Anaemia in low-income and middle-income countries

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Anaemia affects a quarter of the global population, including 293 million (47%) children younger than 5 years and 468 million (30%) non-pregnant women. In addition to anaemia's adverse health consequences, the economic effect of anaemia on human capital results in the loss of billions of dollars annually. In this paper, we review the epidemiology, clinical assessment, pathophysiology, and consequences of anaemia in low-income and middle-income countries. Our analysis shows that anaemia is disproportionately concentrated in low socioeconomic groups, and that maternal anaemia is strongly associated with child anaemia. Anaemia has multifactorial causes involving complex interaction between nutrition, infectious diseases, and other factors, and this complexity presents a challenge to effectively address the population determinants of anaemia. Reduction of knowledge gaps in research and policy and improvement of the implementation of effective population-level strategies will help to alleviate the anaemia burden in low-resource settings.

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Introduction

Anaemia is a major public health problem affecting 1·62 billion people globally.[1] Although the prevalence of anaemia is estimated at 9% in countries with high development, in countries with low development the prevalence is 43%.[1] Children and women of reproductive age are most at risk, with global anaemia prevalence estimates of 47% in children younger than 5 years, 42% in pregnant women, and 30% in non-pregnant women aged 15–49 years,[1] and with Africa and Asia accounting for more than 85% of the absolute anaemia burden in high-risk groups. Anaemia is estimated to contribute to more than 115 000 maternal deaths and 591 000 perinatal deaths globally per year.[2] The consequences of morbidity associated with chronic anaemia extend to loss of productivity from impaired work capacity, cognitive impairment, and increased susceptibility to infection,[3] which also exerts a substantial economic burden.[4]

We review present understanding of the epidemiology, clinical assessment, pathophysiology, and consequences of anaemia, focusing on women of reproductive age and children in low-income and middle-income countries. We discuss the multifactorial causes of anaemia and the co-occurrence of multiple risk factors in different populations and identify potential barriers to effective anaemia prevention and control.

Epidemiology

Anaemia is characterised by reductions in haemoglobin concentration, red-cell count, or packed-cell volume, and the subsequent impairment in meeting the oxygen demands of tissues.[5] Table 1 shows the criteria adopted by WHO to define anaemia status by haemoglobin concentration.[6] Physiological characteristics such as age, sex, and pregnancy status, as well as environmental factors such as smoking and altitude affect haemoglobin concentration. There has been continued discussion about the appropriateness of the thresholds used to define anaemia and their applicability to different populations, which has implications for epidemiological surveillance, monitoring, and targeting.[7,8] For example, several studies have shown that the population distribution of haemoglobin is lower in black people than in white people.[7,9,10] Only a few studies from low-income and middle-income countries have, however, examined the applicability of these guidelines to other populations.[10,11] The use of moderate-to-severe anaemia (haemoglobin <90 g/L) has been recommended for disease surveillance, especially in high-prevalence countries, as changes in the high end of the distribution are likely to shift more rapidly than those at the low end, so are more helpful in monitoring progress.[12]

The WHO Global Database on Anaemia for 1993–2005, covering almost half the world's population, estimated the prevalence of anaemia worldwide at 25%.[1] About 293 million children of preschool age, 56 million pregnant women, and 468 million non-pregnant women are estimated to be anaemic (figure 1, webappendix p 1).[1] Africa and Asia are the most heavily affected regions, with Africa having the highest prevalence of anaemia, and Asia bearing the greater absolute burden.[6]

Determinants of the prevalence and distribution of anaemia in a population involve a complex interplay of political, ecological, social, and biological factors (figure 2). At the country level, anaemia prevalence is inversely correlated with economic development

Search strategy and selection criteria

We searched PubMed using the search terms "anaemia", "tropical anaemia", "iron deficiency", and in combination with "nutrition", "infectious disease", "helminths", "hookworm", "schistosomiasis", "malaria", "HIV/AIDS", "thalassaemias", "hemoglobinopathies", "treatment", "iron", "fortification", "supplementation", "developing countries", "Africa", and "Asia". We focused on publications from the past 10 years, including reviews. We also searched publications from international organisations including WHO, World Bank, and UNICEF, as well as reports from non-governmental agencies, conference discussions, and book chapters. We reviewed reference lists of publications and reports identified by this search strategy and selected those deemed relevant to this Review.

	Haemoglobin concentration (g/L)
Non-pregnant women (>15 years)	<120
Pregnant women	<110
Children (0·5–4·9 years)	<110
Children (5·0–11·9 years)	<115
Children (12·0–14·9 years)	<120
Men (>15 years)	<130

Table 1: **Thresholds of haemoglobin used to define anaemia in different subpopulations, at sea level[6]**

(webappendix p 2). Children and women of reproductive age, in part because of their physiological vulnerability, are at high risk, followed by elderly people, and men.[1] Consequently, assessments of anaemia as well as interventions and policies to reduce anaemia largely focus on women and children. Adolescents are also a key group, with adolescent girls being targeted for intervention before the onset of childbearing.[13]

Anaemia is socially patterned by education, wealth, occupation (eg, agricultural workers), and residence.[14–16] In most settings, anaemia is a marker of socioeconomic disadvantage, with the poorest and least educated being at greatest risk of exposure to risk factors for anaemia and its sequelae. Analysis of nationally representative Demographic and Health Surveys undertaken in 32 selected low-income and middle-income countries (panel 1) suggests substantial variation in the prevalence of anaemia between countries. The proportion of women with anaemia varies—for example, being 61% (Benin) and 18% (Honduras), with half or more women having anaemia in a third of the countries (webappendix p 5). In 23 of the 32 countries, the proportion of children with anaemia was 50% or higher.

Anaemia is patterned by socioeconomic factors, especially by household wealth (table 2). Our pooled analysis showed that the risk of anaemia among women living in the lowest wealth quintiles was 25% higher than among those in the highest wealth quintile (table 2). Women with no education were more likely to be anaemic than were those with greater than secondary education. Conditional on women's socioeconomic status, relative risk of anaemia differed by urban or rural setting. Patterning of anaemia by socioeconomic status was also noted for children (table 2). A child living in a household in the lowest wealth quintile was 21% more likely to be anaemic than were those in the highest wealth quintile. Risk of anaemia was also raised in children whose mothers had no education. Conditional on demographic and socioeconomic factors, mother's anaemia status was among the strongest predictors of anaemia in children (table 2).

