

## Original Article

# Intersectoral and eco-nutritional approaches to resolve persistent anemia in Indonesia

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Anemia in Indonesia has been of concerning persistence in all age groups for some 75 years since independence. The relationships between anemia and nutrition are complex being evident with compromised general health and nutrition. Increased micronutrient intakes, especially iron and folic acid, has alleviated the problem, but encouraged nutrient-specific micronutrient interventions as attractive policy directions as if anemia were a stand-alone disease irrespective of associated disorder. Concerted action to deal with the fundamental causality has been missing. Much of the pathogenetic pathway may be nutritional, but its multifactoriality is ultimately socioecological. Given the intransigence and progression of societal and ecosystem dysfunction, it can be expected that failure to recognize their causal importance will further entrench endemic anemia. This review deliberates the practical measures taken to recognize anemia by symptomatology, food and nutrition surveys, screening (fingerpick blood), nutrition assessment, and blood loss (menstrual and faecal). It identifies vulnerable groups including premenopausal and pregnant women, children and adolescents, unwell adults, and the dependent aged. Risk settings include food insecurity, infectious disease, non-communicable disease, inheritance and epigenetics, and socioeconomic disadvantage. Underlying socio-ecological problems are livelihood, food systems, cultural habits, belief systems, and social networks and activities. With this framework, policy directions could deal more comprehensively and effectively with the socioecological complexity which underpins and limits progress towards anemia eradication at a time of intense global food and health insecurity. It will require co-operative intersectoral and eco-nutritional approaches which take into account the need for universal, sustainable livelihoods. Recommendations have been made accordingly.

**Key Words:** econutrition, infectious diseases, non-communicable diseases, genetics, policy development

## INTRODUCTION

Anemia is still prevalent worldwide, including in Indonesia.<sup>1-5</sup> It accounts for widespread morbidity which may be as non-descript and under-diagnosed as fatigue or as grave as intergenerational ill-health on account of compromised pregnancy.<sup>6-8</sup> Consecutive 5-year Indonesian Basic Health Research reports in 2008, 2013 and 2018 showed the persistent prevalence of anemia in various at-risk people. In 2008, the prevalence of anemia was 19.7%, 13.1%, and 9.8% in adult women, men, and children, consecutively.<sup>9</sup> In 2008, anemia data on pregnant women could not be considered due to the small sample size. In 2013, the prevalence of anemia were 29.7% and 26.5% in under-five boys and girls; and 22.7% and 37.1% in adult women and pregnant women.<sup>10</sup> In 2018, the prevalence of anemia were 27.2%, 20.3%, 38.5%, and 48.9% in adult women and men, under-five children, and pregnant women consecutively.<sup>11</sup> Anemia affects any at-risk population, under-five children,

adolescents, reproductive-age women, pregnant women, and the aged. Although national data on anemia of the aged are not available, in a selected group of urban Indonesian elderly, Juguan et al reported that anemia was common, and the prevalence was ~25% and 32% in elderly men and women, respectively.<sup>12</sup> Clearly, anemia with its determinants and various health and non-health consequences, contribute to significant public health problems in Indonesia.

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The understanding of erythropoietic and iron physiology and the development of improved screening and diagnostic tools now enable more accurate typing for causality.<sup>13</sup> Pathogenetic biomarkers now include ferritin, transferrin saturation, hepcidin and erythropoietin,<sup>14-16</sup> along with inflammatory markers, enabling more distinction to be made between nutrient deficiency inflammatory anemias and other underlying disease such as chronic kidney disease and, in older people, the myelodysplastic syndrome.<sup>13</sup> The ready availability of a medical and nutritional history, a physical examination, finger prick blood for haematocrit, haemoglobin and microscopy for red cell morphology (and smears for malaria) still go a long way towards establishing the presumptive anemia type (refer to Table 2). However, in many developing countries, including Indonesia, it continues to be regarded principally as nutritional anemia, and is further presumed to be iron-deficiency anemia.<sup>8,13,17-23</sup> It is understandable given that WHO indicates that iron deficiency is the most common cause of anemia globally<sup>24</sup> and the Global Burden of Disease (GBD) reports now refer to inappropriate food intakes as risk factors or 'iron deficiency', rather than anemia, not being a disease, but a manifestation of various diseases.<sup>25,26</sup> Consequently, iron supplementation has been the policy priority to alleviate anemia. Decades of this type of program with increasing budget and different levels of compliance throughout the autonomous provinces and districts across archipelago of Indonesia has not demonstrated uniformly positive outcomes.<sup>27</sup> Fortification and the emerging biofortification of staple foods provide promising food-based approach, but await appropriate evaluation.<sup>27</sup>

