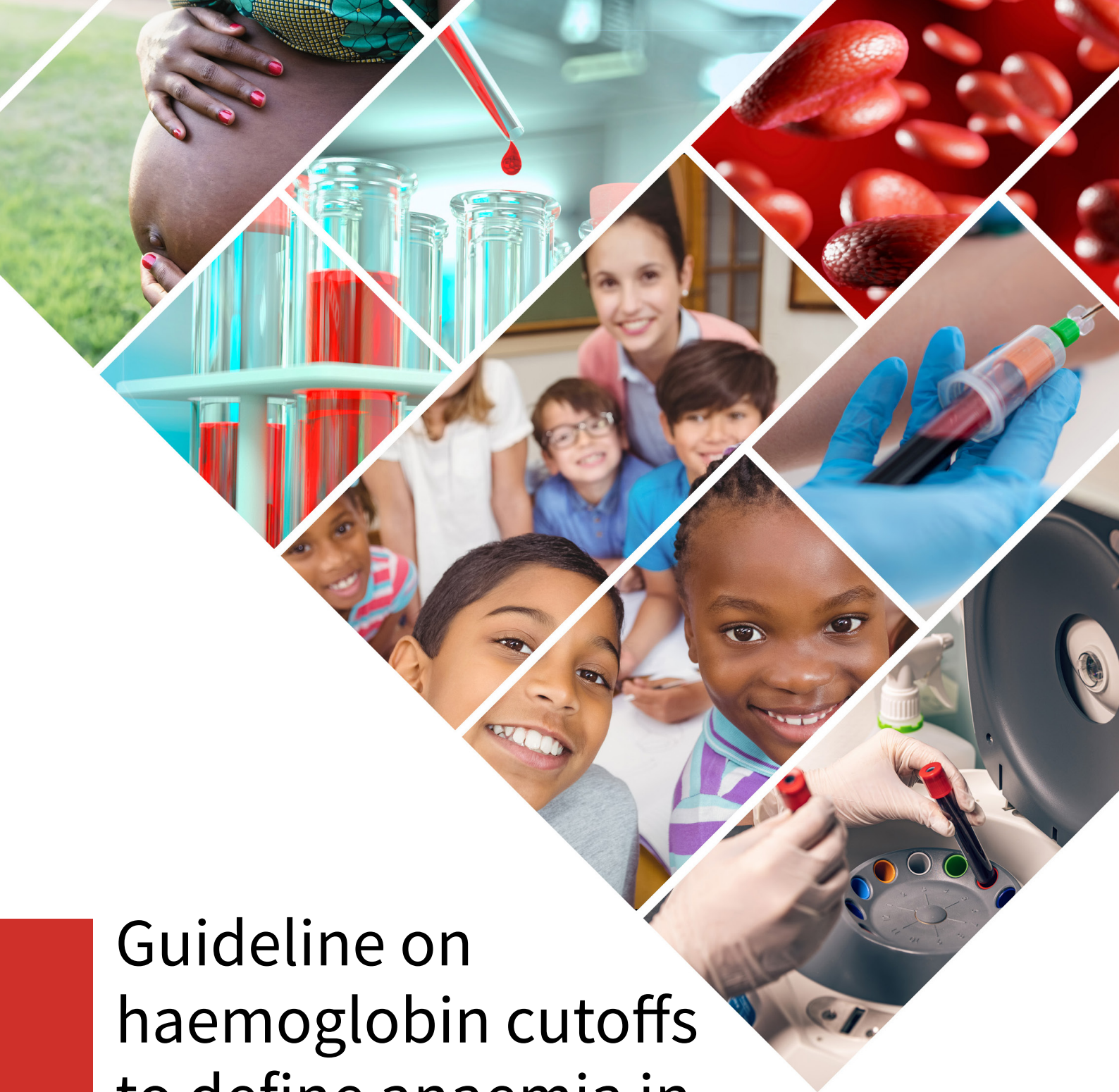




Guideline on haemoglobin cutoffs to define anaemia in individuals and populations



World Health
Organization

Guideline on haemoglobin cutoffs to define anaemia in individuals and populations

Guideline on haemoglobin cutoffs to define anaemia in individuals and populations

ISBN 978-92-4-008854-2 (electronic version)

ISBN 978-92-4-008855-9 (print version)

© World Health Organization 2024

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo>).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: “This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition”.

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization (<http://www.wipo.int/amc/en/mediation/rules/>).

Suggested citation. Guideline on haemoglobin cutoffs to define anaemia in individuals and populations. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at <https://iris.who.int/>.

Sales, rights and licensing. To purchase WHO publications, see <https://www.who.int/publications/book-orders>. To submit requests for commercial use and queries on rights and licensing, see <https://www.who.int/copyright>.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

Cover photograph credits: Wavebreakmedia, Ioan Cseh, DancingMan, Stevica Mrdja, Amynapaloha, and Alessandro Biascioli.

Design and layout: Alberto March.

Contents

Acknowledgements	vii
Abbreviations	viii
Executive summary	ix
Purpose of the guideline	ix
Guideline development methodology	ix
Haemoglobin cutoffs and adjustments	x
1. Haemoglobin cutoffs to define anaemia	xi
Use of statistical and/or clinical outcomes	xi
Normative statement 1.a Haemoglobin cutoffs to define any anaemia	xi
Normative statement 1.b Anaemia severity	xii
2. Adjustments for external factors	xiii
Normative statement 2.a.1 Elevation of residence	xiii
Normative statement 2.a.2 Smoking	xiv
Normative statement 2.b Infection and inflammation	xv
Normative statement 2.c Genetic ancestry/ethnicity/race	xv
3. Measurement of haemoglobin concentrations	xvi
Normative statement 3 Haemoglobin measurement	xvi
4. Haemoglobin concentrations to assess impact of interventions	xvii
Normative statement 4 Assessing impact of interventions	xvii
5. Cutoffs to define the public health significance of anaemia	xviii
Normative statement 5 Public health significance of anaemia	xviii
References	xix
Background	1
Scope and purpose	2
Objectives	3
History of this guideline	3
Existing WHO documents related to this new guideline	4
Technical meetings convened for developing this guideline	5

Summary of the evidence	6
Question 1	
What should be the haemoglobin cutoffs to define anaemia in individuals and in populations?	7
Use of statistical and/or clinical outcomes	9
Normative statement 1.a Haemoglobin cutoffs to define any anaemia	9
Normative statement 1.b Anaemia severity	10
Question 2	
Should haemoglobin cutoffs be adjusted for exposure to external factors or settings known to affect haemoglobin?	12
Question 2.a Should haemoglobin cutoffs to define anaemia be adjusted for elevation of residence and/or smoking?	12
Normative statement 2.a.1 Elevation of residence	13
Normative statement 2.a.2 Smoking	15
Question 2.b Should haemoglobin cutoffs to define anaemia be adjusted by inflammation/infection, particularly in malaria-endemic settings?	16
Normative statement 2.b Infection and inflammation	16
Question 2.c Should haemoglobin cutoffs to define anaemia be adjusted by genetic ancestry/ethnicity/race?	17
Normative statement 2.c Genetic ancestry/ethnicity/race	18
Question 3	
How should haemoglobin concentration be measured?	19
Normative statement 3 Haemoglobin measurement	20
Question 4	
Is haemoglobin concentration an adequate marker for assessing the impact of iron interventions?	21
Normative statement 4 Assessing impact of interventions	22
Question 5	
What should be the population cutoffs to define the public health significance of anaemia?	23
Normative statement 5 Public health significance of anaemia	23
Dissemination, implementation, and ethical considerations	26
Dissemination	26
Equity, human rights, and implementation considerations	26
Regulatory considerations	27
Ethical considerations	28
Monitoring and evaluation of guideline implementation	29
Guideline development process	30
Scoping the guideline, evidence appraisal, and decision-making	31
Deliberations on haemoglobin cutoffs for infants and children aged 6–59 months	33
Management of competing interests	34

Plans for updating the guideline	34
References	35
Annex 1. GRADE summary of findings tables	40
Annex 2. Questions in PICO format	47
Question 1	
What should be the haemoglobin cutoffs to define anaemia in individuals and in populations?	47
Question 2	
Should haemoglobin cutoffs be adjusted by exposure to external factors or settings known to affect haemoglobin?	48
Question 3	
How should haemoglobin concentration be measured?	49
Question 4	
Is haemoglobin concentration an adequate marker for assessing the impact of iron interventions?	50
Question 5	
What should be the population cutoffs to define the public health burden of anaemia?	50
Annex 3. Summary of judgements	51
Annex 4. WHO Steering Committee	52
Annex 5. WHO Guideline Development Group	53
Annex 6. Systematic reviews and database analysis team	55
Annex 7. Peer-reviewers	56
Annex 8. WHO Secretariat	57

Acknowledgements

This guideline was coordinated by the Department of Nutrition and Food Safety of the World Health Organization (WHO). Dr Maria Nieves Garcia-Casal prepared this document with technical guidance from the members of the WHO Steering Committee: Dr Lisa Rogers, Dr Juan Pablo Peña-Rosas, and Dr Francesco Branca (Department of Nutrition and Food Safety); Dr Andrea Bosman (Global Malaria Programme); Dr Maurice Bucagu and Dr Yuka Sumi (Department of Maternal, Newborn, Child, and Adolescent Health and Ageing); and Dr Özge Tuncalp Mingard (Department of Sexual and Reproductive Health and Research). The methodologists of this guideline were Dr Susan Norris for the first Guideline development group (GDG) meeting and Dr Maria Nieves Garcia-Casal for the series of second GDG meetings. Other members of the Department of Nutrition and Food Safety who participated in the development of this guideline include Dr Elaine Borghi, Ms Monica Flores-Urrutia, and Dr Laurence Grummer-Strawn.

WHO especially acknowledges Professor Sant-Rayn Pasricha from the Walter and Eliza Hall Institute of Medical Research, Australia, and Dr Maria Elena Jefferds and Dr Andrea Sharma from the United States Centers for Disease Control and Prevention (CDC), United States of America, for their technical support and partnership during the development of this guideline.

Special thanks are extended to the authors of the database analyses and systematic reviews, as well as to the authors of the commissioned literature reviews used to inform this guideline, for their assistance and collaboration in preparing or updating these reviews. We appreciate the feedback provided by a large number of international stakeholders throughout the guideline development process.

WHO gratefully acknowledges the technical input of the members of the GDG involved in this process, especially the co-chairs of two of the meetings on this guideline, Professor Beverly-Ann Biggs, University of Melbourne, Australia (in 2019), and Dr Melissa F. Young, Emory University, United States of America (in 2022). As representatives of technical partners for the project, Dr Pasricha and Dr Jefferds were not GDG members, although they participated in an individual capacity and co-chaired some meetings. A third meeting of the GDG was chaired by WHO.

WHO thanks the peer-reviewers: Dr Omar Dary, United States Agency for International Development (USAID), United States of America; Dr Sorrel Namaste, Demographic and Health Surveys Program, United States of America; Dr Nelly Zavaleta, Instituto de Investigación Nutricional, Peru; and Dr Michael Zimmermann, Swiss Federal Institute of Technology, Switzerland, for their thoughtful feedback on a preliminary version of this guideline.

Thanks are due to Dr Susan Norris, Ms Marion Blacker and Ms Rebekah Thomas from the WHO Guidelines Review Committee Secretariat, and members of the WHO Guidelines Review Committee for their technical support throughout the process. Thanks are also due to Ms Alma Alic from the WHO Department of Compliance and Risk Management and Ethics for her support in the management of conflicts of interest procedures.

WHO thanks USAID for their generous financial support. WHO also acknowledges CDC, especially the International Micronutrient Malnutrition Prevention and Control programme, and the Bill & Melinda Gates Foundation, for providing financial support to the work of the Department of Nutrition and Food Safety. These partners did not participate in the development of or voting on the normative statements.

Donors, observers, and external peer-reviewers did not participate in any decision related to the guideline development process, including the composition of research questions, membership of the guideline groups, conduct and interpretation of the evidence synthesis, or guidance formulation.

Abbreviations

CDC	United States Centers for Disease Control and Prevention
CI	Confidence interval
DECIDE	Developing and Evaluating Communication Strategies to support Informed Decisions and Practice based on Evidence
GDG	Guideline development group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
NHANES	National Health and Nutrition Examination Survey
PICO	Population, intervention, comparator, outcome
SD	Standard deviation
UNICEF	United Nations Childrens Fund
USAID	United States Agency for International Development
VMNIS	Vitamin and Mineral Nutrition Information System
WHO	World Health Organization
YLD	Years lived with disability

Executive summary

Anaemia is a global public health concern, especially afflicting adolescent girls, women 15–49 years of age, pregnant women, and children in low- and middle-income countries. WHO estimates that in 2019 30% (571 million) of women aged 15–49 years, 37% (32 million) of pregnant women, and 40% (269 million) of children 6–59 months of age were affected by anaemia, with the WHO African Region and South-East Asia Region being most affected (1).

Accurate characterization of anaemia is critical to understand the burden and epidemiology of this problem, for planning public health interventions, and for the clinical care of people across the life course (2). Multiple interventions are aimed at alleviating the burden of anaemia in many low-, middle-, and high-income countries worldwide, and decisions around the choice of intervention and their implementation and monitoring is founded on measuring the prevalence and distribution of anaemia in different segments of the population, notably the most vulnerable groups (3).

Purpose of the guideline

This guideline aims to help Member States and their partners in their efforts to make informed decisions on the appropriate tools to support assessing and reducing the global burden of anaemia as an important public health priority. The WHO [Global nutrition targets 2025](#) include a 50% reduction in the prevalence of anaemia in women of reproductive age (4). The 2030 [Sustainable Development Goals \(SDGs\)](#) (5), in particular, Goal 2: End hunger, achieve food security and improved nutrition and promote sustainable agriculture and Goal 3: Ensure healthy lives and promote well-being for all at all ages, encompass alleviation of anaemia (6). This guideline will also support Member States in their efforts to achieve the global targets of the [Comprehensive implementation plan on maternal, infant and young child nutrition](#) (7) and the [Global strategy for women's, children's and adolescents' health \(2016–2030\)](#) (8).

Appropriate guidelines for measuring haemoglobin and defining anaemia are crucial for both clinical and public health medicine but require consideration of a range of complexities across different populations.

The normative statements in this guideline are intended for a wide audience, including policy-makers, their expert advisers, and technical and programme staff at ministries and organizations involved in the design, implementation, and scaling-up of actions for addressing anaemia. Other end-users of the guideline include nongovernmental and other organizations and professional societies involved in the planning and management of anaemia actions, as well as health professionals including clinicians, managers of nutrition and health programmes, national blood services, and public health policy-makers in all settings.

The objective of this guideline is to provide updated, locally adaptable, clear, evidence-informed normative statements on the use of haemoglobin concentrations to assess anaemia and on best approaches in its measurement in individuals and populations. The purpose of the guideline is to improve the diagnosis of anaemia, grounded in gender, equity and human rights approaches, with the aim of leaving no one behind, thereby informing the development of nutrition and health policies.

Guideline development methodology

WHO developed the present evidence-informed normative statements using the procedures outlined in the [WHO handbook for guideline development](#) (9). The evidence that informed haemoglobin cutoffs to define anaemia in individuals and populations was based on a commissioned analysis of haemoglobin concentrations from healthy populations and systematic reviews. When possible, the [Grading of Recommendations Assessment, Development and Evaluation \(GRADE\)](#)¹ methodology was followed to prepare evidence profiles related to preselected topics, based on up-to-date systematic reviews and other narrative syntheses of the evidence.

¹ The GRADE approach defines the overall rating of confidence in the body of evidence from systematic reviews as the extent to which one can be confident of the effect estimates across all outcomes considered critical to the recommendation. Each of the critical outcomes had a confidence rating based on certainty of evidence – high, moderate, low, or very low. High-certainty evidence indicates that we are very confident that the true effect lies close to that of the estimate of the effect. Moderate-certainty evidence indicates that we are moderately confident in the effect estimate and that the true estimate is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low-certainty evidence indicates that our confidence in the effect estimate is limited, and the true effect may be substantially different from the estimate of the effect. Very low-certainty evidence indicates that we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of effect.

The GDG consisted of content experts, clinicians, and public health specialists. After consideration of topics generated by a via a two-stage international consultation on priority areas, the GDG developed five questions in the PICO (population, intervention, comparator, outcome) format.

A team of systematic reviewers, acting as resource persons, participated in the guideline development process by presenting evidence and identifying research priorities. The GDG considered additional factors for the implementation of revised haemoglobin cutoffs to diagnose anaemia at both the individual and the public health level, including equitable access to health care. Four technical experts peer-reviewed the draft guideline.

This guideline updates and complements previous recommendations contained in five WHO documents, published between 1968 and 2005, which are summarized in the 2011 WHO publication *Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity* (10). Briefly, haemoglobin cutoffs were first presented in a 1968 WHO document and were based on four published references and one set of unpublished observations. Definitions for mild, moderate, and severe anaemia were first published in 1989 (11). These were slightly modified in a subsequent publication on nutrition in emergencies, which also proposed a classification to determine the public health significance of anaemia in populations (12). Finally, a 2001 guide for programme managers split the age group for children 5–14 years of age and applied a new, lower haemoglobin cutoff for children 5–11 years based on data from the National Health and Nutrition Examination Survey II (NHANES II) of the United States of America (13). The 2001 document also provided haemoglobin adjustments for those residing or working at elevation and for smoking (13).

This publication partially updates and consolidates information from the previous WHO documents. There is still additional valuable information within those documents that has not yet been updated because it was out-of-scope for the current guideline.

Haemoglobin cutoffs and adjustments

The outcome considered by the GDG to be critical for decision-making was the accurate diagnosis of anaemia, considering:

1. the use of anaemia cutoffs at the individual level established using a statistical approach or based on outcomes-related clinical symptoms/functional impairment;
2. the use of adjustments to haemoglobin concentrations to account for elevation of residence/work, smoking, infections (especially malaria), and/or genetic ancestry/ethnicity/race;
3. the comparability of haemoglobin determinations by type of blood sample, methods of analysis, measurement instruments, and international standard materials used at the clinical and public health levels;
4. changes in haemoglobin concentrations in response to interventions that address the direct causes of anaemia; and
5. the anaemia prevalence at population level indicative of a public health problem of mild, moderate, or severe magnitude.

The evidence that informed haemoglobin cutoffs to define anaemia in individuals and populations was based on an analysis of haemoglobin data from healthy populations, general population databases, and systematic reviews. The analysis data from healthy populations has been accepted for publication (14).

1. Haemoglobin cutoffs to define anaemia

Question 1

What should be the haemoglobin cutoffs to define anaemia in individuals and in populations?

1.a How should the cutoffs be defined?

Should they be based on statistical cutoffs, such as percentile-based cutoffs or a reference range of haemoglobin concentrations in apparently healthy populations, or based on outcomes related to clinical symptoms or functional impairment?

1.b How should mild, moderate, and severe anaemia be defined at individual level?

Use of statistical and/or clinical outcomes

Establishing haemoglobin cutoffs for defining anaemia based on outcomes related to clinical symptoms or functional impairment was preferred but not possible for all age groups and trimesters of pregnancy. The evidence of an association between haemoglobin concentration and maternal and newborn health outcomes has been repeatedly reported, but the most relevant outcomes and precise cutoffs are still in development; therefore, the statistical approach was used. The outputs of the statistical approach were haemoglobin values below which only a limited number of healthy individuals would be expected to have anaemia. This approach informed the evaluation and update of current cutoffs.

A key consideration was whether to select the 5th or 2.5th percentile for the haemoglobin concentration cutoffs. The choice of percentile entails trade-offs. For this recommendation, the 5th percentile was selected, which is consistent with original WHO guidance for defining anaemia. The 5th percentile implies that 95% of healthy individuals would have a higher haemoglobin value, and 5% of healthy individuals would still have a lower haemoglobin value than the cutoff and be falsely diagnosed as anaemic. Selecting the higher of the two percentiles is expected to provide more sensitivity to detect individuals with underlying conditions associated with anaemia (e.g. nutritional deficiency, genetic conditions, inflammation, infection), thereby promoting intervention.

Normative statement 1.a Haemoglobin cutoffs to define any anaemia

Analysis of the evidence suggested modification of the current haemoglobin cutoffs for defining anaemia for one population group (children 6–23 months of age) and use of the existing cutoff for pregnant women in the second trimester.

Table 2. Haemoglobin cutoffs to define anaemia in individuals and populations

Population	Haemoglobin concentration (g/L) ^a
Children, 6–23 months	<105
Children, 24–59 months	<110
Children, 5–11 years	<115
Children, 12–14 years, nonpregnant girls	<120
Children, 12–14 years, boys	<120
Adults, 15–65 years, nonpregnant women	<120
Adults, 15–65 years, men	<130
Pregnancy	
First trimester	<110
Second trimester	<105
Third trimester	<110

^a Based on 5th percentile.

Normative statement 1.b Anaemia severity

Changes to current methodology for establishing cutoffs to indicate the severity of anaemia based on haemoglobin concentrations in individuals are not recommended, due to insufficient evidence.

WHO guidance published in 1989 (11) was applied to the updated haemoglobin cutoffs presented in **Table 2** to indicate anaemia severity (**Table 3**). The 1989 guidance considered anaemia to be mild, moderate, or severe when haemoglobin concentrations are above 80%, between 80% and 60%, or less than 60% of the cutoff levels, respectively (**Table 3**). However, after reviewing and recalculating the previous WHO cutoffs for anaemia severity, it was found that the percentages were in general broader (between 85 and 92% of the cutoff value for mild anaemia and between 62 and 70% for severe anaemia).

Therefore, considering: (i) the ample ranges used in previous calculations; (ii) the implications for treatment initiation based on anaemia severity; and (iii) the GDG comments about implications for implementation, the cutoffs for severe anaemia in children aged 6–23 months and for women in the second trimester pregnancy was retained at <70 g/L.

Table 3. Haemoglobin cutoffs to define anaemia severity in individuals

Population	Haemoglobin concentration (g/L)			
	No anaemia	Mild anaemia	Moderate anaemia	Severe anaemia
Children, 6–23 months	≥105	95–104	70–94	<70
Children, 24–59 months	≥110	100–109	70–99	<70
Children, 5–11 years	≥115	110–114	80–109	<80
Children, 12–14 years, nonpregnant girls	≥120	110–119	80–109	<80
Children, 12–14 years, boys	≥120	110–119	80–109	<80
Adults, 15–65 years, nonpregnant women	≥120	110–119	80–109	<80
Adults, 15–65, years men	≥130	110–129	80–109	<80
Pregnancy				
First trimester	≥110	100–109	70–99	<70
Second trimester	≥105	95–104	70–94	<70
Third trimester	≥110	100–109	70–99	<70

Remarks

The remarks in this and the following sections are suggestions intended to provide some considerations for implementation, based on discussions of the GDG.

- The cutoffs in **Table 2** were primarily informed by a WHO commissioned analysis aimed at analysing international databases containing data on haemoglobin and other biochemical and clinical indicators which would enable application of consistent, rigorous criteria to define a healthy individual. These analyses calculated the 5th percentiles of haemoglobin distributions derived from apparently healthy, ethnically diverse populations predominantly from higher-income settings across Australia, China, Europe, North America, and South America.
- Additional data collected in lower-income settings reported heterogeneous, but generally lower, values for 5th percentiles in participants without biochemical evidence of iron and/or vitamin A deficiencies or inflammation (c-reactive protein or α -1-acid glycoprotein). Considering the backdrop of a high burden of infections and inflammation in these settings, with no definitive evidence to exclude their residual effects on haemoglobin concentration, these data were not included in the pooled analysis.