In individual country analyses, in most countries, women in the lowest wealth quintile or with no education were more likely to be anaemic than were those in highest wealth quintile or with greater than secondary education, respectively (webappendix pp 6–9). Similar patterns were reported for children (webappendix pp 10–12). Maternal anaemia was significantly and positively associated with anaemia in children in all countries (webappendix p 10), and the effects were often stronger than socioeconomic factors. Urban–rural differences in anaemia risk were not apparent in most countries for both women and children (webappendix pp 7–9, 11–12).

The second report on the World Nutrition Situation,[23] based on surveillance data available for 1975–90, reported that anaemia prevalence in sub-Saharan Africa and south and southeast Asia probably increased, consistent with the fall in dietary iron supply. Only in the near east and north Africa region were there probable

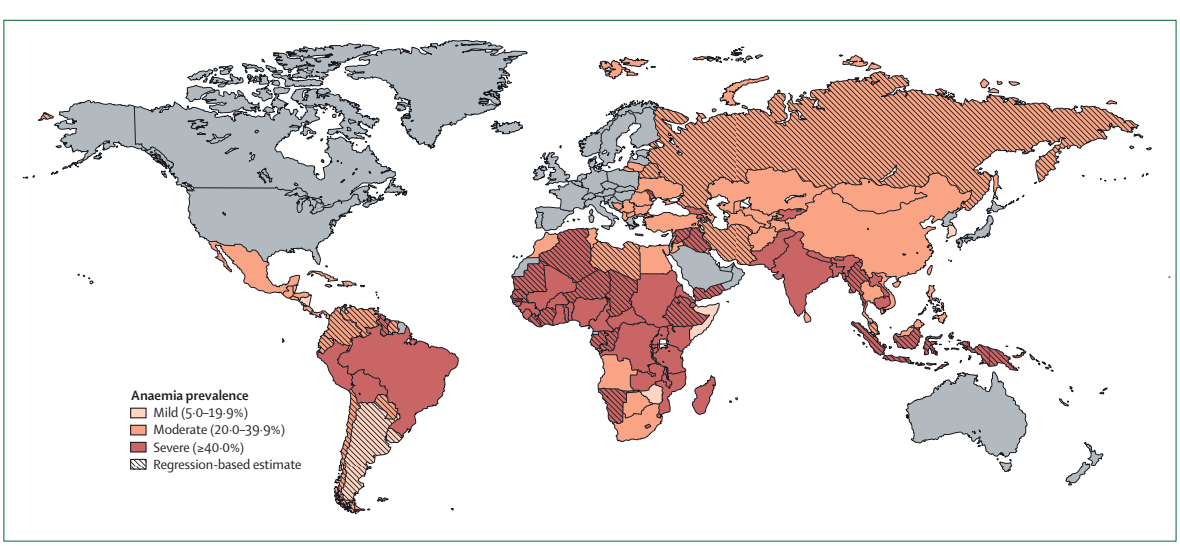

Figure 1: **Global prevalence of anaemia in children of preschool age (0–5 years)**
Adapted from reference 6.

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improvements during this period. Other estimates for 1995–2000 based on several different analytical approaches showed striking variation in trends across countries and regions. Interpolation of prevalence using regression models estimated that global anaemia prevalence fell by 0·16% points per year for non-pregnant women, 0·04% points per year for pregnant women, and 0·36% points per year for children younger than 5 years.[24] However, this overall picture masks regional heterogeneity; for example, among non-pregnant women during this period, trends in anaemia worsened in sub-Saharan Africa (by 0·18% points per year), the middle east and north Africa (by 0·06% points per year), and southeast Asia (by 0·42% points per year). Analysis of Demographic and Health Surveys, which are population-based with standardised methods, suggests that anaemia prevalence has in some cases increased in both women and children over time (webappendix pp 13–14).

Assessment of anaemia

The clinical symptoms and signs of anaemia vary and depend on the cause of anaemia and the speed of onset (panel 2). Medical history of signs and symptoms, clinical examination, blood tests, and additional investigations should ideally be done to confirm the diagnosis of anaemia, along with further investigation to establish the underlying cause. However, in many resource-poor settings, in which access to routine biochemical and haematological testing is scarce, diagnosis relies on history and clinical examination alone.

As part of international guidelines for the Integrated Management of Childhood Illness,[25] clinical assessment for anaemia in sick children involves assessment of palmar pallor. For pregnant women, the specific symptoms assessed during antenatal care are fatigue and dyspnoea, and the signs are conjunctival pallor, palmar pallor, and increased respiratory rate. These symptoms, together with diagnostic testing, result in the classification of anaemia and subsequent treatment options.[26]

Studies have investigated the sensitivity and specificity of clinical signs in diagnosis of anaemia, and these depend on the thresholds used to define anaemia, baseline anaemia prevalence, different phenotypes, and observer training and ability. A meta-analysis of 11 studies[27] assessing the accuracy of clinical pallor in children, mostly from Africa, showed a wide range of sensitivity (29·2–80·9%) and specificity (67·7–90·8%) for different signs of pallor (conjunctiva, palm, and nailbed) using different haemoglobin thresholds for anaemia; no particular anatomical site was deemed highly accurate for prediction of anaemia. In another study of five populations in Nepal and Zanzibar,[28] pallor at any site (conjunctiva, palm, and nailbed) was associated with anaemia, although there were differences in the relative performance of these different anatomical sites in diagnosis of anaemia. The sensitivity of clinical pallor to detect anaemia ranged between 60% and 80%, with a specificity between 92% and 94% in populations in which the prevalence of severe anaemia (haemoglobin <70 g/L) is less than 10%; use of multiple sites to detect pallor maximised sensitivity.[28] The limitation of clinical examination to detect anaemia necessitates the complementary use of blood tests to detect the full extent of the disease.