With the escalating prevalence of non-communicable disease (NCD) and its underlying inflammatory mechanisms, the anemia of inflammation is of increasing relevance.<sup>28-30</sup> Individuals with long-term pharmacotherapy for NCDs, may also suffer from chronic occult blood loss contributing to the development of anemia.<sup>3</sup> Likewise, the major endemic public health problems of pulmonary tuberculosis (TB) and helminthiasis, contribute extensively to the incidence and prevalence of anemia.<sup>3,30</sup> In a tropical country like Indonesia, the benefits and risks of iron and folate tablet supplementation programs in areas endemic for malaria and TB cannot be overlooked.<sup>30</sup>

The genetics and epigenetics of anemia in Indonesia and the extent to which they contribute to anemia preva-

lence and its inadequate rectification by intervention programs are being clarified.<sup>31</sup> Anemia as found in Indonesia is complex in its underlying risk factors and ultimate causality, and in its related health and non-health consequences.

Indonesia is the largest economy in Southeast Asia region and the world's 10<sup>th</sup> largest economy in term of purchasing power. In term of population, Indonesia has a huge number of populations, which is about 250 million people in 2016. This makes Indonesia as the world's fourth most populous nation. Prior to the COVID-19 pandemic, it is predicted that by 2030, Indonesia will emerge as 7 largest economy in the world with \$1.8 trillion market opportunity.<sup>32</sup> Therefore, alleviation of anemia is the cornerstone in materializing this prediction. It is timely to call for another review of anemia and recommend a better strategic approach in formulating the near future policies.

## DEFINITIONS OF ANEMIA AND NUTRITIONAL ANEMIA

Anemia is arguably not a disease, but a manifestation of net erythropoiesis based on various underlying disorders or diseases. It is not generally defined but described by hematologic biomarkers, like low hemoglobin, low hematocrit concentrations, and low red blood cell counts, unable to meet the body's physiologic needs. In Indonesian communities, anemia is often regarded as a health complaint '*kurang darah*' (lack of blood) and '*pucat*' (pale). The World Health Organization uses hemoglobin concentration to define anemia and its severity (Table 1).<sup>33</sup>

Several approaches have been applied to classify anemia. In the hematologic literature, morphologic evaluation of red blood cells is used to classify anemia as presented in Table 2.<sup>34,35</sup> By using cytometric methods, it is nowadays possible to quantify the volume and size of red blood cells, and as a substitute for microscopic blood smear analyses, although the latter has its own value in diagnosing various blood disorders. Morphologic types of red blood cells indicate the potential causes of anemia.<sup>5,34-36</sup>

Nutritional anemia is that seen in association with nutritional deprivation or requiring conjoint nutritional management.<sup>37</sup> This may be evident with chronic energy deficiency (CED),<sup>7</sup> sub-optimal intakes and reduced bio-availabilities of haematonic nutrients (limited dietary di-

**Table 1.** Haemoglobin levels to diagnose anaemia at sea level (g/L)

Population	Non-anaemia <sup>†</sup>	Anaemia <sup>‡</sup>		
		Mild <sup>§</sup>	Moderate	Severe
Children 6-59 months of age	100 or higher	100-109	70-99	lower than 70
Children 5-11 years of age	115 or higher	110-114	80-109	lower than 80
Children 12-14 years of age	120 or higher	110-119	80-109	lower than 80
Non-pregnant women (15 years of age and above)	120 or higher	110-119	80-109	lower than 80
Pregnant women	110 or higher	100-109	70-99	lower than 70
Men (15 years of age and above)	130 or higher	110-129	80-109	lower than 80

References<sup>33,36</sup>

<sup>†</sup>Hemoglobin in grams per litre.

