An Update on Anemia in Less Developed Countries

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Abstract. The highest prevalence of anemia exists in the developing world where its causes are multi-factorial. Anemia is responsible for significant morbidity and mortality, particularly in less developed countries (LDCs). Understanding causes of anemia and potential mechanisms are crucial to our ability to intervene to reduce this burden. In the past decade, our understanding of the etiology and mechanisms of anemia in LDCs has advanced significantly. This review will focus on recent advances in our understanding of the burden of anemia in specific sub-groups, the causes and mechanisms of anemia, and consequences of anemia for the human host.

INTRODUCTION

The highest prevalence of anemia exists in the developing world where its causes are multi-factorial. In the developing world, 42% of children less than five years of age and 53% of children 5–14 years of age are anemic. Anemia has been related to reduced work capacity, reduced ability to execute activities of daily living, poor pregnancy outcomes, and reduced cognitive function. With limited resources and the complex, often multi-factorial nature of anemia in the developing world, combating this problem is a global public health challenge.

This review will focus on recent advances in our understanding of the burden of anemia across different risk groups. In addition, we will discuss how research has revealed specific mechanisms mediating anemia. Finally, we will discuss recent developments in our understanding of complex biologic interactions between varying causes of anemia and the implications these may have for host well-being. It is not the goal of this review to provide an exhaustive summary of all causes of anemia in the developing world; rather we will provide updates where changes in knowledge of the causes, mechanisms, and consequences of anemia have evolved in the past decade.

Defining anemia. Anemia is defined as a condition where there is less than the normal hemoglobin (Hb) level in the body, which decreases oxygen-carrying capacity. World Health Organization (WHO) definitions for anemia differ by age, sex, and pregnancy status as follows: for children 6 months to 5 years of age anemia is defined as a Hb level < 11g/dL, children 5–11 years of age Hb < 11.5 g/dL, adults males Hb < 13 g/dL; non-pregnant females Hb < 12g/dL, and pregnant females Hb < 11g/dL. Severe anemia is defined as Hb < 7.0 g/dL. Because iron deficiency anemia is the leading cause of anemia in the developing world, anemia and iron deficiency anemia are often used interchangeably. There are, however, mild-to-moderate forms of iron deficiency in which the host is not yet anemic, but tissues are functionally iron deficient. In addition, although iron deficiency accounts for most of the anemia that occurs in underprivileged environments, multiple other causes exist independently or coexistent with this micro-nutrient deficiency.

Micro-nutrient deficiencies. Iron deficiency anemia. Iron deficiency is thought to affect the health of more than one billion people worldwide. The WHO/World Bank has ranked iron deficiency anemia as the third leading cause of disability-adjusted life years (DALYs) lost for females 15–44 years of age. For men in this age group, iron deficiency anemia was ranked among the top 10 disease burdens. Most seriously affected are young children and women in less developed countries (LDCs). For young children, this is due to increased iron requirements during periods of rapid growth, which are almost 10 times higher per kilogram of body weight than that of an adult male. In addition, infant and toddler diets are often poor in bio-available iron, particularly post-weaning, in parts of the world where iron fortification programs are not in effect.

Among women, iron deficiency occurs at a higher prevalence than in men due to menstrual iron losses and the extreme iron demands of a growing fetus during pregnancy, which are approximately two times the demands in the non-pregnant state. The growing fetus requires a large supply of iron taken up from maternal blood via transferrin-receptor mediated endocytosis. Once maternal iron stores are depleted, she becomes anemic and transfer of iron to the developing fetus is compromised. With respect to effects of anemia and iron supplements on birth outcomes, studies have provided conflicting results. Although iron has been identified as a key growth factor for the developing fetus, few early studies demonstrated improvements in birth weight or length of gestation with iron supplementation during pregnancy. It should be noted that many of these studies had significant design flaws including unmeasured confounders, lack of iron deficiency in the study population, and insufficient sample size. Studies have, however, associated severe maternal anemia (Hb < 8.0 g/dL) with birth weight values that are 200–400 grams lower than in women with normal Hb levels. In addition, two more recent randomized controlled trials found that iron supplementation led to improved mean birth weight and decreased risk of low birth weight. These studies have led to a re-examination of the role of iron supplementation in improving birth outcomes.