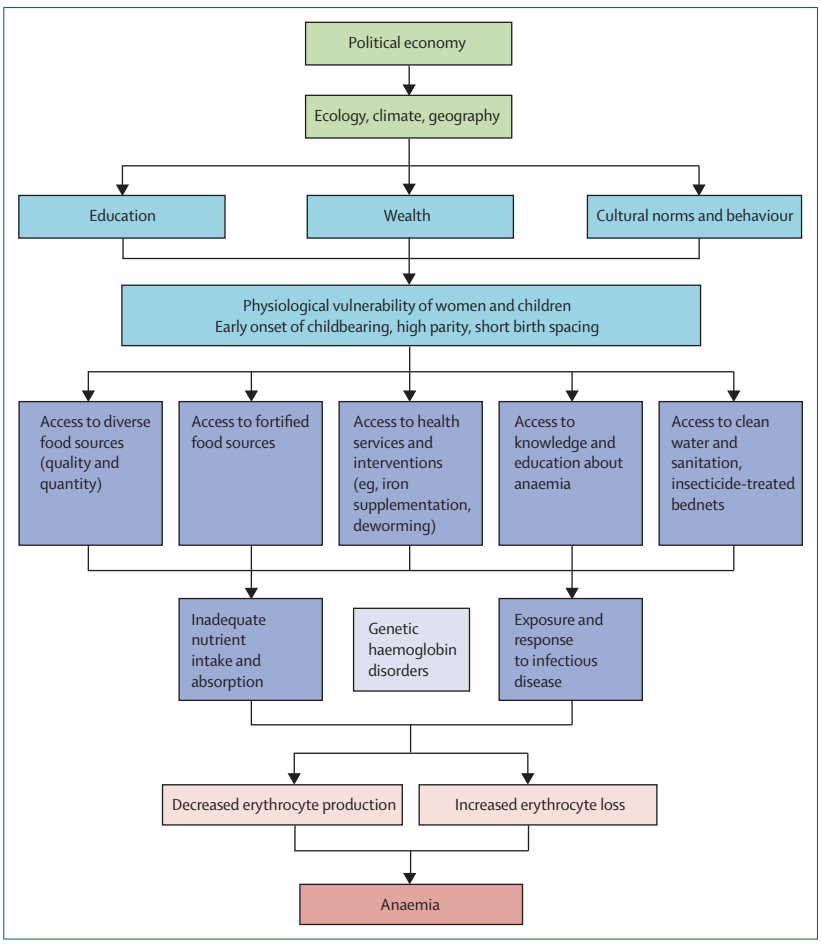

Figure 2: **Conceptual model of the determinants of anaemia**

Several haematological and biochemical indicators are used in diagnosis and assessment of anaemia and iron stores, the relative merits and limitations of which are discussed elsewhere.[29–31] Anaemia status is assessed through haemoglobin concentrations, haematocrit or packed-cell volume, mean cell volume, blood reticulocyte count, blood film analysis, and haemoglobin electrophoresis. Since iron deficiency is one of the key causes of anaemia, additional tests of iron status are also used; these tests include serum or plasma ferritin concentration, total iron-binding capacity, transferrin saturation, transferrin receptor concentration, zinc protoporphyrin concentration, erythrocyte protoporphyrin concentration, and bone-marrow biopsy.[32]

To distinguish between iron-deficiency anaemia and anaemia of chronic or acute disease is difficult, because increased circulating hepcidin seen during inflammation

Panel 1: Epidemiological analysis of anaemia

We used data from Demographic and Health Surveys (DHS; webappendix pp 3–4) to describe the patterns, distribution, and trends in anaemia.[17] DHS are nationally representative household sample surveys measuring indicators of population, health, and nutrition, with special emphasis on maternal and child health.[18] We included all surveys measuring anaemia coded with standardised variables for women and children. The target population in most surveys was all women (or in some cases ever-married women) of reproductive age (15–49 years), and all children born to mothers aged 15–49 years at the time of the survey. Anaemia was ascertained by measurement of the concentration of haemoglobin in capillary blood. Trained investigators removed the first two drops of blood after a finger prick (or heel prick for young children) and drew the third drop into a cuvette for analysis with the HemoCue system. Anaemia is defined as a haemoglobin concentration of less than 120 g/L for women, less than 110 g/L for pregnant women, and less than 110 g/L for children, adjusted for altitude.[6] Mother's age, education (none, primary, secondary or greater), household wealth, and urban or rural residence were included as covariates for analysis of the women's sample, and for child analysis we also include child's age, maternal age at birth (<17, 17–19, 20–24, 25–29, >30 years), and mother's anaemia status. Household wealth was defined in terms of ownership of material possessions,[19] with each mother or child assigned a wealth index based on a combination of different household characteristics provided by DHS. This standardised wealth index was then divided into quintiles for each country.[20,21] We estimated modified Poisson regression models, which allows us to calculate relative risks for non-rare events,[22] to model the risk of having anaemia, for women and children separately, pooled across all countries with country fixed-effect, as well as separately for each country.

blocks iron release from enterocytes and the reticuloendothelial system, resulting in iron-deficient erythropoiesis. Moreover, since serum ferritin is an acute-phase protein, raised concentrations in the presence of inflammation, as with coexisting infection, do not necessarily rule out iron-deficiency anaemia. C-reactive protein (CRP), another marker of inflammation, has therefore been used in conjunction with serum ferritin, although the threshold of CRP that renders the use of serum ferritin unreliable in identifying iron deficiency is unknown, with thresholds of CRP greater than 10–30 mg/L applied.[30]

At the population level, haemoglobin concentration is the most common indicator, because it is inexpensive and easy to measure with field-friendly testing (panel 3). However, it lacks specificity for establishing of iron status. Therefore, concentrations of serum ferritin and transferrin receptor have been recommended as measures of population iron status. Since ferritin is raised in the acute-phase response, this approach underestimates iron deficiency, rendering the threshold of lower than 12–15 µg/L inappropriate in settings in which infectious diseases are prevalent. A meta-analysis of 32 studies[35] assessing the increase in ferritin associated with acute-phase proteins estimated that inflammation increased ferritin by about 30%, leading to an underestimation of iron deficiency by 14% (95% CI 7–21). The combination of serum ferritin with transferrin receptor allows some distinction between inflammation and iron deficiency, although this finding is yet to be validated in population-based surveys.[32] To monitor and assess the effect of interventions on population-level changes in iron status, the WHO and US Centers for Disease Control and Prevention Technical Consultation recommends the use of serum ferritin in combination with haemoglobin.[32,36] However, the complexity of multiple indicators to measure different aspects of anaemia and iron metabolism, the knowledge gaps relating to the choice and thresholds of different indicators, the absence of research comparing the accuracy of different tests for haemoglobin concentration and iron status, and the lack of simple technology to easily measure iron status in the field present a challenge to population assessment of anaemia and iron status.

