11

Risk Factors for Anemia in Preschool Children in Sub-Saharan Africa

Dia Sanou[1,*] and Ismael Ngnie-Teta[2]
[1]*Interdisciplinary School of Health Sciences, Faculty of Health Sciences, University of Ottawa*
[2]*UNICEF – Haiti and Adjunct Professor, Program of Nutrition, University of Ottawa*
Canada

1. Introduction

Iron is a mineral that is found in nature and foods. It is involved in many physiological functions in the body, and poor iron intake can lead to iron deficiency and later to anemia. Iron deficiency anemia (IDA) is the most prevalent nutritional disorder in the world despite iron being the fourth most common element on earth. Anemia is amongst the most important contributing factors to the global burden of disease. According to a recent WHO report on the global prevalence of anemia, one in four people is affected by anemia worldwide (McLean et al., 2009; WHO, 2008), with pregnant women and preschool-age children at the greatest risk. Two thirds of preschool-age children are affected in developing regions of Africa and South East-Asia, and about 40% of the world's anaemic preschool-age children reside in South-East Asia (McLean et al., 2009; WHO, 2008). Of the 293.1 million children who suffer from anemia worldwide, 83 million (28%) are in sub-Saharan Africa, representing 67% of the total population of children of this age group in the continent.

Adverse health consequences of anemia in preschool children include altered cognitive function, impaired motor development and growth, poor school performance, poor immune function and susceptibility to infections, decreased in responsiveness and activity, increased in body tension and fatigue. Even before clinical symptoms are visible, iron deficiency that leads to anemia is detrimental to children and may condemn one third of the world population to live permanently below their full mental and physical potential. Indeed, the impact of iron deficiency anemia on psychomotor development and cognitive function in children under the age of two years may be irreversible despite adequate therapy (Lozoff et al., 2000). Horton & Ross (2003) estimated the median productivity lost due to iron deficiency anemia alone to be about US$2.32 per capita or 4.05% of gross domestic product (GDP). The authors estimated an additional US$14.46 per capita lost in cognitive function, for a total annual loss (cognitive & productive) of about $50 billion in GDP worldwide from iron deficiency anemia. Due to its detrimental effects among children, effective interventions

*Corresponding Author

to improve iron status and reduce the burden of anemia will likely promote health and development.

Anemia is preventable, yet it remains the most widespread nutritional deficiency in the world. Countries, which realized significant progresses in the control of the problem have identified contextual risk factors and implement context relevant programs. In sub-Saharan African, conditions which increase the risk for anemia in children are complex and multidimensional. A first step for evidence-based interventions and policies towards the control and elimination of iron deficiency anemia is a better understanding of these risk factors. The current chapter discusses the determinants of iron deficiency anemia in sub-Saharan Africa children.

2. Definition and conceptual framework

In the literature, the terms anemia, iron deficiency, and iron-deficiency anemia are often used interchangeably, but are not equivalent. Anemia is defined as a significant reduction in hemoglobin concentration, hematocrit, or the number of circulating red blood cells at a level below that is considered normal for age, sex, physiological state, and altitude, without considering the cause of the deficiency (Nestel et al., 2002). Iron deficiency anemia is a condition in which there is anemia due to lack of available iron to support normal red cell production. It is the third and last stage of iron deficiency which starts with depletion of iron stores as reflected by a reduced serum ferritin concentration. The second stage is iron deficient erythropoiesis, characterized by decreased serum iron, transferrin saturation and serum ferritin concentration but with a normal hemoglobin concentration. Because anemia can arise from nutritional factors and from non-nutritional ones, several terms are used to classify anemia, including nutritional anemia, anemia of infection, anemia of chronic diseases, pernicious anemia. For the purpose of this chapter, we focus on the first three that are the most common in developing countries, have modifiable risk factors and can be prevented through appropriate behavioral tailored intervention.

Several factors contribute concurrently in childhood anemia, but their relationships to the onset of anemia are not identical. Therefore, from an epidemiological perspective, it is important to distinguish between the different factors. A causal factor is linked to the onset of a disease or the condition and precedes the disease. A risk factor is an element linked to a person (biologic or hereditary), a behaviour, lifestyle or environment that increases the likelihood of developing the condition and has been found correlated with the condition in epidemiological studies (Last, 2004). When an intervention targeting a factor can reduce the likelihood of the condition developing, the factor is considered a modifiable risk factor. A factor susceptible to increase the onset of a pathological condition is a determining factor or determinant. For example the major causal factors of iron deficiency that lead to anemia are low dietary iron intake, inadequate iron absorption, chronic blood loss, and increased iron demand. However, there are several other factors (non causal relationship) that contribute to anemia including among others sociocultural factors, poverty, maternal factors, chronic conditions secondary to AIDS, tuberculosis and genetic factors such as sickle cell and thalassemia. There are several levels of stratification of anemia risk factors for children including structural and environmental level factors, community level factors, household level factors and individual health and nutrition related factors. Figure 1 summarizes the

multi-level risk factors of anemia in children in developing countries. There is an anthropological perspective that can be seen as a transverse risk factor.

3. Anthropological perspective

Anthropologists believed that agrarian revolution that resulted in changes in dietary behaviours and outbreak of infectious diseases about 10,000 years ago has played an important role in the emergence and spread of iron deficiency and anemia (Denic & Agarwal, 2008; Wander et al., 2009). According to this theory, meat was the main source of energy prior to agrarian revolution. When humans turned from hunting to agriculture, the diet became deficient in bioavailable iron, thus increased the prevalence of iron deficiency and its subsequent anemia. Cultivating plant-based foods has increased calorie intakes, but reduced meat consumption. As a result, iron intake became insufficient to meet individual daily requirements. According to Mann (2007), daily total iron intake decreased from 87 mg in the Palaeolithic age to 15 mg in the twentieth century. In addition, increased consumption of plant-based foods has reduced the intake of absorbable iron because the amount of non-heme iron and inhibitors of iron absorption has increased in the diet, while the amount of heme iron has decreased.

With sedentarization and animal husbandry, carriers of infectious diseases were able to be transmitted from animals to humans leading to emerging or re-emerging human infectious diseases. Thereafter, poor environmental and hygienic conditions, crowding and lifestyle changes have resulted in proliferation and spread of these carriers (Denic & Agarwal, 2007). Several studies suggested that mild to moderate iron deficiency may protect against acute infection (Oppenheimer, 2001; Prentice, 2008; Sazawal *et al.,* 2006). Thus some authors put forward the hypothesis of a potential metabolic adaptation during which the human body self-regulates its iron to a deficiency status, the « iron-deficient phenotype », to prevent the severity of infections when re-infection is a continuous process (Denic & Agarwal, 2007). According to these authors, the important advancement in developed countries to control anemia are more likely due to the successful eradication of infections rather than the quality of diet. In malaria endemic areas such as Africa, the iron deficiency phenotype survived better over time (Denic & Agarwal, 2007; Wander et al., 2009). Therefore, iron substitution therapy in some population groups such as iron supplementation in children with no functional iron deficiency may cause more harm than good (Sazawal et al., 2006; WHO/UNICEF, 2006).

4. Dietary factors

The dietary risk factors for childhood anemia in developing countries include single or combined deficiency of micronutrients such as iron, folic acid, vitamin B6, vitamin B12, vitamin A and copper. Association has been found between anemia and deficiency of vitamin A, riboflavin, protein and other nutrients (Gamble *et al.,* 2004, Semba & Bloem 2002; Thorandenya et al. 2006; Rock et al., 1988). Although nutritional factors are thought to be the most important contributing factors to childhood anemia, their exact contribution to the risk of anemia is not well established and may vary with the level of infection and the diet quality. Magalhaes & Clements (2011) estimated that about 37% of Anemia cases in preschool children in three West African countries namely; Burkina Faso, Ghana and Mali could be averted by treating nutrition related factors alone.

