Revisiting WHO haemoglobin thresholds to define anaemia in clinical medicine and public health

Anaemia exists when circulating red blood cells are insufficient to meet physiological oxygen-carrying needs. Anaemia is conventionally identified when the haemoglobin concentration falls below a defined threshold.[1] Accurate case definition of anaemia is crucial for clinical patient care[1] and for understanding the epidemiology of this problem to plan and monitor public health interventions.[2]

In the clinic, diagnosis of anaemia and assessment of its underlying causes are routine across almost every field of primary and hospital practice. Anaemia might present symptomatically (eg, with fatigue, dizziness, exertional breathlessness, palpitations, exacerbations of cardiac failure, and angina) or be detected incidentally during routine screening (as recommended in some guidelines) or as part of evaluation of almost any medical condition. Identification of anaemia often necessitates more detailed laboratory, genetic, and clinical investigations. Symptoms of anaemia might be lessened if onset is slow because of adaption of oxygen offloading capacity and changes in cardiac output. Thus, severity, chronicity, and clinical effects are essential when considering specific therapeutic approaches for anaemia (eg, transfusion, intravenous iron, erythropoietin).[3] Anaemia might also have long-term consequences: in pregnancy, anaemia is associated with increased risk of caesarean section[4] and maternal mortality, and might contribute to adverse newborn outcomes, including reduced birthweight and gestation duration.[5] Anaemia in children has been linked to impairments in short-term and longer-term cognitive development, which might be irreversible,[6] although definitive evidence from interventional trials remains elusive in young children.[7]

Globally, 41·7% of children younger than 5 years and 32·8% of women of reproductive age were considered anaemic in 2016, with the highest prevalence in low-income countries.[8] Controlling the global burden of anaemia is an important public health priority: the 2025 Global Nutrition Targets pursue a 50% reduction in the prevalence of anaemia in women of reproductive age,[7] while the 2030 Sustainable Development Goals 2 and 3 describe alleviation of anaemia. Decisions to implement, and monitoring of, programmes that integrate nutrition-specific and nutrition-sensitive interventions are predicated on the prevalence of anaemia. Reduction of anaemia might also indicate success of infection control programmes (eg, malaria prevention, deworming).

Appropriate guidelines for measurement of haemoglobin and definition of anaemia are crucial for both clinical and public health medicine, but require consideration of the range of complexities across different populations. Haemoglobin thresholds to define anaemia were first proposed by WHO in 1959. Current thresholds recommended by WHO for men, women, young children, and pregnant women (table) were first proposed in 1968 after technical meetings of a group comprising clinical and public health experts working with data from five studies of predominantly white populations in Europe and North America (appendix). Data from other countries, races, and ages (ie, infants, young children, adolescents, and elderly people) were not available to the panel. These studies were done in an era when laboratory and epidemiological methods were less developed than today. Haemoglobin thresholds to diagnose anaemia proposed by other sources (eg, haematology textbooks), other organisations (eg, the US Centers for Disease Control and Prevention [CDC]), expert clinical organisations, and individual clinical and research laboratories, often differ from WHO recommendations (appendix). Thus, although anaemia remains one of the most common laboratory diagnoses, consensus on the haemoglobin threshold below which it should be defined and the thresholds to establish its severity is limited. WHO is reviewing the use and interpretation of haemoglobin thresholds for assessing

See Online for appendix

	Non-anaemic (g/L)	Mild (g/L)	Moderate (g/L)	Severe (g/L)
Men aged ≥15 years	>130	110–129	80–109	<80
Women aged ≥15 years	>120	110–119	80–109	<80
Pregnant women	>110*	100–109	70–99	<70
Children aged 6–59 months	>110	100–109	70–99	<70†
Children aged 5–11 years	>115	110–114	80–109	<80
Children aged 12–14 years	>120	110–119	80–109	<80

*Threshold is greater than 105 g/L in the second trimester. †Generally, in settings with high malaria transmission, a haemoglobin concentration of 40 g/L or less is an indication for blood transfusion, regardless of the clinical condition of the child; in settings with low malaria transmission, a threshold of 70 g/L is recommended for blood transfusion.

Table: **WHO recommendations for haemoglobin thresholds to define severity of anaemia**

Panel: **Top 15 ranked scoping questions**

1 What anaemia prevalence is indicative of a mild, moderate, or severe magnitude of a public health problem at the population level?
2 Should haemoglobin thresholds to define anaemia differ between males and females?
3 Should haemoglobin thresholds to define anaemia differ in different age groups (eg, infants, preschool children, school children, adolescents, adults, older adults)?
4 How should mild, moderate, and severe anaemia severities be defined?
5 What is the most reliable measure of haemoglobin in population or field-based surveys?
6 At which haemoglobin level should iron supplementation or other intervention at an individual or population level be initiated?
7 What are the effects of different micronutrient deficiencies (eg, iron, folate, vitamin B12, vitamin D) on haemoglobin concentration and anaemia?
8 What is the gold-standard laboratory methodology for determining haemoglobin concentration?
9 How do maternal haemoglobin concentrations affect fetal development (eg, fetal brain development) and pregnancy outcomes?
10 Should haemoglobin thresholds to define anaemia be adjusted for altitude?
11 At which haemoglobin threshold does anaemia negatively affect physical development and growth in children?
12 What proportion of anaemia can be expected to respond to an iron intervention in public health programmes?
13 Is haemoglobin an appropriate measure for monitoring response to various clinical therapies or public health interventions?
14 Which biomarkers/indices aside from haemoglobin should be measured to complement the anaemia diagnosis and assist with defining its aetiology or severity?
15 At which haemoglobin threshold does anaemia negatively affect neurological development, learning, and social interactions?

iron status in individuals and populations. This normative work will follow established evidence-informed guideline development procedures[9] and culminate in updated guidelines for clinical and public health use.