In addition to these technical considerations, operational challenges arise from the different methods and costs. For example, the equipment cost and per-unit cost of testing materials differs: for haemoglobin testing with portable photometers, equipment cost is roughly US$500, unit cost less than $1; for ferritin, immunoassay testing equipment cost is roughly $5000, unit cost $5–10; and for transferrin receptor, immunoassay testing equipment cost is roughly $5000, unit cost $10–15.[32] Thus, technical and operational knowledge gaps, together with paucity of cost–benefit analysis to guide the choice of the haematological and biochemical testing, adds a substantial challenge to assessment of anaemia in low-resource settings.

Causes and types of anaemia

Classification

Anaemia can be broadly classified into decreased erythrocyte production (ineffective erythropoiesis) as a result of impaired proliferation of red-cell precursors or ineffective maturation of erythrocytes; or increased loss of erythrocytes through increased destruction (haemolysis) or blood loss; or both. These processes are broadly determined by nutrition, infectious disease, and genetics (figure 3).[37] Although iron deficiency is thought to be the major cause of anaemia, postulated to account for around 50% of anaemia,[2] there is little evidence to support such estimates. Limitations of existing indicators to measure iron status at the population level and scarcity of data preclude improved understanding of the relative contribution of iron deficiency to anaemia in different settings, although studies in specific populations show that substantial variation exists in the estimated proportion

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of anaemia attributable to iron deficiency. The distribution of haemoglobin among populations with and without iron deficiency also overlaps substantially.[32] Clear distinction between anaemia, iron-deficiency anaemia, and iron deficiency, in view of their independent and interdependent physiological effects, is impeded by data gaps. The terms anaemia and iron-deficiency anaemia are often used interchangeably, further compounding the confusion.

Nutritional anaemias

Nutritional anaemias result from insufficient bioavailability of haemopoietic nutrients needed to meet the demands of haemoglobin and erythrocyte synthesis.[31,38] As human diets have shifted over time from hunter-gatherer to more cultivated cereal-based diets with more heat exposure during food preparation, there has been a large drop in bioavailable haemopoietic nutrients (iron, vitamin B12, and folic acid) and absorption enhancers such as vitamin C. This situation is compounded by increased intake of other dietary factors that reduce the bioavailability of non-haem iron, such as polyphenols (eg, tea, coffee, and spices such as cinnamon), phytates (whole grains, legumes), and calcium (dairy products).[29,39] Moreover, absorption of nutrients that promote haemopoiesis can be affected by physiological and pathophysiological factors—for example, *Helicobacter pylori* is associated with reduced iron stores through several different mechanisms.[40,41]

Restricted access to diverse micronutrient-rich diets, particularly for vulnerable groups, can exacerbate nutritional anaemias. Whereas each of the micronutrients we discuss has specific roles, multiple deficiencies tend to cluster within individuals, and the synergistic effect of these deficiencies is important in the development of anaemia.

Iron deficiency

Iron deficiency occurs when the intake of total or bioavailable iron is inadequate to meet iron demands, or to compensate for increased losses. Iron has an important role in the function of several biological processes, and is an integral part of the haemoglobin molecule wherein Fe^{2+} is bound to the protein-protoporphyrin IX complex to form haem. Lack of available iron thereby results in low haem concentrations and hypochromic microcytic anaemia.

Periods of rapid growth, especially during infancy and pregnancy, result in substantial demands for iron, which accounts for the physiological vulnerability of children and women. Recurrent menstrual loss accounts for roughly 0·48 mg per day, with wide variation depending on menstrual flow.[31,42] During pregnancy, expansion of the red-cell mass and development and maintenance of the maternal-placental-fetal unit results in a substantial increase in iron requirements that range from 0·8 mg per day in the first trimester to 7·5 mg per day in the third trimester.[43,44] Even in developed countries, anaemia during pregnancy is common;[45] however, in developing countries this occurrence is compounded by early onset of childbearing, high number of births, short intervals between births, and poor access to antenatal care and supplementation.[46] The effects of pregnancy and parity on iron status are long-lasting, with differences in iron stores as measured by serum ferritin between nulliparous, uniparous, and multiparous women detectable after menopause.[43]

The intergenerational transfer of poor iron status from mother to child has also been shown in several studies, with maternal iron deficiency increasing the vulnerability of infants to iron deficiency and anaemia.[46–49] Low-birthweight and preterm infants are at increased risk because they are born with reduced iron stores. Iron

	Women (n=370 449)	Children (n=173 464)
Maternal anaemia		
Yes	..	1·20 (1·19–1·21)
No	..	Reference
Education		
None	1·08 (1·07–1·10)	1·09 (1·08–1·10)
Primary	1·04 (1·03–1·05)	1·05 (1·04–1·07)
Secondary or higher	Reference	Reference
Wealth quintile		
Lowest quintile	1·25 (1·23–1·27)	1·21 (1·19–1·22)
Second lowest quintile	1·19 (1·18–1·21)	1·18 (1·16–1·20)
Middle quintile	1·15 (1·13–1·16)	1·14 (1·12–1·16)
Second highest quintile	1·11 (1·09–1·12)	1·10 (1·08–1·12)
Highest quintile	Reference	Reference
Setting		
Urban	0·98 (0·98–0·99)	1·00 (0·99–1·01)
Rural	Reference	Reference

Data are relative risk (95% CI). Models for women were additionally adjusted for age, and models for children were additionally adjusted for child's age and mother's age at birth.

