Non-nutritional anemia: Malaria, thalassemia, G6PD deficiency and tuberculosis in Indonesia

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Anemia affects people worldwide and results in increased morbidity and mortality, particularly in children and reproductive-age women. Anemia is caused by an imbalance between red blood cell (RBC) loss and production (erythropoiesis), which can be caused by not only nutritional factors but also non-nutritional factors, such as inflammation and genetics. Understanding the complex and varied etiology of anemia is crucial for developing effective interventions and monitoring anemia control programs. This review focuses on two interrelated non-nutritional causes of anemia: malaria infection and RBC disorders (thalassemia and G6PD deficiency), as well as tuberculosis. According to the Haldane hypothesis, thalassemia occurs as a protective trait toward malaria infection, whereas G6PD deficiency arises in malaria-endemic regions because of positive selection. Indonesia is a malaria-endemic region; thus, the frequency of thalassemia and G6PD deficiency is high, which contributes to a greater risk for non-nutritional anemia. As Indonesia is the second global contributor to the newly diagnosed tuberculosis, and active pulmonary tuberculosis patients are more anemic, tuberculosis is also a contributing factor to the increasing risk of anemia. Therefore, to reduce anemia rates in Indonesia, authorities must consider non-nutritional causes that might influence the local incidence of anemia, and apply co-management of endemic infectious disease such as malaria and tuberculosis, and of genetic disease i.e. thalassemia and G6PD.

Key Words: hemoglobin, malaria, thalassemia, G6PD, tuberculosis

INTRODUCTION
Anemia affects more than 1.93 billion people worldwide,1,2 mostly children aged <5 years and women.1,3 Anemia increases morbidity and mortality rate, particularly in children and reproductive-age women.4,5 Anemia also contributes to poor birth outcomes,6,7 impaired neurological development in children, and decreased work productivity in adults.7

Anemia is defined by a hemoglobin (Hb) concentration and/or red blood cell (RBC) count below the normal values and insufficient to fulfill an individual’s physiological needs.8 Typically, Hb concentration is the most common hematological assessment method and indicator for the diagnosis of anemia at the population level and in clinical practice. Anemia is caused by an imbalance between RBC loss and production (erythropoiesis). RBC loss may occur because of premature destruction (hemolysis) and/or acute blood loss. Reduced erythropoiesis can be caused by nutritional, inflammatory, and genetic factors. Anemia classification is commonly based on the biological mechanism, such as hemolytic anemia (inflammation), or RBC morphology (e.g., hereditary spherocytosis).9 Understanding the complex and varied etiology of anemia, including the non-nutritional cause, is crucial for developing effective interventions and monitoring anemia control programs. In this review, two interrelated non-nutritional causes of anemia, namely malaria infection and RBC disorders (thalassemia and G6PD deficiency), are discussed. Malaria-endemic regions, such as Indonesia, have a high frequency of thalassemia and G6PD deficiency, which increases the risk for non-nutritional anemia. Discussion also include tuberculosis, which is associated with anemia, since Indonesia is the second global contributor to the increased cases of newly diagnosed tuberculosis. In Indonesia, patients with active pulmonary tuberculosis are more anemic with poor nutritional status. Thus, tuberculosis is also a contributing factor for the increasing risk of anemia.

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ANEMIA AND MALARIA

Malaria, a mosquito-borne disease caused by the parasite belonging to the genus *Plasmodium*, has become a major cause of anemia in tropical regions. In 2018, an estimated 228 million cases of malaria were reported worldwide, compared with 231 million cases in 2017 and 251 million cases in 2010. In 2018, an estimated 405,000 people died of malaria globally, compared with 416,000 estimated deaths in 2017 and 585,000 in 2010. 

Five *Plasmodium* species can infect humans: *Plasmodium falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*. Of these, *P. falciparum* is the more virulent and is responsible for approximately 1–3 million deaths per year, mainly in children and pregnant women. *P. falciparum* infection may cause severe malaria syndrome, including severe anemia (defined as Hb concentration <5 g/dL). By contrast, *P. vivax*, the commonest and most widespread species, is a largely nonlethal malarial species; however, it can also cause severe malaria syndrome because of relapse cases due to the flaring up of hypnozoites in the liver.