- Data in adult men may suggest a higher haemoglobin cutoff (i.e. 135 g/L) but there was uncertainty in the evidence. The GDG decided to retain the cutoff of 130 g/L for men after considering concerns about: iron therapy implications for males; the limited evidence; and the potential unintended consequences of changing the cutoff, such as initiation of iron supplementation programmes in men.
- In developing these cutoffs, a high value was placed on avoidance of harm, given the uncertainty of the evidence and the conflicting results of available proposals.
- The management for individuals with mild, moderate, or severe anaemia could vary depending on the clinical scenario and the underlying cause(s) of the anaemia.
- A clear association between severity of anaemia with clinical or statistical outcomes could be of great value for classifying anaemia severity at clinical/individual level and would help to prevent and treat anaemia.

2. Adjustments for external factors

Question 2

Should haemoglobin cutoffs be adjusted for exposure to external factors or settings known to affect haemoglobin?

- 2.a** Should haemoglobin cutoffs to define anaemia be adjusted for elevation of residence and/or smoking?
- 2.b** Should haemoglobin cutoffs to define anaemia be adjusted by inflammation/infection, particularly in malaria endemic settings?
- 2.c** Should haemoglobin cutoffs to define anaemia be adjusted by genetic ancestry/ethnicity/race?

Question 2.a.1 Should haemoglobin cutoffs to define anaemia be adjusted for elevation of residence?

Normative statement 2.a.1 Elevation of residence

Adjustments of haemoglobin concentrations are recommended to diagnose anaemia in individuals and populations to account for the effect of elevation of place of residency on haemoglobin concentrations.

Table 4 presents a common set of adjustments for use across population groups as an appropriate and practical approach for adjusting haemoglobin concentrations to account for the effect of living at elevations above sea level, especially below 2500 m, where more than 98% of the world's population resides.

Table 4. Adjustments to haemoglobin concentration (g/L) in 500 m increments in elevation^a

Elevation range (metres above sea level)	Adjustments in haemoglobin concentration (g/L) ^b
1–499	0
500–999	4
1000–1499	8
1500–1999	11
2000–2499	14
2500–2999	18
3000–3499	21
3500–3999	25
4000–4499	29
4500–4999	33

^a Adjustments are the amount subtracted from an individual's observed haemoglobin level or added to the haemoglobin cutoff defining anaemia (in g/L).

^b Proposed adjustments for all population groups based on the equation: Haemoglobin adjustment (g/L) = (0.0056384 x elevation) + (0.0000003 x elevation²).

Remarks

- Adjustments for very high elevations >3000 m in **Table 4** are based on data primarily derived from Central and South America.
- Adjustments provided are to be applied by:
 - subtracting the amount recommended from an individual's observed haemoglobin level; or
 - adding the amount recommended to the existing haemoglobin cutoff defining anaemia in g/L.
- When specific information is known about the elevation at the place of residence, use of the formulae provided would enhance precision and accuracy.
- At especially high elevations (>2500 m), tailored adjustments by region and/or ethnicity may be warranted.

Question 2.a.2 Should haemoglobin cutoffs to define anaemia be adjusted for smoking?

Normative statement 2.a.2 Smoking

Haemoglobin concentrations should be adjusted to diagnose anaemia in individuals and populations to account for the effect of smoking on haemoglobin concentrations.

Adjustments to account for smoking are presented in **Table 5**.

Table 5. Adjustments to haemoglobin for smoking status and cigarettes per day^a

Cigarettes per day	Haemoglobin adjustment (g/L)
Smoker, quantity unknown	3
<10	3
10–19	5
>20	6

^a The adjustment consists in the corresponding value in the table added to the haemoglobin cutoff defining anaemia, or subtracted from an individual's observed haemoglobin level.

^b Adjustments based on haemoglobin adjustment (g/L) = $(0.4565 \times \text{cigarette_number}) + (-0.0078 \times \text{cigarette_number}^2)$, solved for the <10 cigarettes/day category using cigarette_number = 9 and for the 10–19 category cigarettes/day using cigarette_number = 19. The adjustment for the >20 cigarettes/day category was solved using cigarette_number = 30. The formula provided may be used in place of the categorical adjustments.

Remarks

- Data on smoking are self-reported and susceptible to inaccuracies. Carbon monoxide exposure may be better addressed using pulse carbon monoxide oximetry for carboxyhaemoglobin to assess all carbon monoxide exposures and eliminate self-reporting biases.
- The largest differences in haemoglobin concentrations between smokers and non-smokers were found in women, who have significantly lower rates of smoking than men, although this may be due to underreporting of smoking quantities. By 30 cigarettes/day the effect size was the same among men and women (6 g/L).
- At the individual level it is unclear whether the difference in haemoglobin with and without adjustment for smoking is physiologically relevant, particularly because the effect of smoking on haemoglobin is complex and, in addition to acute hypoxia, includes chronic hypoxia and end-organ damage. However, corrections at the population level are important in order to accurately report anaemia prevalence rates and efficiently apply health interventions.

Question 2.b Should haemoglobin cutoffs to define anaemia be adjusted by inflammation/infection, particularly in malaria endemic settings?

Normative statement 2.b Infection and inflammation

Haemoglobin concentrations should not be adjusted to diagnose anaemia in individuals and populations to account for the effect of infection and inflammation on haemoglobin concentrations.

Remarks

- Bacterial, viral, and parasitic infections causing inflammation (e.g. malaria, tuberculosis, HIV, hookworm) affect large segments of the population and produce anaemia of various severity. Markers of inflammation (e.g. c-reactive protein and α 1-acid glycoprotein) have been used to adjust biomarkers related to iron metabolism, such as serum ferritin and serum transferrin receptor, although is not the case for haemoglobin adjustments.
- The role of chronic low-grade inflammation in the context of noncommunicable diseases, such as obesity, has been linked to altered iron metabolism and anaemia. However, adjustment of haemoglobin concentration by low-grade inflammation was determined as not the right approach for chronic diseases where anaemia may be a consequence of the condition.
- Additional indicators are required for establishing the underlying cause and magnitude of infection and inflammation, and for determining the course of treatment.

Question 2.c Should haemoglobin cutoffs to define anaemia be adjusted by genetic ancestry/ethnicity/race?

Normative statement 2.c Genetic ancestry/ethnicity/race

Haemoglobin concentrations should not be adjusted to diagnose anaemia in populations to account for the effect of genetic ancestry/ethnicity/race due to insufficient evidence to change current adjustments and the complexity of operationalization.

Remarks

- Among apparently healthy populations, there are observed differences in haemoglobin concentrations across age and population groups. Some of these differences may reflect changes in genes related to haemoglobin production or other aspects of red blood cell production or function. A lower mean haemoglobin concentration (10 g/L difference) has been reported in Black individuals compared to White individuals. When anaemia is diagnosed, the underlying genetic, nutritional, infectious/inflammatory influences, and social determinants of health relevant for the individual or populations should be considered.
- There are concerns about the applicability of existing research due to ubiquitous mixed genetic ancestry worldwide.

3. Measurement of haemoglobin concentrations

Question 3

How should haemoglobin concentration be measured?

- 3.a** What are the acceptable alternative methods for assessing haemoglobin concentration compared to the reference standard (i.e. automated haematology analysers), particularly for population-based or field-based surveys?
- 3.b** What are the key quality control issues pertinent to accurate diagnosis of anaemia?
- 3.c** What blood source(s) are acceptable? How do results vary in capillary blood (finger, heel, ear, single drop, pooled drops) or arterial blood as compared to venous blood (reference)?

Normative statement 3 Haemoglobin measurement

Use of venous blood, automated haematology analysers and high-quality control measures are recommended to measure haemoglobin concentration in individuals and populations.

Remarks

- There is clear variation in haemoglobin concentrations assessed from capillary and venous blood samples; however, the magnitude of variation has not been confirmed. It is therefore not possible to provide adjustments to haemoglobin concentrations measured in capillary blood to make them comparable with venous blood.
- When well maintained in accordance with quality management principles, all accredited instruments should provide acceptably similar results.
- Stakeholders should take into consideration the blood source and type of analyser used during data collection and when tracking changes in haemoglobin concentrations and the prevalence of anaemia over time or comparing between different settings, particularly where the use of venous blood and/or automated analysers are not always feasible.
- Pooling drops of blood from a single capillary prick could be an option for minimizing variability due to blood sampling technique. Also, the effect of sample handling on different analytical methods, for example, length of time between collection and processing, needs to be taken into consideration.
- Where application of the recommendation on using an automated haematology analyser is not possible, consideration could be given to the measurement of haemoglobin using an approved point-of-care blood testing device which has been verified to be calibrated against international reference standards.
- The use of international standards, commutable standards, and calibration materials to achieve appropriate quality control is desirable.
- Quality control points at pre-analytical, analytical and postanalytical levels should be carefully established. Some of them include patient characteristics/disposition/preparation, personnel training, use of international calibration standards, method and frequency of equipment calibration (or validation of the calibration), blood collection, monitoring data collection, recording and analysing results, reproducibility of results, laboratory quality control assessments, and possibly haemoglobin adjustments for elevation and smoking, when warranted.
- The blood source, analytical device, and sample collection protocols should be included in any report of anaemia prevalence.

4. Haemoglobin concentrations to assess impact of interventions

Question 4

Is haemoglobin concentration an adequate marker for assessing the impact of iron interventions?

Normative statement 4 Assessing impact of interventions

Haemoglobin concentrations should be used as one of the markers to assess the impact of iron interventions (e.g. iron supplementation and staple food fortification with iron and other vitamins and minerals) for preventing and treating iron deficiency anaemia throughout the life cycle.

Remarks

- When deciding on the specific interventions to implement for iron deficiency anaemia (supplementation, fortification, nutrition education and combinations of them), policy-makers, programme implementers and clinicians should take into consideration micronutrient status and regional and local variations in the diet, different cultural practices, different methods of food processing and meal preparation, and economic constraints.
- Attention should be paid to the possible adverse effects of excessive iron intakes, especially when considering or implementing iron interventions in malaria-endemic regions or settings where haemoglobinopathies are common.
- Understanding the causes of anaemia will help inform the proper interventions to treat, prevent and/or reduce anaemia. Policy-makers seeking to reduce the prevalence of anaemia should understand and address the local context and intervene through a broad range of pertinent interventions (e.g. iron interventions, malaria prevention) that address this complexity. This comprehensive response will aid in achieving the desired outcomes, avoiding adverse effects and ensuring a tolerable upper level of iron intake is not exceeded from all sources of intake.
- In addition to haemoglobin concentrations, data on programme implementation and the use of biomarkers of iron status (e.g. ferritin, serum transferrin receptor), along with markers of inflammation, are also important for the robust assessment of the response to iron interventions.
- The use of haemoglobin concentration to assess the impact of iron interventions is potentially simple, although implementation may be challenging due to limited access and resources for programmes. In addition, assessing anaemia alone will miss changes in earlier stages of iron deficiency and only capture the more severe stage of iron deficiency anaemia. Considering measuring other biomarkers to address the causes of anaemia is advisable.

5. Cutoffs to define the public health significance of anaemia

Question 5

What should be the population cutoffs to define the public health significance of anaemia?

- 5.a** What anaemia prevalence is indicative of a mild, moderate, or severe (or low, medium, high) problem of public health concern?
- 5.b** Should this classification of anaemia be based on total anaemia alone or should the proportion of mild, moderate, and/or severe anaemia be considered (weighted?) to determine that categorization?

Normative statement 5 Public health significance of anaemia

The current classification of public health significance of anaemia prevalence in populations should be maintained (Table 6). There is a lack of evidence showing a clear association between the severity of the public health burden of anaemia with clinical and/or demographic outcomes. The current expert-based classification has been in use since 2000 and this should be maintained until new evidence becomes available.

Table 6. Classification of public health significance of anaemia in populations based on prevalence estimated from blood levels of haemoglobin

Category of public health significance	Prevalence of anaemia (%)
Severe	40 or higher
Moderate	20.0–39.9
Mild	5.0–19.9
Normal	4.9 or lower

Source: Nutritional anaemias: tools for effective prevention and control. Geneva: World Health Organization; 2017 (2).

Remarks

- The current classification of the public health significance of anaemia is based on expert opinion alone. There was not enough evidence to change the methodology or the current classification.
- The classification of the public health significance of anaemia is based on the total prevalence of anaemia, a sum of the prevalence of mild, moderate, and severe anaemia in a country, and includes all age groups available for analysis.
- A clear association between the public health significance of anaemia with clinical and/or demographic outcomes has been used for planning, initiating, implementing, and evaluating country or regional plans to address anaemia.
- The association between the public health significance of anaemia and clinical outcomes seems clear for moderate and severe anaemia. Associations with social, economic and health indicators are less clear for mild anaemia.
- Countries should consider whether anaemia programmes should be launched based on their national or subnational prevalence of anaemia in a particular age group (e.g. in children, women of reproductive age), physiological status (pregnant women), or severity of anaemia (considering moderate and/or severe anaemia only).
- Countries should have a good understanding of the leading context-specific causes of anaemia (e.g. malaria, other infections, inflammation, iron deficiency) to inform strategies to address the root causes.
- The public health significance of anaemia alone should not be linked to specific interventions. Additional country information (e.g., health, nutrition, economic, social, and political data) should be taken into consideration.
- Countries with limited resources may consider prioritizing strategies to address the causes of moderate and severe anaemia, which have more severe outcomes and lead to higher rates of years lived with disability, while monitoring prevalence to ensure that mild cases are not transitioning to moderate anaemia.

References

1. Anaemia in women and children. In: Global Health Observatory [online database]. Geneva: World Health Organization; 2019 (<https://www.who.int/data/gho/data/indicators>, accessed 19 January 2024).
2. Nutritional anaemias: tools for effective prevention and control. Geneva: World Health Organization; 2017 (<https://iris.who.int/handle/10665/259425>, accessed 19 January 2024).
3. Global anaemia reduction efforts among women of reproductive age: impact, achievement of targets and the way forward for optimizing efforts. Geneva: World Health Organization; 2020 (<https://iris.who.int/handle/10665/336559>, accessed 19 January 2024).
4. Global nutrition targets 2025: policy brief series. Geneva: World Health Organization; 2014 (<https://www.who.int/publications/i/item/WHO-NMH-NHD-14.2>, accessed 19 January 2024).
5. The 17 goals. New York: Department of Economic and Social Affairs, United Nations; 2021 (<https://sustainabledevelopment.un.org/sdgs>, accessed 19 January 2024).
6. Resolution 70/1. Transforming our world: the 2030 Agenda for Sustainable Development. In: Seventieth United Nations General Assembly, New York, 21 October 2015. New York: United Nations General Assembly; 2015 (A/RES/70/1; https://www.un.org/en/development/desa/population/migration/generalassembly/docs/globalcompact/A_RES_70_1_E.pdf, accessed 19 January 2024).
7. Comprehensive implementation plan on maternal, infant and young child nutrition. Geneva: World Health Organization; 2014 (<https://apps.who.int/iris/handle/10665/113048>, accessed 19 January 2024).
8. Global strategy for women's, children's and adolescents' health data portal [online database]. Geneva: World Health Organization; 2015 (<https://www.who.int/data/maternal-newborn-child-adolescent-ageing/global-strategy-data>, accessed 19 January 2024).
9. WHO handbook for guideline development, 2nd edition. Geneva: World Health Organization; 2014 (<https://apps.who.int/iris/handle/10665/145714>, accessed 19 January 2024).
10. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva: World Health Organization; 2011 (<https://iris.who.int/handle/10665/85839>, accessed 19 January 2024).
11. DeMaeyer EM, Dallman P, Gurney JM, Hallberg L, Sood SK, Srikanthia SG. Preventing and controlling iron deficiency anaemia through primary health care. A guide for health administrators and programme managers. Geneva: World Health Organization; 1989 (<https://iris.who.int/handle/10665/39849>, accessed 19 January 2024).
12. The management of nutrition in major emergencies. Geneva: World Health Organization; 2000 (<https://iris.who.int/handle/10665/42085>, accessed 19 January 2024).
13. United Nations Children's Fund, United Nations University, World Health Organization. Iron deficiency anaemia: assessment, prevention and control. A guide for programme managers. Geneva: World Health Organization; 2001 (WHO/NHD/01.3; <https://www.who.int/publications/m/item/iron-children-6to23--archived-iron-deficiency-anaemia-assessment-prevention-and-control>, accessed 19 January 2024).
14. Braat S, Fielding K, Han J, Jackson VE, Zaloumis S, Xu JXH et al. Haemoglobin thresholds to define anaemia from age 6 months to 65 years: estimates from international data sources. *Lancet Haematol.* 2024;S2352-3026(24)00030-9. doi:10.1016/S2352-3026(24)00030-9.

Background

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 cutoff. Accurate case definition of anaemia is crucial for clinical patient care, understanding the epidemiology, and for planning and monitoring of public health interventions. Anaemia has implications at individual and public health levels.

In the clinic, diagnosis of anaemia and assessment of its underlying causes are routine across almost every field of primary care and hospital practice. Anaemia might present symptomatically (e.g. with fatigue, dizziness, exertional breathlessness, palpitations, exacerbations of cardiac failure, and angina) or be detected incidentally during routine screening or as part of an evaluation of almost any medical condition. Anaemia can have long-term consequences: in pregnancy, anaemia is associated with increased risk of caesarean section and maternal mortality, and may contribute to adverse newborn outcomes, including reduced birthweight and gestational duration. Anaemia in children has been linked to impairments in short-term and longer-term cognitive development, which can be irreversible.

Anaemia is a global public health concern, especially afflicting adolescent girls, women 15–49 years of age, pregnant women, and children in low- and middle-income countries. WHO estimates that in 2019 30% (571 million) of women aged 15–49 years, 37% (32 million) of pregnant women, and 40% (269 million) of children 6–59 months of age were affected by anaemia, with the WHO African Region and South-East Asia Region being most affected (1).

The main determinants of anaemia include nutritional deficiencies, genetic haemoglobin disorders, infections (e.g. malaria, schistosomiasis, hookworm), and various conditions (e.g. gynaecological conditions in women, gastrointestinal disease, frequent blood donation and chronic diseases) that lead to blood loss or the destruction of red blood cells. Some reports indicate that iron deficiency anaemia accounts for about 60% of the total global cases of anaemia and is the most significant cause of anaemia-related disability. Infection is also a common cause of anaemia, accounting for about 10–15% of total anaemia cases, with variations by setting and disease burden. An estimated 5% of the global population carry a gene variant of haemoglobin causing a severe disorder, including sickle cell disease or a form of thalassemia, with the percentage being higher in populations in Africa (18%) and Asia (7%). α -thalassaemia carriage might partly explain low haemoglobin concentrations identified in otherwise healthy and well-nourished populations of African Americans. Glucose-6-phosphate dehydrogenase deficiency is another inherited genetic disorder that causes red blood cells to break down prematurely, which can lead to anaemia. This deficiency is one of the most common inherited enzyme abnormalities in humans, and its distribution tends to overlap with areas where malaria is endemic. The proportion of anaemia due to genetic disorders in low- and middle-income countries is likely to rise as other causes (e.g. nutritional deficiencies, infectious diseases) become progressively better controlled (2, 3).

Socioeconomic status, education, and gender inequality are tightly linked to anaemia and affect its prevalence through several pathways. Poverty and low educational attainment are associated with unhealthy living and working conditions—including poor water quality, sanitation, hygiene, and infrastructure—leading to increased disease. Further, the three main contributors to anaemia (nutrition, genetic haemoglobin disorders, and infections) are all fundamentally linked to poverty. In some settings, gender inequality and cultural practices related to marriage and pregnancy increase the risk for developing anaemia. Women and adolescent girls have an especially increased risk of anaemia when their access to health care, education, and household resources is limited (2, 4).

Multiple interventions are aimed at alleviating the burden of anaemia in many low-, middle-, and high-income countries worldwide, and decisions around the choice of intervention and their implementation and monitoring is founded on measuring the prevalence of anaemia and its distribution in different segments of the population, notably the most vulnerable groups such as menstruating women and adolescent girls, pregnant and postpartum women, and young children (4). A reduced prevalence of anaemia may also indicate success of infection control programmes, such as malaria prevention (5) or long-term effects of deworming, in areas where these conditions are endemic.

Emerging, unexpected situations that affect health, food safety or trade can have a profound impact on micronutrient status and anaemia, especially for vulnerable populations including children, women, and older people. The COVID-19 pandemic worsened the already high prevalence of micronutrient deficiencies worldwide. For children, the pandemic also resulted in higher food insecurity and disruption to access to health care and nutrition-related programmes from schools; this situation has been more pronounced in low- and middle-income countries (6).

Scope and purpose

WHO is committed to driving public health impact in every country, ensuring healthy lives and promoting well-being for all at all ages. Through its unique normative function in health, WHO aims to provide global, evidence-informed recommendations on the measurement of haemoglobin and cutoffs to define anaemia in individuals and populations. This *Guideline on haemoglobin cutoffs to define anaemia in individuals and populations* will support the work of WHO regional and country offices and will help Member States and their partners to make evidence-informed decisions to improve access to quality essential health services, support countries' preparedness for health emergencies and address the determinants of health. This guideline will also help in increasing the capacity of countries to tackle anaemia and to prioritize essential actions in national health policies, strategies, and plans.¹

This guideline aims to help Member States and their partners in their efforts to make informed decisions on the appropriate tools to support assessing and reducing the global burden of anaemia as an important public health priority. The WHO [Global nutrition targets 2025](#) include a 50% reduction in the prevalence of anaemia in women of reproductive age (7). The 2030 [Sustainable Development Goals \(SDGs\)](#) (8), in particular, Goal 2: End hunger, achieve food security and improved nutrition and promote sustainable agriculture and Goal 3: Ensure healthy lives and promote well-being for all at all ages, encompass alleviation of anaemia (9). This guideline will also support Member States in their efforts to achieve the global targets of the [Comprehensive implementation plan on maternal, infant and young child nutrition](#) (10) and the [Global strategy for women's, children's and adolescents' health \(2016–2030\)](#) (11).

Appropriate guidelines for measuring haemoglobin and defining anaemia are crucial for both clinical and public health medicine but require consideration of a range of complexities across different populations. Decisions to implement and monitor programmes that integrate nutrition-specific and nutrition-sensitive interventions are often informed by the prevalence and distribution of anaemia across groups within a population, complemented by considerations of the accessibility, availability, acceptability, and quality of the interventions.

The normative statements in this guideline are intended for a wide audience, including policy-makers, their expert advisers, and technical and programme staff at ministries and organizations involved in the design, implementation, and scaling-up of actions for addressing anaemia. Other end-users of the guideline include nongovernmental and other organizations and professional societies involved in the planning and management of anaemia actions, as well as health professionals including clinicians, managers of nutrition and health programmes, national blood services, and public health policy-makers in all settings.

This guideline is intended to contribute to discussions among stakeholders when selecting or prioritizing interventions to be undertaken in their specific context. The document presents the key normative statements and a summary of the supporting evidence. Further details of the evidence base are provided in **Annex 1**, the sections on summary of evidence for each question, and other documents listed in the references.