Table 2: **Relative risk of anaemia in women and children, by household wealth, education, urban or rural residence, and maternal anaemia**

Panel 2: Assessment of anaemia[5]

Dependent on severity, speed of onset, and underlying cause of anaemia:

- Symptoms: fatigue, pallor, exertional dyspnoea, palpitations, angina, claudication, headache, vertigo, light-headedness, faintness, tinnitus, cramps, increased cold sensitivity, anorexia, nausea, change in bowel habits, menstrual irregularities, urinary frequency, and loss of libido
- Signs: pallor (conjunctival, nailbed, palmar, tongue, or generalised), tachycardia, increased arterial pulsation, capillary pulsation, bruits, cardiac enlargement, signs of cardiac failure; specific signs related to specific causes include koilonychia in iron-deficiency anaemia, jaundice in haemolytic anaemia, splenomegaly in hyper-reactive malarial splenomegaly, and bone deformities in thalassaemias

Panel 3: Haemoglobin measurement in population-based surveys

Population-based estimates of anaemia prevalence depend on the sampling design, methods used for assessment of haemoglobin concentrations, and thresholds used to define anaemia.

- Direct cyanmethaemoglobin: gold standard; needs access to laboratory with a spectrophotometer within a few hours of travel time
- Indirect cyanmethaemoglobin: field-friendly; blood dried on filter paper, redissolved in laboratory
- Portable haemoglobin photometers such as HemoCue system:* field-friendly, portable hand-held device; finger-prick or heel-prick (for children) capillary blood samples sampled at site providing immediate results, used in Demographic and Health Surveys[17,33]

*A study comparing the specificity and sensitivity of these tests to the gold standard, on both venous and capillary blood samples, recommended the use of HemoCue with venous blood followed by HemoCue testing of capillary blood for use in remote areas.[34] Furthermore, this system is easy to use, gives immediate results, and has low interobserver error.

deficiency and anaemia in young children are associated with various functional consequences, especially in early childhood development.[50] Although the iron content of breast milk is low, it is highly bioavailable and exclusive breastfeeding for the first 6 months of life is recommended. Inadequate access to fortified complementary foods and iron supplements, and exposure to infections during infant growth increases the risk of anaemia and iron deficiency in young children. Strategies to lower risk of anaemia in early infancy and break the intergenerational cycle of iron depletion include optimisation of maternal nutritional status, delayed cord clamping at delivery, improvement of infant feeding practices, and prevention and treatment of infectious disease.[31,51]

Folic acid deficiency

Folic acid is required for the synthesis and maturation of erythrocytes, and low serum and erythrocyte concentrations of folate can lead to changes in cell morphology and intramedullary death of erythrocytes and reduced erythrocyte lifespan. Folic acid deficiency contributes to megaloblastic anaemia, a condition characterised by cells with large and malformed nuclei resulting from impaired DNA synthesis. During pregnancy, folate demands increase, and women entering pregnancy with poor folate status often develop megaloblastic anaemia; furthermore, lactation places additional demands with preferential uptake of folate by mammary glands over maternal requirements.

The contribution of folate deficiency to anaemia at the population level is unknown because few global data exist, although it is thought to be low in developing countries.[52] Review of epidemiological studies and nutrition surveys from South America did not reveal population-level folate deficiency in Costa Rica, Guatemala, or Mexico, but identified high prevalence of serum folate deficiency in specific subpopulations of Cuban men (64–89%) and Chilean women (25%) before flour fortification.[53] Consumption and preparation of folate-rich food varies greatly by region.

Vitamin B12 deficiency

Vitamin B12 is synthesised only by microorganisms, and its primary source is from ingestion of animal products. Absorption of vitamin B12 involves a complex process by which gastric enzymes and acid facilitate its release from food sources, before being bound by an intrinsic factor secreted by gastric parietal cells, followed by uptake in the distal ileum. Vitamin B12 deficiency can result in a megaloblastic macrocytic anaemia, which is more common in severe vitamin B12 deficiency.[52]

The global prevalence of vitamin B12 deficiency is unknown, but evidence from several developing countries suggests that deficiency is widespread and is present throughout life. In South America, at least 40% of children and adults were vitamin B12 deficient, with prevalences greater than 70% in Africa and Asia.[53,54] However, how much this deficiency contributes to anaemia is unclear, with few data available for the haematological effect of increasing B12 intake at the population level.[52]

The main causes of vitamin B12 deficiency are inadequate dietary intake, especially from vegetarian diets,[55] pernicious anaemia, an autoimmune disorder resulting from autoantibody against intrinsic factor, tropical sprue, and co-infection with *Diphyllobothrium latum*, *Giardia lamblia*, and *H pylori*. Vitamin B12 deficiency is associated with lactovegetarianism in India, and the scarcity of meat products in many south Asian diets.[56–59] The prevalence of pernicious anaemia is unknown, but reports from several African countries suggest that it could be more prevalent than was previously thought.[60,61]

Vitamin A deficiency

Vitamin A deficiency is common in Africa and southeast Asia, affecting an estimated 21% of children of preschool age and 6% of pregnant women, and accounting for around 800 000 deaths of women and children worldwide.[2] Vitamin A deficiency results from low dietary intake of preformed vitamin A from animal products and carotenoids from fruits and vegetables. Vitamin A plays an important part in erythropoiesis and has been shown to improve haemoglobin concentration and increase the efficacy of iron supplementation.[62] The mechanisms are not fully understood, but are suggested to operate through effects on transferrin receptors affecting the mobilisation of iron stores, increasing iron absorption, stimulating erythroid precursors in the bone marrow, and reducing susceptibility to infections.

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Soil-transmitted helminths

Infectious diseases can contribute to anaemia through impaired absorption and metabolism of iron and other micronutrients or increased nutrient losses. Of soil-transmitted helminth infections, hookworms (*Necator americanus* and *Ancylostoma duodenale*) are the major cause of anaemia, and are commonly found in sub-Saharan Africa and southeast Asia, with an estimated 576–740 million infections.[63,64] In the tropics and subtropics, where ecological conditions allow larval development, hookworm infections are overdispersed or highly aggregated in areas of poverty, where poor water, sanitation, and infrastructure result in endemicity, often concentrated in small populations within these areas.[65,66] Co-infection with several species is common.

Hookworms can cause chronic blood loss, with the severity dependent on the intensity of infection, the species of hookworm (*A duodenale* is more invasive than *N americanus*),[67] host iron reserves, and other factors such as age and comorbidity. Systematic review of 12 studies of deworming during pregnancy[68] showed that women with light hookworm infection (1–1999 eggs per g of faeces) had a standardised mean difference of haemoglobin that was 0·24 lower (95% CI –0·36 to –0·13) than in those with no hookworm. Adult parasites invade and attach to the mucosa and submucosa of the small intestine, causing mechanical and chemical damage to capillaries and arterioles. By secreting anticlotting agents, the parasite ingests the flow of extravasated blood, with some recycling of lysed erythrocytes and blood. Hookworm disease results when chronic blood loss exceeds iron reserves, inducing iron-deficiency anaemia.