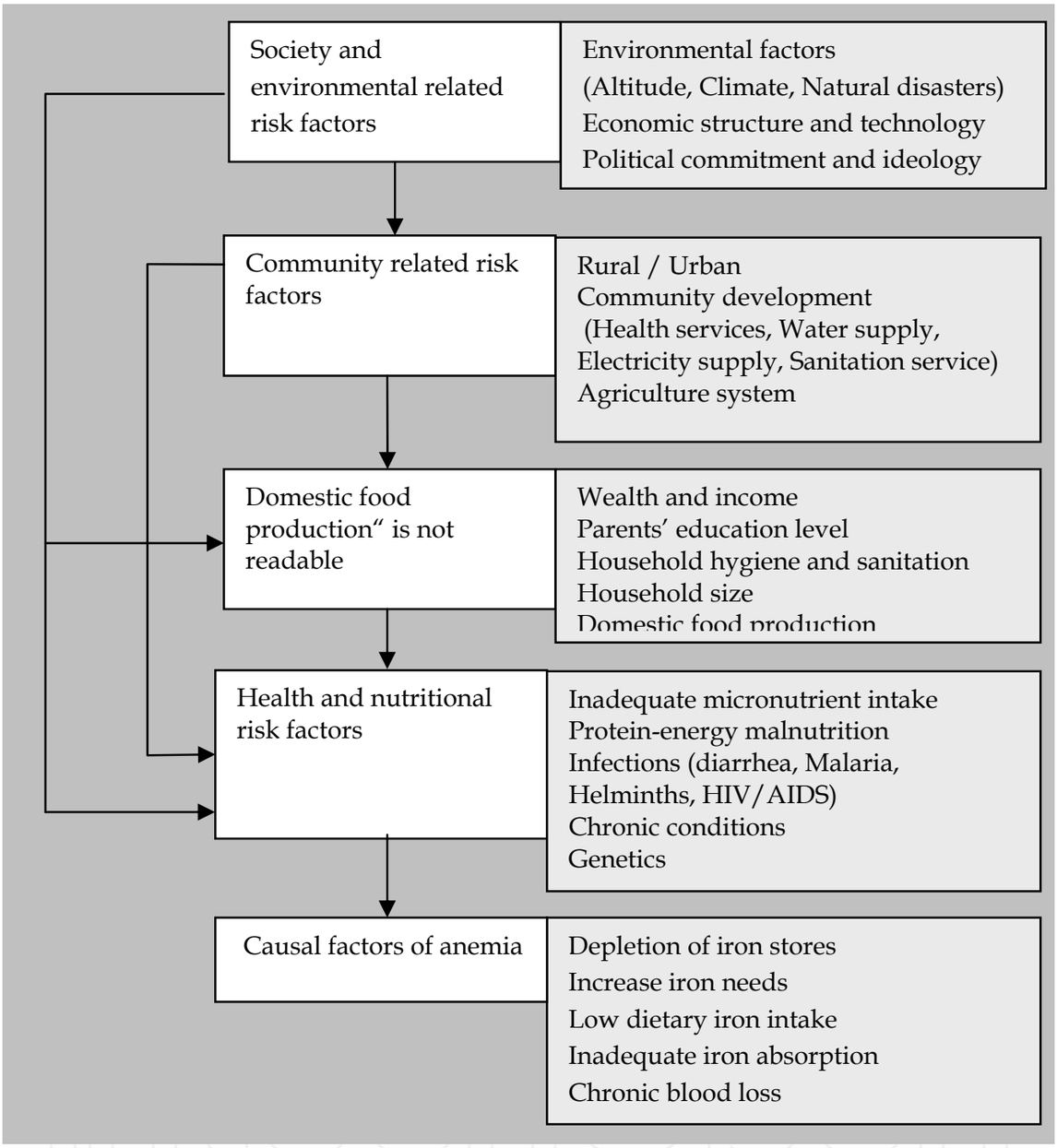


Fig. 1. Simplified conceptual framework for determinants of anemia among children (adapted from Ngnie-Teta et al, 2007).

4.1 Iron deficiency

The leading cause of anemia worldwide is iron deficiency due to inadequate intake or malabsorption of dietary iron. The adequacy of dietary iron depends on the intake and the bioavailability, which in turn are contingent to the nature of the food and the composition of the overall diet. In many developing countries, the amount of iron in the diet is usually enough to cover body needs, however because it is mainly provided by plant based food in the form of non-heme iron, its bioavailability is very low (Adish et al., 1998; Sanou et al., 2011; Zimmermann et al., 2005)

Iron is present in food in two forms: heme iron and non-heme iron. Heme is a component of hemoglobin and myoglobin and heme iron is mainly provided by animal tissues such as meat, poultry, fish and shellfish. Heme iron represents about 40% of animal tissue iron and is easily absorbed. However, it contributes to less than 15% of the total dietary iron, and may represent less than 1% in some countries where consumption of animal foods is very low (Monsen *et al.,* 1978). Most of the dietary iron is provided in the form of non-heme iron that is comprised of non-heme iron component of animal tissues, iron from eggs, milk and plant-based foods. The absorption rate of non-heme iron is very low and depends on iron status and combined effects of enhancers and inhibitors of iron absorption (Monsen et al., 1978). Enhancers of iron absorption include animal tissues (meat, poultry, and fish) and vitamin C and organic acids (Diaz *et al.* 2003; Reddy *et al.* 2000). Dietary factors that can reduce the absorption of iron (inhibitors) are phytates and some groups of polyphenols such as tannins (Reddy *et al.,* 2000; Sandberg et al., 1999), high intake of calcium and zinc (Lind *et al.,* 2003; Lynch, 2000), and cow's milk (Kibangou *et al.* 2005). Studies conducted in different regions of the world with high prevalence of anemia showed strong correlation between iron stores and absorbable iron intakes while there is no evidence of association between total iron intake, iron deficiency and anemia (Zimmermann *et al.,* 2005; Talata *et al.* 1998; Adish *et al.,* 1998).

4.2 Other micronutrient deficiencies associated with anemia

Other micronutrients are directly or indirectly involved in red blood cell metabolism. Vitamin B_6 (pyridoxal phosphate) for example is required for activation of Δ-aminolevulinic acid synthase that is necessary for heme synthesis. Vitamine B_9 (folate) and B_{12} (cobalamine) deficiencies result in immature erythrocyte leading to macrocytic anemia (Gropper *et al.,* 2005). Poor vitamin A status has been associated with Anemia (Gamble et al., 2004; Semba & Bloem 2002) and vitamin A supplementation has been shown to reduce the prevalence of Anemia (Semba *et al.,* 2001). Copper is an enzymatic cofactor of ceruloplasmin (ferroxydase) that is involved in iron mobilisation during the hemoglobin synthesis. Therefore, a deficiency of copper may contribute to iron deficiency anemia (Gropper *et al.,* 2005). It has been suggested that because of some similarities metabolic pathways of iron and zinc, high level zinc intake in the form of supplement may reduce the effectiveness of iron supplementation programmes aimed at reducing the burden anemia (Lind *et al.,* 2003).

4.3 Severe acute malnutrition

Acute malnutrition resulting from inadequate dietary intake of nutrients and/or from acute infection and disease may also lead to mild to moderate anemia. Several hypotheses have been put forward to explain the relationship between anemia and protein-energy malnutrition; 1) adaptation to lower tissue-metabolic requirements for oxygen transport, 2) the reduction of protein required for hematopoiesis and 3) the reduction of survival time of red blood cells and the maturation of the erythroblasts (MacDougall *et al.,* 1982). Some authors however consider that the anemia of PEM is the outcome of a complex haematological process in which iron and other micronutrient deficiencies interplay (Awasthi *et al.,* 2003).

5. Infections

Infections are the second most important cause of anemia after iron deficiency and contribute in some settings to up to 50% of the cases (Asobayire *et al.,* 2001; Stoltzfus *et al.,* 2000). Children are particularly affected by infection-related anemia because of their lower immune response

and their frequent exposure to poor sanitation and environmental conditions which favour the transmission and spread of parasites. Infections including malaria, hookworms, schistosomia, etc. are highly prevalent in developing countries and may negatively affect the nutritional status and growth of children. Studies conducted in many regions of Africa found positive associations between the presence and density of infection and chronic undernutrition, anemia and poor cognition (Brooker et al., 1999; Calis et al., 2008a; Friedman et al., 2005; Osazuwa et al. 2011; Sanou et al. 2008; Tolentino & Friedman, 2007). Regardless, the parasites or bacteria causing the anemia are different, all cases of anemia due to infection share some common pathways; 1) resulting iron deficiency through reduction of iron intake due to poor appetite and blood loss; 2) hemolysis i.e increased red blood cell destruction; 3) decreased red cells production and; 4) resulting inflammation. These mechanisms will be discussed later together with some pathways that are specific to each infection.