¹ This publication is a WHO guideline. A WHO guideline is any document, whatever its title, containing WHO recommendations about health interventions, whether they be clinical, public health or policy interventions. A recommendation provides information about what policymakers, health-care providers or patients should do. It implies a choice between different interventions that have an impact on health and that have ramifications for the use of resources. All publications containing WHO recommendations are approved by the WHO Guidelines Review Committee.

Objectives

The objective of this guideline is to provide updated, locally adaptable, clear, evidence-informed normative statements on the use of haemoglobin concentrations to assess anaemia and on best approaches in its measurement in individuals and populations. The purpose of the guideline is to improve the diagnosis of anaemia, grounded in gender, equity and human rights approaches, with the aim of leaving no one behind, thereby informing the development of nutrition and health policies.

This guideline is aligned with WHO's Thirteenth General Programme of Work 2019–2023,¹ endorsed by the World Health Assembly in May 2018, specifically enabling countries to provide high-quality, people-centred health services based on primary health care strategies and comprehensive essential service packages through collaboration and coordination among diverse sectors.

History of this guideline

WHO first proposed haemoglobin cutoffs to define anaemia in 1959. The current cutoffs for men, women, young children, and pregnant women recommended by WHO were first proposed in 1968 after technical meetings of clinical and public health experts working with data from five studies of populations in Europe and North America with predominantly European ancestry. Data from other countries, a wider range of races, and for certain age groups (i.e. infants, young children, adolescents, and elderly people) were not available at the time (**Table 1**). These studies were done in an era when laboratory and epidemiological methods were less developed than today.

Table 1. Previous haemoglobin levels (g/L) to diagnose anaemia at sea level

Population	No anaemia	Mild	Anaemia	
			Moderate	Severe
Children, 6–59 months	≥110	100–109	70–99	<70
Children, 5–11 years	≥115	110–114	80–109	<80
Children, 12–14 years	≥120	110–119	80–109	<80
Nonpregnant women, 15 years and above	≥120	110–119	80–109	<80
Pregnant women	≥110	100–109	70–99	<70
Men, 15 years of age and above	≥130	110–129	80–109	<80

Source: Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva: World Health Organization; 2011 (12).

¹ Thirteenth General Programme of Work 2019–2023. Geneva: World Health Organization; 2019 (<https://www.who.int/about/what-we-do/thirteenth-general-programme-of-work-2019-2023>, accessed 14 January 2023).

Existing WHO documents related to this new guideline

This guideline updates and complements previous information contained in five WHO documents, published between 1968 and 2005, which are summarized in the 2011 WHO document *Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity* (12). Briefly, haemoglobin cutoffs were first presented in a 1968 WHO document (13) and were based on four published references and one set of unpublished observations. Definitions for mild, moderate, and severe anaemia were first published in 1989 (14). These were slightly modified in a subsequent publication on nutrition in emergencies, which also proposed a classification to determine the public health significance of anaemia in populations (15). Finally, a 2001 guide for programme managers split the age group for children 5–14 years of age and applied a new, lower haemoglobin cutoff for children 5–11 years based on NHANES II data (16). The 2001 document also provided haemoglobin adjustments for those residing or working at elevation and for smoking (16).

This guideline partially updates and consolidates information from the previous WHO documents. There is still additional valuable information within those documents that has not yet been updated because it was out-of-scope for the current guideline.

- *Nutritional anaemias* is a report of an international group of experts convened by WHO in Geneva, Switzerland from 13–17 March 1967 (13). The consultation was called 3 years after the start of a worldwide multicountry collaborative study in India, Israel, Mexico, Poland, South Africa, the United Kingdom of Great Britain and Northern Ireland, the United States of America, and Venezuela (Bolivarian Republic of). The study investigated iron metabolism in pregnancy as well as the role of hookworm in anaemia during pregnancy, and further tested the procedures for examining whole blood and serum.
- *Preventing and controlling anaemia through primary health care* (14) was published after a May 1987 meeting of the International Nutritional Anaemia Consultative Group in Quito, Ecuador. This publication aimed to help health administrators and programme managers to develop and implement suitable strategies for preventing and controlling iron deficiency anaemia.
- *The management of nutrition in major emergencies* (15) was published by WHO in response to the World Declaration and Plan for Action in Nutrition that urged governments to provide sustainable assistance to refugees, displaced and war-affected populations where high rates of malnutrition and micronutrient deficiencies occur.
- *Iron deficiency anaemia: assessment, prevention and control, a guide for programme managers* (16), a document published in 2001, is mainly based on a consultation organized by WHO, the United Nations Children's Fund (UNICEF), and the United Nations University held in Geneva, Switzerland, 6–10 December 1993. The purpose of this consultation was to provide scientists and national authorities with a timely and authoritative review of iron deficiency anaemia, and to help managers of national micronutrient malnutrition prevention and control programmes to identify effective measures for fighting iron deficiency anaemia.
- *Assessing the iron status of populations* (17) is a report of a joint technical consultation by WHO and the United States Centers for Disease Control and Prevention (CDC) held in Geneva, Switzerland, 6–8 April 2004, with the participation of 34 experts. The objectives were: to review the indicators currently available to assess iron status; to select the best indicators for assessing the iron status of populations and for evaluating the impact of interventions to control iron deficiency in populations; and to identify priorities for research related to assessing the iron status of populations.

Technical meetings convened for developing this guideline

WHO started this project for updating haemoglobin cutoffs to define anaemia in individuals and populations by convening a prioritization exercise via a two-stage international consultation in 2015. Six subtopics were established, including the physiology of anaemia, haemoglobin thresholds for different population groups, definition of anaemia across clinical and environmental contexts, approach to development of anaemia cutoffs, laboratory, equipment, regulatory and diagnostic considerations, and guidance for implementation. After input from the WHO Steering Committee, to advise and support this normative work, and based on the identified subtopics and the normative needs identified at various technical meetings organized by WHO, the available evidence was presented to the GDG. Three GDG meetings were held.

- First meeting: 6–8 November 2019.
- Second meetings: 1–3 June 2022, 15–17 June 2022, and 29 June–1 July 2022.
- Third meeting: 8 June 2023.

The first GDG meeting developed and prioritised five key questions and identified topics for further discussions, technical meetings, or research. The questions are detailed in **Annex 2** and mainly relate to the review of cutoffs and haemoglobin adjustment factors to diagnose anaemia. The manner of the questions made them difficult to formulate in the PICO format. Preparation of the evidence-to-decision frameworks was therefore more complex than developing standard WHO recommendations, since the questions did not always fit the PICO format or cover all domains of evidence-to-decision frameworks.

Certain technical questions needed consideration before haemoglobin cutoffs could be addressed. The questions related to the review of adjustments in haemoglobin concentrations to account for differences in settings and populations such as elevation above sea level of the place of residence, smoking, genetic background, and infection and inflammation. They also encompassed the type of blood sample and the method of haemoglobin concentration determination. These topics were addressed in three technical meetings of experts from those fields.

The objectives of the second GDG meetings were to: discuss the results and conclusions from the three technical meetings; formulate normative statements on the use and interpretation of haemoglobin concentrations for assessing anaemia status in individuals and populations and determining their strength taking into account benefits, harms, values and preferences, feasibility, equity, ethics, acceptability, resource requirements, and other factors, as appropriate; define implications for further research and gaps; and discuss implementation and evaluation considerations of the guideline.

The third GDG meeting discussed the rationale of a WHO proposal to separate haemoglobin cutoffs for children aged 6–59 months into two groups (6–23 months and 24–59 months). This proposal differed from the output in the previous meeting in July 2022, where the GDG voted for a single cutoff for the age range from 6 to 59 months. The rationale for this proposal was: (i) to maintain consistency in the criteria used for defining the other age groups; (ii) the consistent differences in haemoglobin concentrations (5–9 g/L) of children 6–23 months versus 24–59 months reported in additional publications reviewed during the series of second GDG meetings ([18–20](#)); (iii) notable differences in growth and nutrient requirements between the two age groups; and (iv) additional analysis obtained after the GDG meeting in July 2022, which supported the separation of the age groups. The same health inclusion criteria were applied to the data in both the original and additional analyses.

Summary of the evidence

Although anaemia remains one of the most common laboratory diagnoses, consensus on the haemoglobin cutoffs below which it should be defined and the cutoffs to establish its severity is limited. Defining cutoffs for anaemia requires estimation in a reference population of healthy individuals. This entails a detailed consideration of factors which influence haemoglobin concentration in apparently healthy individuals of diverse genetic backgrounds as they pass through the life course and live in different environments. An apparently healthy individual may be defined as an individual with physical well-being for their age and physiological status, without detectable diseases or infirmities.

Physiological, environmental, and genetic factors might need to be considered when defining haemoglobin cutoffs. Variations in haemoglobin across the lifecycle (particularly in early life, during pregnancy, and with age) are not always considered in laboratory practice. In response to hypoxia, such as from elevation above sea level or smoking, haemoglobin concentrations increase. Additionally, about 5% of the world's population carries a clinically relevant haemoglobinopathy or thalassaemia mutation.

In modern clinical laboratories, haemoglobin is conventionally measured photometrically using variations of the cyanmethaemoglobin method across several automated platforms. International reference standards ensure validation and calibration of these approaches. Non-invasive techniques for measurement of haemoglobin concentration are emerging. Ensuring appropriate standardization of haemoglobin measurements across this range of methods is essential to ensure high-quality detection of anaemia in all settings.

The outcome considered by the GDG to be critical for decision-making was the accurate diagnosis of anaemia, considering:

1. the use of anaemia cutoffs at individual level established using a statistical approach or based on outcomes-related clinical symptom/functional impairment;
2. the use of adjustments to account for elevation of residence, smoking, infections (especially malaria), inflammation, and/or genetic ancestry/ethnicity/race;
3. the comparability of haemoglobin determinations by type of blood sample, methods of analysis, measurement instruments, and international standard materials used at the clinical and public health levels;
4. the changes in haemoglobin concentrations in response to interventions that address the direct causes of anaemia; and
5. the anaemia prevalence at population level indicative of a public health problem of mild, moderate, or severe magnitude.

The evidence that informed haemoglobin cutoffs to define anaemia in individuals and populations was based on an analysis of haemoglobin data from healthy populations, general population databases, and systematic reviews. The section **Scoping the guideline, evidence appraisal and decision-making** details the methodology used. The key questions and outcomes guiding the evidence review and synthesis are listed in **Annex 2**.

In addition to the direct and indirect evidence and its overall certainty, other considerations were discussed by the GDG. Guideline users may wish to refer to the remarks within the evidence summaries, including the considerations on implementation.

Question 1

What should be the haemoglobin cutoffs to define anaemia in individuals and in populations?

1.a How should the cutoffs be defined?

Should they be based on statistical cutoffs, such as percentile-based cutoffs or a reference range of haemoglobin concentrations in apparently healthy populations, or based on outcomes related to clinical symptoms or functional impairment?

1.b How should mild, moderate, and severe anaemia be defined at the individual level?

Braat et al. (18) from the Walter and Eliza Hall Institute of Medical Research, Australia, a WHO collaborating centre, proposed haemoglobin cutoffs to define anaemia through the lifecycle. These cutoffs were based on analysis of data from national surveys and population and cohort studies, including: the Australian Health Survey; the Benefits and Risks of Iron intervention in Children randomized controlled trial, Bangladesh; the China Health and Nutrition Survey; the Generation R cohort study, Netherlands (Kingdom of the); the Health Survey for England; NHANES II, United States of America; the National Health and Nutrition Survey, Ecuador; and the Applied Research Group for Kids, Canada.

The large-scale datasets in ethnically diverse populations included sufficient clinical and laboratory information on individuals to allow selection of a healthy reference sample. The reference population of healthy individuals was defined as people:

- **without** reported underlying medical conditions; recent clinical illness; biochemical evidence of iron deficiency or inflammation, other nutrient deficiencies, or renal/hepatic impairment (where available); and
- **with** normal body mass index and taking no medications other than non-iron nutritional supplements.

Although the data on health indicators varied among the surveys, this was a rigorous and conservative approach with a high number of exclusions resulting in an apparently healthy reference population. The underlying populations were generally multi-ethnic.

For estimating the anaemia cutoffs and the confidence interval around this estimate, either a parametric (normal distribution) or non-parametric (distribution-free) approach can be taken. Since the reference distribution appeared reasonably normal for all studies with a simple random sample design, the parametric method was employed as the preferred method. Data were pooled using both a fixed and random effects model. The fixed effect model was preferred as authors propose that cutoffs across these studies represent an estimate of the same underlying value (18).

Braat et al. (18) also presents a proposal for haemoglobin cutoffs to define anaemia in pregnant women in the first and second trimesters. Data were insufficient to inform setting cutoffs for pregnant women in the third trimester, due to limitations in sample sizes from NHANES II.

For all but one of the surveys included in Braat et al., venous blood samples were used to assess haemoglobin concentrations using an automated analyser. The one exception is the Benefits and Risks of Iron intervention in Children project, which used venous samples analysed on a HemoCue 301+ point-of-care device (HemoCue AB, Ängelholm, Sweden).

Although the criteria for a healthy population in the Braat et al. analysis was the basis for the GDG discussions, other evidence was also presented. This additional evidence included studies from which selection of participants was based on different inclusion criteria, which are described below.

Sachdev et al. (19) examined data from the large-scale, nationally representative Comprehensive National Nutrition Survey of children and adolescents aged 0–19 years in India, to assess the age-specific and sex-specific percentiles of haemoglobin and cutoffs to define anaemia in a healthy population. To obtain a healthy population, participants with iron, folate, vitamin B₁₂, and retinol deficiencies; inflammation; variant haemoglobins (haemoglobin A2 and haemoglobin S); and a history of smoking were excluded. Age-specific and sex-specific haemoglobin 5th percentiles derived for this healthy population were compared with current WHO cutoffs. The Comprehensive National Nutrition Survey collected venous blood samples from

49 486 individuals; 41 210 participants had a haemoglobin value, 8087 of whom were included. Compared with existing WHO cutoffs, the study cutoffs for haemoglobin were lower at all ages, usually by 10–20 g/L, but more so in children of both sexes aged 1–2 years and in girls aged 10 years or older.

Addo et al. (20), evaluated and analysed data collected from 30 household, population-based nutrition surveys of children aged 6 to 59 months and nonpregnant women aged 15 to 49 years during 2005 to 2016 across 25 countries. To define a healthy population, persons with iron deficiency (ferritin <12 µg/L for children or <15 µg/L for women), vitamin A deficiency (retinol-binding protein or retinol <20.1 µg/dL), inflammation (c-reactive protein >5 mg/L or α-1-acid glycoprotein >1 g/L), or known malaria were excluded. Survey-specific, pooled haemoglobin 5th percentile cutoffs were estimated. A total of 79 950 individuals were included in the original surveys. The final healthy sample was 13 445 children (39.9% of the original sample of 33 699 children: 6750 [50.2%] boys, mean [standard deviation, SD] age 32.9 [16.0] months) and 25 880 women (56.0% of the original sample of 46 251 women, mean [SD] age 31.0 [9.5] years). Survey-specific haemoglobin 5th percentiles among children ranged from 79.0 g/L (95% CI = 75.4–82.6 g/L in Pakistan) to 112.3 g/L (95% CI = 111.4–113.3 g/L in the United States of America), and among women from 88.3 g/L (95% CI = 77.7–98.8 g/L in Gujarat, India) to 120.9 g/L (95% CI = 120.0–121.7 g/L in the United States of America). Inter-survey variance around the haemoglobin 5th percentile was low (3.5% for women and 3.6% for children). Pooled 5th percentile estimates were 96.5 g/L (95% CI = 92.6–100.4 g/L) for children and 108.1 g/dL (95% CI = 103.5–112.7 g/L) for women. The authors concluded that current WHO cutoffs to define anaemia are higher than the pooled 5th percentile of haemoglobin among the biochemically healthy individuals in this study.

In addition to data from Braat et al., data from the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) study and from INTERBIO-21st, an extension aimed at improving the characterization of the fetal growth restriction, were analysed to propose haemoglobin cutoffs for pregnancy by trimester (21, 22). The INTERGROWTH-21st project was carried out between 2009 and 2016 across eight diverse, geographically delimited, urban areas. At each visit, information was collected about the pregnancy, as well as the results of blood tests taken as part of routine antenatal care. All study sites assessed haemoglobin concentration from venous blood samples using commercially available methods (23). Measurement of ferritin and other iron biomarkers were not available. The gestational age-specific percentiles for maternal haemoglobin proposed were based on prospective study throughout pregnancy of 3502 healthy, well-nourished women from eight countries, whose healthy babies were followed up to 2 years of age. The highest median maternal haemoglobin concentration was at 14 weeks of gestation (121.4 g/L) and the lowest was between 31 and 32 weeks of gestation (114.6 g/L), but values rose progressively thereafter to a median concentration of 118.7 g/L at 40 weeks of gestation.

The INTERBIO-21st study comprised two components: fetal study and neonatal study. The fetal component monitored fetal growth from early pregnancy (14 weeks) up to delivery, whereas the neonatal component monitored these infants up to 2 years. Among the variables collected were detailed biological parameters (e.g. haemoglobin) of the mothers and documentation of maternal and fetal outcomes (24). The authors concluded that, when compared to a reference value of 110 g/L, women with haemoglobin levels below 95 g/L had an increased risk of adverse neonatal outcomes, which doubled with haemoglobin values below 80 g/L. A U-shaped relationship between maternal haemoglobin and adverse neonatal outcomes was also demonstrated, with an increased risk of adverse neonatal outcomes among women with haemoglobin concentrations of 140 g/L or more (22).

The limitations of the INTERGROWTH project are the lack of haemoglobin data collected at <14 weeks of gestation and the lack of data on ferritin, which gives rise to the possibility that women with iron deficiency may have been included in the sample. Also, most of the included women received iron and folic acid supplementation as standard care.

As noted by the WHO guidance published in 1989, although anaemia is often graded as mild, moderate, and severe, the haemoglobin values for these three categories vary and are arbitrary (14). The 1989 guidance considered anaemia to be mild, moderate, or severe when haemoglobin concentrations were above 80%, between 80% and 60%, or less than 60% of the cutoffs, respectively. According to the 1989 guidance, given the relatively small differences between age and sex groups, mild anaemia was diagnosed when the haemoglobin concentration was above 100 g/L but below the cutoff, moderate anaemia when the concentration was

70–100 g/L, and severe anaemia when it was below 70 g/L. Similar severity limits were presented in the WHO document from the year 2000 on the management of nutrition in major emergencies (15).

Use of statistical and/or clinical outcomes

Establishing haemoglobin cutoffs for defining anaemia based on outcomes related to clinical symptoms or functional impairment was preferred but not possible for all age groups and trimesters of pregnancy. The evidence of an association between haemoglobin concentration and maternal and newborn health outcomes has been repeatedly reported, but the most relevant outcomes and precise cutoffs are still in development (22, 25–28); therefore, the statistical approach was used. The outputs of the statistical approach were haemoglobin values below which only a limited number of healthy individuals would be expected to have anaemia. This approach informed the evaluation and update of current cutoffs.

A key consideration was whether to select the 5th or 2.5th percentile for the haemoglobin concentration cutoffs. The choice of percentile entails trade-offs. For this recommendation, the 5th percentile was selected, which is consistent with original WHO guidance for defining anaemia. The 5th percentile implies that 95% of healthy individuals would have a higher haemoglobin value, and 5% of healthy individuals would still have a lower haemoglobin value than the cutoff and be falsely diagnosed as anaemic. Selecting the higher of the two percentiles is expected to provide more sensitivity to detect individuals with underlying conditions associated with anaemia (e.g. nutritional deficiency, genetic conditions, inflammation, infection), thereby promoting intervention.

Normative statement 1.a Haemoglobin cutoffs to define any anaemia

Analysis of the evidence suggested modification of the current haemoglobin cutoffs for defining anaemia for one population group (children 6–23 months of age) and use of the existing cutoff for pregnant women in the second trimester.

The updated cutoffs to define anaemia in individuals and populations are presented in **Table 2**.

Table 2. Haemoglobin cutoffs to define anaemia in individuals and populations^a

Population	Haemoglobin concentration (g/L)
Children, 6–23 months	<105
Children, 24–59 months	<110
Children, 5–11 years	<115
Children, 12–14 years, nonpregnant girls	<120
Children, 12–14 years, boys	<120
Adults, 15–65 years, nonpregnant women	<120
Adults, 15–65 years, men	<130
Pregnancy	
First trimester	<110
Second trimester	<105
Third trimester	<110

^a Based on the 5th percentile.

Normative statement 1.b Anaemia severity

Changes to current methodology for establishing cutoffs to indicate the severity of anaemia based on haemoglobin concentrations in individuals are not recommended, due to insufficient evidence.

WHO guidance published in 1989 (14) was applied to the updated haemoglobin cutoffs presented in **Table 2** to indicate anaemia severity (**Table 3**). The 1989 guidance considered anaemia to be mild, moderate, or severe when haemoglobin concentrations are above 80%, between 80% and 60%, or less than 60% of the cutoff levels, respectively (**Table 3**) (3). However, after reviewing and recalculating the previous WHO cutoffs for anaemia severity, it was found that the percentages were in general broader – between 85 and 92% of the cutoff value for mild anaemia and between 62 and 70% for severe anaemia.

Therefore, considering: (i) the ample ranges used in previous calculations; (ii) the implications for treatment initiation based on anaemia severity; and (iii) the GDG comments about implications for implementation, the cutoffs for severe anaemia in children aged 6–23 months and for women in the second trimester pregnancy was retained at <70 g/L.

For severe anaemia, 70 g/L is 67% of the cutoff (105 g/L) for defining any anaemia in children 6–23 months, which compares well with the percentage used in other age groups (e.g. 80 g/L for the group of girls 12–17 years old is 67% of the cutoff of 120 g/L). Likewise, the use of 70 g/L in pregnant women in the second trimester represents 67% of the cutoff (105 g/L), which compares well with the use of 70 g/L for pregnant women in the first and third trimesters, which is 64% of the cutoff of 110 g/L. For mild anaemia, 95 g/L is 90% of the cutoff of 105 g/L.

Table 3. Haemoglobin cutoffs to define anaemia severity in individuals

Population	Haemoglobin concentration (g/L)			
	No anaemia	Mild anaemia	Moderate anaemia	Severe anaemia
Children, 6–23 months	≥105	95–104	70–94	<70
Children, 24–59 months	≥110	100–109	70–99	<70
Children, 5–11 years	≥115	110–114	80–109	<80
Children, 12–14 years, nonpregnant girls	≥120	110–119	80–109	<80
Children, 12–14 years, boys	≥120	110–119	80–109	<80
Adults, 15–65 years, nonpregnant women	≥120	110–119	80–109	<80
Adults, 15–65 years, men	≥130	110–129	80–109	<80
Pregnancy				
First trimester	≥110	100–109	70–99	<70
Second trimester	≥105	95–104	70–94	<70
Third trimester	≥110	100–109	70–99	<70

Remarks

The remarks in this and the following sections are suggestions on considerations for implementation based on the discussion of the GDG.

- The cutoffs in **Table 2** were primarily informed by a WHO commissioned analysis aimed at analysing international databases containing data on haemoglobin and other biochemical and clinical indicators which would enable application of consistent, rigorous criteria to define a healthy individual. These analyses calculated the 5th percentiles of haemoglobin distributions derived from apparently healthy, ethnically diverse populations predominantly from higher-income settings across Australia, China, Europe, North America, and South America.