The pathophysiology of anemia caused by malaria infection is complex and influenced by multiple factors. During malaria infection, merozoite-stage parasites invade RBCs to undergo the asexual intraerythrocytic developmental cycle. This results in a noticeable loss in RBCs due to parasite maturation and macrophage-mediated disruption of infected RBCs in the bone marrow. However, the principal contributor to anemia severity is the accelerated disruption of uninfected RBCs, as observed in severe malaria cases caused by *P. falciparum* and *P. vivax*. Studies have revealed that, similar to infected RBCs, uninfected RBCs also exhibit reduced deformability, which may impair microcirculatory flow and trigger splenic retention and phagocytosis, thereby contributing to malarial anemia. Moreover, studies have reported that increased apoptosis and accelerated senescence of uninfected RBCs, as well as the destruction of non-parasitized RBCs through opsonization and complement dysregulation, greatly contribute to anemia caused by falciparum and vivax malaria. Furthermore, malarial anemia is compounded by defective development of RBCs in the bone marrow (dyserythropoiesis), which is mainly caused by the release of various immune mediators by both the host and parasite cells.

In many developing countries burdened by malaria, the destruction of RBCs induced by the parasite at the end of the infection exacerbates pre-existing anemia; this typically due to malnutrition, helminthiasis, or inherited disorders related to RBCs, such as hemoglobinopathies. The level of transmission also influences anemia severity. In areas with high malaria transmission (e.g., sub-Saharan Africa), where most of the patients have developed immunity because of frequent exposure to malaria infection, anemia is predominantly observed in young children (aged <5 years). As the children grow into adulthood, they develop immunity against the malaria infection, such that in adolescence nearly all malaria infections are asymptomatic. By contrast, in regions with unstable and low transmission of malaria, in which protective immunity from malaria is not achieved, the age group that is most affected by malarial anemia tends to shift toward adolescents and young adults.

Malaria is highly endemic in Eastern Indonesia, and most infections occur on the islands of Papua and East Nusa Tenggara, as illustrated in Figure 1.
parasite incidence in Indonesia was 0.84 in 2018 and 0.93 in 2019.35 According to a related study conducted in Southern Papua, malaria infection due to *P. falciparum, P. vivax,* and *P. malariae* contributes to severe anemia risk, particularly in patients infected by mixed *Plasmodium* species, thus contributing to increased mortality risk.36 Moreover, the burden of malaria-related anemia during pregnancy is overwhelming: almost 50% of pregnant mothers in Indonesia are anemic.37 Malaria infection is a risk in approximately 6.3 million annual pregnancies in Indonesia.37 Anemia is closely correlated with malaria infection, and in endemic regions, malaria is a major cause of anemia as well as a large contributor to maternal anemia during pregnancy, resulting in poor birth outcomes.38,39

Asymptomatic microscopic parasitemia is associated with increased risk of anemia40 and adverse birth outcomes, including prematurity delivery and low birth weight newborns.41 In the Asia–Pacific region, 70% of pregnancies occur in malaria-endemic regions, of which 7% occur in Indonesia.37 Malaria contributes to increased risk of anemia among women living in Sumba and Papua, independent of nutritional status (determined by body mass index and mid-upper arm circumference; Table 1).42 Studies on the burden of malaria in West Sumba Regency, where malaria transmission is seasonal, revealed that anemia prevalence increased in younger children (aged <10 years) during the wet season.43 Subsequent studies monitoring the efficacy of an antimalarial drug reported that the common clinical manifestation in the patients screened and involved in the studies was mild to severe anemia (Asih et al.44 and unpublished data, Eijkman Institute). Common concomitant genetic disorders that are also prevalent in Sumba include thalassemia, G6PD, and Southeast Asian ovalosytosis.45,46

The management of anemia in malaria endemic areas requires an intersectoral approach between nutritionists, hematologists, and infectious disease practitioners. This is because iron supplementation, rather than the provision of nutritious food as with biofortified grains and legumes, and bioavailability generated by food biodiversity, can exacerbate malaria, even to the point of overwhelming parasitosis.47-51 This consideration applies to placental malaria in particular where even periconceptional iron is a risk factor.52,53

### Table 1. Risk factors for anemia in women living in Sumba and Papua

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-anemic (N=1481)</th>
<th>Anemic (N=2993)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malnourished, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1094 (73.9)</td>
<td>2105 (70.3)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>387 (26.1)</td>
<td>888 (29.7)</td>
<td>1.19 (1.04-1.37)†</td>
<td>1.36 (1.17-1.59)†</td>
</tr>
<tr>
<td>Malaria, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1387 (93.7)</td>
<td>2731 (91.2)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>94 (6.3)</td>
<td>262 (8.8)</td>
<td>1.42 (1.11-1.81)‡</td>
<td>1.44 (1.13-1.84)‡</td>
</tr>
</tbody>
</table>

MUAC: mid-upper arm circumference; OR: odds ratio; 95% CI: 95% confident interval.