<sup>§</sup>'Mild' is a misnomer: iron deficiency is already advanced by the time anemia is detected. The deficiency has consequences even when no anemia is clinically apparent.

**Table 2.** Morphologic assessment of anemia, and its potential risk factors and causes.

Morphology of anemia	MCV	Risk factors and causes
Microcytic	MCV <82fL	Iron deficiency Anemia of inflammation (chronic disease) Thalassemias
Normocytic	MCV=82–98fL	Vitamin A deficiency Anemia of inflammation (chronic disease) Renal disease
Macrocytic	MCV >98fL	Bone marrow failure (aplastic anemia, leukemia) Folate deficiency Vitamin B12 deficiency

MCV: mean corpuscular volume.

References<sup>5,34,35</sup>.

versity and food intake quality, vitamins, elements, essential fatty acids, and other bioactive food components),<sup>37</sup> excessive nutrient loss by way of the gut (malabsorption, intestinal parasitosis, atrophic gastritis), reproductive tract (menstrual loss, lactation), integument or intravascular haemolysis (inherited or acquired including malaria),<sup>31</sup> with inflammatory diseases (including over-fatness) and in association with a wide range of chronic diseases.<sup>30</sup> It is responsive, at least in part, to nutrition support if an oral, enteral or parenteral portal is available and losses can be met by intake or the underlying cause addressed. Non-nutritional anemia is where none of these situations apply.

#### MISCONCEPTIONS AND UNDER RECOGNITION OF CAUSES, RISK FACTORS OR COMORBIDITIES FOR NUTRITIONAL ANEMIA

Many stakeholders have perceived nutritional anemia to be iron-deficiency anemia. Iron-deficiency anemia has been diagnosed without the assessment of iron status. This perception obtains because iron-deficiency anemia represents about half of nutritional anemia in developing countries including Indonesia, and because iron supplementation with acceptable recipient compliance has partly improved hemoglobin concentrations,<sup>4,7,38</sup> and, therefore, reduced morbidity and mortality related to IDA.<sup>39-41</sup> However, some reports indicate that anemia associated with iron deficiency is much less than 50% in *reproductive age women*, especially in developing countries, where the prevalence of anemia may be >40%, with a high burden of infection and inflammation.<sup>2,29</sup> Meta-analysis of anemia in pregnant Indonesian women by Lipoeto et al<sup>7</sup> has demonstrated that chronic energy deficiency, not iron deficiency, is the key determinant of anemia. Therefore, to reduce the burden of anemia in reproductive age Indonesian women by 50% in 2030 (as stipulated by the World Health Assembly and the Food and Agriculture Organization SDGs - Sustainable Development Goals as Target 2.2),<sup>42</sup> it is timely to consider other underlying causes of anemia in Indonesia like infection burden, and to implement targeted intervention strategies.

Indonesia has the second highest incidence of *tuberculosis (TB)* after India.<sup>43</sup> WHO acknowledges that TB is a communicable disease that is a major cause of ill health, one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent

(ranking above HIV/AIDS). Nutritional factors are involved in susceptibility to it in Indonesia.<sup>44</sup> Without adequate treatment, chronic TB infection leads to malnutrition with further health consequences like anemia.<sup>45-48</sup> In a case-control study, Karyadi et al<sup>49</sup> reported that ~60% of active TB patients vs 20% of healthy controls were anemic.<sup>50</sup> Anemia in TB individuals is related to inflammation as evidenced by high ferritin concentrations in TB-associated anemia,<sup>48,51</sup> and adequate treatment of TB, not iron supplementation, to some extent, improves the hemoglobin status. Excess of iron due to iron supplementation to active TB sufferers potentially leads to exacerbation of TB and worsens the outcome of TB since M tuberculosis scavenges iron from the host-cell transferrin-iron acquisition pathway, which enhances its growth in the alveolar macrophages.<sup>52,53</sup>