- Additional data collected in lower-income settings reported heterogeneous, but generally lower, values for 5th percentiles in participants without biochemical evidence of iron and/or vitamin A deficiencies or inflammation (c-reactive protein or α -1-acid glycoprotein). Considering the backdrop of a high burden of infections and inflammation in these settings, with no definitive evidence to exclude their residual effects on haemoglobin concentration, these data were not included in the pooled analysis.
- Data in adult men may suggest a higher haemoglobin cutoff (i.e. 135 g/L) but there was uncertainty in the evidence. The GDG decided to retain the cutoff of 130 g/L for men after considering concerns about iron therapy implications for males, the limited evidence, and the potential unintended consequences of changing the cutoff, such as initiation of iron supplementation programmes in men.
- In developing these cutoffs, a high value was placed on avoidance of harm, given the uncertainty of the evidence and the conflicting results of available proposals.
- The management for individuals with mild, moderate, or severe anaemia could vary depending on the clinical scenario and the underlying cause(s) of the anaemia.
- A clear association between severity of anaemia with clinical or statistical outcomes could be of great value for classifying anaemia severity at clinical/individual level and would help to prevent and treat anaemia.

Research gaps

- To enable the definition of functional thresholds, research is needed on the haemoglobin concentrations below which clinical symptoms, increased risk of mortality, increased risk of morbidity, developmental impairment (cognitive, psychomotor, language, physical), and/or other conditions requiring further clinical investigation (e.g. genetic condition, nutritional deficiency, chronic bleeding) are observed to occur.
- Further consideration should be given to establishing the optimal criteria to define a healthy population using the statistical approach.
- Future studies should prospectively define 5th percentiles in healthy populations across all geographical regions, including infants, and men and women aged >65 years.

Summary of judgements

The GDG considered there were large desirable effects and trivial undesirable effects related to reviewing the cutoffs, although there were no studies specifically designed to address the need for review. They based their judgement on the importance of correct diagnoses of anaemia at both the clinical and public health levels and because current cutoffs were established in the 1960s and 1980s based on limited evidence. The GDG felt that reviewing cutoffs to define anaemia and its severity could improve decisions about implementation of public health interventions and treatment of anaemia at the individual level.

A further advantage of reviewing anaemia cutoffs is a positive impact on equity. The GDG felt that harmonized, evidence-based guidelines for haemoglobin cutoffs to define anaemia would ensure all people in the world have access to the same definition. No studies were available to address costs, acceptability, and feasibility implications, but the group considered that reviewing haemoglobin concentration cutoffs to define anaemia in individuals and populations was acceptable and feasible to key stakeholders since, in general, improved anaemia cutoffs would benefit patients across the world, including a broad range of clinical, laboratory, public health and research settings.

Question 2

Should haemoglobin cutoffs be adjusted for exposure to external factors or settings known to affect haemoglobin?

- 2.a** Should haemoglobin cutoffs to define anaemia be adjusted for elevation of residence and/or smoking?
- 2.b** Should haemoglobin cutoffs to define anaemia be adjusted by inflammation/infection, particularly in malaria-endemic settings?
- 2.c** Should haemoglobin cutoffs to define anaemia be adjusted by genetic ancestry/ethnicity/race?

Question 2.a Should haemoglobin cutoffs to define anaemia be adjusted for elevation of residence and/or smoking?

Evidence-to-decision frameworks for these questions (elevation of residence and smoking) were based on data prepared by the CDC Division of Nutrition, Physical Activity, and Obesity, a technical partner of this project (29, 30). The CDC presented this work for consideration by the GDG as part of the WHO process of guideline development but were not involved in decision-making.

Question 2.a.1 Should haemoglobin cutoffs to define anaemia be adjusted for elevation of residence?

In 2019, Sharma et al. (29) proposed updated haemoglobin adjustments for elevation above sea level and smoking based on an analysis using data derived from a large dataset comprising the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia project and additional region-specific surveys.

The analyses included 13 population-based surveys and one cohort study, all conducted after 2000. All WHO regions except the WHO South-East Asia Region were represented. The dataset included 68 193 observations among preschool-aged children (6–59 months) and nonpregnant women of reproductive age (15–49 years) with data on haemoglobin and elevation (–28 m to 4000 m).

Generalized linear models were used to assess the robustness of associations under varying conditions, including controlling for inflammation-corrected iron and vitamin A deficiency, or restricting to an apparently healthy population with no evidence of iron and vitamin A deficiency. Results were consistent across model specifications. Models were also adjusted for age, sex (preschool-aged children only), and survey to account for potential unmeasured confounding and the underlying difference in mean haemoglobin associated with each location.

The study confirmed that haemoglobin should be adjusted for elevation and that current cutoffs may under-adjust haemoglobin for those residing at lower elevations and over-adjust haemoglobin for those residing at higher elevations. Haemoglobin adjustment concentrations among preschool-aged children and nonpregnant women of reproductive age differed by 1 g/L for all elevations above sea level.

A second analysis by the same group examined the relationship between haemoglobin and elevation (ranging from –6 m to 3834 m) among school-aged children (5–14 years) using nine population-based surveys ($n = 26\,518$) (30). Generalized linear models were used to assess the robustness of associations adjusting for potential confounders and varying conditions including controlling for iron and vitamin A deficiency. The haemoglobin adjustments among school-aged children were consistent with the adjustments proposed for preschool-aged children and nonpregnant women of reproductive age.

To assess the consistency of the previous findings, the group performed a third analysis of population-based data from preschool-aged children, nonpregnant women of reproductive age, and infants aged 1–5 months residing at a range of higher elevations (Dr Laura Pompano, CDC, unpublished data, December 2023).

This work included data from six population-based surveys from Guatemala (four surveys), Nepal, and Peru, together with 5 years of data from the Nutritional State Information System in Peru on infants and

preschool-aged children who attended health centres as part of the Growth and Development Programme. This analysis included a total of 170 971 infants, 3 134 207 preschool-aged children, and 41 034 nonpregnant women of reproductive age residing at elevations ranging from 0 m to 5012 m. Generalized linear models were used to assess the relationship between haemoglobin and elevation; models controlled for age, sex, and survey.

These findings were consistent with elevation adjustments previously proposed. At elevations above 2500 m, adjustments may vary more by region due to known epigenetic differences. Data at elevations above 2500 m were limited primarily to countries in Central and South America, where the nonlinear association between haemoglobin and elevation tended to become stronger at higher elevations compared with Nepal. Nearly all data from locations >4000 m elevation were from Peru.

An ad hoc, all-ages, analysis was done that combined the population-based data from the three analyses to maximize representation across all regions and age groups ($n = 3\,440\,932$). Generalized linear models were adjusted for age, sex, and survey. Data were weighted to equalize country representation. A slight age gradient in the association between haemoglobin and elevation was noted. Preschool-aged children had a 25% lower change in haemoglobin concentration by elevation than nonpregnant women of reproductive age. However, the difference in haemoglobin adjustments in the age-group-specific models compared to the all-ages model was 3 g/L or less at any elevation. A common set of haemoglobin adjustments across age groups is likely to be an appropriate and practical approach for adjusting haemoglobin for elevation, especially at elevations below 2500 m (Dr Andrea Sharma, CDC, personal communication, December 2023).

Normative statement 2.a.1 Elevation of residence

Adjustments of haemoglobin concentrations are recommended to diagnose anaemia in individuals and populations to account for the effect of elevation of place of residency on haemoglobin concentrations.

Table 4 presents a common set of adjustments for use across population groups as an appropriate and practical approach for adjusting haemoglobin concentrations to account for the effect of living at elevations above sea level, especially below 2500 m where more than 98% of the world's population resides.

Table 4. Adjustments to haemoglobin concentration (g/L) in 500 m increments in elevation^a

Elevation range (m above sea level)	Adjustments in haemoglobin concentration (g/L) ^b
1–499	0
500–999	4
1000–1499	8
1500–1999	11
2000–2499	14
2500–2999	18
3000–3499	21
3500–3999	25
4000–4499	29
4500–4999	33

^a Adjustments are the amount subtracted from an individual's observed haemoglobin level or added to the haemoglobin cutoff defining anaemia (in g/L).

^b Proposed adjustments for all population groups based on the equation: Haemoglobin adjustment (g/L) = $(0.0056384 \times \text{elevation}) + (0.0000003 \times \text{elevation}^2)$.

Remarks

- Adjustments for very high elevations >3000 m in **Table 4** are based on data primarily derived from Central and South America.
- Preschool-aged children were found to have a 25% lower change in haemoglobin concentration by elevation than nonpregnant women of reproductive age. However, the difference in haemoglobin adjustments in the age-group-specific models compared to the all-ages model was 3 g/L or less at any elevation.
- Adjustments provided are to be applied by:
 - subtracting the amount recommended from an individual's observed haemoglobin level, or
 - by adding the amount recommended to the existing haemoglobin cutoff defining anaemia in g/L.
- When specific information is known about the elevation at the place of residence, use of the formulae provided would enhance precision and accuracy.
- At especially high elevations (>2500 m), tailored adjustments by region and/or ethnicity may be warranted.

Research gaps

- Given the growing body of evidence showing differences between populations living at very high elevation (>2500 m) in different regions, future analyses should include data from a greater number of countries and population groups (such as infants, pregnant women, men, and older individuals) to help confirm whether and to what extent adjustments are required that are specific to that region and/or genetic background.
- Further research is needed to understand differences in observed haemoglobin concentrations among populations with gene variants limiting haemoglobin concentrations (production or maintenance) or those with epigenetic adaptations to living at very high elevation (>2500 m) and the nuances of adjusting haemoglobin for elevation between different ethnicities within a region.
- There were limited elevation data for some age groups. These gaps are important from the perspective of iron regulation at elevation because infants and pregnant women have particularly high iron requirements.
- There are several research groups worldwide working on the regional, genetic, and environmental reasons for the differences among populations living at the same high elevations. This work should also address aspects related to acceptability and equity of haemoglobin adjustments by populations.

Summary of judgements

The GDG considered the current evidence on the effects of adjusting haemoglobin concentrations by elevation of place of residence is of moderate quality since data and modelling for elevations above 3000–3500 m were obtained from limited samples, mainly from Central and South America.

The GDG members agreed on the value and on the positive effects of adjustments although they recognized that there may be costs associated with having to revise and implement new adjustments. The group considered that the haemoglobin adjustments by elevation are acceptable to stakeholders, cost-effective, and have a positive impact in equity. The adjustments were considered feasible to implement especially because adjustments for elevation have been in use since 2001 and also because an accurate definition of anaemia is critical to understand its incidence and distribution, to apply effective health interventions, and to improve the health and nutrition status of individuals and populations.

Question 2.a.2 Should haemoglobin cutoffs to define anaemia be adjusted for smoking?

The same data sources used for analysis of adjustments by elevation (29) were also analysed to explore the effect of smoking on haemoglobin concentrations, covering a broad range of age groups and geographical regions. Analyses included 19 826 observations among women of reproductive age with data on haemoglobin and smoking (status or daily cigarette quantity). Adjustments for smoking and elevation were additive and overall, mean haemoglobin was 3.3 g/L (95% CI 2.5–4.0) higher among smokers than in non-smokers across all surveys. The association between smoking and haemoglobin concentration was stronger in women than in men. For example, female smokers aged 15–49 years had an average of 2.6 g/L higher haemoglobin than non-smokers while male smokers had an average increase of 1.1 g/L (adjusted for elevation, age, survey, and iron deficiency).

In the WHO technical meeting on considerations for adjustments of haemoglobin concentrations to define anaemia by elevation above sea level and smoking in October 2020, attendees discussed whether adjustments for cigarette smoking should be made. Experts expressed concern that the mean differences between smokers' and non-smokers' haemoglobin levels were relatively small and also that, despite smoking increasing haemoglobin concentration via carbon monoxide exposure, there are additional physiological consequences which also affect haemoglobin, particularly in heavy and long-term smokers. The experts considered it important to prioritize the need for improved carboxyhaemoglobin measures to account for self-reporting errors and to adjust for other carbon monoxide exposures.

Normative statement 2.a.2 Smoking

Haemoglobin concentrations should be adjusted to diagnose anaemia in individuals and populations to account for the effect of smoking on haemoglobin concentrations.

Adjustments to account for smoking are presented in **Table 5**.

Table 5. Adjustments to haemoglobin for smoking status and cigarettes per day^a

Number of cigarettes per day	Haemoglobin adjustment (g/L) ^b
Smoker, quantity unknown	3
<10	3
10–19	5
>20	6

^a The adjustment consists in the corresponding value in the table added to the haemoglobin cutoff defining anaemia, or subtracted from an individual's observed haemoglobin level.

^b Adjustments based on haemoglobin adjustment (g/L) = (0.4565 × cigarette_number) + (−0.0078 × cigarette_number²), solved for the <10 cigarettes/day category using cigarette_number = 9, and for the 10–19 category cigarettes/day using cigarette_number = 19. The adjustment for the >20 cigarettes/day category was solved using cigarette_number = 30. The formula provided may be used in place of the categorical adjustments.

Remarks

- Data on smoking are self-reported and susceptible to inaccuracies. Carbon monoxide exposure may be better addressed using pulse carbon monoxide oximetry for carboxyhaemoglobin to assess all carbon monoxide exposures and eliminate self-reporting biases.
- The largest differences in haemoglobin concentrations between smokers and non-smokers were found in women, who have significantly lower rates of smoking than men, although this may be due to underreporting of smoking quantities. By 30 cigarettes/day the effect size was the same among men and women (6 g/L).
- At the individual level it is unclear whether the difference in haemoglobin with and without adjustment for smoking is physiologically relevant, particularly because the effect of smoking on haemoglobin is complex and, in addition to acute hypoxia, includes chronic hypoxia and end-organ damage. However, corrections at the population level are important in order to accurately report anaemia prevalence rates and efficiently apply health interventions.

Research gaps

- The relative impact of different carbon monoxide sources including smoking, second-hand smoke, air pollution, and indoor cooking smoke still needs to be defined.
- Future studies might benefit from using biochemical assessments of carbon monoxide exposure such as carbon monoxide oximetry to measure carboxyhaemoglobin levels.
- Implementation research is needed on when and how to collect information on smoking habits and exposure.
- Further studies are needed on the effect of e-cigarette use and exposure on haemoglobin concentrations.

Summary of judgements

The GDG had moderate certainty about the desirable effects of adjusting haemoglobin concentrations by smoking, since the quality of the evidence was very low. They considered that there are positive effects in adjusting haemoglobin concentrations by smoking, although at the individual level it is unclear whether the difference in haemoglobin with and without adjustment for smoking is physiologically relevant. The group agreed on the value and positive effects of adjustments, although they were unsure about the costs associated with the implementation of new adjustments or about the equity of such adjustments, especially for certain cultures, for women, and for elderly people. Adjustments for smoking were considered acceptable to stakeholders, cost-effective, and feasible to implement since they have been in use since 2001 in some settings.

Question 2.b Should haemoglobin cutoffs to define anaemia be adjusted by inflammation/infection, particularly in malaria-endemic settings?

The December 2021 WHO technical meeting on the role of infections, inflammation, and genetic ancestry as determinants for adjusting haemoglobin cutoffs to define anaemia, included discussion on the high number of illnesses and conditions known to affect haemoglobin concentration via multiple mechanisms, which poses a challenge to determining the feasibility of adjusting haemoglobin concentrations for inflammation and infection. Regarding malaria, there is a strong association between severe malarial anaemia and mortality in locations with varying degrees of endemicity, with substantial increases in mortality at haemoglobin concentrations below 40 g/L (31, 32).

Bacterial, viral, and parasitic infections causing inflammation (e.g. malaria, tuberculosis, HIV, hookworm) affect large segments of the population and produce anaemia of various severities (33–37). Markers of inflammation (e.g. c-reactive protein and α 1-acid glycoprotein) have been used to adjust biomarkers related to iron metabolism such as serum ferritin and serum transferrin receptor.

Chronic low-grade inflammation in the context of noncommunicable diseases, such as obesity, has been linked to altered iron metabolism and anaemia. However, adjustment of haemoglobin concentration by low-grade inflammation may not be the right approach for chronic diseases where anaemia may be a consequence.

Experts felt that due to vast differences in the origins and severities of infection and inflammation, and in the pathways that lead to reduced haemoglobin concentrations, it is not feasible to establish an adjustment factor for haemoglobin concentrations to account for the role of infection and inflammation.

Normative statement 2.b Infection and inflammation

Haemoglobin concentrations should not be adjusted to diagnose anaemia in individuals and populations to account for the effect of infection and inflammation on haemoglobin concentrations.

Remarks

- Bacterial, viral, and parasitic infections causing inflammation (e.g. malaria, tuberculosis, HIV, hookworm) affect large segments of the population and produce anaemia of various severity. Markers of inflammation (e.g. c-reactive protein and α 1-acid glycoprotein) have been used to adjust biomarkers related to iron metabolism, such as serum ferritin and serum transferrin receptor, although is not the case for haemoglobin adjustments.
- The role of chronic low-grade inflammation in the context of noncommunicable diseases, such as obesity, has been linked to altered iron metabolism and anaemia. However, adjustment of haemoglobin concentration by low-grade inflammation was determined as not the right approach for chronic diseases where anaemia may be a consequence of the condition.
- Additional indicators are required for establishing the underlying cause and magnitude of infection and inflammation, and for determining the course of treatment.

Research gaps

- Cost-effectiveness data are needed to determine the convenience of establishing adjustments in haemoglobin concentration by infection/inflammation.
- Studies on the health equity implications of accurate adjustments for infection/inflammation are needed.
- There is a need for improvements in accurate, field-friendly measurement of inflammation to determine its contribution to anaemia or its role in haemoglobin concentration.

Summary of judgements

The evidence on desirable effects of no adjustments of haemoglobin concentration by infection/inflammation was considered large, with small undesirable effects, since a high number of illnesses and conditions are known to affect haemoglobin concentration via multiple mechanisms, which complicates the determination of the appropriateness and feasibility of adjustments. The group considered that there is no important uncertainty around not adjusting haemoglobin concentrations by infection/inflammation. The GDG considered that the balance of benefits/harms of adjusting haemoglobin concentrations is not clear since the effect of infection/inflammation on haemoglobin is complex and the mechanisms causing anaemia might not warrant adjustment, leading to the undesirable effect of introducing error in the interpretation of haemoglobin concentrations. However, for individuals and populations, it is necessary to determine whether anaemia is caused by infection/inflammation, although adjustments are not required. Determining the cause of anaemia is critical to plan, implement, monitor, and evaluate nutrition interventions. No adjustments of haemoglobin concentrations by infection/inflammation were considered to be acceptable, feasible, and with a clear impact on health equity.

Question 2.c Should haemoglobin cutoffs to define anaemia be adjusted by genetic ancestry/ethnicity/race?

Although race/ethnicity correlates with genetic ancestry, it captures different information. Race and ethnicity are self-ascribed or socially ascribed identities and are often assigned to people by police, hospital staff, or others based on physical characteristics. Genetic ancestry is the genetic origin of one's population. Genetic exchange among people from different ancestries is an important characteristic of many populations and may correlate with an individual's risk for certain genetic diseases.

There is evidence showing differences in haemoglobin concentration by genetic background. For a 2019 multivariate analysis of 23 657 haemograms from 7318 pregnancies and 6870 pregnant women in Italy, the authors categorized the women's ethnicity as African, Asian, Caucasian, or Other. They found that women in the African and Asian categories had lower haemoglobin and haematocrit concentrations than women in the Caucasian category. Compared with women in the Caucasian category, those in the African category had mean haemoglobin and haematocrit values that were 2.4 (95% CI 3–1.7) g/L and 0.7 (95% CI 0.8–0.5)% lower, respectively; women in the Asian category had values that were 1.1 (95% CI 1.9–0.3) g/L and 0.3 (95% CI 0.5–0.1)% lower, respectively (38).

In 2019, Varghese et al. (39) used standard statistical methods to assess the haemoglobin distributions of healthy nonpregnant women of who self-identified as Asian, Black, Hispanic, or White. Data were obtained from nine rounds of NHANES, United States of America, and two rounds of the National Diet and Nutrition Survey, United Kingdom of Great Britain and Northern Ireland. The mean haemoglobin concentrations of women identifying as Black, Hispanic, or Asian were lower than those identifying as White. The authors calculated a cutoff for mild anaemia in Asian women at 112.2 g/L and noted that use of this cutoff in place of the WHO cutoff of 120 g/L would result in a 17.9% decrease in the prevalence of anaemia in India (39).

In 2015, Lim (40) investigated racial/ethnic differences in reference intervals of common biochemical and haematological laboratory tests using NHANES 2011–2012 data and included 3077 participants aged 18–65 years who reported their race/ethnicity as Asian, Black, Hispanic, or White. Quantile regression analyses adjusted for sex showed that in the Asian, Black, and Hispanic populations, the lower or upper percentile for all except five laboratory tests (glucose, phosphorus, potassium, total bilirubin, and uric acid) differed from the values in the White population. For example, the normal range for people who reported their race as Asian was significantly shifted to higher values in globulin and total protein and to lower values in creatinine, haematocrit, haemoglobin, mean cell haemoglobin, mean cell haemoglobin concentration, and mean platelet volume. The authors concluded that race/ethnicity may need to be incorporated into the development of reference intervals for biochemical and haematological laboratory tests (40).

In 2021, Weyand and McGann argued that the inclusion of separate thresholds for different races validates the common misperception that there are physiological differences between Black and White people (41).

In 2020, Jallow et al. reported a disproportionately high genetic diversity in African populations that, coupled with a high prevalence of iron deficiency, indicates the need for further investigations on the genetic influences of low iron status in sub-Saharan Africa (42).

Kang et al. described consistently lower haemoglobin concentrations in people whose ethnicity was categorized as African American than those categorized as European, as well as consistently higher proportions of African American women identified as anaemic based on current thresholds (43). The authors constructed linear mixed-effects models to explore ethnic differences in iron status biomarkers in population-based data from the published literature. People categorized in the original studies as East Asian had significantly higher concentrations of iron status indicators (serum ferritin, transferrin saturation, and haemoglobin) than those who were categorized as African American, European, or South Asian (43).

The 2001 WHO document *Iron deficiency anaemia: assessment, prevention and control, a guide for programme managers* states: “For populations of African extraction, recent analysis indicates that achieving a similar screening performance (sensitivity and specificity) requires a haemoglobin criterion that is 10 g/L (0.62 mmol/L) lower than current cutoffs” (16).

The 2017 WHO document: *Nutritional anaemias: tools for effective prevention and control*, indicates that individuals of African heritage have haemoglobin concentrations that are significantly lower than those of individuals of European descent, and that it has been suggested to include adjustments for ethnicity to the WHO thresholds for determining anaemia (2). The suggested adjustments are the subtraction of 6–10 g/L, depending on genetic background. The same document indicates that Black individuals have lower haemoglobin concentrations than White individuals; these differences are not explained by health, nutrition, or socioeconomic status, and are observed across the age spectrum. Even after accounting for iron status and known gene mutations such as α -thalassaemia, glucose-6-phosphate deficiency, and sickle-cell trait, which occur more commonly in populations of African descent, differences in haemoglobin by race still existed in one study of more than 32 000 individuals (2).

Normative statement 2.c Genetic ancestry/ethnicity/race

Haemoglobin concentrations should not be adjusted to diagnose anaemia in populations to account for the effect of genetic ancestry/ethnicity/race due to insufficient evidence to change current adjustments and the complexity of operationalization.