Anemia criteria: hemoglobin <11 mg/dL for pregnant women or hemoglobin <12 mg/dL for nonpregnant women.4 Malnourished: mid-upper arm circumference <23 cm.37

†Unadjusted logistic regression. †Adjusted logistic regression after controlling for underweight, malnourished, and malaria status.

**p<0.010, ***p<0.001

**ANEMIA AND THALASSEMIA**

Haldane (1949)44 proposed that the high frequency of thalassemia in Mediterranean populations might be due to natural selection that resulted in increased prevalence of protective traits toward malaria infection; this is known as the Haldane hypothesis or malaria hypothesis. As a result of this survival advantage against malaria, inherited RBC disorders such as thalassemias are the most common diseases attributable to single defective genes. Considering its selective pressure in the human genome, malaria is regarded as an evolutionary force of some genetic diseases that mainly present as abnormal Hbs and RBC enzyme deficiencies.55

The thalassemias—characterized by decreased Hb production—are the most common inherited hemoglobin disorders and also the most common human monogenic diseases.56 The two main types of thalassemia are α and β thalassemia, referring to the affected globin chains.57,58 On the basis of globin chain expression, thalassemia can be classified as α+ and α0 or β+ and β0.59 Although these disorders are most common in tropical and subtropical regions, they are now encountered in most countries because of global population migration and marriage between ethnic groups. Of all globin disorders, α thalassemia is the most widely distributed and occurs at high frequencies throughout tropical and subtropical regions; in these areas, carrier frequency can reach up to 80%–90% in the population.60,61 For β thalassemia, the carrier frequency is approximately 1.5% of the global population (80–90 million people), with approximately 60,000 individuals with clinical manifestations born annually.62

Thalassemias are a heterogeneous group of anemias that result from defective synthesis of the globin chains of adult hemoglobin. In Southeast Asia, α-thalassemia, β-thalassemia, hemoglobin E (HbE), and hemoglobin Constant Spring (HbCS) are prevalent. HbE and HbCS are hemoglobin variants that cause a decrease in hemoglobin production. HbE mutation alternates the mRNA splicing, whereas HbCS mutation produces unstable mRNA due to a stop codon shift that causes longer but unstable mRNA, resulting in the reduction of the α-globin chain. The gene frequencies of α0-thalassemia in Indonesia range from 1.5% to 11.8% and that of α-thalassemia from 3.2% to 38.6% (unpublished data, Eijkman Institute).63 The gene frequencies of β-thalassemia in Indonesia vary from 0.5% to 17.45% for the HbE mutation and 0.5% to 5.4% for the
other β-thalassemia mutations (unpublished data, Eijkman Institute).

**α-Thalassemia**

α-Thalassemia is an autosomal recessive hereditary RBC disorder due to mutations in the α-globin genes, causing a decrease in or absence of α-globin chain production; it is characterized by microcytic hypochromic anemia. The clinical phenotype of α-thalassemia varies from almost asymptomatic to lethal hemolytic anemia. α-thalassemia is a condition related to a defect in the production of α-globin chains, which form a tetrameric molecule together with β- or γ- globin chains of the hemoglobin molecule. Healthy individuals have four α-globin genes; two sets of two tandemly encoded (in cis) genes, located on chromosome 16 in band 16p13.3.60

The α-globin chains are subunits for both fetal (α2β2) and adult (α2β2) hemoglobin; therefore, homozygous α-thalassemia can cause anemia in fetuses and adults.58 The most frequent mutation of α-thalassemia is deletion of one (α+-thalassemia) or both (α°-thalassemia) of the α-globin genes. The severity of clinical and hematological phenotypes (degree of microcytic hypochromic anemia) is closely correlated with the reduction of α-globin chain synthesis in each mutated α gene.64

**β-Thalassemia**

The other autosomal recessive hereditary RBC disorder is β-thalassemia, which is caused by mutations in the β-globin gene. β-thalassemia is characterized by the reduction in or absence of β-globin chain synthesis, resulting in reduced Hb, decreased RBC production, and anemia. On the basis of the clinical manifestations, β-thalassemia is classified as thalassemia major, thalassemia intermedia, and thalassemia minor.59,62

The beta globin gene maps in the short arm of chromosome 11 at position 15.4. Approximately 200 β-globin gene mutations have been reported.65 β-globin gene mutations result in a reduction or absence of β-globin chains production, with variable phenotypes ranging from severe anemia to clinically asymptomatic. The clinical severity of β-thalassemia is associated with the imbalance between the α-globin and non-α-globin chains.