Folic acid. Folic acid is necessary for cell growth and repair and essential for the formation and maturation of red blood cells. Deficiency of folate leads to slowing of DNA synthesis and impaired cell proliferation. This, in turn, leads to intramedullary death of many of these abnormal cells and shortened lifespan of circulating red blood cells. As early as the 1950s, pre-natal folate supplementation was recognized as a means to prevent pregnancy-related megaloblastic
anemia. Pregnancy, in particular, is associated with increased folate demands because of the rapid growth of the fetus and utero-placental organs. Lactation presents a continuation of this demand, with mammary glands taking up folate preferentially, at the expense of maternal hematopoietic requirements.

Despite public health interventions globally to provide peri-conceptual folate to reduce the risk of neural tube defects, many developing countries still have high rates of folate insufficiency. This is due to dietary inadequacies, lack of education regarding folate supplementation for women of reproductive age, and lack of food fortification programs. For example, a study conducted in Malawi in the late 1990s found a prevalence of folate deficiency of 21–34% among pregnant women, depending on cut-off values used.

Interactions between malaria and folate metabolism present further challenges. *Plasmodium* spp. synthesize folate; therefore, malarial parasitism increases the red blood cell folate levels of the host and hampers assessment of folate status, without actually providing a significant folate source to the human host. Furthermore, recurrent malaria hemolysis stimulates production of red blood cell precursors, increasing the demand for folate. This can lead to folate depletion and megaloblastic anemia, which can be profound, particularly during pregnancy. Further complicating this issue, one class of anti-malarial drugs act by inhibiting the production of folate by inhibiting dihydrofolate-reductase. Although the action of these drugs is many times more potent for the enzyme of *Plasmodium* spp. than for that of mammals, overdoing can cause megaloblastic anemia in humans. At the appropriate dosing, these drugs prevent malarial hemolysis, reducing demand for folate and preventing megaloblastic anemia.

**Vitamin B<sub>12</sub>**. Vitamin B<sub>12</sub>, which is synthesized by microorganisms, is primarily obtained by eating foods from animal sources. It is necessary for the synthesis of red blood cells and deficiencies of this micro-nutrient are associated with megaloblastic anemia. Given a normal diet contains a large excess of B<sub>12</sub> and efficient storage of the vitamin in the liver, deficiency states were thought to be rare. Recent studies, however, have led to a re-assessment of the importance of vitamin B<sub>12</sub> deficiency, indicating that its prevalence is greater than originally thought. According to these studies, the prevalence of vitamin B<sub>12</sub> deficiency was 18% and 41% among pre-school children in Kenya and Mexico, respectively, 16% among pregnant women in Malawi, and 40% among individuals in all age groups in Latin America. Diets with little or no animal protein, as is often the case in the developing world, coupled with malabsorption related to parasitic infections of the small bowel, may be causative. The contribution of B<sub>12</sub> deficiency to the worldwide prevalence of anemia, however, has not been well-established.

**Vitamin A**. Studies suggest that vitamin A can improve hematologic indicators and enhance the efficacy of iron supplementation. Vitamin A is thought to positively influence Hb levels by 1) stimulation of human erythroid precursors 2) enhancing iron availability to the bone marrow by mobilizing it from storage forms such as ferritin, 3) decreasing risk of infection and infection-related anemia, and 4) enhancing absorption of iron from the gut. Hematologic improvement, including increased Hb and serum iron concentration, have been shown to occur with vitamin A supplementation among children and, in some studies, pregnant women. In randomized controlled trials, vitamin A has been shown to lead to increased Hb levels in different pediatric age ranges and at various dosing frequencies. For example, among Thai school children with conjunctival xerosis (clinical sign of vitamin A deficiency), a single oral dose of vitamin A led to a 3 g/L increase in the Hb level after two weeks compared with placebo. With respect to pregnant women, the effect of vitamin A on the risk of anemia is more variable. Two studies demonstrated increases in Hb levels during pregnancy compared with placebo or iron alone. Recently, van den Broek and others found that vitamin A supplementation during pregnancy did not decrease the risk of anemia, although the authors note that the prevalence of vitamin A deficiency in the population was lower than expected. Among pregnant women infected with human immunodeficiency virus (HIV), daily vitamin A supplementation did not lead to an improved Hb concentration in Tanzania. Reasons for disparate results among pregnant women include 1) low prevalence of vitamin A deficiency in study populations, 2) inadequate dosage in the context of poor absorption, 3) increased requirements that may occur in specific disease states such as malnutrition and HIV, and/or 4) hemodilution during the second trimesters of pregnancy, which may obscure any benefit.

