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# Anemia epidemiology, pathophysiology, and etiology in low- and middle-income countries

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## Abstract

Anemia affects a third of the world's population and contributes to increased morbidity and mortality, decreased work productivity, and impaired neurological development. Understanding anemia's varied and complex etiology is crucial for developing effective interventions that address the context-specific causes of anemia and for monitoring anemia control programs. We outline definitions and classifications of anemia, describe the biological mechanisms through which anemia develops, and review the variety of conditions that contribute to anemia development. We emphasize the risk factors most prevalent in low- and middle-income countries, including nutritional deficiencies, infection/inflammation, and genetic hemoglobin disorders. Recent work has furthered our understanding of anemia's complex etiology, including the proportion of anemia caused by iron deficiency (ID) and the role of inflammation and infection. Accumulating evidence indicates that the proportion of anemia due to ID differs by population group, geographical setting, infectious disease burden, and the prevalence of other anemia causes. Further research is needed to explore the role of additional nutritional deficiencies, the contribution of infectious and chronic disease, as well as the importance of genetic hemoglobin disorders in certain populations.

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Author contributions

C.M.C. was responsible for overall manuscript conception, interpretation, and writing; P.S.S. contributed to manuscript conception, interpretation of data, and reviewed and wrote manuscript sections.

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**Keywords**

anemia; iron deficiency anemia; nutritional anemias; anemia of inflammation

## Introduction

Anemia—a condition in which hemoglobin (Hb) concentration and/or red blood cell (RBC) numbers are lower than normal and insufficient to meet an individual's physiological needs[1]—affects roughly one-third of the world's population.[2] Anemia is associated with increased morbidity and mortality in women and children,[3,4] poor birth outcomes,[5,6] decreased work productivity in adults,[7] and impaired cognitive and behavioral development in children.[8] Preschool children (PSC) and women of reproductive age (WRA) are particularly affected.

Establishing appropriate Hb thresholds to define anemia is essential for ensuring that anemia is correctly identified, and its negative effects prevented. As important, understanding the diverse and complex etiology of anemia is crucial for developing appropriate interventions that address the context-specific causes of anemia and for monitoring the success of anemia control programs. To that end, the primary aims of this paper are to outline definitions and classifications of anemia; describe the biological mechanisms through which anemia develops; review the variety of factors and conditions that contribute to anemia development, emphasizing those most prevalent in low- and middle-income countries (LMICs); and identify research needs. Although our primary focus is on anemia and its etiology at a population level, the information we present on definitions and classifications of anemia, as well as its etiology, is relevant to individual-level assessment by clinicians.

## Materials and methods

We reviewed the peer-reviewed literature on definitions and classifications of anemia, global magnitude and epidemiology of anemia, and causes of anemia, including their biological mechanisms and public health significance. We identified references through PubMed searches on relevant search terms (see below) and the "snowball" method in which references of references are identified. We also consulted gray literature, particularly documents relevant to defining anemia and nutritional status published by international organizations. To provide estimates of the global magnitude of anemia and to elucidate the etiology of anemia, we used three principal sources: (1) recent analyses by WHO on global anemia prevalence between 1995 and 2016 using population-representative data on PSC and WRA from 257 sources representing 107 countries;[9,10] (2) a recent global analysis of anemia burden between 1990 and 2010 in 20 age groups and both sexes from 187 countries that also performed cause-specific attribution to 17 conditions from the Global Burden of Diseases, Injuries and Risk Factors 2010 Study;[2] and (3) recent analyses from the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project, a large-scale collaborative study to examine the factors associated with anemia in 29,000 PSC (6−59 months of age) from 16 population-based surveys and 27,000 nonpregnant WRA (15−49 years of age) from 10 population-based surveys representing countries in all six WHO geographic regions.[11]

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### Search terms

Anemia AND: causes, classification, etiology, risk factors, assessment, iron deficiency, vitamin A deficiency, folate deficiency, B12 deficiency, riboflavin deficiency, malaria, infection, infectious disease, schistosomiasis, hookworm, intestinal helminths, HIV, tuberculosis, obesity, overweight, undernutrition, underweight, stunting, wasting, child development, motor development, cognitive development, birth outcomes, birth weight, premature birth, growth, mortality, work productivity, poverty, education; nutritional anemias; anemia of inflammation; anemia of chronic disease; thalassemia, α-thalassemia, β-thalassemia; sickle cell disease; sickle cell disorders; hemoglobinopathies; hemoglobin disorders; hepcidin; iron deficiency anemia.

## Defining anemia

Anemia is alternately defined as a reduced absolute number of circulating RBCs[12] or a condition in which the number of RBCs (and subsequently their oxygen-carrying capacity) is insufficient to meet physiologic needs.[1] Though most commonly diagnosed by a low Hb concentration or a low hematocrit,[12] anemia can also be diagnosed using RBC count, mean corpuscular volume, blood reticulocyte count, blood film analysis, or Hb electrophoresis.[13] At the population level and in clinical practice, Hb concentration is the most common hematological assessment method used[14] and the most common indicator used to define anemia. The critical role of Hb to carry oxygen to the tissues explains the most common clinical symptoms of anemia, which include fatigue, shortness of breath, bounding pulses or palpitations, and conjunctival and palmar pallor.[15] Clinical signs[16] and medical history are used to diagnose anemia when hematological data are unavailable, but they are limited in their ability to detect anemia.[17] Severe anemia (defined by WHO as Hb <70 g/L in children under 5 years of age and Hb <80 g/L in all other age groups,[1] though other definitions, including Hb <50 g/L, are used) is of particular importance clinically, as it can result in high-output heart failure and death.[12]

Defining an abnormally low Hb concentration requires understanding how Hb naturally varies by age, sex, pregnancy status, genetic and environmental factors, and, potentially, race. Hb varies with age, most dramatically in the first months of life (Fig. 1).[18] In the newborn, normal Hb concentrations are between 17 and 21 g/L, their highest point during life.[18,19] Hb concentration then decreases through the first 2−3 months of life before increasing again in childhood,[18,20] and then levels off throughout adulthood before declining again in older age.[21] Sex differences in Hb concentrations begin in puberty (because of the effect of menstruation on iron stores and, subsequently, anemia) and continue throughout the reproductive years.[22,23] During pregnancy, because of the expansion of blood volume and consequent dilution effect, Hb concentration naturally declines during the first and second trimesters, rising gradually again in the third trimester.[24] Apart from physiological factors, behavior and environmental conditions, such as altitude and smoking, can also affect Hb concentrations.[1]