A meta-analysis of 14 randomised controlled trials[69] of deworming in sub-Saharan Africa and Asia showed a significant increase in mean haemoglobin (1·71 g/L, 95% CI 0·70–2·73), with an increased response in those provided with iron supplementation. A more recent meta-analysis of deworming in non-pregnant populations[70] showed the beneficial effect of anthelmintic treatment, and the differential effects of coadministration with praziquantel to target other parasites, or iron supplementation to replenish iron stores, or both; for example, albendazole together with praziquantel increased mean haemoglobin by 2·37 g/L (95% CI 1·33–3·50).

Malaria

Malaria causes between 1 million and 3 million deaths every year,[71] a burden falling overwhelmingly on Africa. *Plasmodium falciparum* is the most pathogenic species and can lead to severe anaemia, and subsequent hypoxia and congestive heart failure.[72] Our knowledge of the mechanisms of malaria-related anaemia has evolved substantially,[72] and can be broadly characterised as increased erythrocyte destruction and decreased erythrocyte production, with mechanisms probably acting simultaneously and affected by factors such as age, pregnancy, malarial species, previous exposure, and prophylaxis.

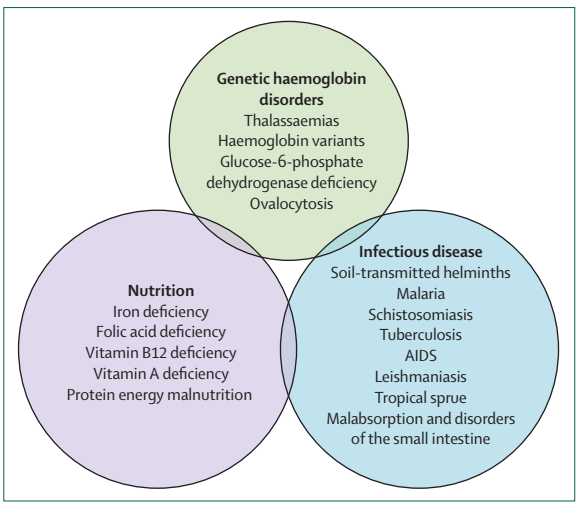

Figure 3: **Causes of anaemia in countries with low or middle incomes[5]**

The interaction between malaria and iron and folate supplementation has been the subject of intense research and controversy in recent years,[73] intensified by the results of two cluster-randomised double-blind intervention trials[74,75] of iron and folate in preschool children in Zanzibar and Nepal. In Zanzibar, an area of high *P falciparum* endemicity, the increased risk of severe morbidity and mortality in children receiving iron and folate supplementation was shown to outweigh the benefits.[74] The subsequent WHO-led Expert Consultation[76] emphasised the need to exercise caution against universal iron supplementation for children younger than 2 years in malaria-endemic regions where appropriate screening and clinical care are scarce, together with other recommendations. Subsequently, a systematic review of 68 randomised and cluster-randomised trials[77] covering 42 981 children did not identify any adverse effect of iron supplementation on risk of clinical malaria or death, in both anaemic and non-anaemic children, in malaria-endemic areas. However, this finding relates to settings in which there are adequate regular malaria surveillance and treatment services in place, which might not be the case in many low-resource settings. Thus, treatment of children with iron supplements should be accompanied by adequate screening for and treatment of malaria.

Other malaria control strategies have had a beneficial effect on anaemia. A systematic review of the effect of insecticide-treated bednets for prevention of malaria[78] showed a beneficial effect on haemoglobin in children. Use of insecticide-treated bednets compared with no bednets increased absolute packed-cell volume by 1·7%, whereas use of treated bednets compared with untreated bednets increased absolute packed-cell volume by 0·4%.

Analysis of nine trials of 5445 children examining the effect of malaria chemoprophylaxis and intermittent prevention revealed significant reduction of severe anaemia (RR 0·70, 95% CI 0·52–0·94).[79]

Schistosomiasis

More than 90% of schistosomiasis occurs in sub-Saharan Africa, where there are an estimated 192 million cases affecting children and young adults,[80] with *Schistosoma haematobium* accounting for about two-thirds of these. Several cross-sectional studies and randomised trials of different treatment options have examined the association between *Schistosoma* spp and anaemia.[81] However, of the two randomised trials of monotherapy, only one[82] showed a significant effect of treatment of children with praziquantel of about 10 g/L increase in haemoglobin concentration in a *Schistosoma japonicum* endemic area in the Philippines, 6 months after the intervention.

The mechanisms underlying schistosomiasis-related anaemia are not well understood. Postulated mechanisms include iron deficiency from blood loss from haematuria (*S haematobium*) and bloody diarrhoea (*S japonicum* and *S mansoni*); splenic sequestration or increased haemolysis by the hypertrophic spleen, or both; autoimmune haemolysis; and anaemia of chronic disease driven by proinflammatory cytokines.[81] Several mechanisms are likely to be in operation, depending on the species, intensity of infection, and host interactions.

HIV/AIDS

Anaemia is the most common haematological complication associated with HIV infection, and is a marker of disease progression and survival.[83] The burden of HIV/AIDS-related anaemia falls predominantly on sub-Saharan Africa, where women and children are most at risk.[84] The mechanism of HIV/AIDS-related anaemia is multifactorial, resulting from HIV infection and the induced anaemia of chronic disease, AIDS-related illnesses, and antiretroviral treatment. Further research is needed to assess the burden and effect of strategies for HIV/AIDS prevention and treatment on anaemia.[85]

Genetic causes

Genetic haemoglobin disorders, which result from structural variation or reduced production of globin chains of haemoglobin, can result in anaemia. Estimates of the burden of haemoglobin disorders suggest that at least 5·2% of the global population, and more than 7% of pregnant women, are carriers of a significant haemoglobin variant.[86] There is substantial regional variation, with the burden falling overwhelmingly on the African and southeast Asian regions, where 18·2% and 6·6% of the population, respectively, carry a significant haemoglobin variant.[86] Although extensive research has investigated the distribution and functional consequences of these genetic haemoglobin disorders, their contribution to the global anaemia burden remains unclear.[87] Micromapping studies are needed to estimate their prevalence in different populations,[88] which could also have implications for prevalence estimation of anaemia in populations in which these variants are present.[8]