Malaria is highly endemic in the eastern part of Indonesia, namely East Nusa Tenggara and Papua.<sup>31,54</sup> It is evident in many studies that, in endemic malaria, so called malaria-associated anemia is prevalent. The pathophysiology of anemia is described by Malik et al.<sup>31</sup> In the eastern part of Indonesia, malaria-associated anemia may worsen anemia related to malnutrition,<sup>1,8,9</sup> helminthiasis,<sup>55</sup> and inherited disorders related to red blood cells like hemoglobinopathies.<sup>31</sup>

In *malaria* endemic areas, anemia and iron/folate deficiency seem to protect individuals against malaria infection.<sup>31,56-59</sup> Despite the unknown definitive mechanisms for this phenomena, available data reveal that iron supplementation in young children living in an endemic area may increase the risk of malaria-related hospitalization and mortality.<sup>60-63</sup> Morbidity among breast-fed infants given iron supplementats is dependent on hemoglobin concentration, being greater when Hb was ≥110 g/L.<sup>64</sup> Reticulocytosis stimulated by iron supplementation,<sup>64</sup> with a younger and larger RBC population increases susceptibility to the malarial parasite and may lead to overwhelming parasitosis, especially in infants.<sup>63,65</sup>

In pregnant women, malaria-associated anemia is complex. It leads to adverse pregnancy outcomes like low-birth weight due to preterm delivery and intra-uterine growth retardation, most likely caused by placental malaria.<sup>66-68</sup> Iron deficiency may confer protection against malaria and all-cause mortality during early childhood, while needed for optimal neurodevelopment.<sup>57</sup> The management of anemia in malaria-endemic areas needs

consideration of whether at-risk people have access to effective primary health care; and whether effective malaria case management is in place.<sup>31,56,66</sup> Malaria management and prevention arrangements must be in place prior to iron and folate supplementation. Interventions with biofortified grains and legumes, and bioavailability generated by food biodiversity, are safer and more preferable than iron and or folate supplementation. Since *helminthiasis* may co-exist with malaria and contribute to anaemia as well, its conjoint management is also required.<sup>31,56,66,69</sup>

### THE NEED TO BE INTERSECTORAL AND ECO-NUTRITIONAL WITH ANEMIA

Perhaps one of the major weaknesses in many accounts of anemia and nutritional anemia in any form, is the lack of eco-nutritional context. Human biology is strongly connected to its ecosystem, and any disturbance leads potentially to ecosystem health disorder.<sup>71,72</sup> As a megadiverse country, Indonesia is rich in plant food and animal species, which support hematinic nutriture for its human population. Therefore, iron- and vitamin B-rich foods are usually available for the sustenance of Indonesian communities with their diverse traditional food cultures. Yet, studies of nutritional anemia, rarely connect background dietary pattern and *consumption of local nutrient-dense foods*. The consumption of a biodiverse diet means not only consumption of iron-replete foods, but also good sources of vitamin C, which enhances iron absorption. This may mean a reduction in phytate-rich foods consumption, as phytate inhibits iron absorption, but this may be resolved by food culture inclusive of foods with phytase so retaining inositol since phytate is a hexaphosphate. There is evidence that inositol is protective against metabolic disease, as in diabetic neuropathy.<sup>72,73</sup> This illustrates how the consumption of biodiverse foods can foster better health outcomes.<sup>74</sup> (Table 3) Practical guidelines to obtain food variety scores can be developed by way of food variety check lists as for Australians, but instead for Indonesians.<sup>71</sup>