The WHO Hb cutoffs for anemia (Table 1) are widely applied globally and are sex, age, and pregnancy specific.[1] These cutoffs were first established in 1968 by a nutritional anemia study group at WHO using statistical cutoffs rather than thresholds linked to meaningful

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health outcomes.[25] Hb cutoffs were modified slightly since then to allow for additional age divisions among children, adjustment for children in the 5−11 age group based on data of noniron-deficient children from the United States, and creation of the categories of "mild," "moderate," and "severe" anemia.[26,27] Cutoffs were also supported by findings among participants of the Second National Health and Nutrition Examination Survey (NHANES II) who were not iron deficient.[14] The need for separate cutoffs based on ethnicity/race has been proposed (e.g., individuals of African descent have lower Hb concentrations than do Caucasian populations, at least partially due to the greater prevalence of genetic Hb disorders in persons of African descent), as have revisions to the cutoffs for particular age groups (e.g., very young infants).[28–32]

## Global magnitude of anemia

Approximately one-third of the world's population (32.9%) was estimated to suffer from anemia in 2010.[2] The population groups most vulnerable to anemia include (1) children under 5 years of age (42% with anemia in 2016), particularly infants and children under 2 years of age; (2) WRA (39% with anemia in 2016); and (3) pregnant women (46% with anemia in 2016).[33,34] Females were consistently at greater risk of anemia than men across almost all geographic regions and in most age groups.[2] Other at-risk groups include the elderly, as the prevalence of anemia among adults over 50 years of age rises with advancing age,[35] though data are limited.

The prevalence of anemia also varies by geographic region. Sub-Saharan Africa, South Asia, the Caribbean, and Oceania had the highest anemia prevalence across all age groups and both sexes in 2010.[2] At the country level, anemia among WRA and children under 5 years of age is a moderate-to-severe public health problem (20% or greater as defined by WHO) in the majority of WHO member states.[9,10]

Progress on decreasing anemia has been overall slow and uneven. For all age groups and both sexes, anemia is estimated to have decreased roughly seven percentage points between 1990 and 2016, from 40% to 33%.[2] The WHO Global Nutrition Target 2025 on anemia aims to reduce anemia in WRA by 50% by 2025.[36] Based on a global prevalence of 29–38% anemia among WRA (nonpregnant and pregnant, respectively) as of 2011, a reduction of 1.8–2.4 percentage points per year would be required to meet this target.

## Pathophysiology of anemia: consequences for development, growth, birth outcomes, and work productivity

Anemia has significant consequences for human health, as well as for social and economic development. In 2010, anemia accounted for 68.4 million years of life lived with disability, or 9% of the total global disability burden from all conditions.[2] Anemia has been associated with negative health and development outcomes, including neonatal and perinatal mortality, low birth weight,[37] premature birth,[5,38] and delayed child development.[39]

The negative effects on health and development outcomes from anemia arise from the impacts of decreased oxygen delivery to tissues (in which multiple organ systems may be

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affected), as well as effects related to the underlying causes of anemia, which are difficult to disentangle. For example, in iron deficiency anemia (IDA), decreased iron availability has well-established negative effects on brain development and functioning even prior to anemia development.[40]

## Etiology of anemia: conceptual models, biological mechanisms, and classifications

At a biological level, anemia develops because of an imbalance in erythrocyte loss relative to production; this can be due to ineffective or deficient erythropoiesis (e.g., from nutritional deficiencies, inflammation, or genetic Hb disorders) and/or excessive loss of erythrocytes (due to hemolysis, blood loss, or both). Anemia is frequently classified based on the biological mechanism of causation (e.g., IDA, hemolytic anemia, and anemia of inflammation (AI)) and/or the RBC morphology. Table 2 displays a partial list of several common anemias and the biological mechanisms through which they develop and RBC parameters that characterize their presentation and distinguish them from each other.[41] Most anemias have a characteristic RBC appearance, which can provide insights to the diagnosis of anemia. However, as Table 2 displays, multiple factors can cause a similar type of RBC morphology.[41] Furthermore, as anemia may have multiple causes, even in the same individual, hematological manifestations of a particular cause can be masked by another. For example, the hallmark of anemia caused by vitamin B12 or folate deficiencies is macrocytic anemia. Concomitant ID, which causes microcytosis, may mask entirely the effects of the B12 or folate deficiency. Although indices exist in clinical practice for distinguishing anemia etiology based on RBC parameters (e.g., IDA versus β-thalassemia—both cause hypochromia and microcytosis), their reliability for discriminating between causes varies.[42,43]

Figure 2 is a conceptual model of the etiology of anemia identifying how distal factors contribute to more proximate determinants of anemia, such as food insecurity, clean water, and sanitation, and, ultimately, the most immediate causes of anemia (e.g., nutritional deficiencies, disease, inflammation, and Hb disorders).[13,44,45] Many of these determinants are interrelated. Poverty, for example, is a major determinant of health and nutrition, and poor socioeconomic position is linked to a greater risk of anemia among women and children.[13,46] Similarly, low education level is also associated with a greater risk of anemia.[13] A recent analysis of 53 demographic and health surveys with Hb data found that anemia among PSC (affecting 70% of the PSC population studied) was strongly associated with maternal anemia, household wealth, maternal education, and low birth weight.[47]

It is important to note that the primary causes of mild and moderate anemia tend to differ from the principal causes of severe anemia. Though there are limited studies on the etiology of severe anemia,[48] malaria is frequently identified as a principal cause of severe anemia, particularly in African children. In the BRINDA project, the most consistent predictors of severe anemia in population-based surveys of PSC were malaria, poor sanitation, underweight, and inflammation (in African countries only); stunting, vitamin A deficiency (VAD), and rural location were also significant determinants in high/very high infection

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countries.[49] In a study of Malawian PSC, factors associated with severe anemia included malaria, bacteremia, hookworm infection, HIV infection, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and vitamin A (VA) and B12 deficiencies.[48] In this population, iron deficiency (ID) was protective of severe anemia, likely due to the relationship between iron and infection. In Kenyan PSC, severe anemia was associated with malaria, inflammation, and stunting, while predictors of more moderate forms of anemia were ID, malaria, and α-thalassemia.[50] Severe anemia is also a comorbidity of severe acute malnutrition (SAM); for example, in India, of hospital-based children with SAM, 67% also had severe anemia.[51]

As identified in Figure 2, and reflected in global analyses of anemia burden between 1990 and 2010, the most proximal risk factors for anemia include nutritional deficiencies, disease/infection, and genetic Hb disorders.[52] These conditions and several others, which are also prevalent causes of anemia in LMIC, will be discussed in more detail below.