5.1 Malaria

The highest prevalence of childhood Anemia worldwide is found in malaria endemic regions. The WHO recent estimation of the global prevalence of anemia 1993-2005 suggested that between 31% and 90% of children in malaria-endemic areas of Africa suffer from anemia (WHO, 2008). Anemia is a common manifestation of the malaria infection and severe anemia can contribute to malaria mortality through hypoxia and cardiac failure (Memendez et al., 2000). Various *Plasmodium* species cause malaria, yet *P. falciparum* is the most critical for anemia in children. Contrary to iron deficiency anemia that develops slowly, *P. falciparum* causes severe and profound anemia within 48 hours of the onset of the fever. Other Plasmodium that can contribute to malaria include *P. vivax and P malariae*.

Table 1 shows the pathophysiology of malaria induced anemia. Philips and Pasvol (1992) summarized the pathophysiology of malarial anemia as follows, "anemia occurs when red cells are destroyed more rapidly than they can be replaced, or when red cell production falls below the minimal level required to maintain the steady state". Potential causes of increased red blood cell destruction include alteration of the red cell membrane rigidity and deformability, "loss of infected cells by rupture or phagocytosis, removal of uninfected cells due to antibody sensitization or other physico-chemical changes, and increased reticuloendothelial activity, particularly in organs such as the spleen" (Nuchsongsin et al., 2007; Park et al., 2008; Phillips & Pasvol, 1992). Factors leading to decreased red cell production include bone marrow hyploplasia and dyserythropoiesis. The severity of the malaria induced anemia is correlated with the density of the parasitaemia.

Although there is a consensus that clinical malaria causes severe anemia, there is limited evidence on the effect of asymptomatic malaria on severe anemia. While some authors reported that asymptomatic malaria does not significantly impact Haemoglobin level (Nkuo et al. 2002), some studies have demonstrated that asymptomatic malaria can cause homeostatic imbalance and lower Haemoglobin level in children (Kurtzhals et al. 1999); thus contributing to mild to moderate anemia (Price et al. 2001; Sowunmi et al., 2010; Umar et al. 2007). Imbalances of cytokines such as TNF-α, IL-6, IL-10 and IFN-γ resulting from malaria related-inflammation can induce changes in iron absorption and distribution, thus contributing to iron deficiency and subsequent iron deficiency anemia (Cercamondi et al., 2010; Shaw & Friedman, 2011). Bed net use is well documented as effective anemia prevention strategy (Korenromp et al., 2004, TerKuile, 2001). An exhaustive review of impact of malaria control on risk of anemia among children (Korenromp et al., 2004), estimates the protective effect of bed net on severe anemia to be 60%.

Mechanism	Comments
Increased erythrocyte destruction	
Non-immune mediated haemolysis	Rupture of parasitized red blood cells (PRBC) following invasion of RBC by malaria parasites
	Phagocytosis of parasitized (PRBC) and unparasitized red blood cells (NPRBC) due to proliferation and hyperactivity of macrophages in the reticuloendothelial system; thus shortening their life span
	Premature removal of NPRBC from the circulation due to reduce deformability and membrane binding of parasite components
	Increased clearance of parasitaemia due to splenic hypertrophy and hypersplenism (increased activity of the spleen that filters malaria infected RBC from the circulation)
Auto-immune haemolysis	Increased premature removal and clearance of unparasitized RBC due to immunoglobulin and complement activation leading to an extravascular haemolysis
	Hapten induced intravascular haemolysis due to the use of quinine that acts as a hapten combining with RBC protein to become antigenic
Decreased erythrocyte production	
Morphological abnormalities of the bone marrow	Aberrations of erythroblast morphology, macrophage hyperplasia, erythroid hypolasia and failure of reticulocyte release following a repeated attacks of malaria
Dyserythropoiesis	Morphological abnormalities of the eryhtroid series including multinuclearity of the normoblasts, intercytoplasmic bridging, karyorrhexis, incomplete and unequal mitotic nuclear divisions in some individuals with malaria
suppression of erythropoietin (EPO) synthesis	Suppression of EPO synthesis by inflammatory mediators such as TNF in some adults with malaria
Imbalances of cytokines (Inflammation induced anemia)	Bone marrow depression, dyserythropoeisis and erythrophagocytosis following low interleukine (IL-10 and IL-12) or excess of T helper cell type 1 (th1), cytokines THF-a et TNF-x, and nitric acid (NO)
Inflammation induced erythroid hypoplasia	Suppression of normal response to erythropoietin due to an autologous serum factor that may suppress the growth of early precursors of RBC including the burst-forming unit-erythron (BFU-E) and the colony-forming unit erythron (CFU-E).
Concomitant infections	Increased susceptibility to secondary infections due to reduced immune systems following malaria infection
Anti-malarial drugs	
Antifolate antimalarial	Megaloblastic anemia due to overdosing of pyremethamine and/or trimethoprim
	Quinine induced intravascular auto-immune haemolysis

Table 1. Pathophysiology mechanisms of malaria-related anemia (Memendez et al., 2000; Phillips & Pasvol, 1992).

Price et al. (2001) reported that treatment failure in uncomplicated malaria can lead to anemia. It has also been suggested that child undernutrition, particularly stunting modify the associations between malaria and anemia (Verhoef et al. 2002). Verhoef et al (2002) reported that stunting impairs host immunity, increases inflammation, and increases iron demand in developing erythroblasts, thus increasing the malaria-associated anemia.

5.2 Hookworms

Helminths are a group of intestinal nematodes that are recognized as a major public health problem in many developing countries. The effects on anemia are well documented for four species, namely trichomonas (*Trichuris trichiura),* ankylostoma (*Necator americanus*, A*ncylostoma duodenale*), hookworm (*Hymelolepis nana*) and ascaris (*Ascaris lumbricoides*). It is believed that the burden of hookworm is the most important particularly on severe anemia and is mostly due to extracorporeal blood loss in the stools resulting from a parasite release of a coagulase in the blood. *A. duodenale* was found more harmful than *N. americanum* and Skeletee (2003) for example estimated that it can cause approximately 0.25 mL blood loss per parasite per day during pregnancy.

According to a study done in Kenyan preschool children, hookworm contributed to 4% of anemia cases in children and heavy infection with hookworm increases the risk of anemia by 5 (Brooker et al., 1999). However, the authors did not find any association between hookworm and hemoglobin concentration likely due to the relatively low prevalence of the infection. Indeed, the burden of hookworm is directly related to the intensity of infection, the infecting species and the individual's nutritional status.

Calis et al. (2008a) also reported that the likelihood of developing severe anemia was increased by 4.8 in hookworm infected Malawian preschool children. In West Africa, a risk mapping approach using geostatistical models estimated that 4.2% of anemia cases in preschool children could be averted by treating hookworm (Magalhaes & Clements, 2011). *Trichomonas trichiura*, the causal agent of Trichuris Dysentery Syndrome has been associated with growth failure and Anemia. The anaemic effect of *T. trichiura* is thought to be linked to the blood consumption by the worm, inflammation induced anemia and reduced dietary iron intake due to decreased appetite (Shaw & Friedman, 2011).

Intervention studies have shown positive associations between mass deworming and decreased prevalence of anemia, physical performance, cognitive scores, growth and general morbidity among children from developing countries. Further, there is evidence that effectiveness of iron interventions such as supplementation and dietary approaches may be reduced when activities aiming at controlling infections are not part of the strategies (Davidson *et al.,* 2005). Therefore, it is recommended to include deworming in interventions targeting iron status at the community level.

5.3 Human schistosomiasis

Three major species of schistosomiasis have been identified as the most prevalent worldwide and cause human disease. These species that are endemic in some rural areas of Africa include *Schistosoma haematobium S. mansoni and S. japonica* (Friedman et al., 2005; Dianou *et al.,* 2004). Although most attention has been on schoolchildren, some studies have examined the relationship between schistosomiasis and anemia in preschool children (Brooker et al., 1999; Magalhaes & Clements, 2011; Talata et al., 1998). Friedman et al. (2005) described four mechanisms underlying the relationship between schistosome infections and

anemia: 1) iron deficiency due to extracorporeal blood loss of iron; 2) splenic sequestration iii) auto-immune hemolysis and; 4) anemia of inflammation. It is also important to mention that infection may reduce appetite and disturb the intakes, absorption and metabolism of dietary iron.