Remarks

- Among apparently healthy populations, there are observed differences in haemoglobin concentrations across age and population groups. Some of these differences may reflect changes in genes related to haemoglobin production or other aspects of red blood cell production or function. A lower mean haemoglobin concentration (10 g/L difference) has been reported in Black individuals compared to White individuals. When anaemia is diagnosed, the underlying genetic, nutritional, infectious/inflammatory influences, and social determinants of health relevant for the individual or populations should be considered.
- There are concerns about the applicability of existing research due to ubiquitous mixed genetic ancestry worldwide.

Research gaps

- Further research is needed on single nucleotide polymorphisms, novel variants or altered effects of known single nucleotide polymorphisms in iron or haemoglobin regulation.
- Further studies of the genetic basis for ethnic differences in iron metabolism and its effect on disease susceptibility among different ethnic groups are needed to inform population-specific recommendations and personalized nutrition interventions for iron-related disorders.
- Further global health research is needed that looks not only at the prevalence but also at the causes of anaemia (e.g. additional testing for markers of iron, infection/inflammation, and potentially genetic haemoglobin disorders) to inform the choice of intervention.

Summary of judgements

There was a high uncertainty about the desirable and undesirable effects of adjustments of haemoglobin concentration by genetic ancestry and the GDG considered the evidence as very low quality. The group noted that there is no new evidence base from which to set/update haemoglobin reference ranges for different genetic groups. The balance of effects, and cost-effectiveness, favours no adjustments of haemoglobin concentrations by genetic ancestry, since it seems unfeasible to generate other adjustments to cutoffs based on genetic backgrounds due to the complexity of genetic testing.

Another point of discussion was the substantial research needs in the race/ethnicity/genetic ancestry field in the context of discussion of haemoglobin cutoffs adjusted by race/ethnicity/genetic ancestry, especially recognizing how underrepresented some genetic backgrounds have been in the literature thus far. The group also considered that generating the data necessary to update current adjustments is not feasible for most Member States.

Question 3

How should haemoglobin concentration be measured?

- 3.a** What are the acceptable alternative methods for assessing haemoglobin concentration compared to reference standard (i.e. automated haematology analysers) particularly for population-based or field-based surveys?
- 3.b** What are the key quality control issues pertinent to accurate diagnosis of anaemia?
- 3.c** What blood source(s) are acceptable? How do results vary in capillary blood (finger, heel, ear, single drop, pooled drops), or arterial blood as compared to venous blood (reference)?

Blood sample collection site, measurement device, methodological errors, individual variations, and other factors have been reported to influence haemoglobin concentration. There is evidence supporting a biological variability between capillary and venous blood after accounting for device and sampling variability and/or error, the magnitude of which is likely to vary by sex, possibly age, and other factors. Although it is easier to control all potential factors influencing the quality of the measurement and interpretation in more controlled settings than in less controlled field settings, high-quality data could be obtained in all settings (44–47).

Automated analysers are optimal for measuring haemoglobin for clinical laboratories. Non-invasive and invasive point-of-care analysers are considered feasible for field settings because of their portability, cost, and weight, but have variable comparability to the reference. Most studies have compared the point-of-care analysers developed by HemoCue (Ängelholm, Sweden) to the reference, as these are frequently used to measure haemoglobin in public health population-based surveys in field settings and other settings requiring low technological solutions that provide immediate haemoglobin results (e.g. blood donation). Studies with HemoCue show high variability in results depending on the model, blood source, and field conditions (47).

Normative statement 3 Haemoglobin measurement

Use of venous blood, automated haematology analysers and high-quality control measures are recommended for the assessment of haemoglobin concentration in individuals and populations.

Remarks

- There is clear variation in haemoglobin concentrations assessed from capillary and venous blood samples; however, the magnitude of variation has not been confirmed. It is therefore not possible to provide adjustments to haemoglobin concentrations measured in capillary blood to make them comparable with venous blood.
- When well maintained in accordance with quality management principles, all accredited instruments should provide acceptably similar results.
- Stakeholders should take into consideration the blood source and type of analyser used during data collection when tracking changes in haemoglobin concentrations and the prevalence of anaemia over time or comparing between different settings, particularly where the use of venous blood and/or automated analysers are not always feasible.
- Pooling drops of blood from a single capillary prick could be an option for minimizing variability due to blood sampling technique. Also, the effect of sample handling on different analytical methods, for example, length of time between collection and processing, needs to be taken into consideration.
- Where application of the recommendation on using an automated haematology analyser is not possible, consideration could be given to the measurement of haemoglobin using an approved point-of-care blood testing device which has been verified to be calibrated against international reference standards.
- The use of international standards, commutable standards, and calibration materials to achieve appropriate quality control is desirable.
- Quality control points at pre-analytical, analytical, and postanalytical levels should be carefully established. Examples include patient characteristics/disposition/preparation, personnel training, use of international calibration standards, method, and frequency of equipment calibration (or validation of the calibration), blood collection, monitoring data collection, recording and analysing results, reproducibility of results, laboratory quality control assessments, and possibly haemoglobin adjustments for elevation and smoking, when warranted.
- The blood source, analytical device, and sample collection protocols should be included in any report of anaemia prevalence.

Research gaps

- Validation of the comparability of pooled capillary drops and venous blood is needed. If validated, standard operating procedures to optimize methods for collection and processing of pooled capillary drops should be developed.
- High-quality studies are needed to determine variations in haemoglobin concentrations from the same individuals based on different blood specimen types, body positions, collection methods, training and supervision of staff, and quality of data collection.

- Further investigation is needed on the effect of hydration status and fasting on haemoglobin concentrations, especially in hot climates.
- The clinical implications of the difference in haemoglobin concentration between venous and capillary blood in otherwise healthy individuals requires investigation.
- New quantitative methods and analysers practical in field settings are needed, with consideration of performance and their ability to be portable and field friendly.
- Approaches are needed for the integration of data from different surveys where there is variation in blood sources and analysis methods. This will aid tracking progress towards global and country anaemia reduction goals.
- Continued development, validation, and testing of non-invasive methods for haemoglobin measurement is needed.

Summary of judgements

The GDG considered that there is substantial evidence on the desirable effects of using venous blood, automated haematology analysers, and high-quality control standards for assessing haemoglobin concentration or adjusting haemoglobin values.

There is value in using the gold standard practice for haemoglobin determination, and the positive effects of clear knowledge of comparable methodologies to measure haemoglobin and correct diagnosis of anaemia at individual and at population levels are clear. Harmonized, evidence-based guidelines validating the use of venous blood, automated haematology analysers and high-quality control standards for assessing haemoglobin concentration would have a positive impact on health equity and would help ensure that the same definition of anaemia is available to all. The use of best practices for haemoglobin determinations were considered acceptable to stakeholders, cost-effective and feasible to implement.

Question 4

Is haemoglobin concentration an adequate marker for assessing the impact of iron interventions?

A WHO-commissioned overview of reviews focused on nutrition-specific interventions to control micronutrient malnutrition and increase the intake of micronutrients through supplementation, food fortification, and enhancement of food diversity and quality (48). The objective was to summarize the evidence from systematic reviews of randomized controlled trials, regarding the benefits or harms of nutrition-specific interventions for preventing and controlling anaemia in anaemic or non-anaemic, apparently healthy, populations throughout the life cycle.

The nutrition-specific interventions considered for this overview of reviews included: (i) supplementation (daily or intermittent oral iron, vitamins, or any other mineral); (ii) fortification (iron alone or other vitamins and minerals, multiple micronutrient powders, lipid-based nutrient supplementation, complementary foods, fortified staple foods, and biofortified foods); and (iii) dietary diversity and quality improvement (increasing food variety through education and provision of foods rich in minerals and vitamins, use of iron-containing cooking pots and fish-shaped iron ingots, general nutrition education and counselling).

The primary outcomes were haemoglobin concentration, anaemia, and iron deficiency anaemia; secondary outcomes were iron deficiency, severe anaemia, and adverse effects (e.g. diarrhoea, vomiting).

This overview included 75 systematic reviews; half were rated as being of high methodological quality and the remainder were rated as medium quality. The number of trials included in these systematic reviews ranged from two to 90 trials, and the number of participants ranged from 52 to over 310 000. At least 67 of the reviews were conducted in low- and middle-income countries, with populations from different cultural and economic backgrounds.

The authors concluded that, compared to no treatment, daily iron supplementation may increase haemoglobin levels and reduce the risk of anaemia and iron deficiency anaemia in infants, preschool and

school-aged children, and pregnant and nonpregnant women. For infants, iron fortification of foods and for children, use of iron-containing cooking pots may have prophylactic benefits for malaria endemicity low-risk populations. In any age group, only a limited number of reviews assessed interventions to improve dietary diversity and quality (48).

Normative statement 4 Assessing impact of interventions

Haemoglobin concentrations should be used as one of the markers to assess the impact of iron interventions (e.g. iron supplementation and staple food fortification with iron and other vitamins and minerals) for preventing and treating iron deficiency anaemia throughout the life cycle.

Remarks

- When deciding on the specific interventions to implement for iron deficiency anaemia (supplementation, fortification, nutrition education and combinations of them), policy-makers, programme implementers and clinicians should take into consideration micronutrient status and regional and local variations in the diet, different cultural practices, different methods of food processing and meal preparation, and economic constraints.
- Attention should be paid to the possible adverse effects of excessive iron intakes, especially when considering or implementing iron interventions in malaria-endemic regions or settings where haemoglobinopathies are common.
- Understanding the causes of anaemia will help inform the proper interventions to treat, prevent and/or reduce anaemia. Policy-makers seeking to reduce the prevalence of anaemia should understand and address the local context and intervene through a broad range of pertinent interventions (e.g. iron interventions, malaria prevention) that address this complexity. This comprehensive response will aid in achieving the desired outcomes, avoiding adverse effects, and ensuring a tolerable upper level of iron intake is not exceeded from all sources of intake.
- In addition to haemoglobin concentrations, data on programme implementation and the use of additional biomarkers of iron status (e.g. ferritin, serum transferrin receptor) along with markers of inflammation are also important for the robust assessment of the response to iron interventions.
- The use of haemoglobin concentration to assess the impact of iron interventions is potentially simple, although implementation may be challenging due to limited access and resources for programmes. In addition, assessing anaemia alone will miss changes in earlier stages of iron deficiency and only capture the more severe stage of iron deficiency anaemia. Considering measuring other biomarkers to address the causes of anaemia is advisable.

Research gaps

- Due to the scarcity of data, future trials should focus on infants <6 months of age, adolescents, women aged 50 to 65 years, men aged 19 to 65 years, and older persons.
- The evidence reviewed predominantly included nutrition-specific interventions in apparently healthy populations. Studies are needed on the effect of these interventions in populations at higher risk of anaemia due to acute or chronic infections, acquired bone marrow disorders, inflammation, or inherited anaemia.
- Studies on haemoglobin response in iron replete individuals that receive iron interventions, by iron dose and status, are needed to determine whether there are associated adverse risks with iron supplementation in these populations.
- Iron biomarkers and measurement of other functional outcomes may be required to evaluate interventions, which is more expensive than determining haemoglobin concentrations alone. There is a need for accurate, accessible, and affordable assays for measuring iron status and inflammation.

Summary of judgements

When reviewing and voting on the evidence-to-decision framework for this question, all GDG members found substantial evidence supporting the desirable effects of using haemoglobin concentration to assess the impact of iron interventions, with undesirable effects being moderate to small, with a moderate certainty of evidence. GDG members also considered that there is value and clear benefits from using haemoglobin concentration to assess the impact of iron intervention, although the cost/resources required to implement the measurement of haemoglobin could be variable. The group considered that iron supplementation and food fortification have increased impact on equity and acceptability and are feasible to implement.

Question 5

What should be the population cutoffs to define the public health significance of anaemia?

- 5.a** What anaemia prevalence is indicative of a mild, moderate, or severe (or low, medium, high) problem of public health concern?
- 5.b** Should this classification of anaemia be based on total anaemia alone or should the proportion of mild, moderate, and/or severe anaemia be considered (weighted?) to determine that categorization?

Accurate characterization of the prevalence of anaemia and its severity at the public health level is critical to understand the burden and epidemiology of this problem and for planning public health interventions. Current classification of the public health significance of anaemia in populations indicates there is a mild, moderate, or severe public health problem when anaemia prevalence is 5.0–19.9, 20.0–39.9, and $\geq 40\%$, respectively (5, 6). This categorization was proposed in 2000 as part of a manual on the management of nutrition in major emergencies. It was further stated that interventions should be seriously considered if the prevalence exceeds 20%. The methodology for deriving these ranges was not provided and it is assumed they were established through expert consensus.

There is no new evidence to support or change this categorization. The group was presented with demographic and socioeconomic evidence showing that, for example, in 2013 anaemia was responsible for 8% of all non-fatal health loss for all diseases, lower than the total disability caused by low back and neck pain (106 million years lived with disability [YLD]), but similar to disability due to asthma, diabetes, and cardiovascular disease combined (61.3 million YLD) (49). The Global Burden of Disease Study of 2017 identified iron deficiency anaemia as one of the five greatest causes of YLD, accounting for 34.7 million YLD (50). The Global Burden of Disease Study of 2019 indicated that the burden of anaemia was lower in regions with higher socioeconomic development. Globally, most cases were attributable to dietary iron deficiency, as well as to haemoglobinopathies and haemolytic anaemias (51). This sociodemographic approach highlights the importance of defining the public health burden of anaemia in order to catalyse public health policies. As a reference for the investment needed to address anaemia, it has been suggested that: interventions with an incremental cost of US\$ 200 or less per disability-adjusted life-year averted could be considered for publicly funded health care in low-income countries; interventions costing US\$ 200–500 could be considered in lower-middle-income countries; and interventions costing US\$500–1000 could be considered in upper-middle-income countries (52).

Normative statement 5 Public health significance of anaemia

The current classification of public health significance of anaemia prevalence in populations should be maintained (Table 6). There is a lack of evidence showing a clear association between the severity of the public health burden of anaemia with clinical and/or demographic outcomes. The current expert-based classification has been in use since 2000 and this should be maintained until new evidence becomes available.

Table 6. Classification of public health significance of anaemia in populations based on prevalence estimated from blood levels of haemoglobin

Category of public health significance	Prevalence of anaemia (%)
Severe	40 or higher
Moderate	20.0–39.9
Mild	5.0–19.9
Normal	4.9 or lower

Source: Nutritional anaemias: tools for effective prevention and control. Geneva: World Health Organization; 2017 (2).

Remarks

- The current classification of the public health significance of anaemia is based on expert opinion alone. There was not enough evidence to change the methodology or the current classification.
- The classification of the public health significance of anaemia is based on the total prevalence of anaemia, a sum of the prevalence of mild, moderate, and severe anaemia in a country, and includes all age groups available for analysis.
- A clear association between the public health significance of anaemia with clinical and/or demographic outcomes has been used for planning, initiating, implementing, and evaluating country or regional plans to address anaemia.
- The association between the public health significance of anaemia and clinical outcomes seems clear for moderate and severe anaemia. Associations with social, economic, and health indicators are less clear for mild anaemia.
- Countries should consider whether anaemia programmes should be launched based on their national or subnational prevalence of anaemia in a particular age group (e.g. in children, women of reproductive age), physiological status (pregnant women), or severity of anaemia (considering moderate and/or severe anaemia only).
- Countries should have a good understanding of the leading context-specific causes of anaemia (e.g. malaria, other infections, inflammation, iron deficiency) to inform strategies to address the root causes.
- The public health significance of anaemia alone should not be linked to specific interventions. Additional country information (e.g. health, nutrition, economic, and social data) should be taken into consideration.
- Countries with limited resources may consider prioritizing strategies to address the causes of moderate and severe anaemia, which have more severe outcomes and lead to higher rates of YLD, while monitoring prevalence to ensure that mild cases are not transitioning to moderate anaemia.

Research gaps

- Further global health research is needed focus not only on the presence or absence of anaemia, but also on its causes and severity.
- There is a need to identify and measure the social determinants of clinical and/or sociodemographic indicators to base the public health of significance of anaemia classification.
- A definition of the severity of the public health problem of anaemia prevalence based on clinical and/or sociodemographic outcomes is needed.

Summary of judgements

The group decided to maintain the current classification of the public health significance of anaemia based on the lack of new evidence to analyse desirable or undesirable effects of changing the current classification. From the global and national perspectives, this could help countries to gauge whether they need an intervention, and global organizations to know where the priority countries/areas for intervention are. The decision was also based on the acceptability by stakeholders, low cost, and feasibility of continuing with the current expert-based classification, which has been in use since 2000.

The GDG decided that the current classification could have a high value for stakeholders to prioritize countries in need of assistance and for countries to plan, implement, monitor, and evaluate nutrition interventions in their populations. Also, the group considered that keeping the current classification will probably help to increase equity, although they were not sure about the cost-effectiveness or the balance of desirable and undesirable effects, because more robust data are needed to make an informed decision.

Dissemination, implementation, and ethical considerations

Dissemination

This guideline will be disseminated through electronic media such as webinars, slide presentations and the World Wide Web, through the [WHO Nutrition](#) mailing lists, social media, the [WHO nutrition website \(53\)](#), and the [WHO e-Library of Evidence for Nutrition Actions \(54\)](#). eLENA compiles and displays WHO guidelines related to nutrition, along with complementary documents such as: systematic reviews and other evidence that informed the guidelines; biological and behavioural rationales; and additional resources produced by Member States and global partners. In addition, the guideline will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, universities, other United Nations agencies and nongovernmental organizations. Derivative products that are useful for end-users, such as summaries and collation of normative statements related to implementation of haemoglobin cutoffs to define anaemia in individuals and populations, may be developed.

Particular attention will be given to improving access to these guidelines for stakeholders that face more, or specific, barriers in access to information, or to those that play a crucial role in implementation, for example, policy-makers and decision-makers at subnational level that disseminate the contents of the guideline. Disseminated information may emphasize the benefits of a correct anaemia diagnosis in individuals, populations, or regions where anaemia and its consequences are of public health significance. This is particularly important in rural communities or highly isolated settings where access to facilities for haemoglobin measurement and anaemia diagnosis is often limited or difficult.

The executive summary of the guideline may be translated into the other five United Nations languages and disseminated through the WHO regional offices. Specialized technical assistance will be provided to any WHO regional office willing to translate the full guidelines into any of these languages and support countries in implementation for impact.

Equity, human rights, and implementation considerations

This guideline is intended to help Member States and their partners make informed decisions about what interventions are best suited to their context, needs, resources and ongoing programmes, observing existing human rights standards and pursuing health equity.¹ If Member States decide to adopt the normative statements contained in this guideline at either the national or subnational level, a thorough assessment of the policy implications concerning this decision is needed. The following considerations seek to support Member States to adopt/use the haemoglobin cutoffs and measurement practices that will lead to correct anaemia diagnoses, which will help in the prevention and control of anaemia at the individual and population levels.

As this is a global guideline, it should be adapted to the context of each Member State. Prior to implementation, a public health programme should have well-defined objectives that take into account available resources, existing policies, suitable delivery platforms and suppliers, communication channels, and potential stakeholders. Ideally, the normative statements on assessing anaemia should be implemented as part of an integrated programme on health and nutrition.

The adoption and adaptation of these normative statements should be framed under the existing national strategy on prevention and control of anaemia. The adoption of the cutoffs and best practices to measure haemoglobin as part of interventions aimed at preventing and treating anaemia should be considered in the context of that strategy, including consideration of the costs, feasibility, accessibility, and acceptability. Such considerations should include the various stakeholders, such as decision-makers, law-makers, programme managers, users' organizations, and organizations with opposing views. A mapping exercise of the different stakeholders and their interests and forms of involvement in the intervention is a useful practice (55).

¹ Equity in health refers to the absence of unjust differences in health, which are avoidable by reasonable action (57). Thus, the implementation of the interventions informed by this guideline should contribute to preventing or mitigating systematic differences in haemoglobin measurement and anaemia diagnosis across populations, including health inequities that may be exacerbated or created as a result of their implementation.

Sound data obtained under the best quality standards and methods and a robust baseline or database on the prevalence of anaemia across the population is the optimal foundation for any programme. Data should be disaggregated as much as possible, in order to identify health inequities across population groups. Some of the most useful and common stratifiers include those grouped under the acronym PROGRESS-Plus: **P**lace of residence; **R**ace, ethnicity, culture and language; **O**ccupation; **G**ender and sex; **R**eligion; **S**ocioeconomic status; and **S**ocial capital; plus other relevant social determinants (e.g. age, disability status, migration status, health-system configuration, political environment) (56). The disaggregation of data is also useful for monitoring and evaluation of programmes. WHO has developed guidance on health equity in order to support Member States in this respect: the WHO *Handbook on health inequality monitoring with a special focus on low- and middle-income countries* (57) and the WHO *Health equity assessment toolkit* software application (58). These resources will assist Member States in the assessment of within-country health inequalities and can inform the process of adaptation for Member States adopting this guideline.

Access to and availability of an accurate anaemia diagnostics should be promoted when the need is identified, irrespective of geographical, cultural, or economic factors. In addition to socioeconomic barriers, context-specific gender and social norms within households may affect women's and adolescent girls' ability to seek health services and consume sufficient, safe, and nutritious food to meet their dietary needs. In the context of haemoglobin measurement, even slight changes in geographical placement, in culturally adapted communication strategies, and in the price of the test could affect accessibility. Concurrent measures can contribute to prevent and mitigate health inequities that are produced as a result of differential access to an accurate anaemia diagnosis.

To help prevent misconceptions, culturally appropriate communication strategies should be developed to disseminate accurate and evidence-based information on anaemia diagnosis and why it is important for health and development. Likewise, programmes at national and subnational levels should be culturally appropriate to the target populations, in order to increase the acceptability, adoption, and sustainability. Such approaches should also identify any resistance, via actions or behaviours based on well-established practices or social beliefs, which affect adoption of and adherence to the proposed cutoffs, adjustments, and methods. The involvement of local leaders and use of local languages and culturally relevant representations is a reasonable strategy.

Acceptability and adoption are better achieved if they are accompanied by simple and easy-to-access information that can be understood by different population groups. Information must be disseminated in a manner that aims to ensure that these normative statements are perceived as appropriate by all actors involved.

Ideally, anaemia diagnosis should be part of a coordinated and comprehensive programme aiming to prevent and control anaemia. A coordinated and comprehensive anaemia detection programme may include several aspects, including appropriate cutoffs for all sex, age, pregnancy status, ethnic groups, and populations living in different settings. It should also include the best practices for haemoglobin measurement. The programme should have well-defined objectives that take into account available resources, existing policies, suitable delivery platforms and suppliers, communication channels, and potential stakeholders. Anaemia prevention and control programmes, including haemoglobin measurement and anaemia diagnosis, should be coordinated with antenatal care programmes, malaria prevention and treatment programmes, and nutrition-specific and nutrition-sensitive programmes to be effective. They should also be coupled programmes on community involvement, education, and sanitation. In order to achieve this coordination, policy-makers need to determine the multisectoral approaches that represent the most appropriate allocation of resources, produce the greatest benefits, and optimize the results of the programme objectives.

Regulatory considerations

A general legislation framework for technical specifications, including standards and regulations, could be placed at different levels of anaemia prevention and control programmes. Competent authorities should determine whether the standards and methods for haemoglobin determinations should be mandatory or voluntary. This decision may be based on the severity and extent of public health need. Input from all involved sectors when developing the regulations and standards, including public institutions, academia, research organizations and communities, will help to ensure a realistic approach.

