Determinants of Anemia in South East Asian Countries

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Introduction

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 [1]. Although iron deficiency is thought to be the major cause of anaemia, postulated to account for around 50% of anaemia, there is little evidence to support such estimates [2]. 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 of anaemia attributable to iron deficiency. The distribution of haemoglobin among populations with and without iron deficiency also overlaps substantially [3,4]. Clear distinction between anaemia, iron-deficiency anaemia, and iron deficiency, in view of their independent and inter-dependent physiological effects, is impeded by data gaps. The terms anaemia and iron-deficiency anaemia are often used interchangeably, further compounding the confusion [4].

Nutritional Anemias

Nutritional anaemias result from insufficient bioavailability of haemopoietic nutrients needed to meet the demands of haemoglobin and erythrocyte synthesis [4,5]. 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 bioavailabiity of non-haem iron, such as polyphenols (eg, tea, coffee, and spices such as cinnamon), phytates (whole grains, legumes), and calcium (dairy products) [6,7]. 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 [8,9].

Restricted access to diverse micronutrient-rich diets, particularly for vulnerable groups, can exacerbate nutritional anaemias. Whereas each of the micro-nutrients have 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 vulnerabiity of children and women. Recurrent menstrual loss accounts for roughly 0•48mg per day, with wide variation depending on menstrual flow [10]. 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•8mg per day in the first trimester to 7•5mg per day in the third trimester [11,12]. Even in developed countries, anaemia during pregnancy is common [13]; 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. 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 [11].

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 [14-17]. Low¬ birth weight and preterm infants are at increased risk because they are born with reduced iron stores. Iron deficiency and anaemia in young children are associated with various functional consequences, especially in early childhood development [18]. 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 [19].

Available meta-analyses suggest that iron supplementation would increase the mean blood haemoglobin concentration by 8.0g/L in children, 10.2g/L in pregnant women and 8.6g/L in non-pregnant women [20]. Applying these shifts to estimated blood haemoglobin concentrations indicates that about 42% of anaemia in children would be amenable to iron supplementation and about 50% of anaemia in women could be eliminated by iron supplementation [20].

Folic acid deficiency

Folic acid is required for the synthesis and maturation of erythrocytes. The low serum and erythrocyte concentrations of folate can lead to changes in cell morphology and intra-medullary death of erythrocytes and reduced erythrocyte life span. 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 [4].

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 [21]. 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 [21]. Consumption and preparation of folate -rich food varies greatly by region.

Vitamin B12 deficiency

Vitamin B12 is synthesized only by micro-organisms, 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 [22].

The prevalence of vitamin B12 deficiency is unknown, but evidence from several developing countries in SE Asia region suggests that deficiency is widespread and is present throughout life. In South America, at least 40% of children and adults were vitamin B12 deficient. The prevalences greater than 70% in Africa and Asia have been documented [23,24]. 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 [20].

The main causes of vitamin B12 deficiency are inadequate dietary intake, especially from vegetarian diets [23], pernicious anaemia, an autoimmune disorder resulting from auto-antibody against intrinsic factor, tropical sprue, and co-infection with Diphyllobothrium latum, Giardia lamblia, and H pylori.

Vitamin B12 deficiency is associated with lacto-vegetarianism and the scarcity of meat products in South Asian diets [25-27]. The prevalence of pernicious anaemia is unknown, but reports from several developing countries suggest that it could be more prevalent than was previously thought [28-30].

Vitamin A deficiency

Vitamin A is involved in creation of red blood cells, improves haemoglobin concentration, improves efficacy of iron supplementation, and reduces susceptibility to infections. Vitamin A deficiency is common in countries in South East Asia region, affecting an estimated 21% of children of preschool age and 6% of pregnant women [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 [31]. The mechanisms are not fully understood, but are suggested to operate through effects on transferrin receptors affecting the mobilization of iron stores, increasing iron absorption, stimulating erythroid precursors in the bone marrow, and reducing susceptibility to infections.

The scientific evidence exists on the influence of vitamin A and iron supplementation in anaemic pregnant women. Improvement in vitamin A status contribute to the control of anaemia in pregnant women. In children also, following supplementation of vitamin A, a significant increase in the levels of hemoglobin, hematocrit and plasma iron has been documented. Evidence suggests that apart from deficiency of iron, vitamin A deficiency may also have a contributory role in the development of anemia in children.