Even though thalassemia is closely associated with anemia, some of the hematologic features of the RBCs could appear normal in the thalassemia trait, as observed in our population studies in several ethnic groups in Indonesia (Table 2). The prevalence of anemia (according to Hb concentration) in the population of Banjarmasin and Ternate was 11.4% (67/587; cutoff is <12 g/dL for women individuals and <13 g/dL for men individuals; according to the World Health Organization criteria5). We applied trait thalassemia screening according to the complete blood count, Hb analysis, and blood smear of these 67 individuals with anemia; we noted that only approximately 82% exhibited an indication of thalassemia (microcytic hypochromic). If molecule detection were also included, the confirmed thalassemia cases would be even lower. However, those with nonconfirmed thalassemia with microcytic hypochromic anemia could still harbor

### Table 2. Clinical characteristics of individuals with and without anemia in the Banjarmasin and Ternate population

<table>
<thead>
<tr>
<th>Population</th>
<th>Variable</th>
<th>Non-anemic</th>
<th>Anemic</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=179)</td>
<td>(N=19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Banjarmasin</td>
<td>Age [years, median (IQR)]</td>
<td>20.0 (19.0-21.0)</td>
<td>19.0 (19.0-20.0)</td>
<td>0.175</td>
</tr>
<tr>
<td></td>
<td>Sex [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>74 (41.7)</td>
<td>1 (5.3)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>105 (58.3)</td>
<td>18 (94.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hb [mg/dL, median (IQR)]</td>
<td>14.1 (13.3-15.2)</td>
<td>10.8 (10.6-11.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>MCV [fL, median (IQR)]</td>
<td>84.7 (82.3-87.5)</td>
<td>80.0 (71.4-82.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>MCH [pg, median (IQR)]</td>
<td>28.3 (27.4-29.2)</td>
<td>24.4 (21.4-26.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>MCHC [g/dL, median (IQR)]</td>
<td>33.2 (32.5-33.8)</td>
<td>31.2 (30.6-32.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>RDW [n (%)]</td>
<td>13.4 (13.0-13.9)</td>
<td>15.7 (14.7-17.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>HbA2 [n (%)]</td>
<td>2.8 (2.7-2.9)</td>
<td>2.6 (2.5-2.9)</td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td>HbE [n (%)]</td>
<td>0.3 (0.0-0.5)</td>
<td>0.0 (0.0-0.4)</td>
<td>0.281</td>
</tr>
<tr>
<td></td>
<td>HbE [n (%)]</td>
<td>2 (1.0)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Ternate</td>
<td>Age [years, median (IQR)]</td>
<td>20.0 (17.0-21.0)</td>
<td>19.5 (18.8-20.0)</td>
<td>0.185</td>
</tr>
<tr>
<td></td>
<td>Sex [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>146 (42.8)</td>
<td>1 (2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>195 (57.2)</td>
<td>47 (97.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hb [mg/dL, median (IQR)]</td>
<td>14.0 (13.1-15.6)</td>
<td>11.2 (9.6-11.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>MCV [fL, median (IQR)]</td>
<td>82.9 (80.4-85.2)</td>
<td>74.6 (66.6-79.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>MCH [pg, median (IQR)]</td>
<td>28.2 (26.9-29.3)</td>
<td>23.4 (19.9-25.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>MCHC [g/dL, median (IQR)]</td>
<td>33.8 (32.9-34.9)</td>
<td>31.4 (29.5-32.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>RDW [n (%)]</td>
<td>13.6 (13.1-14.3)</td>
<td>15.7 (14.8-19.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>HbA2 [n (%)]</td>
<td>2.8 (2.6-2.9)</td>
<td>2.5 (2.3-2.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>HbE [n (%)]</td>
<td>0.3 (0.2-1.0)</td>
<td>0.2 (0.0-0.9)</td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td>HbE [n (%)]</td>
<td>4 (1.2)</td>
<td>2 (4.2)</td>
<td>0.162</td>
</tr>
</tbody>
</table>