**Infectious diseases.** *Infection with HIV.* Anemia is significantly more prevalent among individuals infected with HIV than in their uninfected age-, sex-, and pregnancy-status-matched counterparts. Among individuals with HIV, anemia has been identified as a marker for disease progression and has been associated with decreased survival. One recent study found that even after controlling for important potential confounders such as CD4 cell count, clinical stage, and body mass index, moderate and severe anemia were associated with an increased relative hazard of all-cause mortality of 2.06 and 3.19, respectively, among Tanzanian women with HIV. As HIV disease severity progresses within individuals, the likelihood of developing anemia increases. This, in turn, has been shown to negatively impact quality of life, particularly health-related quality of life. In particular, HIV-related anemia has been related to decreased energy, poor physical functioning, and decreased global health.

The predominant cause of anemia in the context of HIV is anemia of inflammation (AI), also known as anemia of chronic disease. AI is characterized by decreased red blood cell production through a series of mechanisms mediated, in part, by pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-6. Recently, the putative link between inflammation and AI has been identified in the form of hepcidin. Hepcidin, which is produced by the liver in response to inflammation, is thought to mediate many of the mechanisms of AI. These mechanisms include suppression of the normal response of bone marrow to erythropoietin, decreased synthesis of erythropoietin, dyserythropoiesis (disturbances of bone marrow cellular division), and alterations in iron metabolism such that iron is sequestered into storage forms, such as ferritin, which make it less bioavailable.

One study conducted among Ugandan infants with and without infections with HIV found the prevalence of iron deficiency anemia (Hb < 11.0 g/dL and ferritin < 12 μg/L) to be approximately equal in each group, but the prevalence of any anemia was much higher in HIV-infected infants than in
uninfected infants (90.9% versus 76.9%). The excess anemia was attributed to AI. In another study conducted among antiretroviral-naïve HIV-infected children in South Africa, investigators found the prevalence of anemia increased with HIV disease stage from 42% for children with no evidence of immunosuppression to 85% for children with severe immunosuppression. In addition, iron deficiency anemia was present in only 17% of the children, lending further support for the role of AI in the pathogenesis of HIV-related anemia. Am. duodenale is one of the most important parasitic diseases in humans, caused primarily by parasite release of anticlotting agents (i.e., coagulase, a blood thinner), which cause ongoing blood loss in the stool caused by this parasitic infection. Blood loss is increased. Among pregnant women, anemia exists at a higher prevalence among HIV-infected versus uninfected women. Three studies conducted in sub-Saharan Africa (Burkina Faso, Tanzania, Côte d’Ivoire) demonstrated prevalences of anemia among HIV-infected women of 78.4%, 83%, and 82.7%, respectively. Two of these studies compared anemia in HIV-positive and HIV-negative pregnant women and found a significantly higher prevalence of anemia among women with HIV. Thus, HIV is contributing to the already enormous burden of anemia during pregnancy in LDCs.