Soil-Transmitted Helminthes

Around two billion people globally are estimated to be infested with helminths, and 300 million of them have severe and permanent impairments. Poor people in developing countries endure the burden of diseases caused by soil-transmitted nematodes which inhabit the gastrointestinal tract. Reduced food intake, impaired digestion, malabsorption, and poor growth rate are frequently observed in these children [32].

There is no global database on the prevalence of helminth infestation or estimates of its contribution to anemia. Scientific evidence show that in areas with high prevalence of helminthiasis (50-80%) a significant association exists with anemia prevalence. Observational data suggest an inverse relation between intestinal helminthiasis and haemoglobin concentrations [33]. However, intervention trials using anthelmintic drugs have provided conflicting evidence; some authors have documented improvements in haemoglobin concentration, whereas other investigators have found no such benefit. Routine administration of intestinal anthelmintic drugs results in a marginal increase in haemoglobin, which could translate on a public health scale into a small reduction in the prevalence of anaemia in populations with a relatively high prevalence of intestinal helminthiasis [4].

Hookworm

About one quarter of the world's population has hookworm infection, one of the commonest of the soil-transmitted helminthiases. It is prevalent throughout the tropics and subtropics, wherever there is faecal contami¬nation of the environment. 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 [34].

The course and outcome of pregnancy, growth, and development during childhood and the extent of worker productivity are diminished during hookworm disease. The severity of anemia caused by hookworms has consistently been found to depend on the number of worms present per person. Hookworms infectious diseases can contribute to anaemia through impaired absorption and metabolism of iron and other micronutrients or increased nutrient losses. The chronic blood loss gradually depletes body iron stores, leading eventually to iron deficiency anaemia which may be widespread and often severe in an infected community. Infections due to two species of hookworm, Ancylostoma duodenale and Necator americanus, almost ubiquitous over large areas of the tropics and subtropics and of persistently high prevalence, continue to be major causes of iron deficiency anaemia and associated ill-health [35].

Of soil-transmitted helminth infections, hookworms (Necator americanus and Ancylostoma duodenale) are the major cause of anaemia, and are commonly found in southeast Asia, with an estimated 576-740 million infections [34,35]. In the tropics and subtropics, where ecological conditions allow larval development, hookworm infections are over dispersed or highly aggregated in areas of poverty, where poor water, sanitation, and infrastructure result in endemicity, often concentrated in small populations within these areas [36,37]. Co-infection with several species is common.

Blood loss in hookworm infection has been estimated as 0.20ml per worm per day (range 0.14-0.26ml) for A. duodenale and 0.04ml per worm per day (range 0.02-0.07ml) for *N. americanus*. Over a period, even small hookworm loads may cause sufficient blood loss to deplete body iron reserves. For example, a blood loss of 1ml per day (equivalent to 0.347mg of iron at a haemoglobin level of 100g/litre of blood) would cause a loss of 250mg of iron in 2 years, or the equivalent of the total body iron stores in a woman of 50kg. 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*) [38], host iron reserves, and other factors such as age and co-morbidity. Systematic review of 12 studies of deworming during pregnancy [39] showed that women with light hookworm infection (1-1999 eggs per g of faeces) had a standardized mean difference of haemoglobin that was 0•24g/L lower (95% CI -0•36 to -0•13) than in those with no hookworm.

A meta-analysis of 14 randomized controlled trials [40] of deworming in sub-Saharan Africa and Asia showed a significant increase in mean haemoglobin (1•71g/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 popu¬lations [41] showed the beneficial effect of anthelmintic treatment, and the differential effects of co-administration 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•37g/L (95% CI 1•33-3•50) [41].

Helicobacter Pylori

It has been hypothesized that H. pylori may lead to IDA by sequestering and utilizing iron, thus competing with the hu¬man host. Another potential mechanism is that the bacteria exerts a negative effect on body iron balance by chronic blood loss from the gastrointestinal tract. There is evidence to support that *H. pylori* associated hemorrhagic gastritis is associated with iron deficiency [42].