## Nutritional anemias: iron, vitamins A and B12, folate, and riboflavin

Nutritional anemias result when concentrations of hematopoietic nutrients—those involved in RBC production or maintenance—are insufficient to meet those demands.[13] Causes of nutrient deficiency include inadequate dietary intake, increased nutrient losses (e.g., blood loss from parasites, hemorrhage associated with childbirth, or heavy menstrual losses), impaired absorption (e.g., lack of intrinsic factor to aid vitamin B12 absorption, high intake of phytate, or *Helicobacter pylori* infection that impair iron absorption), or altered nutrient metabolism (e.g., VA or riboflavin deficiency affecting mobilization of iron stores). While nutrient supplementation is a common preventive and treatment strategy for nutritional anemias—for example, iron supplementation for the prevention of IDA—the bioavailability and thus absorption from different nutrient supplement preparations can vary, potentially limiting their impact.[53]

ID is considered the most common nutritional deficiency leading to anemia, though other nutritional deficiencies can also cause anemia, including deficiencies of vitamins A, B12, B6, C, D, and E, folate, riboflavin, copper, and zinc.[54] Several of these nutrients—vitamins A, B6, and B12, folic acid, and riboflavin—are needed for the normal production of RBCs; other nutrients, such as vitamins C and E, may protect RBCs through their antioxidant function.[55] Trace elements, such as copper and zinc, are found in the structures of enzymes that act on iron metabolism (e.g., copper and ceruloplasmin).[56] Copper may also contribute to anemia development through reductions in erythropoietin (EPO) and antioxidant enzymes that require copper, thus increasing oxidative stress and reducing RBC life span;[57] the mechanisms through which zinc deficiency is associated with anemia are not as well characterized.[57] The extent to which each of these deficiencies contributes to the global anemia burden is still a subject of investigation. While some of these nutrient deficiencies are rare and may contribute little to the burden of anemia globally, deficiencies in multiple micronutrients likely have a synergistic effect on anemia development.[58]

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## Iron deficiency

ID develops when dietary iron intake cannot meet iron needs over a period of time, especially during periods of life when iron requirements are particularly high (e.g., during periods of rapid growth and development, such as infancy and pregnancy) or when iron losses exceed iron intake. ID typically evolves in three stages: storage iron depletion, iron-deficient erythropoiesis, and IDA (defined as concomitant ID plus anemia).[59] The WHO recommends assessing iron status using serum ferritin or soluble transferrin receptor (sTfR).[60,61] Serum ferritin, a measure of body storage iron and a sensitive measure of ID, is elevated by the acute phase response; sTfR levels when high indicate tissue ID, but sTfR may also be affected by inflammation and other causes of erythropoiesis.[60,61] Because of the effect of inflammation on many biomarkers of iron status, acute phase proteins (e.g., C-reactive protein (CRP) and alpha-1-acid glycoprotein (AGP)) should be assessed when possible.[60] A fuller review of iron status indicators, outside the scope of the paper here, is available elsewhere.[61]

Estimates from the late 1990s placed the number of individuals affected by ID at 2 billion, and ID has long been assumed to contribute to approximately 50% of anemia cases globally.[62,63] A recent systematic analysis of global anemia data that calculated cause-specific attribution for 17 conditions related to anemia ranked ID as the most common cause in almost all global regions examined.[2] The WHO used the change in Hb concentration from iron supplementation studies to estimate the "proportion of all anemia amenable to iron" as 50% of anemia among nonpregnant and pregnant women, and 42% of anemia in children.[9] Recent analyses from the BRINDA project indicated that along with age and malaria, ID was one of the factors most consistently associated with anemia, though the proportion of anemic children and women with ID varied by infectious disease burden.[46,49] Another study that assessed the role of ID in anemia burden among PSC and nonpregnant WRA, across a range of countries with varying rankings on the Human Development Index, showed that between approximately a quarter to a third of anemia among PSC and WRA was associated with ID.[64] In countries where the prevalence of anemia was greater than 40% and in countries where inflammation levels were high, ID played a much smaller role.[64] Thus, while ID remains a primary cause in many settings, the proportion of anemic individuals with ID varies by contextual factors, and poor iron nutrition cannot be assumed to be the primary cause in all cases. Yet, iron interventions (e.g., supplementation, fortification, and dietary interventions) are central to most anemia control programs, and WHO currently has 17 guidelines on iron supplementation.[65] Given the complex etiology of anemia, the extent to which ID accounts for the anemia burden continues to be investigated.

## Vitamin A deficiency

VAD is prevalent in many LMICs, particularly among PSC, pregnant women, and WRA. In 2005, the WHO estimated that 190 million PSC and 9.1 million pregnant women from regions at risk of VAD were VA deficient (based on serum retinol concentrations), which represents a third of PSC and 15% of pregnant women from these countries.[66]

VAD and anemia have been observed to occur in the same populations for decades, and significant correlations between VA status biomarkers and Hb have been described in