5.4 HIV/AIDS

Anemia is a common hematological manifestation in Human immunodeficiency (HIV-infection), and has been identified as a marker for disease progression and survival (Calis et al., 2008b). A review of the global literature on HIV-related anemia in children by Calis et al. (2008b) revealed that mild to moderate anemia was more prevalent and hematocrit levels lower in HIV-infected children as compared to uninfected children. The authors also found that Anemia prevalence was higher in children with more advanced disease. However, blood loss and hemolysis are not common in HIV-infection. The suspected pathogenetic mechanisms for HIV-related anemia likely include decreased production of erythrocytes and subsequent inflammation. Further, based on findings from Uganda (Totin et al., 2002) and South Africa (Eley et al., 2002) that have suggested that iron deficiency anemia is equally affecting both HIV-infected and uninfected children, Shaw & Friedman (2011) concluded that HIV-related anemia is an Anemia of inflammation.

5.5 Bacteremia

The most common anemia inducing bacteria reported in the literature *is Helicobacter pylori* (Digirolamo *et al.* 2007; Dubois & Kearney 2005). *H. pylori* is thought to cause anemia through three mechanisms: 1) reduced iron absorption due to hypochlorhydria resulting from impaired secretion of gastric acid; 2) inflammation and; 3) competing iron demands of the bacteria and the host (Shaw & Friedman, 2011). Nontyphoid *Salmonella* has been also independently associated with anemia in children (Calis et al. 2008a; Dubois et al., 2005).

Although not investigated, it is possible that other species that can cause bloody dysentery such as *Shigella* and *Enteroinvasive E. coli* contribute to anemia. Comorbid conditions such as fever and respiratory infection often resulting from bacterial infection have been correlated with anemia (Stoltzfus *et al.,* 2000; Howard *et al.,* 2007). Diarrheal illness is associated with loss of iron and decreased absorption of nutrients needed to maintain normal Hb status. It is also likely that as demonstrated for other nutrient deficiencies, diarrhea shares many common causes with anemia (Tomkins, 1986).

Further due to the high susceptibility of HIV-infected children to opportunistic infection, bacteria may also act as synergetic factors in HIV-related anemia. A number of studies have reported biological synergisms between pathogens for disease progression (Ezeamama et al., 2008; Robertson et al., 1992). Ezeamama et al. (2008) investigated the effect of codistribution of schistosomiasis, hookworm and trichuris infection on paediatric anemia and found that hookworm and *S. japonicum* infections were independent risk factors for anemia and that co-infections of hookworm and either *S. japonicum* or *T. trichiura* were associated with higher levels of anemia than would be expected if the effects of these species had only independent effects on anemia. More recently, Magalhaes & Clements (2011) found that hookworm/S. haematobium coinfection significantly increased the likelihood of pediatric anemia as compared to individual infestation with one of these pathogens.

6. Inflammation and chronic diseases

Anemia of inflammation also termed the anemia of chronic disease (ACD) is the second most prevalent type of anemia after anemia of iron deficiency. It is observed in patients with chronic infectious disease (tuberculosis, meningitis, pulmonary infection to name a few), non-infectious chronic conditions (rheumatoid arthritis, Crohn disease, burn patients, etc.) or chronic neoplasic conditions (leukemia, carcinoma, Hodgkin disease, etc.) (Weiss & Goodnough, 2005). The pathophysiological mechanisms are not well understood, but it is believed that they are similar to the indirect pathways by which infection causes anemia. Anemia of chronic inflammatory diseases is immune driven and includes several pathways regulated by different immune and inflammatory mediators (Weiss & Goudnough, 2005):

- decreased red blood cell half-life because of dyserythropoiesis, red blood cell damage and increased erythrophagocytosis (TNF-α);
- inadequate erythropoietin responses for the degree of anemia in most, but not all (e.g. systemic-onset of juvenile chronic arthritis) (IL-1 and TNF-α);
- impaired responsiveness of erythroid cells to erythropoietin (IFN-γ, IL-1, and TNF-α);
- inhibited proliferation and differentiation of erythroid cells (IFN-γ, IL-1, TNF-α, and α-1-antitrypsin); and
- pathological iron homeostasis caused by increased DMT-1 (IFN-γ) and TfR (IL-10) expression in macrophages, reduced ferroportin 1 expression (IFN-γ and IL-6-induced high hepcidin levels) in enterocytes (inhibition of iron absorption) and macrophages (inhibition of iron recirculation), and increased ferritin synthesis (TNF-α, IL-1, IL-6, IL-10) (increased iron storage).

In a review published in New England Journal of Medicine, Weiss & Goudnough (2005) carefully discussed these mechanisms and summarized them in a single figure (Figure 2).

Recent studies have identified hepcidin as the main iron regulatory hormone in human (Andrews & Schmidt, 2007, Ganz, 2003). Hepcidin is an antimicrobial hormone that is synthesized in response to liver iron levels, inflammation, hypoxia and anemia. The persistence of inflammation results in excess hepcidin which in the circulation binds ferroportin on enterocytes and macrophages. The excess of hepcidin lowers iron absorption and prevents iron recycling, which results in hypoferremia and iron-restricted erythropoiesis, despite normal iron stores (functional ID), and anemia of chronic disease. In acute inflammation-related anemia (e.g. trauma or surgery), inflammatory responses are mediated by cytokine production mainly IL-6 and IL-8 (Weiss & Goudnough, 2005). Indeed, during inflammation, cytokines such as interleukin IL-6 stimulates the human hepcidin gene (HAMP) which in turns induces hepcidin secretion in the hepatocytes (Nicolas *et al.,* 2002; Nemeth *et al.*, 2004). In contrast, decreased hepcidin expression due to iron deficiency, anemia and hypoxia may lead to hereditary haemochromatosis (HH type I, mutations of the HFE gene) and type II (mutations of the hemojuvelin and hepcidin genes). In persisting iron deficiency due to decreased iron absorption and/or chronic blood loss, anemia of chronic disease evolves to anemia of chronic disease with a true iron deficiency (ACD + ID).

It is also important to keep in mind that the links between anemia and infection are bilateral and may be mutually beneficial. Indeed iron deficiency may protect against adverse effects of infections on iron status (Denic & Agarwal 2007; Sazawal *et al.,* 2006; Oppenheimer, 2001; Weinberg 1984).

