-Saharan children with malaria, and increases severe anemia (< 7g/dL) from 3% to 8% [2].

Infection with *Plasmodium falciparum* is an independent risk factor for anemia [9, 16] (Table 1). Indeed, *P. falciparum* digests hemoglobin and releases hemozoin, the plasmodium pigment, which inhibits erythropoiesis in bone marrow [23, 38]. But these parasites also stimulate hepcidin production, independently of inflammation, thereby reducing iron absorption [23]. In two cohorts of children with malaria from Kenya [39] and Côte d'Ivoire [40] (Tables 1–2) with or without biological inflammation, hepcidin was higher, and all the more so the younger the child. Following anti-malarial treatment, hepcidin rapidly falls [41]. Moreover, malaria increases hepcidin production more than any other kind of inflammation [41] (Table 1).

Fears have arisen regarding iron supplementation and the risk of encouraging malaria and other infections. Since *Plasmodium* requires free intracytoplasmic iron to multiply, iron supplementation could stimulate infections. Iron supplementation stimulates erythropoiesis, but *Plasmodium vivax* prefers reticulocytes (unlike *P. falciparum*). Zinc protoporphyrin (produced through erythropoiesis in cases of iron deficiency) can inhibit the formation of hemozoin and create a toxic environment for anti-malarial treatments. Therefore, some authors recommend treating malaria before beginning iron supplementation [42]. The meta-

analysis performed by Gera and Sachdev found that iron supplementation caused no additional risk of upper or lower respiratory tract infections, diarrhea, or malaria [43]. Furthermore, a Cochrane review found that intermittent and preventative anti-malarial treatments had no effect on 6-month mortality and hospitalization of anemic children, whether or not they were taking iron supplements [44]. Nor is iron supplementation responsible for increased clinical or severe malaria in pediatric patients, and iron supplementation combined with anti-malarial treatments can reduce forms of clinical malaria [45]. This means that iron supplementation can be prescribed, when required, parallel to the prevention and treatment of malaria [45].

3.9 Digestive and urinary parasitosis

Parasites are the third most common cause of infectious diarrhea in sub-Saharan children [46]. Schistosomiasis, hookworm and whipworm cause loss of blood, and hence also iron. Intestinal bleeding caused by *Schistosoma mansoni* and *S. japonicum* eggs may be compensated by partial reabsorption of luminal iron [47]. On the other hand, *S. haematobium* causes hematuria and therefore a loss of non-absorbable iron. This loss may reach 1 mg of iron or more every day (equal to or greater than menstruation) [47]. Hookworms feed on the digestive lining and produce an anticoagulant that causes intestinal bleeding [47]. Infection with *Trichuris trichiura* causes inflammation of the intestine, with blood loss and dysentery [47].

In a pediatric population of 591 children aged 6–14 years in Côte d'Ivoire, 55% were infested with worms (primarily hookworms) [48]. Anti-worm treatments reduced the prevalence of anemia [48] (Table 2). There is a correlation between hookworm and ferritinemia, independent of malaria and geophagia [30] (Table 1).

Although *Giardia lamblia* is a predominant cause of parasitic gastroenteritis [46] and can cause stunting [49], there was no association with anemia in sub-Saharan children [49, 50].

3.10 Other main causes of iron malabsorption

In the case of refractory iron deficiency anemia in which other causes have been ruled out, European and North American pediatric gastroenterology guidelines consider looking for *Helicobacter pylori* [51]. Africa has the highest rate of *H. pylori* infection in the world (70.1%), and children are not spared (14.2% in Ghana, 44.3% in Uganda, 73.3% in Kenya) [52]. However, there are no data on iron deficiency due to *H. pylori* infection in Africa.

Celiac disease is another possible cause of iron malabsorption and anemia, but it seems to be less prevalent or under-diagnosed in sub-Saharan Africa compared with the rest of the world [53]. The exact prevalence of celiac disease in children is not known due to a lack of large studies.

Other digestive causes such as inflammatory bowel disease or enteropathy have a more pronounced clinical presentation than *H. pylori* infection or celiac disease in most cases, and iron deficiency is usually not the only symptom.

4. Iron deficiency treatments

The treatment of malaria and worms, the correction of factors that stimulate inflammation, the fight against geophagia as well as more hygienic living conditions are all prerequisites for overcoming iron deficiency [10, 11].

In some parts of sub-Saharan Africa, it is difficult to achieve the WHO recommendations for iron intake in infants aged 6–23 months from diet alone [54]. When the prevalence of anemia is 40% or more in young children, guidelines generally recommend that children of normal birthweight receive oral iron (2 mg/kg per day of elemental iron for 3 months) between the

ages of 6 months and 2 years, and that children with a low birthweight receive the same amount of iron starting at 2 months [45].