Hb: hemoglobin; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width; HbA2: hemoglobin subunit alpha 2; HbF: fetal hemoglobin; HbE: hemoglobin E. World Health Organization anemia criteria were employed: hemoglobin <12 mg/dL for women or hemoglobin <13 mg/dL for men.6

The \( p \) values were calculated using either the Wilcoxon–Mann Whitney U test for continuous variables or Fisher’s exact test for categorical variables. Significant \( p \) values are in bold \((p<0.05)\). Unpublished data, Eijkman Institute.
thalassemia traits because a comprehensive molecular screening has not yet been conducted; in this case, screening was only performed for the most common mutations. Microcytic hypochromic anemia could result from not only thalassemia but also iron deficiency because thalassemia can coexist with iron deficiency. However, in cases where thalassemia is not confirmed, the microcytic hypochromic anemia is most likely due to iron deficiency. Hence, nutritional anemia could coexist with RBC disorders, such as thalassemia.

We included hemoglobin analysis when screening for thalassemia, either in patients at our genetic clinic or as part of our population studies. We observed that RBC morphology (microcytic hypochromic) was similar between thalassemia and iron deficiency anemia and noted that this similarity could obscure the real cause of the underlying anemia because both abnormalities are commonly noted in the Indonesian population. Therefore, iron status must be examined to confirm the cause of the anemia, which is crucial to determining prevention, therapy, and management strategies. However, government guidelines do not include iron status examination for determining the cause of anemia. The current policy is to provide iron supplementation for every person with anemia. Thus, we propose complete blood count and iron status screening in the Indonesian population in cases where iron supplementation does not improve iron content.

**ANEMIA AND GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY**

Another genetic disorder associated with the selective pressure of malaria is glucose-6-phosphate dehydrogenase deficiency (G6PDd), which has been reported to confer resistance to malarial infection.66–68 Population genetic analyses of the G6PD locus have supported the association between G6PDd and malaria; these studies have revealed that the frequency of G6PD gene mutations have increased recently in certain geographic regions where malaria is endemic, as a result of positive selection.69,70

The G6PD gene is located on chromosome X and maps to Xq28, making the disorder X-linked; consequently, men can only be hemizygous G6PD normal or hemizygous G6PD deficient. Women can either be homozygous G6PD normal, homozygous G6PD deficient, or heterozygous because women have two G6PD alleles. Similar to most X-linked genes, G6PD is affected by the random X-chromosome inactivation phenomenon, and somatic cells in G6PD heterozygous women are a mosaic of G6PD-normal and G6PD-deficient RBCs.71,72

G6PDd is a common RBC enzyme disorder worldwide, affecting approximately 400 million people. The clinical manifestations of G6PDd are broad, ranging from asymptomatic to acute hemolytic anemia, renal failure, and death. These manifestations result from mutations in the G6PD gene that cause instability in the produced enzyme. Approximately 400 biochemical variants are known, but only 186 mutations have been genotyped.74 These mutations are region- or ethnic-specific. In Indonesia, G6PDd is most prevalent in malaria-endemic areas, such as south Lampung, central and south Kalimantan, and most of eastern Indonesia, such as Sumba and Papua. Certain variants, such as Vanua-Lava, Viangchan, Coimbra Shunde, are found predominantly in eastern Indonesia.75,76

Most individuals with G6PDd do not exhibit any symptoms unless exposed to exogenous agents that trigger oxidative stress resulting in acute hemolytic anemia. In affected individuals, a defect in the G6PD enzyme causes RBCs to break down prematurely in response to oxidative medication, infections, or fava beans, leading to hemolytic anemia that may be severe and life-threatening.77 We noted no difference in G6PD enzyme activity between those with and without anemia in normal conditions (i.e., not exposed to oxidative agents), whereas older age and being a woman increased the risk for acute hemolytic anemia (Table 3).

**TUBERCULOSIS**

Anemia is also found in association with tuberculosis. In Taiwan’s nationwide population-based study covering 12 years of data, iron deficiency anemia was associated with a 99% increased incidence of tuberculosis compared with the matched group, which supports the hypothesis that individuals with micronutrient deficiency, including iron deficiency, are more susceptible to infections.78 Data from study conducted in Indonesia showed that patients with active pulmonary tuberculosis are more anemic with