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multiple countries and populations including preschool and school-age children, adolescents, and adults.[67] VA supplementation has been shown to increase Hb concentrations, hematocrit, and some iron status indices, even when administered in the absence of iron supplements.[55,67] VAD is thought to cause anemia through multiple mechanisms, including the role of retinoids in erythropoiesis, VA's importance for immune function, as well as VA's well-established role in iron metabolism.[67] In contrast to IDA, which is marked by a depletion of iron stores, anemia due to VAD is marked by an increase in iron stores in the liver and spleen and increased serum ferritin concentrations.[68] The anemia of VAD has alternatively been described as hypochromic or microcytic and hypochromic, but other factors—including other nutritional deficiencies and infections—occurring simultaneously may cause inconsistencies in RBC parameters.[67] BRINDA analyses showed that among PSC, VAD was associated with anemia in close to half of the surveys (5/12) and across levels of infectious disease burden.[49] Among WRA in the BRINDA project where ID and VAD were both assessed, VAD and ID were associated with anemia in all surveys (5/5 surveys) in both high- and low-infection burden groups.[46] Estimates as to how much anemia would be reduced by addressing VAD warrants additional research. In addition, like iron status indices, VA biomarkers are affected by inflammation, thus complicating the assessment of anemia due to VAD in settings where infectious disease is prevalent.[69]

## Deficiencies of B vitamins (riboflavin, B12, and folate)

Several B vitamins are involved in Hb synthesis or iron metabolism, including riboflavin (B2), pyridoxine (B6), cobalamin (B12), and folate. Deficiencies of these nutrients have been associated with anemia; however, the extent to which they contribute to the global burden of anemia varies and in some cases is unclear. Vitamin B6 deficiency is rare[55] and will not be addressed here.

Both vitamin B12 (cobalamin) and folate deficiency can lead to macrocytic anemia. Deficiencies of these nutrients affect DNA synthesis and cell division in the bone marrow (megaloblastic changes), such as hypersegmented neutrophils on the peripheral blood smear.[70] Folate deficiency can also lead to decreased erythrocyte life span. Vitamin B12 deficiency in LMIC most commonly results from low dietary intake of the nutrient. Its bioavailable forms are only found in animal-source foods; but vitamin B12 deficiency can also result from malabsorption, particularly in the elderly among whom gastric atrophy is common,[71] in cases of pernicious anemia, an autoimmune disease in which autoantibodies are formed against intrinsic factor essential for B12 absorption, and in bacterial and parasitic coinfections.[13,72] Folate deficiency tends to be more common in populations relying on unfortif ied wheat or rice as a staple food and that consume low amounts of legumes and green leafy vegetables.[71] Pregnant women, preterm infants, and individuals living in malaria-endemic regions (as folate is needed for malarial parasite growth)[73] are at high risk of folate deficiency.[55] For women during pregnancy, folate demands increase; and starting pregnancy with poor folate status can lead to megaloblastic anemia, which is further exacerbated by the additional folate needs for lactation.[13]

Data on the prevalence of vitamin B12 and folate deficiencies at the national level are limited.[74] Out of seven countries with national data on B12 status (measured using different

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indicators, including serum vitamin B12, homocysteine, or methylmalonic acid) primarily from the Americas and Europe, five had levels of deficiency greater than 5% (the level above which the authors of the study considered B12 deficiency a problem of public health significance).[74] In the BRINDA project, among the 10 surveys of WRA, four measured vitamin B12 status;[46] among these, vitamin B12 deficiency was very low (<3%) in Mexico and the United States, but higher (approximately 15%) in Côte d'Ivoire and Colombia.[46] In the global review of vitamin B12 and folate status by McLean *et al.*, folate deficiency was estimated to be of public health significance (>5% deficient) in six out of eight countries with national data, and particularly affected groups included PSC in Venezuela (33.8%), pregnant women in Costa Rica (48.8%) and Venezuela (25.5%), and the elderly in the United Kingdom (15.0%).[74] In the BRINDA project surveys of WRA, the prevalence of folate deficiency was >80% in both Côte d'Ivoire and Georgia, but <3% in Mexico and the United States.[46]

The contribution of B12 and folate deficiencies to the global prevalence of anemia is unknown though data suggest that it may be minimal. One review indicated that a high prevalence of B12 or folate deficiency did not necessarily correlate with a high prevalence of anemia except possibly for women (and their infants and children) consuming vegetarian diets who were B12 deficient.[43] Supporting this, the BRINDA project showed that vitamin B12 and folate deficiencies were not significantly associated with anemia, though sample sizes for studies that measured these deficiencies were limited.[46]

Riboflavin's role as a cofactor in redox reactions is an important part of iron metabolism, and riboflavin deficiency in animals can decrease iron mobilization from stores, decrease iron absorption, increase iron losses,[75] and impair globin production.[55] Riboflavin deficiency is thought to be common in many populations[75] and has been documented in pregnant and lactating women, infants, school-age children, adolescent girls, and the elderly in both high-income and LMICs, especially where consumption of milk/dairy products and meat (primary riboflavin sources) is low.[75] Whether riboflavin deficiency is a primary contributing factor to anemia in humans remains unclear. Riboflavin supplements provided along with iron supplements have been shown to have a greater effect on Hb concentration than iron supplements alone among children and pregnant women in some studies, though not all.[76] In a longitudinal study of Chinese adults, inadequate riboflavin intake was associated with anemia at baseline and increased risk of anemia during a 5-year follow-up period.[77] However, in schoolchildren in Côte d'Ivoire, riboflavin deficiency was not associated with Hb concentration or anemia despite a prevalence of riboflavin deficiency of 65%, though it was associated with ID.[76]

## Other conditions associated with anemia: undernutrition and overweight/obesity

Stunting, wasting, and underweight have been associated with anemia in some studies,[49,78,79] but not all.[80] In analyses from the BRINDA project, stunting, underweight, and wasting were associated with anemia in PSC in more than half of the surveys (9/15, 10/15, and 5/15, respectively) for which these variables were available.[49] These manifestations of poor nutritional status are associated with anemia due to similar factors (though not constituting a causal relationship), including poor maternal nutrition, inadequate home and

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community environments, inadequate complementary feeding practices leading to poor micronutrient and animal-source food intake, contaminated water and poor sanitation, suboptimal breastfeeding practices, and clinical and subclinical infections.[81]

While more related to ID than anemia per se, overweight and obese individuals have an increased risk for ID, as data from multiple countries show.[82] The primary link between these conditions is thought to be through hepcidin, a peptide hormone produced predominantly by the liver and responsible for iron homeostasis, and which is elevated in the presence of inflammation.[83] The chronic subclinical inflammation present in overweight and obese individuals increases hepcidin levels, resulting in reduced iron absorption.[82] However, Hb concentrations tend to be within the normal range.[82,83]

## Anemia of inflammation and infection, and primary diseases associated with anemia globally

Many diseases are associated with anemia through multiple mechanisms, including disease-specific effects on blood loss, hemolysis or erythropoiesis, and through the effects of inflammation on iron metabolism. The presence of an inappropriately low reticulocyte count for the degree of anemia is used clinically to indicate conditions due to nutritional deficiencies, decreased erythropoietin levels, aplastic anemia, or inherited bone marrow failure syndromes.[70] In global analyses of anemia burden between 1990 and 2010, hookworm, schistosomiasis, and malaria constituted three primary causes of anemia.[2] Below, we describe AI as well as the specific mechanisms for several predominant diseases associated with anemia and prevalent in LMICs.