For implementing a standardized programme for anaemia diagnosis, a well-designed monitoring system is an essential component to ensure that cutoffs, samples, equipment, quality, and safety standards are followed as set out in the regulations and standards. National authorities should establish procedures, methodologies, and reporting requirements to evaluate programmes; allocation of responsibilities between the different actors; and a monitoring mechanism.

Ethical considerations

Ethics refers to standards of what is right or wrong and fair or unfair, which can advise people on what to do and not do in terms of rights, obligations and benefits to society and individuals. Ethics is central to science, research, policy-making, and implementation. Every field of human action, including public health nutrition, is subject to facing ethical challenges.

Ethical principles lead to consideration of whether an intervention is: producing benefits to individuals and communities; preventing harms, also at the individual and societal levels; distributing health benefits across social groups (i.e. how much an intervention is contributing to health equity); and respecting and promoting the exercise of human rights.

An assessment of the accessibility and acceptability of an anaemia control programme or survey can inform programme design and development, in order to increase therapeutic adherence to iron supplementation and the understanding and acceptance of haemoglobin determinations to evaluate the impact of the programme. This is particularly relevant in settings where the prevailing social norms and determinants may set unequal conditions and opportunities for different groups. In some settings, for example, gender norms may create unequal opportunities for girls and boys at any age, both within and out of school; in other settings, social perceptions around ethnicity and race intervene in how certain population groups access and use an intervention.

The correct diagnosis of anaemia and the process involved to achieve it, must be informed by the right to health, and duty-bearers should take into account the corresponding human rights instruments when designing the intervention and also during its implementation. Anaemia diagnosis and control may raise ethical challenges about how to best benefit populations, avoid unintended harms, and promote the principles of equity and social justice.

Sound implementation of this guideline, as informed by these considerations, can contribute to systematic detection of facilitators and barriers to achieving the programme goals, and to better design any scaling-up strategy (59).

Monitoring and evaluation of guideline implementation

A plan for monitoring and evaluation with appropriate indicators, including equity-oriented indicators, is encouraged at all stages (57). The impact of this guideline can be evaluated within countries (i.e. monitoring and evaluation of the programmes implemented at national or regional scale) and across countries (i.e. the adoption and adaptation of the guideline globally).

WHO is committed to supporting countries to reduce anaemia and has recently developed a comprehensive framework for action to prevent, diagnose and manage anaemia through a multisectoral approach (60). The framework sets forth ways to address the direct causes, risk factors, and broad social inequities that are fundamental drivers for anaemia. It describes the necessarily comprehensive approach that brings together multiple sectors and actors and identifies key action areas to improve the diagnosis, prevention, and management of anaemia, driving progress towards national and global targets. This guideline is key for supporting countries in the initial, and monitoring, phases of anaemia prevention and control programmes. WHO and UNICEF have also established an Anaemia Action Alliance (61), bringing partners across sectors together to support implementation of this guideline and the framework at the country level. A dedicated section of the WHO Global Health Observatory contains up-to-date global, regional, and country data on anaemia for the areas of maternal, newborn, child, and adolescent health and ageing (62). Since 1991, WHO has hosted the Micronutrients Database as part of the [Vitamin and Mineral Nutrition Information System \(VMNIS\)](#) (63). Part of WHO's mandate is to assess the micronutrient status of populations, monitor and evaluate the impact of strategies for the prevention and control of micronutrient malnutrition, and track related trends over time. The Department of Nutrition and Food Safety manages the VMNIS Micronutrient Database through a network of regional and country offices, and in close collaboration with national health authorities.

For evaluation at the global level, the WHO Department of Nutrition for Health and Development has developed a web-based [Global targets tracking tool](#) (64) that allows users to explore scenarios to achieve the rates of progress required to meet the WHO [Global nutrition targets 2025](#), including target 2 of a 50% reduction of anaemia in women of reproductive age (7). The tool also serves as a central platform for sharing information on nutrition actions in public health practice implemented around the world (64). By sharing programmatic details, specific country adaptations and lessons learned, this platform will provide examples of how guidelines are being translated into actions. The [Global database on the Implementation of Nutrition Actions \(GINA\)](#) (65) provides valuable information on the implementation of numerous nutrition policies and interventions.

An efficient system for the routine collection of relevant data, including relevant determinants of health, therapeutic adherence, and measures of programme performance, is critical to ensure programmes are effective and sustained and drivers to the achievement of the right to health for all population groups. Monitoring differences across groups in terms of the accessibility, availability, acceptability, and quality of the interventions contributes to the design of better public health programmes. Creation of indicators for monitoring can be informed by social determinants of health approaches, so that inequities can be identified and tackled. It is particularly important to design sound implementation strategies to serve as the basis for scaling-up efforts. Appropriate monitoring requires suitable data, so attempts towards collecting and organizing information on the implementation are also fundamental.

Guideline development process

This guideline was developed in accordance with the WHO evidence-informed guideline development procedures outlined in the *WHO handbook for guideline development* (66). The steps in this process included: (i) identification of priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of normative statements, including research priorities; (v) planning for dissemination; (vi) equity, human rights, implementation, regulatory, and ethical considerations; and (vii) impact evaluation and updating of the guideline.

In 2015, WHO initiated a review of global guidelines on haemoglobin cutoffs to define anaemia. The activities included retrieving, summarizing, and assessing the currently available evidence to inform updated WHO normative statements on the use and interpretation of haemoglobin concentrations for assessing anaemia in individuals and in populations.

A WHO Steering Committee (**Annex 4**), led by the Department of Nutrition and Food Safety, was established with representatives from relevant WHO departments with an interest in the provision of scientific nutrition advice. Advisers from the WHO regions participated in the meetings of the GDG as part of the Steering Committee. The Steering Committee guided and provided overall supervision of this guideline development process. Two additional groups were formed: the GDG and a systematic reviews team.

The GDG was established in 2019 (**Annex 5**) and comprised 14 experts with a range of technical skills, diverse perspectives, wide geographical representation, and gender balance. They consisted of content experts, methodologists, and representatives of potential stakeholder and beneficiaries. The list of members of the GDG came from suggestions from all WHO departments with an interest in the provision of scientific nutrition advice; WHO expert advisory panels (67); members of previous guideline development groups; and those identified through a call for experts published on the WHO Nutrition website and distributed to the WHO Nutrition mailing list.

The GDG consisted of experts in nutrition, micronutrients, maternal and child nutrition, public health, epidemiology, clinical practice, malaria, infectious diseases, health equity, behaviour science, programme evaluation, haematology, diagnostic methods, biomarkers for anaemia, bioethics, genetics, haemoglobinopathies, blood donation, transfusion, and blood safety. Its role was to advise WHO on: (i) the scope of the guidelines and priority questions for which systematic reviews of evidence were commissioned; (ii) the choice of important outcomes for decision-making; (iii) the interpretation of evidence with explicit consideration of the overall balance of risks and benefits; and (iv) the formulation of final drafting of the normative statements, taking into account existing evidence as well as diverse values and preferences.

As resource persons, the systematic reviews team members, participated in the guideline development process by presenting evidence and identifying research priorities. They participated only in the open meetings and were informed that they were not allowed to participate in the decision-making process (**Annex 6**).

Five technical experts were invited to peer-review the draft guideline. The final draft guideline was peer-reviewed by four content experts, who provided technical feedback (**Annex 7**). These peer-reviewers were identified through various expert panels within and outside WHO. Peer-reviewers are not involved in the guideline development process (66) and are only asked to provide comments on the final draft guideline. Their role is to identify any errors or missing data and to comment on clarity, setting-specific issues, and implications for implementation, not to change the normative statements formulated by the GDG. Reviews from such individuals or organizations on a draft guideline may be helpful in anticipating and dealing with controversy, improving the clarity of the final document, and promoting engagement with all stakeholders.

This document is a WHO guideline and, after executive clearance, represents the decisions, policy, or views of WHO.

Scoping the guideline, evidence appraisal, and decision-making

WHO started this project for updating haemoglobin cutoffs to define anaemia in individuals and populations by convening a prioritization exercise via a two-stage international consultation. Six subtopics were established: physiology of anaemia; haemoglobin cutoffs for different population groups; definition of anaemia across clinical and environmental contexts; approach to development of anaemia cutoffs; laboratory, equipment, regulatory, and diagnostic considerations; and implementation of WHO's haemoglobin threshold guidelines.

Based on the identified subtopics and the normative needs identified at various technical meetings organized by WHO, 17 background papers were commissioned (3, 26–29, 46, 68–79), and the available evidence was presented to the GDG, after input from the WHO Steering Committee to advise and support this normative work.

The first GDG meeting, held in Spain on 6–8 November 2019, developed and prioritized PICO questions and identified topics for further discussions, technical meetings, or research.

The PICO questions were drafted by technical staff at the Department of Nutrition and Food Safety, based on the policy and programme guidance needs of Member States and their partners, although the questions related to the review of haemoglobin cutoffs and adjustment factors to diagnose anaemia did not always fit the format or cover all domains of the evidence-to-decision frameworks.

The evidence was searched systematically for all PICO questions. WHO documents and databases (Cumulative Index to Nursing and Allied Health Literature, Cochrane Library, Google Scholar, Medline, Ovid, PubMed, ScienceDirect, and Scopus) were searched. Databases of clinical trials and WHO databases were searched for ongoing studies, and the grey literature was also reviewed. The search was performed without time or language limitations and snowballing was used with selected reviews and systematic reviews to identify additional references. Due to the nature of the PICO questions and the guideline objective of reviewing cutoffs to define anaemia in individuals and populations, the identification of geographically diverse datasets of raw data for setting cutoffs and reviewing adjustments was prioritized.

The questions were discussed and reviewed by the WHO Steering Committee and the GDG and were modified as needed. The GDG scored the relative importance of each outcome from one to nine (where a score of seven, eight, or nine indicated that the outcome was critical for a decision; a score of four, five, or six indicated that it was important; and a score of three, two, or one indicated that it was not important). A special issue of 17 papers in the *Annals of the New York Academy of Sciences*, including systematic or desk reviews on the priority questions, was the basis for developing the final PICO questions after the first GDG meeting (3, 26–29, 46, 68–79). The key questions, along with the outcomes that were identified as critical for decision-making, are listed in PICO format in **Annex 2**.

WHO convened three technical meetings after the first GDG meeting in 2019 to address several key issues that had been identified as needing addressing before the need for adjustments to account for differences in settings and populations could be considered.

- In October 2020, a technical meeting on considered adjustments of haemoglobin concentrations to define anaemia by elevation above sea level and smoking.
- In April 2021, a technical meeting was held on considerations to determine haemoglobin concentrations to define anaemia in the lifecycle, particularly during pregnancy and to discuss the basis for the revision of the cutoffs to define anaemia focusing on a statistical approach and/or a functional/clinical outcomes approach.
- In December 2021, a third technical meeting considered the role of infection, inflammation, and genetic ancestry as potential determinants for adjustments of haemoglobin concentrations to define anaemia, especially at the population level. This meeting also addressed considerations about blood sampling and analytical methods used for haemoglobin determinations.

Participants of these technical meetings were instructed to declare any interest relevant to the meeting, prior to their participation. At the beginning of each meeting, conflicts of interest were addressed and publicly declared, with no significant conflicts recorded.

The series of second GDG meetings was held virtually on 1–3 June, 15–17 June, and 29 June–1 July 2022. The objectives were to:

- formulate normative statements on the use and interpretation of haemoglobin concentrations for assessing anaemia status in individuals and populations and determine their strength, taking into account benefits, harms, values and preferences, feasibility, equity, ethics, acceptability, resource requirements, and other factors, as appropriate;
- define implications for further research and gaps; and
- discuss implementation and evaluation considerations of the guideline.

The evidence that informed the haemoglobin cutoffs to define anaemia in individuals and populations was based on a commissioned haemoglobin concentration analysis of healthy population databases (18), general population databases (18–22), and systematic reviews (48). For identification of unpublished studies or studies still in progress, a standard procedure was followed to contact more than 10 international organizations working on anaemia prevention and control interventions. In addition, the [ClinicalTrials.gov](#) online database of the National Library of Medicine, United States of America (80), and the [International Clinical Trials Registry Platform](#) (81), which is hosted by WHO, were systematically searched for trials in progress. No language restrictions were applied in the search.

When possible, since some of the questions did not apply to this format due to their intrinsic nature, evidence summaries and profiles were prepared according to the [GRADE](#) approach, to assess the overall certainty of the evidence (82, 83). GRADE considers: the study design; the limitations of the studies in terms of their conduct and analysis; the consistency of the results across the available studies; the directness (or applicability and external validity) of the evidence with respect to the populations, interventions, and settings where the proposed intervention may be used; and the precision of the summary estimate of the effect. The GRADE approach could only be used for a subsection of the questions.

The GDG interpreted the evidence, taking in consideration the Developing and Evaluating Communication Strategies to support Informed Decisions and Practice based on Evidence (DECIDE) framework (84). DECIDE is an evidence-to-decision tool that includes intervention effects, values, resources, equity, acceptability, and feasibility criteria to guide the formulation of the normative statements (85, 86).

The certainty of the direct evidence for the critical outcomes was moderate, and for three of the questions was considered very low. The GRADE summary of findings table for the response of haemoglobin concentrations to nutrition interventions in infants, children and adolescents is shown in **Annex 1**. Readers are directed to the overview of reviews (48) for other tables on interventions and population groups.

The draft normative statements were discussed and voted on at the second GDG meetings, including judgements on harms and benefits and taking into account: (i) desirable and undesirable effects; (ii) the certainty of the available evidence; (iii) values and preferences related to the intervention in different settings; and (iv) the cost and feasibility of the intervention in different settings (**Annex 3**). The WHO Secretariat (**Annex 8**) gathered and circulated a summary of the results to the GDG.

If there was no unanimous consensus (primary decision rule), more time was given for deliberations and a second round of online balloting took place. If no unanimous agreement was reached, a two thirds vote of the GDG was required for approval of the proposed normative statements (secondary decision rule). Divergent opinions could be recorded in the guideline. The results from voting forms are kept on file by WHO for up to 5 years. WHO staff present at the meeting, as well as the systematic reviews teams involved in the collection and grading of the evidence, did not participate in the consensus-building process. Two co-chairs with expertise in managing group processes and interpreting evidence were nominated at the opening of each consultation, and the GDG approved their nomination. Members of the WHO Secretariat were available at all times, to help guide the overall meeting process, but did not vote and did not have veto power.

Deliberations on haemoglobin cutoffs for infants and children aged 6–59 months

During the series of second GDG meetings, while addressing the cutoffs to define anaemia in individuals (**Table 2**), there was discussion about cutoffs for infants and children 6–59 months and a proposal from some members of the GDG was presented. The GDG voted in favour of this new proposal of having a single cutoff of <105 g/dL for the whole 6–59-month age group. This differed from the WHO proposal of separate cutoffs for the age groups 6–23 months and 24–59 months, which was based on there being a consistent difference in haemoglobin concentrations between the two age groups. This raised concerns from some GDG members because: the proposed single cutoff was based on a completely unsupported and separate analysis from Braat et al. (18); the evidence was mixed; and the criteria for the definition health were unclear and inconsistent.

During the drafting of this guideline, and after discussions within the WHO Nutrition and Food Safety Department, it was found that in the analysis of the evidence in Braat et al. (18) and in other publications (19, 20), there is indeed a consistent difference in haemoglobin concentrations between the two age groups. In the data from the Comprehensive National Nutrition Survey in India (19), the difference between the two age groups is 9 g/L, under the assumptions that: (i) the number of boys and girls is the same; (ii) the data children aged 1 year and 2 years can be averaged to represent 6–23 months; and (iii) the data for children aged 3 years, 4 years, and 5 years can be averaged to represent 24–59 months. For the data in Addo et al. (20), the difference between the two age groups is 5 g/L, under the assumption that the sample size for the 22 surveys is one third for 6–23 months age group and two thirds for the 24–59 months age group. These findings were supported by the analysis of an additional database from Ecuador by the Braat et al. authors, which was obtained after the GDG meeting in July 2023. These new data were held to the same health inclusion criteria as the other databases in the original Braat et al. analysis (18).

Within WHO, there was also discussion about the significance and implications of a single haemoglobin cutoff for infants and children from 6 months to 5 years of age, when there are noted differences in growth and nutrient requirements. The relatively large increase (10 g/L) in cutoffs (i.e. from <105 to <115 d/L between the ages of from 59 months and 5 years) was also noted. It was felt that the current evidence and physiological changes occurring in these children supported separation cutoffs for infants and children 6–23 months, 24–59 months, allowing for changes in cutoffs to occur in a transitioned manner. The WHO proposed cutoff presents a gradual increase from 105 g/L at 23 months, to 110 g/L at 59 months, and to 115 g/L from 5 years of age. By contrast, with the original GDG proposal, the cutoff for a 4.5-year-old child would be 105 g/L and would increase to 115 g/L (10 g/L increase) 6 months later when the child reaches 5 years of age.

A third GDG meeting was convened on 8 June 2023 to discuss the rationale of the WHO proposal to separate haemoglobin cutoffs for children from 6 to 59 months of age into two groups (6–23 months, and 24–59 months). The rationale was: (i) to maintain consistency with the health criteria used for defining the other age groups; (ii) analysis of other publications reviewed during the second GDG meeting (18–20) also showed consistent differences in haemoglobin concentrations between children 6–23 months and 24–59 months, ranging between 5 g/L and 9 g/L; (iii) there are noted differences in growth and nutrient requirements between those two age groups; and (iv) additional analysis by Braat and colleagues obtained after the GDG meeting in July 2022 supported the separation of the age groups.

Seven GDG members participated in the online meeting and voted. The proposal and presentations were sent to the four members unable to attend the meeting, along with a request to vote. The result was: yes, eight votes; no, one vote; no answer, two votes.

Management of competing interests

According to the processes recommended in the *WHO handbook for guideline development* (66), all experts participating in WHO meetings must declare any interest relevant to the meeting, prior to their participation. The responsible technical officer and the WHO Steering Committee reviewed the declarations-of-interest statements for all GDG members, before finalization of the group composition and invitation to attend a GDG meeting.

All participants, members of the GDG, and systematic reviews teams of the guideline development meetings, submitted a declaration-of-interests form, along with their curriculum vitae, before each meeting. Participants of these meetings participated in their individual capacity and not as institutional representatives. In addition, they verbally declared any interests that could be perceived to affect their objectivity and independence in providing advice to WHO at the beginning of each meeting. The procedures for management of competing interests strictly followed the *Guidelines for declaration of interests (WHO experts)* (87). The management of the perceived or real conflicts of interest declared by the members of the GDG that are relevant to this guideline was as follows.¹

Dr Rachel Hammonds declared she has worked as a consultant for UNICEF in Kenya to highlight the importance of testing and treating women of reproductive age for anaemia. She was asked to verbally disclose this to the other participants at the start of the GDG meetings.

Dr Crystal Karakochuck declared she has worked as a consultant for WHO in themes related to anaemia. She was asked to verbally disclose this to the other participants at the start of the GDG meetings.

Dr Harshpal Singh Sachdev declared he has done research and published substantially on anaemia, including a recent publication on haemoglobin thresholds in Indian children and adolescents. He was asked to verbally disclose this to the other participants at the start of the GDG meetings.

Dr Melissa F. Young declared she has received funding for research on anaemia. She was asked to verbally disclose this to the other participants at the start of the GDG meetings.

The names of the GDG members, along with a description of the objectives of the meeting, were published on the WHO website prior to the first GDG meeting (88), for public notice and comment. No additional information on any interests or biases relating to the individuals being considered for membership of the GDG were brought to light from the public notice.

Plans for updating the guideline

The WHO Secretariat will continue to follow research developments in the area of anaemia detection, diagnosis and control, particularly for areas in which the evidence was limited and the quality of evidence was found to be very low. If the guideline merits an update, or if there are concerns about the validity of the guideline, the Department of Nutrition and Food Safety, in collaboration with other WHO departments or programmes, will coordinate the guideline update, following the formal procedures of the *WHO handbook for guideline development* (66).

¹ A conflict-of-interest analysis must be performed whenever WHO relies on the independent advice of an expert in order to take a decision or to provide recommendations to Member States or other stakeholders. The term "conflict of interest" means any interest declared by an expert that may affect or be reasonably perceived to affect the expert's objectivity and independence in providing advice to WHO. WHO's conflict-of-interest rules are designed to avoid potentially compromising situations that could undermine or otherwise affect the work of the expert, the committee, or the activity in which the expert is involved, or WHO as a whole. Consequently, the scope of the inquiry is any interest that could reasonably be perceived to affect the functions that the expert is performing.

References

1. Anaemia in women and children. In: Global Health Observatory [online database]. Geneva: World Health Organization; 2019 (<https://www.who.int/data/gho/data/indicators>, accessed 19 January 2024).
2. Nutritional anaemias: tools for effective prevention and control. Geneva: World Health Organization; 2017 (<https://iris.who.int/handle/10665/259425>, accessed 19 January 2024).
3. Chaparro CM, Suchdev PS. Anemia epidemiology, pathophysiology, and etiology in low- and middle-income countries. *Ann N Y Acad Sci.* 2019;1450(1):15-31. doi:10.1111/nyas.14092.
4. Global anaemia reduction efforts among women of reproductive age: impact, achievement of targets and the way forward for optimizing efforts. Geneva: World Health Organization; 2020 (<https://iris.who.int/handle/10665/336559>, accessed 19 January 2024).
5. Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. *Cochrane Database Syst Rev.* 2004;(2):CD000363. doi:10.1002/14651858.CD000363.pub2.
6. Zhu PH, Mhango SN, Vinnakota A, Mansour M, Coss-Bu JA. Effects of COVID-19 pandemic on nutritional status, feeding practices, and access to food among infants and children in lower and middle-income countries: a narrative review. *Curr Trop Med Rep.* 2022;9(4):197-206. doi:10.1007/s40475-022-00271-8.
7. Global nutrition targets 2025: policy brief series. Geneva: World Health Organization; 2014 (<https://iris.who.int/handle/10665/149018>, accessed 19 January 2024).
8. The 17 goals. New York: Department of Economic and Social Affairs, United Nations; 2021 (<https://sustainabledevelopment.un.org/sdgs>, accessed 19 January 2024).
9. Resolution 70/1. Transforming our world: the 2030 Agenda for Sustainable Development. In: Seventieth United Nations General Assembly, New York, 21 October 2015. New York: United Nations General Assembly; 2015 (A/RES/70/1; https://www.un.org/en/development/desa/population/migration/generalassembly/docs/globalcompact/A_RES_70_1_E.pdf, accessed 19 January 2024).
10. Comprehensive implementation plan on maternal, infant and young child nutrition. Geneva: World Health Organization; 2014 (<https://apps.who.int/iris/handle/10665/113048>, accessed 19 January 2024).
11. Global strategy for women's, children's and adolescents' health data portal [online database]. Geneva: World Health Organization; 2015 (<https://www.who.int/data/maternal-newborn-child-adolescent-ageing/global-strategy-data>, accessed 19 January 2024).
12. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva: World Health Organization; 2011 (<https://iris.who.int/handle/10665/85839>, accessed 19 January 2024).
13. Nutritional anaemias. Report of a WHO scientific group. Geneva: World Health Organization, 1968 (<https://iris.who.int/handle/10665/40707>, accessed 19 January 2024).
14. DeMaeyer EM, Dallman P, Gurney JM, Hallberg L, Sood SK, Srikantia SG. Preventing and controlling iron deficiency anaemia through primary health care. A guide for health administrators and programme managers. Geneva: World Health Organization; 1989 (<https://iris.who.int/handle/10665/39849>, accessed 19 January 2024).
15. The management of nutrition in major emergencies. Geneva: World Health Organization; 2000 (<https://iris.who.int/handle/10665/42085>, accessed 19 January 2024).
16. United Nations Children's Fund, United Nations University, World health Organization. Iron deficiency anaemia: assessment, prevention and control. A guide for programme managers. Geneva: World Health Organization; 2001 (<https://www.who.int/publications/m/item/iron-children-6to23--archived-iron-deficiency-anaemia-assessment-prevention-and-control>, accessed 19 January 2024).
17. World Health Organization, Centers for Disease Control and Prevention. Assessing the iron status of populations, second edition. Geneva: World Health Organization; 2004 (<https://iris.who.int/handle/10665/75368>, accessed 19 January 2024).