*Socio-cultural factors* affect food habits and dietary patterns. In many cultural contexts with patrilineal and matrilineal systems, marginal income generation, intra-household food distribution is discriminatory, with women and children getting less nutritious foods at meal-time.<sup>75-79</sup> In many Indonesian ethnic groups, food avoidance is traditionally practised, sometimes based on valid observation over generations; for example, pregnant mothers may not be allowed to consume fish as it is

believed to cause helminth infestation. The increasingly wide use of smart phones may affect these traditions for better or worse, but provide opportunity for anemia mitigation.<sup>80,81</sup>

Inter-sectoral and eco-nutritional approaches enable us to develop *practical measures which recognise anemia* by symptomatology, food and nutrition surveys, screening (fingerpick blood), nutrition assessment, and blood loss (menstrual and faecal). They identify *vulnerable groups* including premenopausal and pregnant women, children and adolescents, unwell adults and the dependent aged. *Risk settings* include food insecurity, infectious disease, non-communicable disease, inheritance and epigenetics and socioeconomic disadvantage. *Underlying socio-ecological problems* are livelihood, food systems, cultural habits, belief systems, and social networks and activities (Figure 1).

### ANEMIA AND THE COVID-19 PANDEMIC

Since the first two confirmed covid cases in early March 2020 in Indonesia, no decline in incidence has been in evidence by the end of 2020. By mid-December 2020, there were more than 600,000 positive COVID-19 cases with almost 20,000 deaths. The clinical syndromes of SARS-CoV-2 infection are many. The most common symptoms are fever (77%), dry cough (81%), expectoration (56%), headache (34%), myalgia or fatigue (52%), diarrhea (8%), and haemoptysis (3%). Three percent have shortness of breath on hospital admission. The median time from exposure to onset of illness is 4 days (ranges 3-5 days), and from onset of symptoms to first hospital admission is 2 (ranges 1-4) days. On hospital admission, ground-glass opacity (GGO) is the most common radiologic finding on chest computed tomography (CT) (56.4%). No radiographic or CT abnormality is found in 17.9% patients with nonsevere disease and in 2.9% of patients with severe disease. Lymphocytopenia is present in 83.2% of admissions, and of prognostic consequence for disease severity and mortality.

Anemia is an independent risk factor for adverse outcomes of community-acquired pneumonia, and this appears to apply with COVID-19 infection. Tao et al have reported that, among 222 COVID-19 patients, ~35% were anemic.<sup>81</sup> Of those who were anemic, 58% and 42% were classified as having mild or moderate to severe anemia, respectively. In severe COVID-19 patients, hemoglobin concentrations is lower than in those with mild COVID-19. With respect to anemia, serum iron deficiency is found in COVID-19 patients and associated with disease severity and mortality. However, the relationship between iron deficiency and susceptibility to infection is moot. There is no evidence that iron supplementation in COVID-19 patients mitigates clinical progression of the disease.

The most evidence-based nutritional approach to COVID-19 and its complications, even where vaccination becomes available, is to enhance innate immunity and to ensure the most optimal health and nutritional status compatible with physical (not social) isolation and compromised food systems.<sup>83-85</sup>

**Table 3.** Required food variety score to achieve dietary adequacy.

Total food variety score	Dietary adequacy
30 or more per week	Very good
25–29 per week	Good
20–24 per week	Fair
Less than 20 per week	Poor
Less than 10 per week	Very poor

The concept of dietary adequacy embraces that of essential nutrient adequacy, but also takes into account other food components and food properties.<sup>71</sup>