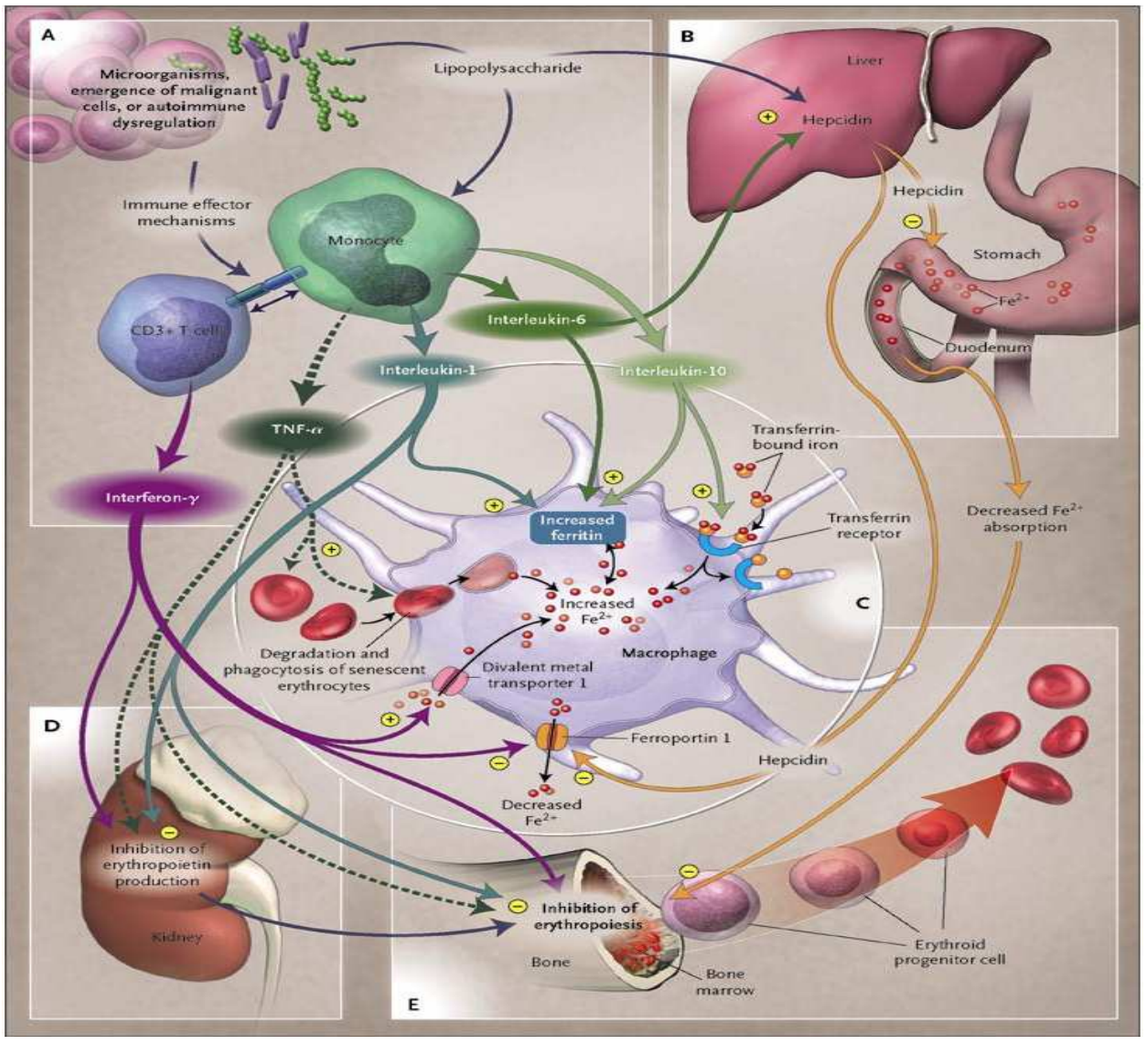


Fig. 2. Pathophysiological mechanisms of anemia of chronic diseases (Weiss & Goudnough, 2005) - reproduced with the permission from the authors and the New England Journal of Medicine -

In Panel A, the invasion of microorganisms, the emergence of malignant cells, or autoimmune dysregulation leads to activation of T cells (CD3+) and monocytes. These cells induce immune effector mechanisms, thereby producing cytokines such as interferon-γ (from T cells) and tumor necrosis factor α (TNF-α), interleukin-1, interleukin-6, and interleukin-10 (from monocytes or macrophages). In Panel B, interleukin-6 and lipopolysaccharide stimulate the hepatic expression of the acute-phase protein hepcidin, which inhibits duodenal absorption of iron. In Panel C, interferon-γ, lipopolysaccharide, or both increase the expression of divalent metal transporter 1 on macrophages and stimulate the uptake of ferrous iron (Fe2+). The antiinflammatory cytokine interleukin-10 up-regulates transferrin receptor expression and increases transferrin-receptor–mediated uptake of transferrin-bound iron into monocytes. In addition, activated macrophages phagocytose and degrade senescent erythrocytes for the recycling of iron, a process that is further induced by TNF-α through damaging of erythrocyte membranes and stimulation of phagocytosis. Interferon-γ and lipopolysaccharide down-regulate the expression of the macrophage iron

transporter ferroportin 1, thus inhibiting iron export from macrophages, a process that is also affected by hepcidin. At the same time, TNF-α, interleukin-1, interleukin-6, and interleukin-10 induce ferritin expression and stimulate the storage and retention of iron within macrophages. In summary, these mechanisms lead to a decreased iron concentration in the circulation and thus to a limited availability of iron for erythroid cells. In Panel D, TNF-α and interferon-γ inhibit the production of erythropoietin in the kidney. In Panel E, TNF-α, interferon-γ, and interleukin-1 directly inhibit the differentiation and proliferation of erythroid progenitor cells. In addition, the limited availability of iron and the decreased biologic activity of erythropoietin lead to inhibition of erythropoiesis and the development of anemia. Plus signs represent stimulation, and minus signs inhibition (Weiss & Goudnough, 2005).

7. Genetic polymorphisms

Some hemoglobinopathies such as sickle-cell disease, thalassaemias, glucose-6-phosphate deshydrogenase are common in many developing countries (Deyde et al., 2002; Simpore *et al.,* 2003; Thurlow *et al.,* 2005*)*. These disorders are particularly found in malaria endemic areas and have been associated with Anemia. Glucose-6-phosphate deshydrogenase for example is correlated with chronic haemolytic Anemia (Lang *et al.,* 2002; van Bruggen *et al.,* 2002).

Sickle cell Anemia is highly prevalent in West Africa, with a frequency of the trait of 15% to 30% (WHO, 2006). Many studies suggested that these red cell polymorphisms are a human body adaptation against adverse effects of malaria. Sickle cell for example results from genetic mutation of allele A in allele S or C of the β chain to provide resistance against *Plasmodium* effect (Modiano *et al.* 2008; Rihet *et al.* 2004). In Gambia and Burkina Faso, it has been reported that sickle-cell trait is associated with protection against malaria, malaria Anemia and even cerebral Anemia (Hill, 1991; Modiano et al., 2008). In central Burkina Faso, the prevalence is expected to increase if the malaria prevalence does not decrease (Modiano et al., 2008).

Data from the National Health and Nutrition Examination Survey» (NHANES I, II et III) of the USA consistently show hemoglobin levels of Black Americans are usually lower than for their white and hispanic counterparts at all ages, regardless of the iron, health et socioeconomic status (Johnson-Spear & Yip, 1995). This finding has resulted in an adjustment of Haemoglobin cut-off for population origin 1 g/L below the normal cut-off for other population groups (Nestel et al., 2002). Although the causes of this difference is not well established, it is hypothesized that high prevalence of hemoglobinopathies such as thalassaemias and chronic inflammations as well as other genetic disorders may be important contributing factors (Beutler & West, 2005).

8. Socio-economic risk factors

The socioeconomic status, commonly measured by household income and/or household assets is a key determinant of anemia. There is strong evidence that that children living in low income household are at greater risk of anemia compared to those with higher income. Limited access to food and poor sanitation are often correlated to low income and to some extent, explain the higher risk of anemia among these children (Osorio et al., 2004). Moreover, the diet of children living in poor families is usually monotonous, even when there is enough

food to eat. A study by Ag Bendech et al. (1996) in Burkina Faso showed that even though almost all the family enrolled were having three meals per day, only children from the wealthiest families were taken two or three different meals while their peers from middle income and poor households had the same meals for breakfast, lunch and dinner. The authors also reported that animal source foods which are rich in bioavailable iron were limited, contributing to only 9% of the total protein intake in poor households, 19% in middle income households and up to 41% in wealthiest households (Ag Bendech et al., 1996).

Parent's level of education constitutes another well documented determinant of anemia in children. Educated parents are more likely to have well paid job and also more likely to adopt healthier dietary behavior. In Brazil, Osorio's et al. (2004) found that mean hemoglobin level of children whose mothers attended secondary schools (9 years of schooling) was 11.5 g/dl, 11.2 for mothers with 5-8 years in school and 10.8 g/dl for mothers with less than 4 years of schooling. De Pee et al. (2002) report similar results among Palestinian children with risk of anemia twice higher for children from non-educated mothers. Even in developed countries, low level of education is associated with higher risk of anemia (Sargent et al., 1996; Soh et al., 2004).

Community level factors play an important role in the risk of anemia. Several studies have shown that living in rural areas increases the risk of child malnutrition (Kuate-Defo, 2001 ; Sommerfelt, 1991) and anemia (Bentley 2003; Osorio et al. 2001; Osorio et al., 2004; Ngnie-Teta et al., 2007). Altitude also affects the risk of anemia. Indeed, the amount of oxygen decrease with altitude, hence reducing the saturation ability of hemoglobin to capture oxygen (Cohen & Haas, 1999). This should be counterbalanced by an increased number of red blood cells. Therefore hemoglobin cut-offs have been adjusted for different age groups according to the altitude (Nestel *et al.,* 2002).

Due to increasing use of multilevel, modelling neighbourhood contribution to the risk of disease could now be quantified. A recent study in West Africa reported significant contribution of community factors of 14% to 19% to the prevalence of moderate-to-severe anemia (Ngnie-Teta et al., 2007; 2008). This reflects the variability in the risk of anemia attributable to the differences between communities, regardless of individual and households characteristics.