### Anemia of inflammation

Anemia of chronic disease or AI is generally normocytic with a low reticulocyte count and characterized to be mild-to-moderate (Hb concentrations 8−10 g/L).[84] In AI, proinflammatory cytokines released in the host defense response to infection (IL-6 in particular, but other cytokines are also involved) alter iron metabolism so that iron is sequestered within cells of the reticuloendothelial system (liver and spleen) and intestinal enterocytes, and RBC production and life span are reduced.[84–86] The effects on iron metabolism are mediated by hepcidin such that inflammatory cytokines increase its production, which downregulates the expression of ferroportin in intestinal enterocytes, macrophages, and hepatocytes, thus blocking iron absorption and mobilization of iron from stores into circulation.[82,85,86] Inflammatory cytokines also contribute to shortened RBC life span (potentially by activating macrophages), as well as impairing the production and function of EPO and inhibiting normal erythroid progenitor cell proliferation and differentiation.[84,86,87]

AI has been called the second most common cause of anemia after IDA,[84,86] and while disease/infections are the top causes of anemia,[2] the proportion of global anemia due to inflammation is not known, and likely varies by setting and disease burden. Among PSC in the BRINDA project, inflammation (as assessed through the measurement of CRP and/or AGP) was generally associated with anemia across countries (9/10 surveys). However, in a

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pooled analysis of countries by infection burden (reflecting sanitation, drinking water quality, and prevalence of malaria, diarrhea, or schistosomiasis), inflammation was associated with anemia in the high- and very high–infection burden groups, but not in the low- and moderate-infection groups. Among anemic PSC in low-, moderate-, high-, and very high-infection burden countries, 9.1%, 13.7%, 37.4%, and 70.3%, respectively, also had inflammation (any level).[49] Thus, in countries with higher infectious disease burden, the role of inflammation is likely larger than in countries with lower infectious disease burden. Among WRA, inflammation was significantly associated with anemia in countries with high and low (but not moderate) infectious disease burden; the odds of anemia among WRA with inflammation were 90% and 50% more than the odds among WRA without inflammation in high- and low-infection countries, respectively. In the elderly, roughly 10−32% of anemia is thought to be due to inflammation, as circulating IL-6 levels rise with increasing age, though there are multiple other causes of anemia—including ID and other pathologies—that become more common with advancing age.[88]

## Soil-transmitted helminth infections

Hookworm (*Necator americanus* and *Ancylostoma duodenale*) is the primary soil-transmitted helminth associated with anemia. Hookworm attaches to and feeds from the intestinal mucosa causing blood (and iron) loss and, depending on underlying iron status as well as the presence of other risk factors, can lead to IDA. Hookworms are common in sub-Saharan Africa and Southeast Asia, particularly in areas with poverty, poor water, sanitation, hygiene, and infrastructure, causing an estimated 576−740 million infections.[89] The severity of blood loss and subsequent anemia risk from hookworm infection is determined by several factors: (1) the intensity of infection (e.g., the number of hookworms an individual harbors), (2) the species of hookworm, and (3) whether there is coinfection with multiple parasites. Moderate- and heavy-intensity hookworm infections are associated with lower Hb in schoolchildren, while in adults, any level of infection is associated with lower Hb.[90] Children with poor iron status to begin with, however, may still be negatively affected by even light hookworm infections.[90] *A. duodenale* infection is associated with a greater risk of ID and anemia because of a fivefold greater blood loss, as compared with *N. americanus*.[91] However, the two species overlap geographically and both are endemic to many areas.[91] Coinfection with multiple parasites, such as *Schistosoma* sp., *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), or *Plasmodium*, has been shown to have an additive effect on anemia risk, with a greater effect than would be expected if these species had independent effects on anemia.[79,92,93] Antihelminthic treatment—particularly albendazole, and albendazole administered with praziquantel—has beneficial effects on Hb.[90]

In a systematic analysis that ranked the causes of global anemia burden in 2010 by prevalence, hookworm infection was ranked as the third and fourth most prevalent causes among males and females, respectively, though anemia due to hookworm decreased between 1990 and 2010, particularly for males.[2] Anemia due to hookworm infection was a predominant cause of anemia in East Asia and Oceania.[2] Hookworm infections tend to be less common among PSC (e.g., <2.5 years old) and may not contribute significantly to anemia among this most vulnerable group.[94] However, in a study of causes of severe anemia

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in Malawian children, hookworm infections were more common and more intense in children with severe anemia, and three-fourths of infected children were under 2 years of age (and thus would not be the focus of current treatment regimens).[48] The authors speculated that younger children might be more vulnerable to severe hematologic complications from heavy hookworm infections.

## Schistosomiasis

Schistosomiasis is a parasitic disease carried by freshwater snails infected with one of five varieties of the *Schistosoma* parasite and primarily occurs in sub-Saharan Africa. It affects an estimated 240 million people in up to 78 countries and reaches peak intensity and prevalence in 10−15-year-olds.[95,96] The exact mechanisms of schistosomiasis-induced anemia are not well understood, and the relationship may also depend on the species of *Schistosoma* parasite causing the infection. Data are most consistent for a causal relationship between *S. japonicum* and anemia, though anemia has been associated with the other two primary species—*S. haematobium* and *S. mansoni*—as well.[96] Schistosomiasis, similarly to hookworm, has been shown to lead to blood loss, particularly if the intensity of infection is high, which can contribute to IDA.[96] In fact, Schistosomiasis is linked to cognitive impairment, which may be at least in part due to the resulting ID.[96] Schistosome infection may also contribute to anemia through splenic sequestration of erythrocytes, deceased RBC life span, autoimmune hemolysis, or AI.[96] Schistosomiasis is a primary cause of anemia in sub-Saharan Africa, particularly among females.[2] In addition, between 1990 and 2010, schistosomiasis as a cause of anemia increased for both sexes but slightly more among females.