18. Braat S, Fielding K, Han J, Jackson VE, Zaloumis S, Xu JXH et al. Haemoglobin thresholds to define anaemia from age 6 months to 65 years: estimates from international data sources. *Lancet Haematol*. 2024;S2352-3026(24)00030-9. doi:10.1016/S2352-3026(24)00030-9.
19. Sachdev HS, Porwal A, Acharya R, Ashraf S, Ramesh S, Khan N et al. Haemoglobin thresholds to define anaemia in a national sample of healthy children and adolescents aged 1–19 years in India: a population-based study. *Lancet Glob Health*. 2021;9(6):e822-31. doi:10.1016/S2214-109X(21)00077-2.
20. Addo OY, Yu EX, Williams AM, Young MF, Sharma AJ, Mei Z et al. Evaluation of hemoglobin cutoff levels to define anemia among healthy individuals. *JAMA Netw Open*. 2021;4(8):e2119123. doi:10.1001/jamanetworkopen.2021.19123.
21. Ohuma EO, Young MF, Martorell R, Ismail LC, Peña-Rosas JP, Purwar M et al. International values for haemoglobin distributions in healthy pregnant women. *EClinicalMedicine*. 2020;29-30:100660. doi:10.1016/j.eclinm.2020.100660.
22. Ohuma EO, Jabin N, Young MF, Epie T, Martorell R, Peña-Rosas JP et al. Association between maternal haemoglobin concentrations and maternal and neonatal outcomes: the prospective, observational, multinational, INTERBIO-21st fetal study. *Lancet Haematol*. 2023;10(9):e756-66. doi:10.1016/S2352-3026(23)00170-9.
23. Villar J, Altman DG, Purwar M, Noble JA, Knight HE, Ruyan P et al; International Fetal and Newborn Growth Consortium for the 21st Century. The objectives, design and implementation of the INTERGROWTH-21st Project. *BJOG*. 2013;120 Suppl 2:9-26. doi:10.1111/1471-0528.12047.
24. Kennedy SH, Victora CG, Craik R, Ash S, Barros FC, Barsosio HC et al. Deep clinical and biological phenotyping of the preterm birth and small for gestational age syndromes: the INTERBIO-21st newborn case-control study protocol. *Gates Open Res*. 2019;5;2:49. doi:10.12688/gatesopenres.12869.2.
25. Ali SA, Tikmani SS, Saleem S, Patel AB, Hibberd PL, Goudar SS et al. Hemoglobin concentrations and adverse birth outcomes in South Asian pregnant women: findings from a prospective maternal and neonatal health registry. *Reprod Health*. 2020;17 Suppl 2:154. doi:10.1186/s12978-020-01006-6.
26. Jung J, Rahman MM, Rahman MS, Swe KT, Islam MR, Rahman MO et al. Effects of hemoglobin levels during pregnancy on adverse maternal and infant outcomes: a systematic review and meta-analysis. *Ann N Y Acad Sci*. 2019;1450(1):69–82. doi:10.1111/nyas.14112.
27. Young MF, Oaks BM, Tandon S, Martorell R, Dewey KG, Wendt AS. Maternal hemoglobin concentrations across pregnancy and maternal and child health: a systematic review and meta-analysis. *Ann N Y Acad Sci*. 2019;1450(1):47–68. doi:10.1111/nyas.14093.
28. Young MF, Oaks BM, Rogers HP, Tandon S, Martorell R, Dewey KG et al. Maternal low and high hemoglobin concentrations and associations with adverse maternal and infant health outcomes: an updated global systematic review and meta-analysis. *BMC Pregnancy Childbirth*. 2023;23(1):264. doi:10.1186/s12884-023-05489-6.
29. Sharma AJ, Addo OY, Mei Z, Suchdev PS. Reexamination of hemoglobin adjustments to define anemia: altitude and smoking. *Ann N Y Acad Sci*. 2019;1450(1):190–203. doi:10.1111/nyas.14167.
30. Kanu FA, Jefferds ME, Williams AM, Suchdev PS, Sharma AJ. Association between hemoglobin and elevation among school-aged children: a verification of proposed adjustments. *Am J Clin Nutr* doi:10.1016/j.ajcnut.2023.04.014.
31. World malaria report 2021. Geneva: World Health Organization; 2021 (<https://iris.who.int/handle/10665/350147>, accessed 19 January 2024).
32. White N. Anaemia and malaria. *Malar J*. 2018;17(1):371. doi:10.1186/s12936-018-2509-9.
33. Wiciński M, Liczner G, Cadelski K, Koźnierzak T, Nowaczewska M, Malinowski B. Anemia of chronic diseases: wider diagnostics – better treatment? *Nutrients*. 2020;12(6):1784. doi:10.3390/nu12061784.
34. Fraenkel PG. Anemia of inflammation: a review. *Med Clin North Am*. 2017;101(2):285-96. doi:10.1016/j.mcna.2016.09.005.
35. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. *Blood*. 2019;133(1):40-50. doi:10.1182/blood-2018-06-856500.

36. Ganz T. Anemia of Inflammation *N Engl J Med*. 2019;381:1148-57. doi:10.1056/NEJMra1804281.
37. Gelaw Y, Getaneh Z, Melku M. Anemia as a risk factor for tuberculosis: a systematic review and meta-analysis. *Environ Health Prev Med*. 2021;26(1):13-29. doi:10.1186/s12199-020-00931-z.
38. Chiossi G, Palomba S, Costantine MM, Falbo AI, Harirah HM, Saade GR et al. Reference intervals for hemoglobin and hematocrit in a low-risk pregnancy cohort: implications of racial differences. *J Matern Fetal Neonatal Med*. 2019;32(17):2897-04. doi:10.1080/14767058.2018.1452905.
39. Varghese JS, Thomas T, Kurpad AV. Evaluation of haemoglobin cut-off for mild anaemia in Asians – analysis of multiple rounds of two national nutrition surveys. *Indian J Med Res*. 2019;150(4):385-89. doi:10.4103/ijmr.IJMR_334_18.
40. Lim E, Miyamura J, Chen JJ. Racial/ethnic-specific reference intervals for common laboratory tests: a comparison among Asians, Blacks, Hispanics, and White. *Hawaii J Med Public Health*. 2015;74(9):302-10 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4578165/>, accessed 19 January 2024).
41. Weyand A, McGann P. Eliminating race-based reference ranges in haematology: a call to action. *Lancet Haematol* 2021;8:e462-66. doi:10.1016/S2352-3026(21)00106-X.
42. Jallow MW, Cerami C, Clark TG, Prentice AM, Campino S. Differences in the frequency of genetic variants associated with iron imbalance among global populations. *PLoS One*. 2020;15(7):e0235141. doi:10.1371/journal.pone.0235141.
43. Kang W, Barad A, Clark AG, Wang Y, Lin X, Gu Z, O'Brien KO. Ethnic differences in iron status. *Adv Nutr*. 2021;12(5):1838-1853. doi:10.1093/advances/nmab035.
44. Karakochuk CD, Rappaport AI, Barr SI, Green TJ. Mean hemoglobin concentrations in fasting venous and non-fasting capillary blood of Cambodian women using a hemoglobinometer and an automated hematology analyzer. *Clin Chem Lab Med*. 2017;55(11):e247-50. doi:10.1515/cclm-2017-0118.
45. Larson LM, Braat S, Hasan MI, Mwangi MN, Estepa F, Hossain SJ et al. Preanalytic and analytic factors affecting the measurement of haemoglobin concentration: impact on global estimates of anaemia prevalence. *BMJ Glob Health*. 2021;6(7):e005756. doi:10.1136/bmjgh-2021-005756.
46. Neufeld L, Larson L, Kurpad A, Mburu S, Martorell R, Brown K. Hemoglobin concentration and anemia diagnosis in venous and capillary blood: biological basis and policy implications. *Ann NY Acad Sci*. 2019;450:172-89. doi:10.1111/nyas.14139.
47. Whitehead RD Jr, Zhang M, Sternberg MR, Schleicher RL, Drummeh B, Mapango C et al. Effects of preanalytical factors on hemoglobin measurement: a comparison of two HemoCue® point-of-care analyzers. *Clin Biochem*. 2017;50(9):513-20. doi:10.1016/j.clinbiochem.2017.04.006.
48. da Silva Lopes K, Yamaji N, Rahman MO, Suto M, Takemoto Y, Garcia-Casal MN et al. Nutrition-specific interventions for preventing and controlling anaemia throughout the life cycle: an overview of systematic reviews. *Cochrane Database Syst Rev*. 2021;9(9):CD013092. doi:10.1002/14651858.CD013092.pub2.
49. Kassebaum NJ; GBD 2013 Anemia Collaborators. The global burden of anemia. *Hematol Oncol Clin North Am*. 2016;30(2):247-308. doi:10.1016/j.hoc.2015.11.002.
50. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390:1211-59. doi:10.1016/S0140-6736(17)32154-2.
51. Safiri S, Kolahi AA, Noori M, Nejadghaderi SA, Karamzad N, Bragazzi N et al. Burden of anemia and its underlying causes in 204 countries and territories, 1990–2019: results from the Global Burden of Disease Study 2019. *J Hematol Oncol*. 2021;14(1):185. doi:10.1186/s13045-021-01202-2.
52. Horton S, Gelband H, Jamison D, Levin C, Nugent R, Watkins D. Ranking 93 health interventions for low- and middle-income countries by cost-effectiveness. *PLoS One*. 2017 Aug 10;12(8):e0182951. doi:10.1371/journal.pone.0182951.
53. Nutrition [website]. Geneva: World Health Organization; 2021 (<https://www.who.int/health-topics/nutrition>, accessed 19 January 2024).

54. e-Library of Evidence for Nutrition Actions (eLENA) [online database]. Geneva: World Health Organization; 2021 (<https://www.who.int/tools/elena/>, accessed 19 January 2024).
55. Blas E, Kurup AS, editors. Equity, social determinants and public health programmes. Geneva: World Health Organization; 2010 (<https://apps.who.int/iris/handle/10665/44289>, accessed 19 January 2024).
56. O'Neill J, Tabish H, Welch V, Petticrew M, Pottie K, Clarke M et al. Applying an equity lens to interventions: using PROGRESS ensures consideration of socially stratifying factors to illuminate inequities in health. *J Clinical Epidemiol.* 2014;67:56-64. doi:10.1016/j.jclinepi.2013.08.005.
57. Handbook on health inequality monitoring with a special focus on low- and middle-income countries. Geneva: World Health Organization; 2013 (<https://apps.who.int/iris/handle/10665/85345>, accessed 19 January 2024).
58. Health equity assessment toolkit. In: Health inequality monitor [online database]. Geneva: World Health Organization; 2021 (https://www.who.int/data/inequality-monitor/assessment_toolkit, accessed 19 January 2024).
59. World Health Organization, ExpandNet. Nine steps for developing a scaling-up strategy. Geneva: World Health Organization; 2010 (<https://apps.who.int/iris/handle/10665/44432>, accessed 19 January 2024).
60. Accelerating anaemia reduction: a comprehensive framework for action. Geneva: World Health Organization; 2023 (<https://iris.who.int/handle/10665/367661>, accessed 19 January 2024).
61. Anaemia Action Alliance. Geneva: World Health Organization; 2023 (<https://www.who.int/teams/nutrition-and-food-safety/anaemia-action-alliance>, accessed 19 January 2024).
62. Maternal, newborn, child and adolescent health and ageing data portal [online database]. Geneva: World Health Organization; 2021 (<https://platform.who.int/data/maternal-newborn-child-adolescent-ageing>, accessed 19 January 2024).
63. Micronutrients Database [online database]. In: Vitamin and Mineral Nutrition Information System (VMNIS). Geneva: World Health Organization; 2021 (<https://www.who.int/teams/nutrition-and-food-safety/databases/vitamin-and-mineral-nutrition-information-system>, accessed 19 January 2024).
64. Global targets tracking tool [online database]. Geneva: World Health Organization; 2021 (<https://www.who.int/tools/global-targets-tracking-tool>, accessed 19 January 2024).
65. Global database on the Implementation of Nutrition Action (GINA) [online database]. Geneva: World Health Organization; 2021 (<https://extranet.who.int/nutrition/gina/en>, accessed 19 January 2024).
66. WHO handbook for guideline development, 2nd edition. Geneva: World Health Organization; 2014 (<https://iris.who.int/handle/10665/145714>, accessed 19 January 2024).
67. Expert advisory panels and committees [website]. Geneva: World Health Organization; 2010 (<https://www.who.int/about/collaboration/expert-advisory-panels-and-committees>, accessed 19 January 2024).
68. Barrera-Reyes PK, Tejero ME. Genetic variation influencing hemoglobin levels and risk for anemia across populations. *Ann N Y Acad Sci.* 2019;1450(1):32-46. doi:10.1111/nyas.14200.
69. Chai KL, Cole-Sinclair M. Review of available evidence supporting different transfusion thresholds in different patient groups with anemia. *Ann N Y Acad Sci.* 2019;1450(1):221-38. doi:10.1111/nyas.14203.
70. Williams AM, Addo OY, Grosse SD, Kassebaum NJ, Rankin Z, Ballesteros KE et al. Data needed to respond appropriately to anemia when it is a public health problem. *Ann N Y Acad Sci.* 2019;1450(1):268-80. doi:10.1111/nyas.14175.
71. Gassmann M, Mairbäurl H, Livshits L, Seide S, Hackbusch M, Malczyk M, Kraut S et al. The increase in hemoglobin concentration with altitude varies among human populations. *Ann N Y Acad Sci.* 2019;1450(1):204-20. doi:10.1111/nyas.14136.
72. Kothari MT, Coile A, Huestis A, Pullum T, Garrett D, Engmann C. Exploring associations between water, sanitation, and anemia through 47 nationally representative demographic and health surveys. *Ann N Y Acad Sci.* 2019;1450(1):249-67. doi:10.1111/nyas.14109.
73. Whitehead RD Jr, Mei Z, Mapango C, Jefferds MED. Methods and analyzers for hemoglobin measurement in clinical laboratories and field settings. *Ann N Y Acad Sci.* 2019;1450(1):147-71. doi:10.1111/nyas.14124.

74. Larson LM, Kubes JN, Ramírez-Luzuriaga MJ, Khishen S, H Shankar A, Prado EL. Effects of increased hemoglobin on child growth, development, and disease: a systematic review and meta-analysis. *Ann N Y Acad Sci.* 2019;1450(1):83-104. doi:10.1111/nyas.14105.
75. Sinharoy SS, Fanzo J. Ethical and human rights considerations related to access to anemia diagnosis. *Ann N Y Acad Sci.* 2019;1450(1):239-48. doi:10.1111/nyas.14125.
76. Jorgensen JM, Crespo-Bellido M, Dewey KG. Variation in hemoglobin across the life cycle and between males and females. *Ann N Y Acad Sci.* 2019;1450(1):105-25. doi:10.1111/nyas.14096.
77. Garcia-Casal MN, Pasricha SR, Sharma AJ, Peña-Rosas JP. Use and interpretation of hemoglobin concentrations for assessing anemia status in individuals and populations: results from a WHO technical meeting. *Ann N Y Acad Sci.* 2019;1450(1):5-14. doi:10.1111/nyas.14090.
78. Cordero D, Aguilar AM, Casanovas C, Vargas E, Lutter CK. Anemia in Bolivian children: a comparative analysis among three regions of different altitudes. *Ann N Y Acad Sci.* 2019;1450(1):281-90. doi:10.1111/nyas.14038.
79. Karakochuk CD, Hess SY, Moorthy D, Namaste S, Parker ME, Rappaport AI et al; HEMoglobin MEasurement (HEME) Working Group. Measurement and interpretation of hemoglobin concentration in clinical and field settings: a narrative review. *Ann N Y Acad Sci.* 2019;1450(1):126-46. doi:10.1111/nyas.14003.
80. Bethesda: National Library of Medicine; 2019 (<https://clinicaltrials.gov/>, accessed 19 January 2024).
81. International Clinical Trials Registry Platform (ICTRP) [online database]. Geneva: World Health Organization; 2019 (<https://www.who.int/clinical-trials-registry-platform>, accessed 19 January 2024).
82. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336:924-26. doi:10.1136/bmj.39489.470347.AD.
83. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J et al. GRADE guidelines: 1. Introduction – GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol.* 2011;64:383-94. doi:10.1016/j.jclinepi.2010.04.026.
84. GRADE Working Group, Cochrane Applicability and Recommendations Methods Group. DECIDE (2011–2015). Evidence to Decision (EtD) framework. London: Cochrane Collaboration; 2015 (<http://www.decide-collaboration.eu/evidencedecision-etd-framework>, accessed 19 January 2024).
85. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M et al; GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ.* 2016;353:i2089. doi:10.1136/bmj.i2089. PMID: 27365494.
86. Schünemann HJ, Mustafa R, Brozek J, Santesso N, Alonso-Coello P, Guyatt G et al; GRADE Working Group. GRADE guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. *J Clin Epidemiol.* 2016;76:89-98. doi: 10.1016/j.jclinepi.2016.01.032.
87. Guidelines for declaration of interests (WHO experts). Geneva: World Health Organization; 2014 (<https://www.emro.who.int/images/stories/polio/doi-guidelines.pdf?ua=1>, accessed 19 January 2024).
88. WHO guideline development group meeting. Use and interpretation of haemoglobin concentrations for assessing anaemia status in individuals and populations. Geneva: World Health Organization; 2019 (<https://www.who.int/news-room/events/detail/2019/11/06/default-calendar/who-guideline-development-group-meeting---use-and-interpretation-of-haemoglobin-concentrations-for-assessing-anaemia-status-in-individuals-and-populations>, accessed 19 January 2024).

Annex 1. GRADE summary of findings tables

The GRADE summary of findings tables in **Annex 1** refer only to question 4: Is haemoglobin concentration an adequate marker for assessing the impact of iron interventions?

Table A1.1. Daily oral supplementation containing iron compared to the same supplementation without iron for prevention or treatment of iron deficiency anaemia in infants, children, and adolescents

Patient or population: Infants, children, and adolescents

Setting: Any country

Intervention: Iron supplementation

Comparison: Daily oral supplementation containing iron compared to the same supplementation without iron for prevention or treatment of iron deficiency anaemia in infants, children, and adolescents

Number of studies	Study design	Certainty assessment					Number of patients		Effect		Certainty (GRADE)
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daily oral supplementation containing iron	Same supplementation without iron	Relative (95% CI)	Absolute (95% CI)	
12	Randomized trials	Not serious	Serious ^a	Not serious	Not serious	None	1042/3083 (33.8%)	1474/3032 (48.6%)	OR 0.40 (0.29 to 0.54)	212 fewer per 1000 (from 271 fewer to 148 fewer)	⊕⊕⊕⊖ Moderate
52	Randomized trials	Serious ^b	Very serious ^c	Not serious	Not serious	Publication bias strongly suspected ^d	6852	6698	–	MD 8.1 higher (6.59 higher to 9.6 higher)	⊕⊖⊖⊖ Very low
9	Randomized trials	Serious ^e	Serious ^f	Not serious	Not serious	Publication bias strongly suspected ^g	693	724	–	MD 24.15 higher (18.99 higher to 29.31 higher)	⊕⊖⊖⊖ Very low

Certainty assessment							Number of patients		Effect		Certainty (GRADE)
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daily oral supplementation containing iron	Same supplementation without iron	Relative (95% CI)	Absolute (95% CI)	
8	Randomized trials	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected ^g	17/1098 (1.5%)	184/975 (18.9%)	OR 0.07 (0.04 to 0.12)	173 fewer per 1000 (from 179 fewer to 162 fewer)	⊕⊕⊕⊖ Moderate
6	Randomized trials	Not serious	Serious ^h	Not serious	Not serious	Publication bias strongly suspected ^g	416/1340 (31.0%)	620/1293 (48.0%)	OR 0.39 (0.32 to 0.47)	215 fewer per 1000 (from 252 fewer to 177 fewer)	⊕⊕⊖⊖ Low

CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MD: mean difference; OR: odds ratio.

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^a Downgraded by one level as the direction is consistent. The substantial heterogeneity (I squared = 83%) is probably driven by the variation in the magnitude of the effect.

^b Downgraded by one level as there is not sufficient information on the random sequence generation and allocation concealment. Further, although many studies were identified as high risk for blinding of participants, most of these studies were identified as low bias for outcome detection. Therefore, not a significant concern. Selective reporting bias was noted for some studies.

^c Downgraded by two levels as both direction and magnitude appear to be inconsistent. Further, there is considerable heterogeneity (I squared = 97%).

^d There appears to be publication bias with most studies concentrated to the left of the funnel plot.

^e There appears to be concerns about random sequence generation and allocation concealment in most studies. In addition, some studies report concerns of attrition bias as well as selective reporting bias.

^f Downgraded by one level as the direction is consistent. The substantial heterogeneity (I squared = 79%) is probably driven by the variation in the magnitude of the effect.

^g There appears to be publication bias for studies with smaller sample size.

^h Downgraded by one level as there is substantial heterogeneity and some inconsistency in direction as well.

Table A1.2. Daily oral supplementation with iron alone compared to no treatment or placebo for prevention or treatment of iron deficiency anaemia in infants, children, and adolescents**Patient or population:** Infants, children, and adolescents**Setting:** Any country**Intervention:** Iron supplementation**Comparison:** Daily oral supplementation with iron alone compared to no treatment or placebo for prevention or treatment of iron deficiency anaemia in infants, children, and adolescents

Number of studies	Certainty assessment						Number of patients		Effect		Certainty (GRADE)
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daily oral supplementation with iron alone	No treatment or placebo	Relative (95% CI)	Absolute (95% CI)	
11	Randomized trials	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected ^a	685/2246 (30.5%)	991/2155 (46.0%)	OR 0.50 (0.44 to 0.56)	161 fewer per 1000 (from 187 fewer to 137 fewer)	⊕⊕⊕⊖ Moderate
9	Randomized trials	Not serious	Serious ^b	Not serious	Serious ^c	None	11/755 (1.5%)	102/744 (13.7%)	OR 0.10 (0.05 to 0.18)	121 fewer per 1000 (from 129 fewer to 109 fewer)	⊕⊕⊖⊖ Low
48	Randomized trials	Serious ^d	Serious ^e	Not serious	Serious ^c	Publication bias strongly suspected ^f	5370	5209	–	MD 9.75 higher (9.57 higher to 9.93 higher)	⊕⊖⊖⊖ Very low
5	Randomized trials	Not serious	Serious ^b	Not serious	Serious ^c	None	396/1041 (38.0%)	529/1006 (52.6%)	OR 0.46 (0.38 to 0.57)	188 fewer per 1000 (from 229 fewer to 139 fewer)	⊕⊕⊖⊖ Low

Certainty assessment							Number of patients		Effect		Certainty (GRADE)
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daily oral supplementation with iron alone	No treatment or placebo	Relative (95% CI)	Absolute (95% CI)	
9	Randomized trials	Serious ^d	Not serious	Not serious	Not serious	Publication bias strongly suspected ^g	521	518	–	MD 23.59 higher (19.95 higher to 27.23 higher)	⊕⊕⊖⊖ Low

CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MD: mean difference; OR: odds ratio.