9. Conclusion

Anemia can result from deficiency of one or several micronutrients but also unfavourable environmental conditions and social determinants of health. Although quantitative and qualitative iron deficiency is thought to be the leading cause, infection such as malaria, schistosomiasis, hookworms, HIV and bacteria can contribute to up to 50% of the cases of anemia in developing regions where these conditions are common. Due to the multi-factorial conditions, the complexity of the risk factors of anemia, and potential interactions among them, a single strategy to control anemia in developing countries may have little success. Country level strategies to tackle anemia should include an emergency nutrition programme that will target severe anemia particularly in children under the age of two and children who live in rural areas, but also a broader nutrition and health programme that may to prevent and treat moderate to mild Anemia. Whatever strategy is used, nutrition education to increase animal sources in the diet where possible in order to enhance bioavailability of iron and to improve sanitation and basic hygiene are highly recommended as complementary measures.

10. Acknowledgement

We are grateful to Dr Weiss Gunter from the Medical University of Innsbruck, Austria and the Publishing Division of the Massachusetts Medical Society, publisher of the New England Journal of Medicine for granting us the permission to use their illustration. Our colleagues and friends who help with the editing of the earlier version of the manuscript namely Dr Nonsikelelo Mathe from the University of Alberta, Canada, Dr Reginald Annan from the International Malnutrition Task Force, University of Southampton, UK and Mrs Sabra Saleh from the Micronutrient Initiative, Dakar Senegal are kindly thanked.

11. References

Adish AA, Esrey ES, Gyorkos TW, Johns T, 1998. Risk factors for iron deficiency anemia in preschool children in northern Ethiopia. *Public Health Nutr* 2(3) : 243–252.

Ag Bendech M, Chauliac M and D Malvy Variability of home dietary habits of families living in Bamako (Mali) according to their socioeconomic status. Sante. 1996;6(5):285-297.

Andrews NC, Schmidt PJ, 2007. Iron Homeostasis. *Ann Rev Physiol* 69 : 69–85.

Awasthi S, Das R, Verma T, 2003. Anemia and undernutrition among preschool children in Uttar Pradesh, India. *Indian Pediatr* 40 : 985–990.

Asobayire FS, Adou P, Davidson L, Cook JD, Hurrell RF, 2001. Prevalence of iron deficiency with and without concurrent anemia in population groups with high prevalence of malaria and infections: a study in Côte d'Ivoire. *Am J Clin Nutr* 74 : 776-782.

Beutler E, West C, 2006. Hematologic differences between African-Americans and whites: the roles of iron deficiency and α-thalassemia on hemoglobin levels and mean corpuscular volume. *Blood* 106(2) : 740–745.

Brooker S, Peshu N, Warn PA, Mosobo M, Guyatt H, Marsh K, Snow RW, 1999. Epidemiology of hookworm infection and its contribution to anemia among pre-school children on the Kenyan coast. *Trans Royal Soc Trop Med Hyg* 93: 240–246.

Calis JCJ, Phiri KS, Faragher EB, Brabin BJ, Bates I, Cuevas LE, et al., 2008a. Severe anemia in Malawian children. *N Engl J Med* 358(9) : 888-899.

Calis JCJ, Boele van Hensbroek MB, de Haan RJ, Moons P, Brabin BJ, Bates I, 2008b. Risk factors and correlates for anemia in HIV treatment-naïve infected patients: a cross-sectional analytical study. *AIDS*. 22(10):1099-112.

Cercamondi CI, Egli IM, Ahouandjinou E, Dossa R, Zeder C, Salami L, Tialsma H, et al. 2010. Afebrile Plasmodium falciparum parasitemia decreases absorption of fortification iron but does not affect systemic iron utilization: a double stable-isotope study in young Beninese women. *Am J Clin Nutr 2010;92:1385–92.*

Chandra J, Jain V, Narayan S, Sharma S, Singh V, Kapoor AK, Batra S, 2002. Folate and cobalamin deficiency in megaloblastic anemia in children. *Indian Pediatr* 39(5):453-7.

Cohen JH, Haas JD, 1999. Hemoglobin correction factors for estimating the prevalence of iron deficiency anemia in pregnant women residing at high altitudes in Bolivia. *Pan Am J Public Health* 6(6) : 392-399.

Davidson L, Nestel P et le comité de pilotage de l'INACG, 2005. *Efficacité et efficience des interventions dans la lutte contre la carence en fer et l'anémie ferriprive.* Washington 6 p.

De Pee S., Bloem M.W., Sari M., Kiess L., Yip R. The high prevalence of low hemoglobin concentration among indonesia infants aged 3-5 months is related to maternal anemia. J. Nutr 2002; 132:2215-21

Denic S, Agarwal MM, 2007. Nutritional iron deficiency: an evolutionary perspective. *Nutrition* 23(7-8) : 603-14.

Deyde V, Lo B, Khalifa I, Ball A, Fattoum S, 2002. Epidemiological profile of hemoglobinopathies in the Mauritanian population. *Ann Hemat* 81 (6): 320-321.

Dianou D, Poda JN, Savadogo LG, Sorgho H, Wango SP, Sondo B,2004. Parasitoses intestinales dans la zone du complexe hydroagricole du Sourou au Burkina Faso. *Vertigo* 5(2) : 1-8.

Diaz M, Rosado JL, Allen LH, Abrams S, García OP, 2003. The efficacy of a local ascorbic acid–rich food in improving iron absorption from Mexican diets: a field study using stable isotopes. *Am J Clin Nutr* 78 : 436–440.

Digirolamo AM, Perry GS, Gold BD, Parkinson A, Provost E, Parvanta I et al., 2007. Helicobacter pylori, anemia, and iron deficiency: relationships explored among Alaska native children. *Pediatr Infect Dis J* 26(10) : 927-934.

Dubois S, Kearney JD, 2005. Iron-deficiency anemia and Helicobacter pylori infection: A review of the evidence. *Am J Gastroent* 100(2) : 453–459.

Eley BS, Sive AA, Shuttleworth M, Hussey GD, 2002. A prospective, cross-sectional study of anemia and peripheral iron status in antiretroviral näive, HIV-1 infected children in Cape Town, South Africa. *BMC Infect Dis* 2(3) Epub 2002

Ezeamama AE, McGarvey ST, Acosta LP, Zierler S, Manalo DL, et al. (2008) The synergistic effect of concomitant schistosomiasis, hookworm, and trichuris infections on children's anemia burden. PLoS Negl Trop Dis 2: e245. doi

Friedman JF, Kanzaria HK, McGarvey ST, 2005. Human schistosomiasis and anemia: the relationship and potential mechanisms *Trends in Parasitology* 21(8):386-92.

Gamble MV, Palafox NA, Dancheck B, Ricks MO, Briand K, Semba RD, 2004. Relationship of vitamin A deficiency, iron deficiency, and inflammation to anemia among preschool children in the Republic of the Marshall Islands. *Eur J Clin Nutr* 58(10) :1396-401.

Ganz T, 2003. Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. *Blood* 102 : 783-788.

Gibson RS, Ashwell M, 2003. The association between red and processed meat consumption and iron intakes and status among British adults. *Public Health Nutr* 6(4) : 341-350.

Gleason GR. Iron deficiency anemia finally reaches the global stage of public health. Nutr Clin Care. 2002 (5):217-9

Gropper SS, Smith JL, Groff JL, 2005. *Advanced nutrition and human metabolism*. 14th ed. Thomson Wadsworth. Belmont CA.

Hill AV, Allsopp CE, Kwiatkowski D, Anstey NM, Twumasi P, Rowe PA, Bennett S, Brewster D, McMichael AJ, Greenwood BM, 1991. Common west African HLA antigens are associated with protection from severe malaria. *Nature* 352(6336):595.

Horton S, Ross J, 2003. The economics of iron deficiency, *Food Policy* 28:51-75.

Howard CT, de Pee S, Sari M, Bloem MW, Semba RD, 2007. Association of diarrhea with anemia among children under age five living in rural areas of Indonesia. *J Trop Pediatr* 53(4) : 238-244.

Jain SK, Williams DM, 1988. Copper deficiency anemia: altered red blood cell lipids and viscosity in rats. Am J Clin Nutr 48(3):637-40.

Johnson-Spear MA, Yip R, 1995. Hemoglobin difference between black and white women with comparable iron status: justification for race-specific anemia criteria. *Am J Clin Nutr* 60 : 117-121.