## Malaria

Malaria caused by *Plasmodium* parasites can cause severe anemia, in addition to other complications, including death. *P. falciparum* is the most prevalent in Africa and responsible for the most malaria-related deaths, and *P. vivax* is predominant outside of sub-Saharan Africa. Nearly half of the world's population is at risk of malaria, though the WHO African region bears a disproportionately high burden of malaria, accounting for 90% of malaria cases and 92% of malaria deaths (as of 2015).[97] Individuals at increased risk of contracting malaria and developing severe disease include infants, PSC, and pregnant women; more than two-thirds of malaria deaths occur among children under 5 years of age.[97]

Malaria commonly exists in areas where ID is also present; ID may protect against severe malaria in humans,[98] and the relationship between iron and malaria is complex. The parasite requires iron for growth, and malaria significantly disturbs iron metabolism and distribution in multiple ways, including through hemolysis, the release of heme, defective erythropoiesis, increased iron in macrophages, and decreased iron absorption.[98] The mechanism for malaria-related anemia is multifactorial, including increased hemolysis of parasitized RBCs, but more importantly, increased destruction of nonparasitized RBCs, which is the primary contributor to anemia development in malaria.[99] Decreased RBC production (suppressed erythropoiesis) during and for days or weeks after acute malaria also contributes to anemia,[13] as do increased red cell clearance and shortened erythrocyte survival.[99] Blood loss is not a cause of anemia due to malaria. Hepcidin is upregulated in malaria infection, which also

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likely contributes to anemia.[98] Malaria control in endemic areas can reduce anemia and severe anemia among children under 5 by 27% and 60%, respectively.[100]

Malaria is one of the primary causes of anemia globally[2] and is a primary cause of severe anemia. Malaria is an even more common cause of anemia in sub-Saharan Africa, particularly West sub-Saharan Africa, where malaria accounted for 25% of anemia prevalence.[2] Among PSC analyzed in the BRINDA project, malaria was consistently associated with anemia in all the surveys conducted in endemic areas (5/5).[49]

### HIV

Anemia is one of the most common hematological abnormalities among individuals infected with HIV; it is typically characterized as a normochromic and normocytic anemia with a low reticulocyte count, normal iron stores, and an impaired EPO response.[101] Anemia prevalence in HIV-positive individuals increases with advancing progression of the disease and is thought to result from several factors, both indirectly and directly related to the virus. HIV infection causes a chronic acute phase response, elevated hepcidin and AI, and altered iron metabolism.[101,102] Opportunistic infections common among HIV-positive patients can also lead to anemia (e.g., malaria and hookworm) as do nutritional deficiencies resulting from the virus.[101] The HIV virus also appears to have direct effects on anemia by affecting hematopoietic progenitor cells and decreasing responsiveness to EPO.[101] Antiretrovirals have been shown to reduce the incidence of anemia and increase Hb levels.[101,102] Finally, anemia among HIV patients is a predictor of the progression to AIDS, as the degree of anemia is correlated with disease progression[101] and is independently associated with mortality.[103]

### Tuberculosis

Anemia is common among tuberculosis (TB) patients and may be more common among those who are coinfected with TB and HIV.[104] In one study from Malawi, more than three-quarters (77%) of TB patients without HIV were anemic, while 88% of TB/HIV coinfected patients were anemic.[105] In Indonesia, 60% of malnourished TB patients were anemic,[106] while in Uganda, 71% of TB/HIV coinfected patients were anemic.[107] Anemia among pulmonary TB patients is thought to result from AI, as well as increased blood loss from hemoptysis (blood in sputum), decreased RBC production, and poor appetite and food intake, leading to poor nutrient status (of iron but also of other nutrients, including selenium in one study[105]).[104] In Tanzania, the Gambia, and South Africa, AI was the primary cause of anemia in TB patients.[108–110]

## Genetic HB disorders

Globally, 330,000 children are estimated to be born each year with a serious inherited Hb disorder (83% with sickle cell anemia or one of its variants; 17% with a form of thalassemia)[31] and approximately 80% of these births occur in LMICs.[111] Roughly, 5% of the global population is estimated to carry a significant Hb variant (e.g., a gene variant that can cause a serious disorder including sickle cell disease or a form of thalassemia); the percentage is much higher in Africa (18%) and Asia (7%).[31] Sickle cell disorders (SCDs),

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which are associated with chronic hemolytic anemia, are the most common genetic Hb disorder found predominantly in sub-Saharan Africa (where it is the most common genetic disorder), followed by β- and α-thalassemia, concentrated in Southeast Asia primarily.[111] Though not discussed in detail here, G6PD deficiency is one of the most common inherited enzyme abnormalities in humans, and its distribution tends to overlap with areas where malaria is endemic.[112] In response to certain triggers—for example, ingestion of fava beans and exposure to the antimalarial primaquine—acute hemolytic anemia can result;[112] G6PD deficiency is estimated to be within the top 35 causes of anemia globally.[2] The proportion of anemia due to genetic Hb disorders—which are currently immutable causes of anemia—in LMICs is only expected to rise as other causes (e.g., nutritional deficiencies and infectious diseases) are better controlled. This requires increased understanding of the contribution of inherited blood disorders to anemia burden; a recent study from Malawi found that 60% of analyzed samples for inherited blood disorders (sickle cell, G6PD deficiency, and α-thalassemia) among PSC in the Malawian Demographic and Health Survey had at least one abnormal result.[113]

## Sickle cell disorders

In sickle cell disease, sickle-shaped RBCs—produced as a result of a defective β-globin chain—block small blood vessels, damage large blood vessels, cause severe pain and residual organ damage, and have a much-shortened life span, leading to chronic hemolytic anemia.[31,114] Children with SCD have an increased risk of infections and malnutrition, which can have negative health repercussions, including painful episodes and increased hemolysis, which can lead to severe acute anemia.[114]