Nutritional supplementation is a key stage in curing iron deficiency, especially through initiatives run in schools.

Within public health programs, it is possible to get more iron into the diet while taking the local diet into account, if not to increase the intake of animal hem iron, which is far more readily absorbed than iron obtained from plants.

4.1 Enriching diet with micronutrients

A number of trials have shown that iron supplementation through food provided at school (milk, biscuits, drinks, corn- and wheat-based meals, salt fortified with iron) reduces the incidence of iron deficiency [10, 11, 23, 55] (Table 2). The results of these studies show that iron deficiency falls first, followed by anemia. However, it is important to select iron with good bioavailability and shelf-life [56].

Iron supplementation may cause diarrhea and increases the risk of infection with opportunistic diseases [57]. The addition of galacto-oligosaccharide prebiotics maintains high abundances of *Bifidobacterium*, reduces enteropathogens and improves iron status, especially in breastfed infants according to the human milk oligosaccharide profile of the mother [58].

Ascorbic acid converts ferric iron into ferrous iron and impedes the action of other inhibitors to iron absorption such as calcium, milk proteins, phytic acid, polyphenols and soy-based products [59]. For this reason, the WHO proposes adding ascorbic acid to food supplements in a 2:1 ratio with iron [56]. Another strategy for increasing the bioavailability of ingested iron is to combat inhibitors of iron absorption with NaFeEDTA (ferric sodium ethylenediaminetetraacetate) or phytase [60]. In the presence of phytic acid, NaFeEDTA increases iron absorption by a factor of two to three. It does not cause flour to oxidize during

storage. NaFeEDTA is approved by the WHO and FAO (Food and Agriculture Organization of the United Nations) with an acceptable daily dose of 0.2 mg of iron per kilogram per day in young children [10, 23]. A meta-analysis confirms improvements in anemia and iron deficiency following fortification with NaFeEDTA [61].

4.2 Biofortification

Biofortification programs are currently under development to increase the production and consumption of local products fortified with iron [18]. Their objective is to enrich these foodstuffs in iron that is more readily absorbed and to combat the inhibition of absorption by phytic acid.

Beans are the most consumed food in Kenya, Burundi and Rwanda [59]. Thus, 66 kg/person per year of beans are consumed in Rwanda and Kenya, compared to just 5 kg/person per year in the USA [62]. Biofortified beans contain double the iron of normal beans (*Phaseolus vulgaris L.*) (57 µg/g of iron compared to 106 µg/g in biofortified beans), but its absorption is limited by phytates, which are more concentrated in biofortified beans [59, 63]. However, the phytate:iron ratio is lower in biofortified beans than in standard beans (11 vs 15), thereby enabling better iron absorption [59].

5. Conclusion

The prevalence of anemia is estimated to stand at 60% of children in Africa, with an accompanying high morbidity and mortality rate. Iron deficiency could explain one third of cases of anemia, but there are often multiple interlinked causes such as pica, malaria, as well as intestinal and urinary parasites.

A number of studies have shown the effectiveness of iron supplementation in schools when children do not eat enough meat. Every micronutrient supplementation and selective

cultivation program that takes local dietary habits into account has shown encouraging results by reducing iron deficiency. In order to optimize results, it is recommended that parasites should be treated before beginning supplementation, and screening for malaria should be carried out in parallel in areas where it is endemic.

All of these initiatives must be implemented to reduce the scourge of iron deficiency in sub-Saharan Africa.

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Tables:

Table 1: Prevalence of anemia, iron deficiency, and iron deficiency anemia as well as associated main risk factors

Table 2: Prevalence of anemia, iron deficiency, and iron deficiency anemia as well as main conclusions in interventional studies

Table 1: Prevalence of anemia, iron deficiency, and iron deficiency anemia as well as associated main risk factors

Study population	Anemia	Iron deficiency	Iron deficiency anemia	Main risk factors for anemia or iron deficiency anemia	Ref.
AFRICA 6–59 months	60.2%		32%	<i>Epidemiologic data</i>	[3]
ANGOLA 5–13 years N=328	21.6%			Age, parasitic infection with <i>H. nana</i>	[49]
BENIN 6–59 months	82.4% (N=681)	23.6% (N=546)	21.2% (N=542)	Mother’s underweight, mother’s occupation, mother’s iron deficiency anemia, stunting, child’s age (12–23 months), inflammation	[15]
CAMEROON Pre-school children	57.6% (N=859)	20.6% (N=838)	16.5% (N=798)	<i>Analysis of national surveys</i>	[8]
CÔTE D’IVOIRE Pre-school children	71.8% (N=879)	15.5% (N=781)	12.0% (N=783)	<i>Analysis of national surveys</i>	[8]
ETHIOPIA 54–60 months N=628	13.6%	9.1%	5.3%	Despite the poor-quality diet, there was a very low prevalence of iron deficiency anemia	[22]
ETHIOPIA (Ethiopian Somali region) 1–5 years N=500	75.1%	91.1%	72.8%	Non-exclusive breastfeeding during the first 6 months of life and lower food variety consumption	[50]
ETHIOPIA Breastfed children aged 6–23 months N=162	52.5%	44.4%	29.6%	Correlation between the micronutrient status of the mothers and the children for ferritin, zinc, and anemia Low consumption of flesh foods in mothers and infants	[27]
GAMBIA 2–6 years N=603		18.6–29.5%	14.0-25.2%	Decrease in hepcidin levels, and increase in prevalence of iron deficiency at the end of the malaria season	[39]
KENYA	26.3%	21.8%	13.3%	<i>Analysis of national surveys</i>	[8]