Each year, more than 330 000 infants are born with these disorders (83% sickle-cell disorders and 17% thalassaemias).[86] Sickle-cell disorders are associated with chronic haemolytic anaemia, and an estimated 2·28 per 1000 conceptions worldwide are affected by sickle-cell disorders.[86] Thalassaemias are highly prevalent in many Mediterranean, middle eastern, and south and southeast Asian countries; an estimated 0·46 per 1000 conceptions worldwide are affected by homozygous β thalassaemia, haemoglobin E/β thalassaemia, homozygous α0 thalassaemia, and α0/α+ thalassaemia (haemoglobin H disease).[86] Only 12% of transfusion-dependent patients with β thalassaemia receive transfusions, and only 39% of those receive adequate iron chelation.[86]

As child survival improves, inherited haemoglobin disorders could become an increasingly important disease burden and cause of anaemia in the future.[89] However, many of the recent advances involving genetic and pharmacological treatments are unlikely to be available in low-resource settings, in which health system requirements for diagnosis and management of these conditions remain poor.[87]

Consequences of anaemia

Background

Much of the knowledge pertaining to the health consequences of anaemia comes from cross-sectional, case-control, and prospective studies examining the association between anaemia or haemoglobin on health outcomes such as maternal mortality, perinatal mortality, and cognitive outcomes, with much of this evidence relating specifically to iron-deficiency anaemia. As such, the causal role and attributable fraction of anaemia toward various outcomes, although highly suggestive, remain to be fully documented.[90]

Maternal and perinatal consequences

Although the causal evidence for adverse consequences is strong for severe anaemia and maternal outcomes, it remains inconclusive for mild-to-moderate anaemia.[90] Assimilation of the evidence from six observational studies of anaemia and maternal mortality used to estimate the magnitude of the association found a combined odds ratio (OR) of 0·75 (95% CI 0·62–0·89) associated with a 10 g/L increase in haemoglobin.[2] The relation between anaemia and perinatal mortality also remains inconclusive;[91] on the basis of a meta-analysis of ten studies, the estimated combined OR for perinatal mortality associated with a 10 g/L increase in haemoglobin was 0·72 (95% CI 0·65–0·81). In a subgroup analysis, the risk in *P falciparum* malaria endemic areas was greater, with a point estimate of 0·65 (0·56–0·75).[2] Yet, more recently, evidence from a large prospective cohort

study in China of more than 160 000 singleton births did not show an association of maternal anaemia with neonatal mortality.[92]

Several studies have investigated the association between anaemia and adverse birth outcomes, namely preterm birth and low birthweight. These studies have had varied results, with heterogeneity in study designs, settings, and populations.[90,93] These heterogeneous findings relating maternal anaemia to perinatal outcomes might also be affected by the dynamics of haemodilution from first to third trimester, and the timing of haemoglobin measurements.[94] Several studies have investigated the effectiveness of iron supplementation (with or without folic acid) in pregnant women; systematic review of 49 randomised and quasirandomised trials covering 23 200 women showed that treatment with iron or iron and folic acid supplementation during pregnancy was associated with increased haemoglobin concentrations at term, and reduced risk of anaemia or iron deficiency at term.[95] However, there was no significant reduction in infant or maternal outcomes, such as preterm birth and low birthweight.[90,93,95]

Cognitive development

Despite substantial research into the association between iron deficiency and cognitive development in children, and several plausible physiological mechanisms, the ability to infer causality from existing studies is limited.[96] Although observational studies have reported associations between iron-deficiency anaemia and poor cognitive and motor development, the evidence from randomised trials has again been inconclusive.[97] In an attempt to quantify this association, a meta-analysis of five studies estimated that a 10 g/L increase in haemoglobin was associated with a 1·73 (95% CI 1·04–2·41) increase in IQ points.[2] However, whether poor cognitive development in iron-deficient children is compounded by other factors affecting social disadvantage, or factors relating to the timing of iron deficiency during cognitive development, is unclear.

Work productivity

The association between iron deficiency and productivity has been extensively investigated.[3] Iron's role in oxygen transport to muscles and other tissues, and its role in other metabolic pathways, show the direct route by which iron deficiency can reduce aerobic work capacity. This link has been supported by randomised field trials of iron supplementation and work productivity in developing countries, including rubber plantation workers in Indonesia, female tea-plantation workers in Sri Lanka, and female cotton-mill workers in China.[3,4] In countries in which physical labour is prevalent, reduced work performance due to anaemia has substantial economic consequences.[4]

Attempts to quantify the economic burden of iron deficiency have focused on the loss of work productivity in adults and cognitive effect in children. The present value of the median physical and cognitive losses associated with anaemia and iron deficiency have been estimated at US$3·64 per head, or 0·81% of gross domestic product in selected developing countries.[98] Although these estimates are based on several assumptions and should be interpreted with caution, they give an idea of the scale of the potential economic consequences of anaemia and iron deficiency. The aggregate effect of small individual losses, especially in developing economies in which physical labour is dominant, accrues to billions of dollars of human capital—for example, in south Asia, the productivity loss is estimated at $4·2 billion annually.[4]

Implementation of anaemia prevention and control interventions

Several strategies exist for anaemia prevention and control, and these include improvement of dietary intake and food diversification, food fortification, supplementation with iron and other micronutrients, appropriate disease control, and education (panel 4). Although we have not reviewed these interventions here, several are low cost and rank among the more cost-effective interventions at the population level.[38,100–107] Furthermore, from a sample of ten developing countries, the median value of the estimated benefit:cost ratios for long-term iron fortification programmes was 6:1, and this ratio increased to 8·7:1 when discounted future benefits attributable to cognitive improvements were included in the estimates.[4,98] Indeed, the high benefit-to-cost ratios of micronutrient supplementation for children (with vitamin A and zinc), fortification with iron (and salt iodisation), biofortification, deworming, school nutrition programmes, and community-based nutrition promotion have placed these interventions among the top ten global