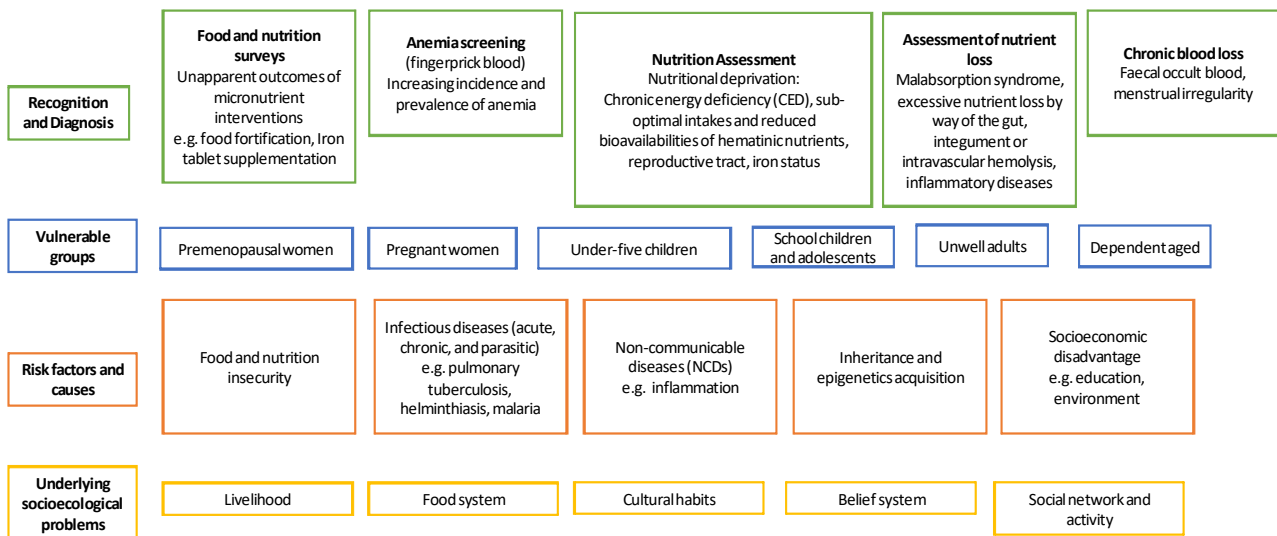


Figure 1. Conceptual framework for anemia in Indonesia.

## RECOMMENDATIONS

- 1) Recognise that, currently, *anemia in Indonesia remains endemic with an underlying societal and epigenetic persistence, and a co-existently high burden of TB, malaria, NCDs and other neglected diseases* as barriers to its mitigation, which constitute an imprimatur for action.
- 2) Recognise that *the endemicity of malaria and linkage with anemia is greatest in the eastern part of Indonesia*, where it is combined notably with inherited anaemias, a situation which might be more effectively addressed by socioculturally enhanced interventions and governance.
- 3) **Empower local government** which, since 2000, has had a consequential role in elevating the livelihoods of Indonesian people, to extend more effectively into the health and nutrition sectors. Intersectoral communication should be encouraged within and beyond the health and nutrition sectors.
- 4) Recognise that most health problems, including anemia, require a 'one package solution', albeit ecological and socio-cultural.
- 5) Mitigate underlying *root and multifactorial socio-ecological causes* and risk factors for anemia in Indonesia.
- 6) Establish *an independent national authority* to integrate evidence-based strategies to reduce the burden of anemia in Indonesia.
- 7) Be *action-orientated*, with vigilant monitoring and evaluation, and to support research in progress for better solutions. Action plans would consider age and gender; women who are adolescent, of reproductive-age, pregnant and lactating would be specifically identified; the endemicity of infectious diseases like TB, malaria, and helminthiasis would be factored in. Biomarkers to allow the differential diagnosis of anemia would include serum ferritin to define not only iron-deficiency anemia, but also to provide an inflammatory marker together with C-reactive protein, and hepcidin, possibly in sub-samples of the target population.

The conceptual framework proposed in this review is intended to provide relevant stakeholder policy direction to deal more comprehensively and effectively with the socioecological complexity which underpins and limits progress towards anemia eradication at a time of intense global food and health insecurity. It will require co-operative intersectoral and eco-nutritional approaches which consider the need for sustainable livelihoods for all and require innovative financial arrangements, for which a consensus is evolving.<sup>86</sup>

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