Pre-school children	(N=827)	(N=918)	(N=827)		
KENYA 4.9–97.1 months N=324		46%		Asymptomatic and febrile malaria contribute to iron deficiency through the increase of hepcidin concentrations	[41]
KENYA 8 Months–8 years N=245		38.2–46.5%	54.9%	Decrease in hepcidin levels, and increase in prevalence of iron deficiency at the end of the malaria season	[39]
KENYA 0.5–3 years N=244	75.8%			Prior or current malaria infection, any current infection with hookworm, <i>Trichuris</i> , <i>Strongyloides</i> , <i>Ascaris</i> , and/or dietary insufficiency	[16]
KENYA 10–18 years N=156	7.1%	14.8%		Geophagy, hookworm, and malaria: independent predictors of ferritinemia when controlling for other helminth infections, age and sex as well as socio-economic and educational background of the children’s families and family size	[30]
KENYA Breastfed children aged 6–10 months N=134	74.6%	82.1%	61.9%	Lower duration of exclusive breastfeeding	[19]
LIBERIA Pre-school children	59.1% (N=1445)	29.8% (N=1416)	21.2% (N=1415)	<i>Analysis of national surveys</i>	[8]
MOZAMBIQUE Pre-school children	70.8% (N=962)	19.3% (N=917)	17.3% (N=917)	<i>Analysis of national surveys</i>	[8]
NIGERIA 6–24 months N=202	70.8%	29.2%	19.3%	Longer duration of exclusive breastfeeding and younger age	[25]
NIGERIA 1–7 years N=96	69%			Longer duration of breastfeeding	[14]
RWANDA Children under 5 years N=545	34.9%	16.8%		<i>P. falciparum</i> infection, younger age, TMPRSS6 736(V) allele	[9]

SIERRA LEONE Pre-school children	76.3% (N=710)	5.2% (N=654)	3.8% (N=668)	Malaria, inflammation	[8, 21]
SOUTH AFRICA Pre-school children	28.9% (N=1049)	21.4% (N=821)	12.3% (N=768)	<i>Analysis of national surveys</i>	[8]
ZAMBIA Schoolchildren 7–15 years N=406	12.1%	18.6%		Geophagia No effects of iron supplementation on geophageous behavior	[29]
ZIMBABWE 3–60 months N=208		26.4%		Any effect of Q248H in protecting against iron deficiency in children exposed to repeated inflammatory conditions	[12]

Table 2: Prevalence of anemia, iron deficiency, and iron deficiency anemia as well as main conclusions in interventional studies

Studied population	Anemia	Iron deficiency	Iron deficiency anemia	Main conclusions related to anemia, iron deficiency or iron deficiency anemia	Ref.
CÔTE D'IVOIRE 6–14 years N=591	70.4%	9.3%		Anthelmintic treatment: decrease of helminth infections and anemia prevalence No improvement of iron status with iron fortification No effect of intermittent preventive treatment of malaria on malaria burden or anemia prevalence	[48]
CÔTE D'IVOIRE 12–36 months N=378	82.8%	34.7%	29.9%	Efficacy of iron fortified complementary food	[23]
CÔTE D'IVOIRE 11–17 years N=41	14.6%	53.7%		Treatment of afebrile malaria reduced inflammation and serum hepcidin and improved iron absorption No effect of treatment of hookworm or <i>S. haematobium</i> infections	[40]
GHANA 5–12 years N=228	63%	68%	46%	Efficacy of cowpea flour fortified with NaFeEDTA	[11]
KENYA 3–8 years N=505	56%	15%	11%	Efficacy of iron-fortified whole maize flour	[10]
KENYA 6.5–9.5 months N=155	74.2%		67.7%	Efficacy of low iron-containing micronutrient powders	[57]
SOUTH AFRICA 6–11 years N=228	27.1%	28.1%		Efficacy of fortified biscuits with iron, iodine, and β -carotene	[55]

NaFeEDTA: ferric sodium ethylenediaminetetraacetate.