Panel 4: **Anaemia prevention and control strategies**

- Improved dietary intake (quality and quantity) and increased food diversity with increased iron bioavailability
- Fortification of staples with iron (mass and home fortification); open-market fortification of selected processed food such as breakfast cereals; targeted fortification of foods for high-risk groups (eg, infant formula);[99] biofortification
- Iron (and folic acid) supplementation (tablets, powders, spreads) to high-risk groups—eg, pregnant and lactating women, children, adolescents, and women of reproductive age
- Disease control (eg, malaria, with insecticide-treated bednets and antimalarial drugs; deworming in helminth-endemic areas; handwashing)
- Improved knowledge and education about anaemia prevention and control, for both civil society and policy makers

	Policy makers	Human resources	Beneficiaries
Policy	Insufficient political priority Poor awareness of the magnitude and consequences of anaemia burden Challenge of coordination of necessary multisectoral policy response (food and agriculture, health systems, water and sanitation, etc)	Limited leadership and capacity of existing human resources to champion anaemia prevention and control	Limited mobilisation of civil society to demand policy attention to address anaemia Challenge of addressing needs of vulnerable groups
Resources	Little financial commitment for anaemia Poor coordination of resources to support multisectoral response Inflexibility of financial disbursements for related health issues (eg, malaria, reproductive health) to be used towards anaemia control	Lack of institutional and operational capacity for scaling up of coverage of high-quality maternal and child health services Challenge of integration of anaemia control into existing programmes and initiatives Poor awareness of need for anaemia prevention and control	Restricted financial access to iron-rich food sources, iron supplements, health services, etc Limited supply and access to iron supplementation and maternal health services to reinforce anaemia prevention
Knowledge	Poor awareness of the magnitude of disease burden due to the insidious, latent presentation of anaemia, and long-term consequences Technical knowledge gaps include: validity and cost-benefit of tests for assessment of anaemia prevalence; challenge of assessment of local determinants of anaemia; challenge of measurement of the effectiveness of interventions; uncertainty as to best strategic response to address anaemia in different groups Poor knowledge about how to coordinate the policy and implementation response to the context-specific causes of anaemia	Technical and operational knowledge gaps to guide more effective implementation Little knowledge of how to integrate anaemia control into existing programmes	Lack of education and information about anaemia prevention, and awareness of benefits of appropriate intervention Poor compliance with iron supplementation Little individual and community awareness of anaemia status due to latent symptoms and signs

***Table 3*: Barriers to effective implementation of anaemia prevention and control strategies**

priorities to address the world's important challenges by the 2008 Copenhagen Consensus.[103]

However, several barriers impede anaemia prevention and control strategies (table 3). Also, there are implementation challenges relating to delivery and scale-up of existing anaemia interventions; addressing implementation knowledge gaps, and maximising opportunity to learn from past failures and successes could improve understanding of how to achieve and sustain impact. Studies that provide evidence to aid policy makers are needed, such as those that evaluate effectiveness and measure the effect of interventions—for example, few studies have assessed the national population-level effectiveness of fortification interventions of staple foods in children.[108]

Another key challenge is meeting the needs of high-risk groups at specific times in their lives—namely, pregnant women, infants (especially preterm or low-birthweight), and adolescent girls, and balancing this strategy with broader population-level approaches. Combination of the different strategies needed during the continuum of care, together with interventions for the general population, present complexity and necessitate assessment of the programme effectiveness, cost-effectiveness, and safety of combinations of interventions, and implementation within the constraints of restricted resources and health systems in these settings.[109] The low coverage of maternal and child health interventions, and the poor quality of these services,[110,111] add to this challenge. For example, although antenatal care coverage is improving, gaps in the delivery of specific interventions (such as iron and folic acid supplementation) remain.[112] Inadequate investment in financial and human resources hampers the implementation of maternal and child health interventions, as does scarce evidence for the effectiveness of policies and practices.[113] Also, evidence from several countries suggests that increased contact with health providers without due attention to the quality of services could fail to improve service delivery.[112] Investment in the quality of community health workers, fostering of community awareness of the benefits of addressing anaemia, and increasing of the social acceptability of interventions through community-based approaches also needs further consideration and could help to improve results.[114]

Crucially, the timely availability and accuracy of data, and its routine use to identify specific performance bottlenecks, target solutions, and assess effect, will underlie the successful implementation of anaemia control strategies. For anaemia in particular, local data collection for decision making is important to guide appropriate targeted packages of interventions to address the different types of anaemia. We remain unclear as to the contribution of different causes of anaemia in different settings; elucidating the pattern of risk factors such as helminth infection and malaria is crucial to identification of local determinants of anaemia. This process might in the interim necessitate alternative strategies such as synergism of data collection, sampling of specific high-risk populations, and development of methods to indirectly estimate clustering of co-infection and anaemia through methods such as prediction modelling or spatial analysis. Geographical information systems can be used to map anaemia and infectious diseases for data analysis, prediction of populations at risk, and planning and monitoring of interventions.[115–117] Improved understanding of the clustering of risk factors and the distribution of co-infection is needed to build the evidence base for strategies offering synergies to address multiple causes with a more coordinated context-specific approach.[117]

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Conclusion

Global inequalities in anaemia reflect the stark differences between developing and developed countries and the differential exposure to the varied determinants of anaemia. Anaemia continues to be an endemic problem of large magnitude, and the increasing trends in several developing countries point to the failures of existing approaches to alleviate this burden. Overcoming political, operational, and technical barriers to anaemia control will foster more effective implementation of policies and strategies. Engagement of diverse stakeholders and building of capacity is needed to effect such change, as is sustained commitment and investment in anaemia reduction.[118,119] Addressing the challenge of anaemia will necessitate a holistic response to both the proximate and distal determinants of anaemia, together with consideration of the intergenerational aspects. Identification of the local determinants of anaemia and improvement of the implementation of contextually appropriate strategies will be crucial for progress in this important global health issue.

Contributors

YB and SVS conceptualised the study and developed the framework for the Review. YB led the writing of the Review. SVS contributed to critical revisions, writing, and supervised the Review. UR and AHS contributed to critical revisions and writing of the Review. EÖ contributed to data analysis and writing. All authors have read and approved the Review.

Conflicts of interest

We declare that we have no conflicts of interest.

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