The gastric juice ascorbic acid was significantly lower in *H. pylori* infected patients compared with uninfected persons. Epidemiologic studies support an association be¬tween *H. pylori* infection and lower iron stores, and small, uncontrolled case series have shown improvement in anemia following *H. pylori* treatment. The available evidence suggests that person

at increased risk of iron deficiency, such as premenopausal women and children, are more likely to develop iron deficiency associated with *H. pylori* infection. However, the evidence that currently exists supports an association be¬tween *H. pylori* infection and IDA, and testing and treatment of persons with unexplained IDA for *H. pylori* infection is recommended.

Malaria

Malaria causes between 1 million and 3 million deaths every year [43-45]. Plasmodium falciparum is the most pathogenic species and can lead to severe anaemia, and subsequent hypoxia and congestive heart failure [46]. Our knowledge of the mechanisms of malaria-related anaemia has evolved substantially [45] and can be broadly characterized as increased erythrocyte destruction and decreased erythrocyte production, with both mechanisms probably acting simultaneously and affected by factors such as age, pregnancy, malarial species, previous exposure, and prophylaxis.

Anemia due to Plasmodium falciparum infection is a major health problem in endemic areas for young children and pregnant women. The anemia is caused by excess removal of non-parasitized erythrocytes in addition to immune destruction of parasitized red cells, and impaired compensation for this loss by bone marrow dysfunction. The pathogenesis is complex. Concomitant infections and nutritional deficiencies also contribute to anemia and may interact with the malarial infection. The current increase in malaria-specific childhood mortality attributed to drug-resistant *P. falciparum* infection, is likely partly related to an increase in severe anemia.

Malaria parasites are believed to affect iron status by reducing intestinal iron absorption, sequestrating iron within the malarial pigment hemeozoin, consuming iron for its own metabolism, stimulating the mobilization of iron to body stores, and releasing iron into the circulation during intravascular hemolysis [43]. The acquisition of iron from the host is essential for survival of pathogenic organisms, and the "nutritional immunity" hypothesis proposes that withholding iron represents a host response to infection and inflammation. Availability of iron for invading organisms is restricted by down regulation of cellular surface transferrin receptors, along with an increase in synthesis of ferritin, shifting iron stores to unavailable compartments [45].

Iron deficiency is prevalent in many malaria-endemic regions, and it is clear that many infants, particularly those born prematurely or with low birth weight, have low total body iron, and are at particular risk of iron deficiency during the first six months of life. Malaria and other infectious diseases have an adverse impact on hemo¬globin levels from the age of approximately three months, and the prevalence of all grades of anemia is highest in the second half of infancy [43].

The interaction between malaria and iron and folate supplementation has been the subject of intense research and controversy in recent years, intensified by the results of two cluster-randomized double-blind inter-vention trials [46-48] 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 [47]. The subsequent WHO led Expert Consultation [48] emphasized 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. Subsequently, a systematic review of 68 randomized and cluster-randomized trials [49] 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 bed nets for prevention of malaria [50] showed a beneficial effect on haemoglobin in children. Use of insecticide-treated bed nets compared with no bed nets increased absolute packed-cell volume by 1•7%, whereas use of treated bed nets compared with untreated bed nets 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) [51].

Iron deficiency per se has been shown to decrease both cell-mediated immune response and bactericidal activity of leukocytes in children. On the other hand, iron status is compromised in infection. The influence of malaria, mild and severe respiratory infections in young children on biomarkers of iron status has been studied and a significant decrease in haemoglobin was seen in children with varying degree of malaria. In children with meager body iron stores, infection tends to aggravate anaemia by blocking iron utilization. It is hypothesized that upon infection, iron is sequestered in the macrophages and hepatocytes and iron absorption decreases, thus limiting iron to the invading pathogen. This also results in decreased plasma iron levels, which if maintained, leads to iron restricted erythropoiesis and ultimately frank anaemia [52].

Acute and Chronic Inflammation

Anaemia is also a consequence of a synergy of inflammation and insufficient bioavailable dietary iron and other haematinic nutrients. It is now widely recognized that infection is a much more important cause of anaemia than previously thought. Over and above the deficit in the intake of haematopoietic nutrients, disease processes also reduce appetite, resulting in further iron deficit. With the onset of the inflammatory response, the plasma

concentrations of several nutrients, including serum iron, decrease significantly. In addition serum ferritin concentration has been shown to parallel the rapid rise in C reactive protein (CRP), both as part of the acute phase response [52].