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^a Publication bias appears to be present for studies with smaller sample size. further, the rest are all concentrated to the right side of the funnel.

^b Inconsistency observed for both magnitude and direction.

^c Several studies report both benefit and harm.

^d Several studies report some concerns about random sequence generation and allocation concealment. Further, selective reporting bias detected in several studies too.

^e Inconsistency observed for magnitude but not direction.

^f Most studies scattered to the left.

^g Some studies fell outside of the funnel plot and the distribution does not appear to be uniform within the funnel plot.

Table A1.3 Daily oral supplementation with iron plus folic acid compared to no treatment or placebo for prevention or treatment of iron deficiency anaemia in infants, children, and adolescents**Patient or population:** Infants, children, and adolescents**Setting:** Any country**Intervention:** Iron supplementation**Comparison:** Daily oral supplementation with iron plus folic acid compared to no treatment or placebo for prevention or treatment of iron deficiency anaemia in infants, children, and adolescents

Number of studies	Study design	Risk of bias	Certainty assessment				Number of patients		Effect		Certainty (GRADE)
			Inconsistency	Indirectness	Imprecision	Other considerations	Daily oral supplementation with iron + folic acid	No treatment or placebo	Relative (95% CI)	Absolute (95% CI)	
2	Randomized trials	Serious ^a	Not serious	Not serious	Not serious	None	22/120 (18.3%)	87/122 (71.3%)	OR 0.09 (0.05 to 0.17)	530 fewer per 1000 (from 603 fewer to 416 fewer)	⊕⊕⊕⊖ Moderate
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected ^b	6/146 (4.1%)	42/159 (26.4%)	OR 0.12 (0.05 to 0.29)	223 fewer per 1000 (from 247 fewer to 170 fewer)	⊕⊕⊕⊖ Moderate
4	Randomized trials	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected ^c	279	285	–	MD 13.4 higher (11.09 higher to 15.72 higher)	⊕⊕⊕⊖ Moderate
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected ^b	146	159	–	MD 33.99 higher (27.66 higher to 40.32 higher)	⊕⊕⊕⊖ Moderate

CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MD: mean difference; OR: odds ratio.

GRADE Working Group grades of evidence**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.**Moderate certainty:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.**Low certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.**Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.^a There are some concerns with random sequence generation and allocation concealment. Further, risk of bias is high for blinding of participants and providers but this does not seem to influence outcome assessment and attrition.^b Only one study has been reported.^c All the data points lie on the central line of the funnel plot and are not distributed on either side.

Table A1.4 Daily oral supplementation with iron plus vitamins and minerals compared to the same vitamins and minerals without iron supplementation for prevention or treatment of iron deficiency anaemia in infants, children, and adolescents

Patient or population: Infants, children, and adolescents

Setting: any country

Intervention: iron supplementation

Comparison: Daily oral supplementation with iron plus vitamins and minerals compared to the same vitamins and minerals without iron supplementation for prevention or treatment of iron deficiency anaemia in infants, children, and adolescents

Number of studies	Study design	Certainty assessment					Number of patients		Effect		Certainty (GRADE)
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daily oral supplementation with iron + vitamins and minerals	Same vitamins and minerals without iron supplementation	Relative (95% CI)	Absolute (95% CI)	
4	Randomized trials	Not serious	Serious ^a	Not serious	Not serious	Publication bias strongly suspected ^b	100/499 (20.0%)	195/537 (36.3%)	OR 0.44 (0.33 to 0.59)	163 fewer per 1000 (from 205 fewer to 111 fewer)	⊕⊕⊖⊖ Low
3	Randomized trials	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected ^c	7/300 (2.3%)	76/336 (22.6%)	OR 0.08 (0.04 to 0.18)	203 fewer per 1000 (from 215 fewer to 176 fewer)	⊕⊕⊕⊖ Moderate
12	Randomized trials	Serious ^d	Serious ^e	Not serious	Not serious	Publication bias strongly suspected ^f	927	922	–	MD 1.35 higher (1.14 higher to 1.56 higher)	⊕⊖⊖⊖ Very low

Number of studies	Study design	Certainty assessment					Number of patients		Effect		Certainty (GRADE)
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daily oral supplementation with iron + vitamins and minerals	Same vitamins and minerals without iron supplementation	Relative (95% CI)	Absolute (95% CI)	
2	Randomized trials	Serious ^g	Serious ^h	Not serious	Serious ⁱ	None	17/217 (7.8%)	80/217 (36.9%)	OR 0.15 (0.08 to 0.26)	288 fewer per 1000 (from 324 fewer to 237 fewer)	⊕⊕⊕⊕ Very low
3	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	162	193	–	MD 16.9 higher (13.59 higher to 20.2 higher)	⊕⊕⊕⊕ High

CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MD: mean difference; OR: odds ratio.

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^a There appears to be inconsistency in magnitude but not direction. There appears to be substantial heterogeneity between studies (I squared = 79%).

^b Points representing studies with smaller sample size (greater standard error) were to the left of the funnel plot and those representing studies with larger sample size (smaller standard error) were to the right side.

^c Points are not randomly scattered, but instead appear to be linear.

^d Multiple studies have a high a risk of bias for one or more domains. Further, several studies have some concerns for random sequence generation and allocation concealment.

^e There appears to be substantial heterogeneity (I squared = 90%) and there appears to be inconsistency in both direction and magnitude.

^f All points appear on the central line of the funnel plot, not randomly scattered.

^g There appear to be some concerns for random sequence generation and allocation concealment.

^h There appears to be significant heterogeneity (I squared = 67%) and inconsistency in both direction and magnitude.

ⁱ Studies report both benefit and harm.

Annex 2. Questions in PICO format

Question 1

What should be the haemoglobin cutoffs to define anaemia in individuals and in populations?

1.a How should the cutoffs be defined?

Should they be based on statistical cutoffs, such as percentile-based cutoffs or a reference range of haemoglobin concentrations in apparently healthy populations, or based on outcomes related to clinical symptoms or functional impairment?

1.b How should mild, moderate, and severe anaemia be defined at individual level?

Table A2.1. Question 1 in PICO format

Population	Apparently healthy individuals/populations (anaemic or non-anaemic) of any sex, age (i.e. infants, children, adults) and pregnancy status in any country
Indicator	Haemoglobin concentrations
Comparator	- Haemoglobin cutoff for anaemia defined by: - statistical aberration below the norm for the group of interest (e.g. using 2.5th percentiles or 2 standard deviations below the mean), or - assessment of cutoffs below which clinical symptoms or functional impairments are noted to occur in populations of interest - Anaemia defined by the haemoglobin concentration below a set cutoff based on age and/or sex to define overall and/or mild, moderate, and severe anaemia
Outcomes	- Accurate diagnosis of anaemia using cutoff defined by: - Statistical aberration below the norm for the defined group (e.g. using 2.5th percentiles, or 2 standard deviations below the mean); or - Assessment of thresholds below which clinical symptoms or functional impairments are noted to occur in populations of interest - Haemoglobin cutoffs below which clinical symptoms, increased risk of mortality, developmental impairment (cognitive, psychomotor, language, physical), and/or other conditions requiring further clinical investigation (e.g. genetic condition, nutritional deficiency, chronic bleeding) are noted to occur in populations of interest. Haemoglobin concentrations below which physical/neurological development, social interactions, and growth in children are affected. Maternal haemoglobin concentrations below which fetal development (e.g. fetal brain development) and pregnancy outcomes are affected - Haemoglobin cutoffs outside the population statistical reference range by age and sex, or below which clinical symptoms or functional impairments are noted to occur in populations of interest, to define overall and/or mild, moderate, and severe anaemia. - Clinical outputs: morbidity (e.g. cardiovascular, respiratory); mortality, growth, and developmental/behavioural/social outcomes (depending on age group, including older persons); productivity (physical, e.g. maximal oxygen uptake [VO₂ max] or educational; pregnancy/birth outcomes; quality of life (daily/usual activity); transfusion - Statistical outputs: 2.5, 5th, 10th percentiles

Question 2

Should haemoglobin cutoffs be adjusted by exposure to external factors or settings known to affect haemoglobin?

- 2.a** Should haemoglobin cutoffs to define anaemia be adjusted for elevation of residence and/or smoking?
- 2.b** Should haemoglobin cutoffs to define anaemia be adjusted by inflammation/infection, particularly in malaria-endemic settings?
- 2.c** Should haemoglobin cutoffs to define anaemia be adjusted by genetic ancestry/ethnicity/race?

Table A2.2. Question 2 in PICO format

Population	Apparently healthy individuals/populations (anaemic or non-anaemic) of any sex, age (i.e. infants, children, adults) and pregnancy status in any country
Indicator	- Haemoglobin concentrations - Acute phase proteins (c-reactive protein and/or a1-acid glycoprotein) - Other biomarkers
Comparator	- Anaemia defined by the haemoglobin concentration below a set cutoff based on elevation of residence/work, smoking, infections (especially malaria), genetic ancestry/ethnicity/race - Haemoglobin concentrations in seasons of low and high infection burden
Outcomes	- Accurate diagnosis of anaemia using cutoff adjustments appropriate for population elevation of residence/work, smoking, infections (especially malaria), genetic ancestry/ethnicity/race - Haemoglobin cutoffs outside the population statistical reference range by elevation of residence, smoking, genetic ancestry/ethnicity/race, and malaria endemicity. - Haemoglobin cutoffs below which clinical symptoms or increased risk of mortality are noted to occur by elevation of residence, smoking, genetic ancestry/ethnicity/race, and malaria endemicity. - Clinical outputs: morbidity (e.g. cardiovascular, respiratory); mortality, growth, and developmental/behavioural/social outcomes (depending on age group, including older persons); productivity (physical, e.g. maximal oxygen uptake [VO₂ max] or educational); pregnancy/birth outcomes; quality of life (daily/usual activity); transfusion - Statistical outputs: 2.5th, 5th, 10th percentiles

Question 3

How should haemoglobin concentration be measured?

- 3.a** What are the acceptable alternative methods for assessing haemoglobin concentration compared to reference standard (e.g. automated haematology analyser) particularly for population-based or field-based surveys?
- 3.b** What are the key quality control issues pertinent to accurate diagnosis of anaemia?
- 3.c** What blood source(s) are acceptable? How do results vary in capillary blood (finger, heel, ear, single drop, pooled drops) or arterial blood as compared to venous blood (reference)?

Table A2.3. Question 3 in PICO format

Population	• Apparently healthy individuals/populations (anaemic or non-anaemic) of any sex, age (i.e. infants, children, adults) and pregnancy status in any country
Index test	• Haemoglobin concentrations measured by any available test • Anaemia diagnosis – any available test
Comparator	• Haemoglobin concentration determinations by cyanmethaemoglobin method, copper sulfate gravimetric method, haemoglobin colour scale method, spun microhematocrit method • Automated, manual, point-of-care testing, quantitative and semiquantitative (Sahli) methods • Use of international standards, commutable standards and calibration materials to achieve quality control
Outcomes	• Comparability of blood samples to be used at clinical and public health levels for accurate haemoglobin determinations: capillary samples (finger, heel, ear, single drop, pooled drops) to venous blood (reference) • Haemoglobin method/equipment to use at clinical and public health levels comparable to reference standard (automated haematology analyser) • Source and handling of blood • Use of international standard materials • Outputs: sensitivity, specificity, predictive value (negative, positive), cost/financial feasibility, limit of detection

Question 4

Is haemoglobin concentration an adequate marker for assessing the impact of iron interventions?

Table A2.4. Question 4 in PICO format

Population	Apparently healthy individuals/populations (anaemic or non-anaemic) of any sex, age (i.e. infants, children, adults) and pregnancy status in any country
Indicator/ intervention	- Haemoglobin concentrations before and after receiving an intervention that increases iron intake or decreases iron loss - Nutrition-specific interventions that have a direct impact on the immediate causes of anaemia
Comparison	Haemoglobin concentrations before and after receiving placebo or a similar intervention without an iron-related component
Outcomes	- Change in haemoglobin concentrations - Change in prevalence of anaemia, iron deficiency anaemia, iron deficiency (as defined by trialist) - Changes in anaemia severity (mild, moderate, and severe)

Question 5

What should be the population cutoffs to define the public health burden of anaemia?

- 5.a** What anaemia prevalence is indicative of a mild, moderate, or severe (or low, medium, high) problem of public health concern?
- 5.b** Should this classification of anaemia be based on total anaemia alone or should the proportion of mild, moderate, and/or severe anaemia be considered (weighted?) to determine that categorization?

Table A2.5. Question 5 in PICO format

Population	- Apparently healthy individuals/populations (anaemic or non-anaemic) of any sex, age (i.e. infants, children, adults) and pregnancy status in any country; or - Particular age/vulnerable groups: infants and young children 6–59 months of age/ nonpregnant women of reproductive age 15–49 years
Indicator	Prevalence of low haemoglobin concentrations (subgrouping by anaemia severity if possible)
Comparator	Social, economic, and health indicators (gross domestic product, infant mortality rate, maternal mortality rate, anaemia, stunting)
Outcomes	- Prevalence of total anaemia in a population higher than a certain level. - Proportion of the total anaemia that is severe (and/or moderate) - Correlation coefficients - Disability-adjusted life-years attributable to anaemia – absolute number, ranking within a country/ population - YLD attributable to anaemia – absolute number, ranking within a country/ population

YLD: years lived with disability.

Annex 3. Summary of judgements

Certainty of evidence	There is a lack of good quality evidence from the systematic reviews in haemoglobin cutoffs to define anaemia and its severity at individual and public health level.
Values and preferences	- The GDG agreed on the value and on the positive effects of reviewing haemoglobin concentrations to diagnose anaemia, and other possible adjustments by other determinants, but recognized that there may be costs associated with having to revise and implement new adjustments. - The group considered that the haemoglobin adjustments are acceptable to stakeholders, cost-effective, and have a positive impact in equity. - Correct diagnosis at the individual and population levels is important in order to accurately report anaemia prevalence rates and efficiently apply health interventions.
Trade-off between benefits and harms	- Benefits of reviewing haemoglobin cutoffs to define anaemia clearly outweigh harms. - The GDG considered that there is a high value and a clear benefit from reviewing cutoffs to define anaemia and its severity because such a review would improve decisions about implementation of public health interventions and decision-making on whether to treat anaemia at the individual level. - Considerations of the balance of effects and cost-effectiveness favour no adjustments of haemoglobin concentrations by genetic ancestry, since the complexity of genetic testing makes adjustments to cutoffs based on genetic background unfeasible. - The GDG found that there was positive value in using the gold-standard practice for haemoglobin determination (using venous blood, automated haematology analysers, and high-quality control standards), and that the positive effects of a clear knowledge of comparable methodologies to measure haemoglobin and the correct diagnosis of anaemia at individual and at population levels were clear.
Equity and human rights	- The differences between urban and rural areas, different levels of educational attainment, and the decision-making level at which community groups operate were considered. - The group concluded that effective interventions to improve nutrition in disadvantaged populations could help to reduce health inequalities. - In general, effective nutrition interventions would be more likely to decrease health inequities only if they are accompanied by concurrent interventions that address the root cause of the anaemia. - In contexts of extended poverty and lack of opportunities, guaranteeing access to anaemia diagnosis and treatment requires addressing the factors that allow for the continuation of exclusion and poverty, which are socially determined and thus modifiable. - Research is needed to set haemoglobin cutoffs adjusted by race/ethnicity/genetic ancestry, especially recognizing how underrepresented some genetic backgrounds have been in the genetic literature thus far.
Costs and feasibility	Costs - The presumed benefits are worth the cost. Feasibility - No studies were available to address cost, acceptability, or feasibility implications, but the group considered that reviewing haemoglobin concentration cutoffs to define anaemia in individuals and populations was acceptable and feasible to key stakeholders, since in general, improved anaemia cutoffs would benefit patients across the world, including a broad range of clinical, laboratory, public health, and research settings.

Annex 4. WHO Steering Committee

Dr Andrea Bosman

Coordinator, Diagnostics, Medicine and Resistance
Global Malaria Programme
World Health Organization
Switzerland

Dr Francesco Branca

Director, Department of Nutrition and Food Safety
World Health Organization
Switzerland

Dr Maurice Bucagu

Medical Officer, Maternal Health Unit
Department of Maternal, Newborn, Child, Adolescent Health and Ageing
World Health Organization
Switzerland

Dr Maria Nieves Garcia-Casal

Scientist, Food and Nutrition Actions in Health Systems
Department of Nutrition and Food Safety
World Health Organization
Switzerland

Dr Juan Pablo Peña-Rosas

Coordinator, Global Initiatives Unit
Department of Nutrition and Food Safety
World Health Organization
Switzerland

Dr Lisa Rogers

Technical Officer, Food and Nutrition Actions in Health Systems
Department of Nutrition and Food Safety
World Health Organization
Switzerland

Dr Yuka Sumi

Technical Officer, Ageing and health
Department of Maternal, Newborn, Child, Adolescent Health and Ageing
World Health Organization
Switzerland

Dr Özge Tuncalp Mingard

Scientist, Maternal Perinatal Health, Prevent Unsafe Abortion
Department of Reproductive Health and Research
World Health Organization
Switzerland

Annex 5. WHO Guideline Development Group

The areas of expertise of each guideline group member are given in italics.

Professor Beverley-Ann Biggs

International and Immigrant Health Group, Department of Medicine
University of Melbourne
Australia
Micronutrient supplementation, clinical infectious diseases

Dr Rachel Hammonds

Law and Development Research Group
University of Antwerp
Belgium
Health equity, behaviour science, programme evaluation

Dr Renuka Jayatissa

Department of Nutrition, Medical Research Institute
Ministry of Health
Sri Lanka
Micronutrients, public health, clinical nutrition,

Dr Crystal Karakochuk

Faculty of Land and Food Systems
University of British Columbia
Canada
Diagnostic methods, biomarkers for anaemia

Dr Heimo Mairbörl

German Center for Lung Research
University Hospital Heidelberg
Germany
Physiology of haemoglobin changes at elevations above sea level

Dr Lynnette Neufeld

Global Alliance for Improved Nutrition
Switzerland
Nutrition, micronutrient programmes, public health, epidemiology

Dr Tarek Owaidah

Department of Pathology and Laboratory Medicine
King Faisal Specialist Hospital & Research Center
Saudi Arabia
Blood banks, transfusions

Dr Kamija Phiri

College of Medicine
University of Malawi
Malawi
Malaria, haematology, global health, epidemiology

Dr Harshpal Singh Sachdev

Sitaram Bhartia Institute of Science and Research
India

Maternal and child nutrition, epidemiology, paediatrics

Dr Elizabeth Tejero

Laboratory of Nutrigenomics and Nutrigenetics
National Institute for Genomic Medicine
Mexico

Genetic variation and nutritional status

Dr Vip Viprakasit

Faculty of Medicine
Mahidol University
Thailand

Genetics, haemoglobinopathies, clinical practice

Professor Pattanee Winichagoon

Institute of Nutrition
Mahidol University
Thailand

Micronutrients, iron metabolism, thalassaemias

Professor Erica Wood

Transfusion Research Unit
Monash University
Australia

Haematology, haemovigilance, blood safety, clinical practice

Dr Melissa F. Young

Hubert Department of Global Health
Emory University
United States of America

Anaemia, micronutrients, maternal and child nutrition, epidemiology, programme evaluation

Dr Crystal Karakochuk was unable to attend the first GDG meeting. Professor Beverley-Ann Biggs and Dr Lynnette Neufeld were unable to continue as GDG members after the first meeting. Dr Rachel Hammond was a GDG member until 21 November 2022; she attended the first and second GDG meetings.

Annex 6. Systematic reviews and database analysis team

The areas of expertise of each member are given in italics.

Dr Eric Ohuma

Centre for Tropical Medicine and Global Health
University of Oxford
United Kingdom of Great Britain and Northern Ireland
Medical statistics

Dr Erica Ota

Graduate School of Nursing Science
St Luke's International University
Japan
Nutrition, systematic reviews

Professor Sant-Rayn Pasricha

Population Health and Immunity Division
Walter and Eliza Hall Institute of Medical Research
Australia
Haematology scientist and clinician

Dr Andrea Sharma

Division of Nutrition, Physical Activity, and Obesity
United States Centers for Disease Control and Prevention
United States of America
Nutrition, epidemiology

Note: Systematic reviews teams participated in technical presentations and in discussions related to those presentations, providing factual information, feedback and clarification when required. They did not participate in or influence the decisions.

Annex 7. Peer-reviewers

Dr Omar Dary

Bureau of Global Health
US Agency for International Development
United States of America

Dr Sorrel Namaste

Demographic and Health Surveys Program
United States of America

Dr Nelly Zavaleta

Instituto de Investigación Nutricional
Peru

Dr Michael Zimmermann

Institute of Food, Nutrition and Health,
Swiss Federal Institute of Technology
Switzerland

Note: The names and affiliations of peer-reviewers are provided here as an acknowledgement and by no means indicate their endorsement of the normative statements in this guideline. The acknowledgement of the peer-reviewers does not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

Annex 8. WHO Secretariat

Dr Elaine Borghi

Coordinator, Monitoring of Nutrition Trends and Food Safety Events Unit
Department of Nutrition and Food Safety

Ms Monica Flores-Urrutia

Technical Officer, Monitoring of Nutrition Trends and Food Safety Events Unit
Department of Nutrition and Food Safety

Dr Maria Nieves Garcia-Casal

Scientist, Food and Nutrition Actions in Health Systems Unit
Department of Nutrition and Food Safety

Dr Laurence Grummer-Strawn

Coordinator, Food and Nutrition Actions in Health Systems Unit
Department of Nutrition and Food Safety

Dr Susan Norris

Director, Department of Research, Ethics and Knowledge Management

Dr Lisa Rogers

Technical Officer, Food and Nutrition Actions in Health Systems
Department of Nutrition and Food Safety

WHO regional offices

Dr Ayoub Al-Jawaldeh

Regional Adviser
WHO Regional Office for Eastern Mediterranean
Cairo, Egypt

Dr Anna Bekele

Regional Adviser
WHO Regional Office for Africa
Brazzaville, Congo

Dr Padmini Angela De Silva

Regional Adviser
WHO Regional Office for South-East Asia
New Dehli, India

Mr Leo Nederveen

Regional Adviser
WHO Regional Office for the Americas
Washington, United States of America

Dr Juliawati Untoro

Technical Lead
WHO Regional Office for the Western Pacific
Manila, Philippines

Dr Kremlin Wickramasinghe

Regional Adviser
WHO Regional Office for Europe
Copenhagen, Denmark

For more information, please contact:

Department of Nutrition and Food Safety

World Health Organization

Avenue Appia 20, CH-1211 Geneva 27, Switzerland

Email: nutrition@who.int

www.who.int/nutrition