Kibangou IB, Bouhallab SH, Gwenaele BF, Allouche S, Blais A, Guerin P, Arhan P, Bougle DL, 2005. Milk proteins and iron absorption: contrasting effects of different caseino-phosphopeptides. *Pediatric Res* 58(4) : 731-734.

Korenromp EL, Armstrong-Schellenberg JR, Williams BG, Nahlen BL, Snow RW, 2004. Impact of malaria control on childhood anemia in Africa -- a quantitative review. *Trop Med Int Health* 9:1050-65.

Kuate-Defo B, 2001. Modelling hierarchically clustered longitudinal survival processes with applications to childhood mortality and maternal health. Canadian Studies Population 28 (2)

Kurtzhals JA, Addae M, Akanmori BD, Dunyo S, Koram KA, Appawu MA, Nkrumah FK, Hviid L, 1999. Anemia caused by asymptomatic *Plasmodium falciparum* infection in semi-immune African schoolchildren. *Trans R Soc Trop Med Hyg* 1999;93:623-627..

Lang K, Roll B, Myssina S, Schittenhelm M, Scheel-Walter HG, Kanz L, et al., 2002. Enhanced erythrocyte apoptosis in sickle cell anemia, thalassemia and glucose-6-phosphate dehydrogenase deficiency. *Cell Phys Bioch* 12 : 365-372.

Lind T, Lonnerdal B, Stenlund H, Ismail D, Seswandhana R, Ekstrom EC, Persson LA, 2003. A community-based randomized controlled trial of iron and zinc supplementation in Indonesian infants: interactions between iron and zinc. *Am J Clin Nutr* 77(4) : 883-890.

Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW, 2000. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. *Pediatrics* 105 : 1-11.

Lynch SR, 2000. The effect of calcium on iron absorption. *Nutr Res Rev* 13 : 141-158.

MacDougall LG, Moodley Gopal, Eyberg C, Quirk M, 1982. Mechanisms of anemia in protein-energy malnutrition in Johannesburg. *Am J Clin Nutr* 35 : 229-235.

Magalhães RJS, Clements ACA, 2011. Mapping the risk of anemia in preschool-age children: the contribution of malnutrition, malaria, and helminth infections in West Africa. PLoS M*edicine*, 8(6): e1000438 doi:10.1371/journal.pmed.1000438

Mann N, 2007. Meat in the human diet: an anthropological perspective. *Nutr Diet* 64 (Suppl. 4) : S102–S107.

Menendez C, Fleming AF, Alonso PL, 2000. Malaria-related anemia. *Parasitol Today 16(11):469-76.*

Mikki N, Abdul-Rahim HF, Stigum H, Holmboe-Ottesen G, 2011. Anemia prevalence and associated sociodemographic and dietary factors among Palestinian adolescents in the West Bank. *East Medit Health J*. 17 (3): 208-217.

McLean E, Coqswell M, Egli I, Wojdyla D, de Benoist B, 2009. Worldwide prevalence of anemia, WHO vitamin and mineral nutrition information system, 1993-2005. *Public Health Nutr.* 12(4):444-54.

Modiano D, Bancone G, Ciminelli BM, Pompei F, Blot I, Simpore J, Modiano G, 2008. Haemoglobin S and haemoglobin C: 'quick but costly' versus 'slow but gratis'

genetic adaptations to Plasmodium falciparum malaria. *Hum Mol Genet* 17(6): 789-799.

Monsen ER, Hallberg L, Layrisse M, Hegsted DM, Cook JD, Walter M, Finch CA, 1978. Estimation of available dietary iron. *Am J Clin Nutr* 31 : 134-141.

Sowunmi A, Gbotosho GO, Happi CT, Fateye BA, 2010. Factors contributing to anemia after uncomplicated *Plasmodium falciparum* malaria in children. *Acta Trop 113(2):155-61.*

Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf T, Pedersen BK, Ganz T, 2004. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. *J Clin Invest* 113 : 1271-1276.

Nestel P et le Comité de pilotage de l'INACG, 2002. *Adjusting hemoglobin values in program surveys.* International Nutritional Anemia Consultative Group (INACG), 6 p.

Ngnie-Teta I, Receveur O, Kuate-Defo B, 2007. Risk factors for moderate to severe anemia among children in Benin and Mali: insights from a multilevel analysis. *Food Nutr Bull* 28(1) : 76-89.

Ngnie-Teta I; Kuate-Defo B; Receveur O, 2009. Multilevel modelling of sociodemographic predictors of various levels of anemia among women in Mali. Public Health Nutrition 12(9):1462-9.

Nicolas G, Chauvet C, Viatte L, Danan JL, Bigard X, Devaux I, et al. 2002. The gene encoding the iron regulatory peptide hepcidin is regulated by anemia, hypoxia, and inflammation. *J Clin Invest* 110 : 1037-1044.

Nkuo-Akenji TK, Ajame EA, Achidi EA, 2002. An investigation of symptomatic malaria parasitaemia and anemia in nursery and primary school children in Buea District Cameroon. Central African journal of medicine. 48 (1-2): 1-4

Nuchsongsin F, Chotivanich K, Charunwatthana P et al. 2007. Effects of Malaria Heme Products on Red Blood Cell Deformability. *Am J Trop Med Hyg* 77(4):617–622.

Oppenheimer SJ, 2001. Iron and its relation to immunity and infectious disease. *J Nutr* 131 : 616S–635S.

Osorio MM, Lira PI, Ashworth A, 2004. Factors associated with Hb concentration in children aged 6–59 months in the State of Pernambuco, Brazil. *Br J Nutr* 91 : 307–315.

Pan WH, Habicht JP, 1991. The non-iron-deficiency-related difference in hemoglobin concentration distribution between blacks and whites and between men and women. *Am J Epidemiol* 134(12) : 1410-1416.

Park YK, Diez-Silva M, Popescu G, Lykotrafitis G, Choi W, Feld MS, Suresh S, 2008. Refractive index maps and membrane dynamics of human red blood cells parasitized by *Plasmodium falciparum PNAS* 105(37):13730–13735

Rock E, Gueux E, Mazur A, Motta C, Rayssiguier Y, 1995. Anemia in copper-deficient rats: role of alterations in erythrocyte membrane fluidity and oxidative damage. *Am J Physiol 269(5 Pt 1):C1245-9.*

Phillips RE & Pasvol G, 1992. Anemia of Plasmodium falciparum malaria. *Baillieres Clin Haematol* 5(2):315-30.

Prentice AM, 2008. Iron metabolism, malaria, and other infections: what is all the fuss about? *J Nutr* 138 (12): 2537-2541.

Price RN, Simpson JA, Nosten F, Luxemburger C, Hkirjaroen L, ter Kuile F, Chongsuphajaisiddhi T, White NJ, 2001. Factors contributing to anemia after uncomplicated falciparum malaria. *Am J Trop Med Hyg* 65:614-622.

Reddy RB, Hurrell RF, Cook RD, 2000. Estimation of nonheme-iron bioavailability from meal composition. *Am J Clin Nutr* 71 : 937–943.

Rihet P, Flori L, Tall F, Traore AS, Fumoux F, 2004. Hemoglobin C is associated with reduced Plasmodium falciparum parasitemia and low risk of mild malaria attack. *Hum Mol Gen* 13(1) : 1–6.

Robertson LJ, Crompton DW, Sanjur D, Nesheim MC (1992) Haemoglobin concentrations and concomitant infections of hookworm and Trichuris trichiura in Panamanian primary schoolchildren. *Trans R Soc Trop Med Hyg* 86: 654–656

Sandberg AS, Brune M, Carlsson NG, Hallberg L, Skoglund E, Rossander-Hulthén L, 1999. Inositol phosphates with different numbers of phosphate groups influence iron absorption in humans. *Am J Clin Nutr* 70 : 240–246.

Sanou D, Turgeon-O'Brien H, Desrosiers T, 2008. Prévalence et déterminants non alimentaires de l'anémie et de la carence en fer chez des orphelins et enfants vulnérables d'âge préscolaire du Burkina-Faso. *Nutr Clin Metab* 22 (1) : 10-19.

Sanou D, Turgeon-O'Brien H, Desrosiers T, 2011. Impact of an integrated nutrition intervention on nutrient intakes, morbidity and growth of rural Burkinabe preschool children. *AJFAND* 11:(4) Epub July 2011. http://www.ajfand.net/Volume11/No4/Sanou9895.pdf

Sargent JD, Stukel TA, Dalton MA, Freeman JL, Brown MJ, 1996. Iron deficiency in Massachusetts communities: Socioeconomic and demographic risk factors among children. *Am J Public Health* 86(4):544-50.