The possibility that chronic inflammatory disease playing an important etiologic role in the anemia of pregnancy in developing countries has not been examined in detail. The contribution of common overt and sub-clinical infections to anemia burden is difficult to quantify; however, it has been either ignored or substantially under¬estimated [4]. The anaemia has been shown to be the consequence of induction of hepcidin expression, brought on by the action of the inflammatory cytokine. Hepcidin is a 25 amino acid hepatocyte-derived peptide that can be increased to up to 100-fold during infections and inflammation causing a decrease in serum iron levels. Urinary or serum hepcidin concentrations are widely altered in anaemia of chronic infection, iron overload, iron deficiency and haemochromatosis. Hepcidin controls plasma iron concentration and tissue distribution of iron by inhibiting intestinal and macrophage iron efflux. Iron per se has also been shown to modulate hepcidin levels. Thus hepcidin is now considered as the iron hormone. The evidence suggests of an interaction of hepcidin (iron hormone) and inflammatory stimuli on iron metabolism and leading to iron deficiency anaemia [53]. There is a relative prevalence of a depression in Hb concentration due to anemia and in¬flammatory disease. In a study on women, almost 20% of those with anemia had no demonstrable deficiencies of iron, vitamin B-12, folate, or vitamin A. However, more than half of the women has CRP was significantly high; thus, the anemia in these women could well have been associated with chronic inflammatory disease. The Inflammation may lead to failure to mobilize iron stores and could be an important factor of iron deficiency anemia.

Deficiency of Iron in Soil

Iron is an important micronutrient element involved in the several metabolic and enzymatic activities in plants. It is essential for the synthesis of chlorophyll and oxidation-reduction activities in green plants. Iron deficiency is commonly observed in horticultural and vegetable crops like citrus, and field crops such as pulses, groundnut, rice etc. Soil deficient in iron leads to poor iron contents of foods grown on it. A study - conducted by the Indian Institute of Soil Science (IISS), Indian Council of Agricultural Research - found that the soils of as many as 174 districts across 13 states in India were deficient in zinc, boron, iron, manganese and copper. The boron deficit was found to be 20 per cent while iron, manganese and copper were deficient by 12.9, 6 and 4.3 per cent of soil samples, respectively [54].

HIV/AIDS

Anaemia is the most common haematological complication associated with HIV infection, and is a marker of disease progression and survival [55]. The burden of HIV/AIDS-related anaemia falls predominantly on sub-Saharan Africa, where women and children are most at risk [56]. 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 [57].

Hemoglobinopathies

Each year, more than 330,000 infants are born with these disorders (83% sickle-cell disorders and 17% thalas¬saemias). Sickle-cell disorders are associated with chronic haemolytic anaemia, and an estimated 2•28 per 1000 conceptions worldwide are affected by sickle-cell disorders [58]. 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). Only 12% of transfusion-dependent patients with β thalassaemia receive transfusions, and only 39% of those receive adequate iron chelation [59].

Haemoglobinopathies are the most common genetic disorders among the people living in Southeast Asia .Hemoglobinopathies refer to a constellation of genetic disorders that affect the structure, function, or production of hemoglobin, the protein that carries oxygen from the lungs to the tissues. The effect of the hemoglobinopathy on hemoglobin is nuanced and varies based on the genetic defect. For defects that affect the structure of the hemoglobin, for example in sickle cell anemias, the hemoglobin level can range from normal in sickle cell trait to severe anemia, in full blown sickle cell disease. In thalassemias too, the thalassemia traits might show normal level of hemoglobin while the more severe disease will present as severe anemia. Other important hemoglobin variants may result in mild anemia.

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. 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 [60]. Although extensive research has investigated the distribution and functional consequences of these genetic haemoglobin disorders, their contribution to the global anaemia burden remains unclear [61]. Micro-mapping studies are needed to estimate their prevalence in different populations, which could also have implications for prevalence estimation of anaemia in populations in which these variants are present [62,63].

As child survival improves, inherited haemoglobin disorders could become an increasingly important disease burden and cause of anaemia in the future [5].

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