The interaction between malaria-related morbidity and HIV infection have received increased attention. In a study conducted in Malawi, investigators examined the relationship between HIV status and risk of malaria morbidity throughout a transmission season. Although this study did not specifically address the risk of anemia, the authors found increased risks for first, second, and overall incidence of malaria parasitemia among HIV-1 seropositive than in seronegative adults. A study in a hospital-based cohort in South Africa that examined risk factors for severe malaria, the risk of severe malaria was almost three times greater for HIV-infected than in uninfected patients. In addition, HIV-infected patients were significantly more likely to have severe anemia. Finally, a study conducted in Uganda found a greater than three-fold increase risk for malaria treatment failure among HIV-infected adults than in uninfected adults. Most treatment failures were caused by new infections, rather than recrudescences. Thus, HIV may contribute to the already enormous toll of malarial anemia by increasing risk for parasitemia, severe anemia, and treatment failure.

Hookworm. On the basis of DALYs, hookworm infection is one of the most important parasitic diseases in humans, outranking schistosomiasis, African trypanosomiasis, Chagas disease, and leprosy. This is due to the fact that infection produces a high degree of long-term morbidity by causing iron deficiency anemia.

The primary morbidity caused by human hookworm infection results from adult parasites causing chronic intestinal blood loss. Thus, in addition to dietary iron deficiency in the developing world, many experience ongoing iron loss in the stool caused by this parasitic infection. Blood loss is caused primarily by parasite release of anticoagulants (i.e., coagulase, a blood thinner), which cause ongoing blood loss in the stool, rather than actual blood consumption by the parasite. For example, Ancylostoma duodenale can cause in excess of 0.25 mL of blood loss per worm per day. Because of already low iron stores among women and young children caused by diets insufficient to meet demands, these populations are most at risk for hookworm-associated iron deficiency anemia.

The development of frank anemia depends on the level of an individual’s iron stores, the intensity of infection, and the infecting species because A. duodenale causes a greater blood loss than Necator americanus. A study conducted in Tanzania that examined 525 school age children compared the degree of anemia and iron deficiency among children infected with each species. Among children infected with N. americanus, anemia was prevalent in 60.5% and iron deficiency in 33.1%. Among children infected with A. duodenale, the prevalence was 80.55% and 58.9%, respectively, which suggested that A. duodenale is associated with a greater burden of iron deficiency.

Anemia caused by hookworm infection has important sequelae. Among adults, chronic hookworm infection causes physical impairment resulting in reduced work capacity or even inability to work. Because iron deficiency is associated with adverse birth outcomes, most notably low birth weight, hookworm infection is likely a major contributor to this outcome. Among children, developmental and behavior impairment have been identified, resulting in recent initiatives to treat school children with antihelmintic drugs. It should be noted, however, that a recent meta-analysis addressing the topic of treatment of soil-transmitted helminths (hookworm, Ascaris, and Trichuris) and cognitive outcomes concluded that a relationship between antihelmintic treatment and improved cognitive performance could not be determined. This meta-analysis was highly controversial, with many published and unpublished differences of opinion.

Recent publications have highlighted the fact that the age intensity of hookworm infection does not follow the same pattern as most helminthic infections, such as schistosomiasis, in which intensity of infection peaks during childhood and adolescence, and then decreases. The intensity of hookworm infection follows a steady increase during childhood and does not reach a peak or plateau until adulthood. In the People’s Republic of China, for example, hookworm infection is more intense among middle-age persons or even those more than 60 years of age. A study conducted in Hainan Province, China, which examined risk factors associated with infection with N. americanus in people ≥ 50 years of age, found that age accounted for 27% of the variation in the intensity of hookworm infection.

The variation in hookworm intensity by age has lead to the conclusion that hookworm infection suppresses the immune system. Recent studies have examined human cellular immune responses to hookworm, as well as mechanisms that hookworms use to suppress the immune system of the host. Unlike most other human helminth infections, age- or exposure-related immunity does not develop in most of the infected people. As a consequence, vaccine development is considered an important goal. Recent progress has been made in the development of recombinant vaccines (in animal models) and clinical trials are expected to begin in the near future.