SCDs were the fifth and seventh top causes of anemia among females and males, respectively, in 2010.[2] Though the sickle cell trait is most prevalent in Africa (where 11 per 1000 conceptions are affected),[31] sickle cell disease accounts for a higher proportion of cases in Western Europe, North America, and other high-income regions due to longer life expectancy in these countries, as well as few other causes.[2]

## Thalassemias

Thalassemias are a group of inherited conditions in which there are defects in the synthesis of one or more of the globin chains that constitute Hb; α-thalassemia is caused by absent/reduced synthesis of the α-globin chain, and β-thalassemia is caused by absent/reduced synthesis of the β-globin chain.[115] This group of autosomal recessive disorders is characterized by hemolytic anemia and impaired erythropoiesis, among other complications depending on the severity of the gene defect, from carriers of the trait who are asymptomatic, to those who experience severe anemia, poor growth and skeletal abnormalities, and death (in the cases of α- or β-thalassemia major).[115]

Globally, approximately 1.7% of the world's population is estimated to carry α- or β-thalassemia trait (e.g., asymptomatic carriers), though within particular ethnic groups—α-thalassemia is most common in individuals from Africa and Southeast Asia, while β-thalassemia is most often found in individuals from the Mediterranean, Africa, and Southeast Asia—the rate can be between 5% and 30%.[115] Thalassemias were estimated as

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the sixth and ninth most prevalent causes of anemia globally among females and males, respectively, but were ranked more highly in Australasia, Central and Eastern Europe, Central and Southeast Asia, North Africa, and the Middle East.[2]

## Potential directions for research

Despite advances in the understanding of anemia etiology, epidemiology, and pathophysiology, important research gaps remain. For example, studies to optimize the assessment of anemia using Hb (e.g., accuracy, cost-effectiveness, and defining thresholds that have physiologic and health significance) would improve the ability to assess anemia burden. Questions also remain on understanding the contribution of nutrition in the etiology of anemia, as well as nonnutritional causes, such as infections and environmental factors, and non-modifiable causes, such as inherited Hb disorders. A challenge for programs is determining how to implement anemia control programs that simultaneously address the context-specific causes of anemia. Without addressing these gaps in knowledge and implementation science, the global goals to reduce anemia burden are likely to fail.

## Summary and conclusions

Anemia continues to be a widespread and significant global health problem that remains to be adequately addressed, particularly in LMICs where progress has been slow and uneven. Though ID remains a primary cause of anemia in most regions, recent work suggests that anemia etiology is complex and context specific. Efforts are needed to further understand how the principal causes of anemia, including ID and other nutritional deficiencies, disease, and Hb disorders, contribute to anemia so that appropriate interventions in specific settings can be implemented. This work will require including biochemical measures of micronutrient status (iron and VA primarily) and markers of inflammation, in addition to hematological indices when assessing anemia clinically and in populations.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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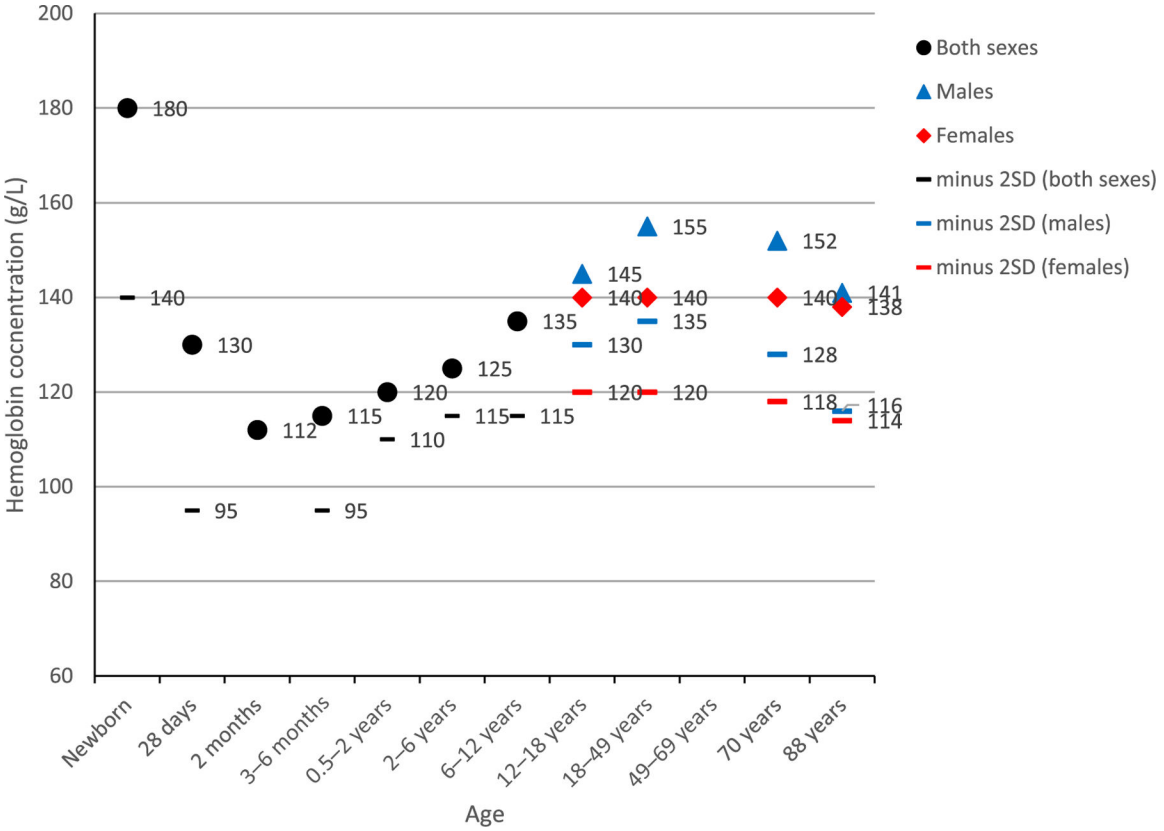


**Figure 1.**

Mean hemoglobin concentrations (and –2 SD values) by age and sex. Compiled from data from the United States, Europe, and Caucasian populations.[18–21]