Sazawal S, Black RE, Ramsan M, Chwaya HM, Stoltzfus RJ, Dutta A, et al., 2006. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. *Lancet* 367 : 133-143.

Semba RD, Bloem MW, 2002. The anemia of vitamin A deficiency: epidemiology and pathogenesis. *Eur J Clin Nutr* 56:271-281

Semba RD, Kumwenda N, Taha TE, Mtimavalye L, Broadhead R, Garrett E, et al., 2001. Impact of vitamin A supplementation on anemia and plasma erythropoietin concentrations in pregnant women: a controlled clinical trial. *Eur J Haematol* 66 : 389-395 .

Shaw FJC, Kuate-Defo B, 2005. Socioeconomic inequalities in early childhood malnutrition and morbidity: modification of the household-level effects by the community SES. Health Place 11:205-25.

Shaw JG, Friedman JF, 2011. Iron deficiency anemia: Focus on infectious diseases in lesser developed countries *Anemia* 260380. Epub 2011 May 15

Simpore J, Nikiema JB, Sawadogo L, Pignatelli S, Blot I, Bere A, et al., 2003. Prévalence des hémoglobinopathies HbS et HbC au Burkina. *Burkina Medical* 32 : 1-13

Skeletee RW, 2003. Pregnancy, nutrition and parasitic diseases. *J Nutr* 133:1661S-1667S

Soh P, Ferguson EL, McKenzie JE, Homs MY, Gibson RS. Iron deficiency and risk factors for lower iron stores in 6-24-month-old New Zealanders. Eur J Clin Nutr. 2004 Jan;58(1):71-9.

Sommerfelt AE. Comparative analysis of the determinants of children's nutritional status. Demographic and Health Surveys World Conference, vol 2, 981-98. 1991 Washington DC, 722-43

Stoltzfus RJ, Chwaya HM, Montresor A, Albonico M, Savioli L, Tielsch JM, 2000. Malaria, hookworms and recent fever are related to anemia and iron status indicators in 0- to 5-y old Zanzibari children and these relationships change with age. *J Nutr* 130 : 1724–1733.

Talata S, Svanberg U, Mduma B, 1998. Low dietary iron availability is a major cause of anemia: a nutrition survey in the Lindi district of Tanzania. *Am J Clin Nutr* 68 : 171–178.

Taylor-Robinson DC, Jones AP, Garner P, 2007. Deworming drugs for treating soil-transmitted intestinal worms in children: effects on growth and school performance. *Cochrane Database of Systematic Reviews Issue* 4. Art. No.: CD000371.

ter Kuile FO, Terlouw DJ, Kariuki SK, et al. Impact of permethrin-treated bed nets on malaria, anemia, and growth in infants in an area of intense perennial malaria transmission in western Kenya. Am J Trop Med Hyg 2003;68:68-77.

Thorandeniya T, Wickremasinghe R, Ramanyake R, Atukorala S, 2006. Low folic acid status and its association with anemia in urban adolescent girls and women of childbearing age in Sri Lanka. *Brit J Nutr.* 95 (3): 511-516.

Thurlow RA, Winichagoon P, Green T, Wasantwisut E, Pongcharoen T, Bailey KB, Gibson RS, 2005. Only a small proportion of anemia in northeast Thai schoolchildren is associated with iron deficiency. *Am J Clin Nutr* 82 : 380–387.

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

Tomkins AM. Protein-energy malnutrition and risk of infection. Proc Nutr Soc 1986;45:289-304.

Totin D, Ndugwa C, Mmiro F, Perry RT, Brooks Jackson J, Semba RD, 2002. Iron deficiency anemia is highly prevalent among human immunodeficiency virus-infected and uninfected infants in Uganda. *Jf Nutr*132(3):423–429.

Umar RA, Jiya NM, Ladan MJ, Abubakar MK, Hassan SW, Nata`ala U, 2007. low prevalence of anemia in a cohort of pre-school children with acute uncomplicated f*alciparum* malaria in Nigeria. *Trends Med Res 2: 95-101.*

van Bruggen R, Bautista JM, Petropoulou T, de Boer M, van Zwieten R, Gomez-Gallego F, et al., 2002. Deletion of leucine 61 in glucose-6-phosphate dehydrogenase leads to chronic nonspherocytic anemia, granulocyte dysfunction, and increased susceptibility to infections. *Blood* 100(3) : 1026 - 1030.

Verhoef H, West C, Veenemans J, Beguin Y, Kok F, 2002. Stunting may determine the severity of malaria-associated anemia in African children. *Pediatrics* 110:E48

Walker FC, Kordas K, Stoltzfus RJ, Black RE, 2005. Interactive effects of iron and zinc on biochemical and functional outcomes in supplementation trials. *Am J Clin Nutr* 82 : 5-12.

Wander K, Shell-Duncan B, McDade TW, 2009. Evaluation of iron deficiency as a nutritional adaptation to infectious disease: An evolutionary medicine perspective. *American Journal of Human Biology*, 2009; 21(2):172-179.

Weinberg, ED. Iron withholding: a defense against infection and neoplasia. *Physiological Reviews,* 1984; 64:65-102.

Weiss G, Goodnough LT, 2005. Anemia of chronic disease. *N Engl J Med* 352 : 1011-1023.

WHO, Sickle-cell anemia. Report by the Secretariat of the World Health Organization for the fifty-ninth world health assembly. 24 April 2006.

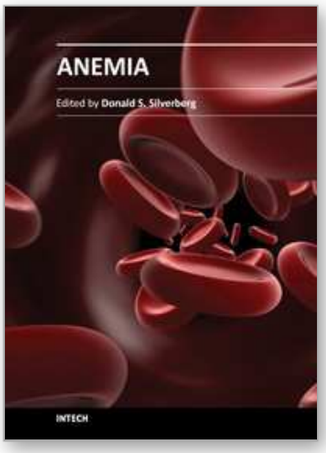
WHO. 2008. Worldwide prevalence of anemia 1993–2005 : WHO global database on anemia / Edited by Bruno de Benoist,

WHO/UNICEF, 2006. *Iron supplementation of young children in regions where malaria transmission is intense and infectious disease highly prevalent*. Joint statement by the World Health Organization and the United Nations Children's Fund. Geneva. 2 p.

WHO/UNICEF, 2006. *Iron supplementation of young children in regions where malaria transmission is intense and infectious disease highly prevalent*. WHO/UNICEF Joint statement. Geneva.

WHO/UNICEF/UNU. *Iron deficiency anemia assessment, prevention and control: a guide for programme managers.* World Health Organization. (WHO/NHD/01.3) Geneva, 2001.

Zimmermann MB, Chaouki N, Hurrell RF, 2005a. Iron deficiency due to consumption of a habitual diet low in bioavailable iron: a longitudinal cohort study in Moroccan children. *Am J Clin Nutr* 81: 115–121.



Anemia

Edited by Dr. Donald Silverberg

ISBN 978-953-51-0138-3
Hard cover, 440 pages
Publisher InTech
Published online 29, February, 2012
Published in print edition February, 2012

This book provides an up- to- date summary of many advances in our understanding of anemia, including its causes and pathogenesis, methods of diagnosis, and the morbidity and mortality associated with it. Special attention is paid to the anemia of chronic disease. Nutritional causes of anemia, especially in developing countries, are discussed. Also presented are anemias related to pregnancy, the fetus and the newborn infant. Two common infections that cause anemia in developing countries, malaria and trypanosomiasis are discussed. The genetic diseases sickle cell disease and thalassemia are reviewed as are Paroxysmal Nocturnal Hemoglobinuria, Fanconi anemia and some anemias caused by toxins. Thus this book provides a wide coverage of anemia which should be useful to those involved in many fields of anemia from basic researchers to epidemiologists to clinical practitioners.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Dia Sanou and Ismael Ngnie-Teta (2012). Risk Factors for Anemia in Preschool Children in Sub-Saharan Africa, Anemia, Dr. Donald Silverberg (Ed.), ISBN: 978-953-51-0138-3, InTech, Available from: http://www.intechopen.com/books/anemia/risk-factors-for-anemia-in-preschool-children-in-sub-saharan-africa

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821