Malaria. In recent years, the already extraordinary estimates of malaria-related morbidity and mortality have been adjusted upward, and morbidity and mortality from other preventable diseases in lower income countries has decreased. It is now estimated that malaria is responsible for 1.2 million deaths and 2.9% of total DALYs from in low and middle income countries. Malaria has a range of manifestations but malaria-related anemia is one of the leading causes of death, with pregnant women and children being the most affected.
In the past decade, our understanding of the mechanisms of *P. falciparum* malaria related anemia has expanded greatly. Although hemolysis is still thought to be the primary mechanism, many other mechanisms are now recognized as contributors. In the early stage of infection, rupture of parasitized red blood cells is the primary cause of the acute decrease in hematocrit. The severity of anemia with acute *P. falciparum* malaria correlates with density of parasitemia. In addition, hypersplenism is thought to contribute to the early anemia of acute malaria, sequestering red blood cells. The persistent, often worsening anemia, that is seen in the weeks after clearance of parasitemia is thought to be caused by a second mechanism, phagocytosis of both parasitized and unparasitized red blood cells by a hyperactive reticuloendothelial system. Finally, malaria is thought to cause AI, as discussed in the section on HIV. Of note, relatively low levels of Th2 cytokines such as interleukin-10 have also been associated with more severe malarial anemia.

The relationship between vitamin A status and malarial anemia is complex. One randomized, double-blind, placebo-controlled trial examined the relationship between vitamin A supplementation in young children in Papua New Guinea and various morbidity outcomes related to *P. falciparum* malaria. Vitamin A significantly reduced the number of febrile *P. falciparum* episodes among all age groups and reduced the geometric mean parasite density, and proportion of children with enlarged spleens among 12–36-month old children. Across all age groups and among specific age strata, however, vitamin A had no significant impact on incidence of infection or anemia, which suggests that risk of infection and anemia may be mediated by different immunologic mechanisms than other clinical morbidities.

**Schistosomiasis.** A number of cross-sectional studies have examined the relationship between the three most prevalent *Schistosoma* spp. that infect humans and anemia. Numerous nutritional deficiencies and infectious diseases co-exist with schistosome infections and are also related to increased risk for anemia. Thus, careful control for confounding variables or use of an experimental design is required to quantify the association between schistosome infection and anemia. Recent cross-sectional studies have better adjusted for potential confounders, which allow a better estimation of the true relationship between schistosomiasis and anemia. These recent studies have observed an inverse relationship between *S. japonicum* intensity of infection and Hb levels, and *S. haematobium* and risk of anemia among young children and adolescents.

Many randomized controlled trials have found that therapy with praziquantel plus albendazole or metrifonate, with efficacy against schistosomes and hookworm, lead to improvements in Hb levels. The use of combination therapy makes inference regarding schistosomiasis-attributable benefits of treatment of anemia difficult, although most authors suggested that part of the improvement in Hb levels was likely caused by reduced schistosomiasis burden.

Only two randomized controlled trials using mono-therapy with a drug with efficacy predominantly against schistosomes have been conducted. A study conducted in a village in Leyte, The Philippines that was endemic for *S. japonicum* showed significantly higher Hb levels six months after therapy in intervention children versus in control children. The magnitude of the effect was approximately 1.1 g/dL. Of note, males experienced a greater increase in Hb levels with treatment than females. The experimental design of this study and the isolation of schistosomiasis support a role for *S. japonicum* in the etiology of anemia in parts of the developing world where it is endemic. Another randomized controlled trial examined praziquantel treatment alone for treatment of infection with *S. haematobium*. No effect of treatment on Hb levels was found, which is unlikely to be caused by a lack of statistical power (n = 104 in the placebo group and 105 in the praziquantel group), low prevalence of anemia (70%), or inadequate follow-up (eight months). However, this null finding may be caused by the exclusion of children with high-intensity infections.

The mechanisms by which schistosome infections may lead to anemia have been debated for decades. There are four proposed mechanism underlying a relationship between schistosomiasis and anemia: 1) iron deficiency caused by extra-corporeal loss, 2) splenic sequestration; 3) autoimmune hemolysis, and 4) AI. Studies suggest that iron loss in the stool may play a role only at higher intensities of infection, with AI being the predominant cause. This is supported by the fact that schistosomiasis leads to significant pro-inflammatory immune responses in human subjects.