Physiological, environmental, and genetic factors might need to be considered when defining haemoglobin thresholds. Variations in haemoglobin across the lifecycle (particularly in early life, during pregnancy, and with age) are not always incorporated in laboratory practice. In response to hypoxia, such as from elevation above sea level and smoking, haemoglobin concentrations increase. About 5·2% of the world's population carries a clinically relevant haemoglobinopathy or thalassaemia mutation.[10] α-thalassaemia carriage might partly explain low haemoglobin concentrations identified in otherwise healthy and well-nourished African American populations.[11]

In modern clinical laboratories, haemoglobin is conventionally measured photometrically with variations of the cyanmethaemoglobin method across several automated platforms; international reference standards ensure calibration of these approaches. In many settings, haemoglobin is also assessed quantitatively with lower-cost approaches, such as cyanmethaemoglobin methods on field calorimeters; semi-quantitatively with Sahli's method and some filter-paper approaches; or with the copper sulfate gravimetric approach. Non-invasive techniques for measurement of haemoglobin concentration are emerging. Ensuring appropriate standardisation of haemoglobin measurements across this range of methods is essential to ensure high-quality detection of anaemia in all settings.

To define priorities and identify key questions for a project to reassess use and interpretation of haemoglobin thresholds to define anaemia, in 2016, we did a scoping exercise via a two-stage international consultation based on the Child Health and Nutrition Research Initiative method[12] (appendix). The first survey allowed respondents to suggest priorities, and the second asked respondents to rank the key questions with established criteria (appendix). A transparent approach was used to identify international experts in anaemia research (based on publication track record [appendix], and ensuring representatives from all WHO regions and low-income and middle-income countries were included); we also contacted organisations (eg, American Society of Hematology) and other groups to suggest experts. Participants in international forums, including the Accelerated Reduction Effort on Anaemia network, were also invited.

The first survey received 123 respondents from 48 countries across all six WHO regions (appendix). The 553 proposed questions spanned many themes (appendix), and were consolidated to form a short-list of 48 questions spanning six subtopics, including physiology of anaemia, haemoglobin thresholds for different population groups, definition of anaemia across clinical and environmental contexts, approach to development of anaemia thresholds, laboratory and diagnostic considerations, and implementation of WHO's haemoglobin threshold guidelines. The second survey received 195 respondents from 64 countries across all six WHO regions (appendix). The complete list of ranked questions is shown in the appendix; a list of the 15 highest-ranked questions is shown in the panel. Questions covered diverse themes, including variation

in thresholds between individuals of different sex and age, categorisation of anaemia severity and the burden of anaemia, optimal clinical and field laboratory measurements of haemoglobin, and antenatal and infant haemoglobin concentrations associated with adverse developmental outcomes. These questions help prioritise the evidence that needs to be sought to reassess WHO anaemia definitions, and existing evidence and data to address them are being summarised in a series of commissioned review papers, which will be published in a peer-reviewed journal.

WHO held a technical meeting (*Use and interpretation of haemoglobin concentrations for assessing anaemia status in individuals and populations*) in Geneva in November, 2017. In preparation for the meeting, WHO issued an open call for authors and selected and commissioned reviews in the topics prioritised from the submitted proposals. Experts at the meeting reviewed evidence on topics, including data on variations in haemoglobin across the lifecycle, effects of haemoglobin concentration on mother and child health, changes in haemoglobin concentrations with elevation above sea level and in smokers, methods for measuring haemoglobin, and ethical and human rights considerations when assessing anaemia. A further session was held at the 59th American Society of Hematology Annual Meeting and Exposition in December, 2017, to share information with the broader haematology community and to ensure they could provide feedback into the process.

Based on normative needs identified at these meetings, WHO and its internal partners will coordinate in the retrieval, summary, and assessment of evidence, as well as in the generation of new data, as needed to address the priorities identified by the consultation. These projects might use a variety of research methods, including prospective studies with data collection, measurement of biomarkers of banked samples, re-analysis of existing databases, functional and physiological studies in human populations, analysis of diagnostic test accuracy, systematic reviews and meta-analyses, and overviews of systematic reviews. Input from key stakeholders, particularly key clinical haematology and public health expert bodies, will be sought. The final evidence will be summarised and presented to a WHO guideline development group after input from a working expert panel. All guidelines will be peer-reviewed before finalisation. This rigorous, inclusive, and transparent approach should enable international harmonisation of haemoglobin thresholds used to define anaemia in both clinical and public health practice.

*Sant-Rayn Pasricha, Katherine Colman, Elizabeth Centeno-Tablante, *Maria-Nieves Garcia-Casal, Juan-Pablo Peña-Rosas*

Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia (S-RP); Medical Research Council (MRC) Human Immunology Unit, MRC Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, University of Oxford, Oxford, UK (S-RP); Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia (KC); and Department of Nutrition for Health and Development, World Health Organization, 1211 Geneva 27, Switzerland (EC-T, M-NG-C, J-PP-R)
garciacasalm@who.int

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