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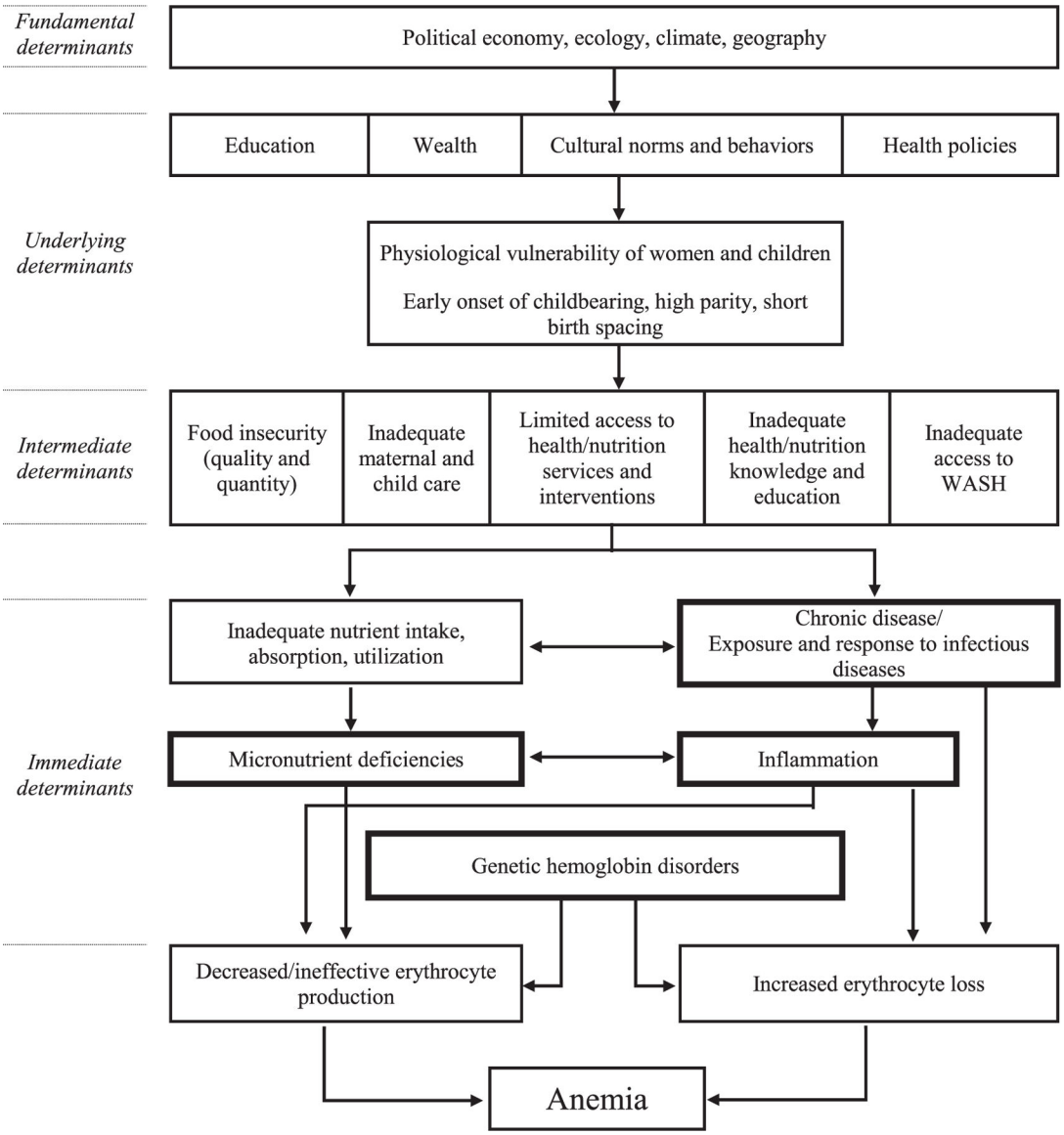


**Figure 2.**

A conceptual model of anemia etiology. Determinants outlined with heavier borders are considered primary contributors to anemia globally. Adapted from Refs. 13,44, and 45.

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**Table 1.**

Hemoglobin (g/L) concentrations to diagnose anemia at sea level[1,a]

| Population | Nonanemic | Anemia | | |
|---|---|---|---|---|
| | | Mild | Moderate | Severe |
| Children 6−59 months of age | ≥110 | 100−109 | 70−99 | <70 |
| Children 5−11 years of age | ≥115 | 110−114 | 80−109 | <80 |
| Children 12−14 years of age | ≥120 | 110−119 | 80−109 | <80 |
| Nonpregnant women (15 years of age and above) | ≥120 | 110−119 | 80−109 | <80 |
| Pregnant women | ≥110 | 100−109 | 70−99 | <70 |
| Men (15 years of age and above) | ≥130 | 110−129 | 80−109 | <80 |

[a]Adjustments recommended for altitude and smoking behaviors prior to applying cutoffs.[1]

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**Table 2.**

Common causes and classifications of anemia[a]

| Increased RBC loss/destruction | | | | Deficient/defective erythropoiesis | | |
|---|---|---|---|---|---|---|
| Blood loss | | Excessive hemolysis | | | | |
| **Acute** | **Chronic** | **Acquired** | **Hereditary** | **Microcytic** | **Normocytic, normochromic** | **Macrocytic** |
| **Postpartum hemorrhage** | • **Heavy menstrual bleeding**<br>• Gastrointestinal blood loss (**hookworm infection,** ulcers, **schistosomiasis**)<br>• Urinary blood loss (**schistosomiasis)** | • Immune mediated<br>• Microangiopathic<br>• **Infection (malaria)**<br>• Hypersplenism | • **Hemoglobin disorders (sickle cell disorders and thalassemias)**<br>• Enzymopathies (G6PD deficiency) | • **Iron deficiency**<br>• **Anemia of inflammation (chronic disease)**<br>• **Thalassemias Vitamin A deficiency** | • **Anemia of inflammation (chronic disease)**<br>• Renal disease<br>• Bone marrow failure (aplastic anemia, leukemia) | • **Folate deficiency**<br>• **Vitamin B12 deficiency** |

[a]Not all potential causes of anemia are identified in this list. Causes that are bolded are discussed in the text and are considered more prevalent causes at the population level in low- and middle-income countries. This table is adapted from Ref. 40.