Understanding these mechanisms is important, given that interventions to address anemia in the context of schistosomiasis will have varying efficacy based on underlying mechanisms. For example, iron therapy in the context of AI will have decreased clinical efficacy.

**Trichuris trichiura.** An estimated 1.049 billion persons harbor *T. trichiura*. The prevalence of infection is high, approaching 95% in areas where it is endemic. Although light infections with *T. trichiura* appear to be asymptomatic, heavy infections and/or *Trichuris* dysentery syndrome (TDS) are characterized by growth stunting and anemia. The anemia may be caused by worm consumption in the context of heavy infections, colonic lesions with associated bleeding, or chronic reduction in food and micro-nutrient intake caused by anorexia-inducing effects of tumor necrosis factor-α released in response to infection. Of note, one study that assessed occult blood loss in persons infected with *T. trichiura* found that trichuriasis does not lead to significant occult gastrointestinal bleeding in the absence of TDS.

**Inherited disorders.** We limit discussion of inherited disorders to those in which recent advances that are relevant to LDCs have been made.

**Sickle cell disease.** Sickle cell disease is an inherited disorder of Hb that is among the most common genetic diseases in the world. It is characterized by lifelong hemolytic anemia and many other significant morbidities largely related to painful and debilitating vaso-occlusive phenomenon. Although research advances have increased the hope of effective therapy in industrialized nations, these expensive pharmacologic, genetic, and stem cell transplantation approaches will remain out of reach of individuals in LDCs. Although the protective effect of the sickle cell trait for death caused by malaria was observed more than 50 years ago, only recently have studies quantified and characterized this protective effect. It is thought that sickle cell trait is protective on the basis of a reduced ability of *P. falciparum* parasites to grow and multiply in HbAS erythrocytes, as well as on
enhanced phagocytosis of infected erythrocytes. More recent studies suggest that the protective effect of the sickle cell trait is mediated not only by innate immune mechanisms, but also by enhanced acquired immunity to the parasite. In one study, the sickle cell trait had no effect on the prevalence of asymptomatic parasitemia, but was 50% protective against mild clinical malaria, 75% protective against admission to the hospital for malaria, and almost 90% protective against severe or complicated malaria. The authors suggest that the protective effect is related to limitation of parasite density.

Thalassemia. Thalassemia is the most common single gene disorder worldwide, resulting from defects in genes producing Hb. It is highly prevalent in many Asian, Mediterranean, and Middle Eastern countries. Heterozygous carriers are clinically normal. Individuals who inherit thalassemia from two carrier parents generally die in utero (α-thalassemia) or in early childhood (β-thalassemia). The intermediate clinical forms of thalassemia result in anemia, with occasional need for transfusions of red blood cells. To date, not much more is understood about the clinical heterogeneity and the natural history of this disorder, which makes it very difficult to design intervention programs for its control, particularly in settings of scarce health care resources.

CONCLUSIONS

In the past decade, our understanding of the etiology and mechanisms of anemia in LDCs has advanced significantly. Assessment of relatively new contributions to the anemia burden of disease such as vitamin A deficiency allow new interventions to be used. In the setting of limited health care resources in LDCs, however, only slow progress has been made toward reducing the prevalence of anemia, due largely to ongoing micro-nutrient deficiencies, and high prevalences of parasitic diseases, HIV, and inherited disorders of Hb. Reducing dietary iron insufficiency, malaria, and hookworm alone would lead to significant decreases in the prevalence of anemia caused by the enormous morbidity toll and high prevalence of these diseases.

Anemia remains one of the glaring health disparities separating LDCs and industrialized countries. With advances such as food fortification programs, availability of effective drugs to treat underlying causes, and sophisticated diagnostic techniques, industrialized nations have outpaced LDCs significantly. It should be noted, however, that implementing current knowledge and fairly low cost interventions such as iron supplementation, malaria prophylaxis, insecticide-treated bed nets, and deworming would bring us a long way in reducing the enormous gap between LDCs and industrialized countries.

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