| Table 3. Predictors of anemia in those with and without G6PD deficiency |
|-----------------------------|-----------------|---------------|----------------|----------------|
| Variable                    | Non-anemic (N=424) | Anemic (N=182) | OR (95% CI)    | p              |
| Age (years)                 | 15.0 (10.0-32.0)  | 30.0 (16.3-40.0) | 1.03 (1.01-1.04) | <0.001 |
| Weight (kg)                 | 39.0 (23.0-48.0)  | 40.0 (34.3-45.0) | 1.01 (1.00-1.03) | 0.045 |
| Sex                         | Reference        | Reference      | Reference      | Reference      |
| Female                      | 210 (49.5)       | 139 (76.4)     | Reference      | Reference      |
| Male                        | 214 (50.5)       | 43 (23.6)      | 0.3 (0.21-0.45) | <0.001 |
| G6PD activity               | Reference        | Reference      | Reference      | Reference      |
| Non-deficient               | 399 (94.1)       | 170 (93.4)     | Reference      | Reference      |
| Deficient                   | 25 (5.9)         | 12 (6.6)       | 1.13 (0.55-2.29) | 0.743 |
| Malaria                     | Reference        | Reference      | Reference      | Reference      |
| Negative                    | 415 (97.9)       | 176 (96.7)     | Reference      | Reference      |
| Positive                    | 9 (2.1)          | 6 (3.3)        | 1.57 (0.55-4.48) | 0.398 |

G6PD: glucose-6-phosphate dehydrogenase; OR: odds ratio; 95% CI: 95% confident interval.
World Health Organization anemia criteria were employed: age <5 years, Hb <11 mg/dL; age 5–11 years, Hb <11.5 mg/dL; age 12–14 years, Hb <12 mg/dL; age >15 years, Hb <12 mg/dL for female individuals or Hb <13 mg/dL for male individuals.8
Data were extracted from Satyagraha et al.72
poor nutritional status as compared to healthy subjects. Indonesia is ranked second (8.5%) as the biggest contributor to the global increase of newly diagnosed tuberculosis, after India (26%) (Figure 2). Nevertheless, similar with malaria, iron supplementation may exacerbate tuberculosis, since the tuberculosis causative pathogen, Mycobacterium tuberculosis, requires iron for essential metabolic pathways. Therefore, in tuberculous areas, iron supplementation approaches to the problem should be avoided without co-management of tuberculosis and monitoring for iron biomarkers, since the management of dietary iron is most likely influential in supporting the outcome of this disease.

CONCLUSION: THE ROLE OF MALARIA, THALASSEMIA, G6PD DEFICIENCY AND TUBERCULOSIS IN ANEMIA IN INDONESIA

The prevalence of anemia is high in Indonesia. The health authorities tend to highlight iron deficiency and/or malnutrition as the cause of anemia. Indonesia is an archipelago country with numerous islands, ethnic groups, cultures, languages, as well as tropical and genetic diseases including malaria, thalassemia, and G6PD deficiency. Multiple malaria infections can cause severe anemia in children or adults living in malaria-endemic areas. Genetic factors that have arisen from malaria pressure in these areas can also cause anemia. Thus, anemia does not occur solely due to malnutrition and iron deficiency but can be due to other internal or external factors, which may play a role in modulating the incidence of anemia in Indonesia. Whenever iron supplementation does not improve anemia status, particularly microcytic hypochromic anemia, practitioners should consider other causes. In our population studies, the prevalence of both thalassemia trait and iron deficiency was high, both of which contribute to the high prevalence of anemia. Therefore, in the management of anemia in the Indonesian population, conducting complete blood count screening, Hb analysis, and iron status examination is necessary, because anemia could be due to either chronic infection (e.g., malaria, tuberculosis) or genetic disorders (e.g., thalassemia and G6PDD). Anemia, particularly in children, may cause irreversible neurological damage that may affect the quality and global competitiveness of future human resources. Anemia in adults limit the quality of people’s work and their productivity. Thus, to eliminate anemia in Indonesia, the authorities should employ a comprehensive and multidisciplinary approach in collaboration with research and government institutions. Anemia elimination in Indonesia requires a knowledge of local pathogens, as well as nutritional factors, especially since iron supplementation may otherwise worsen infectious disease such outcomes as in malaria and tuberculosis.

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REFERENCES
2. Lukito W, Wahlqvist ML. Intersectoral and eco-nutritional approaches to resolve persistent anemia in Indonesia. Asia


67. Cappadoro M, Giribaldi G, O'Brien E, Turrini F, Mannu F, Ulliers D et al. Early phagocytosis of glucose-6-phosphate dehydrogenase (G6PD)-deficient erythrocytes parasitized by Plasmodium falciparum may explain malaria protection in...


