Reviewing haemoglobin thresholds for the determination of anaemia

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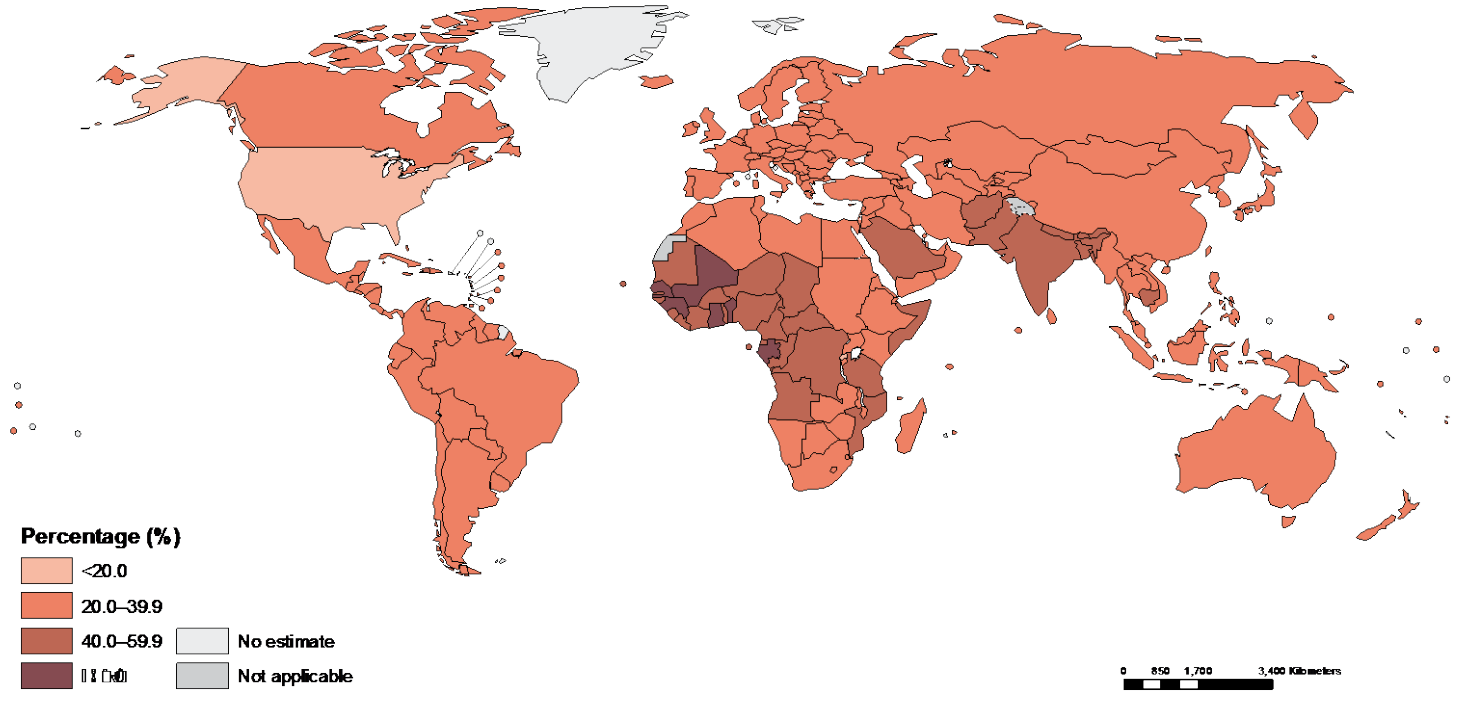
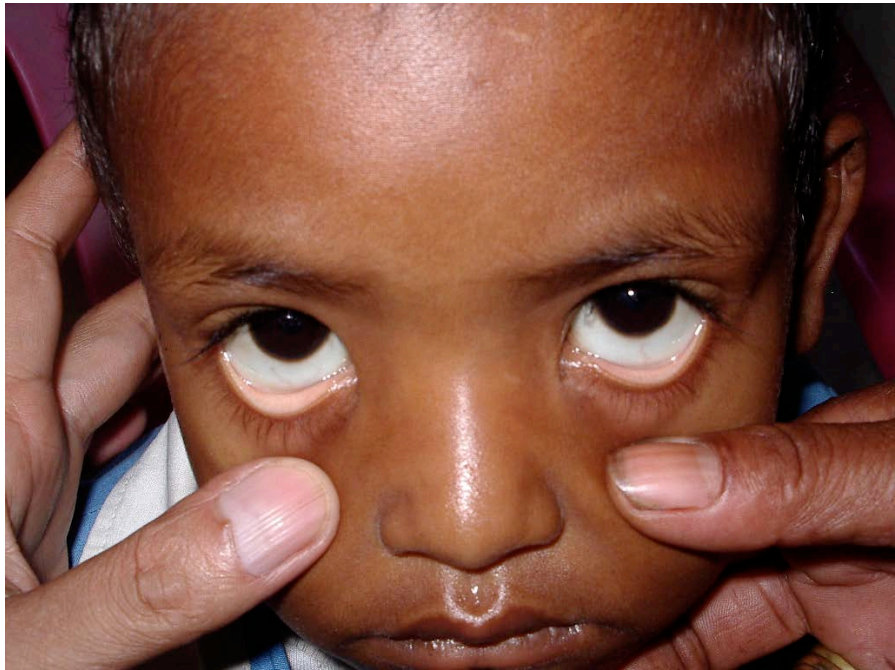
The global burden of anaemia

- 273 million (43%) children globally
- 496 million (29%) non-pregnant women
- 32 million (38%) pregnant women at any time

- **Global Burden of Disease: Anaemia accounted for 8.8% of the total disability from all conditions in 2010.**





Global Nutrition Targets 2025

Causes of anaemia

- Reduced Red Cell Production
- Increased Red Cell Destruction (reduced survival)

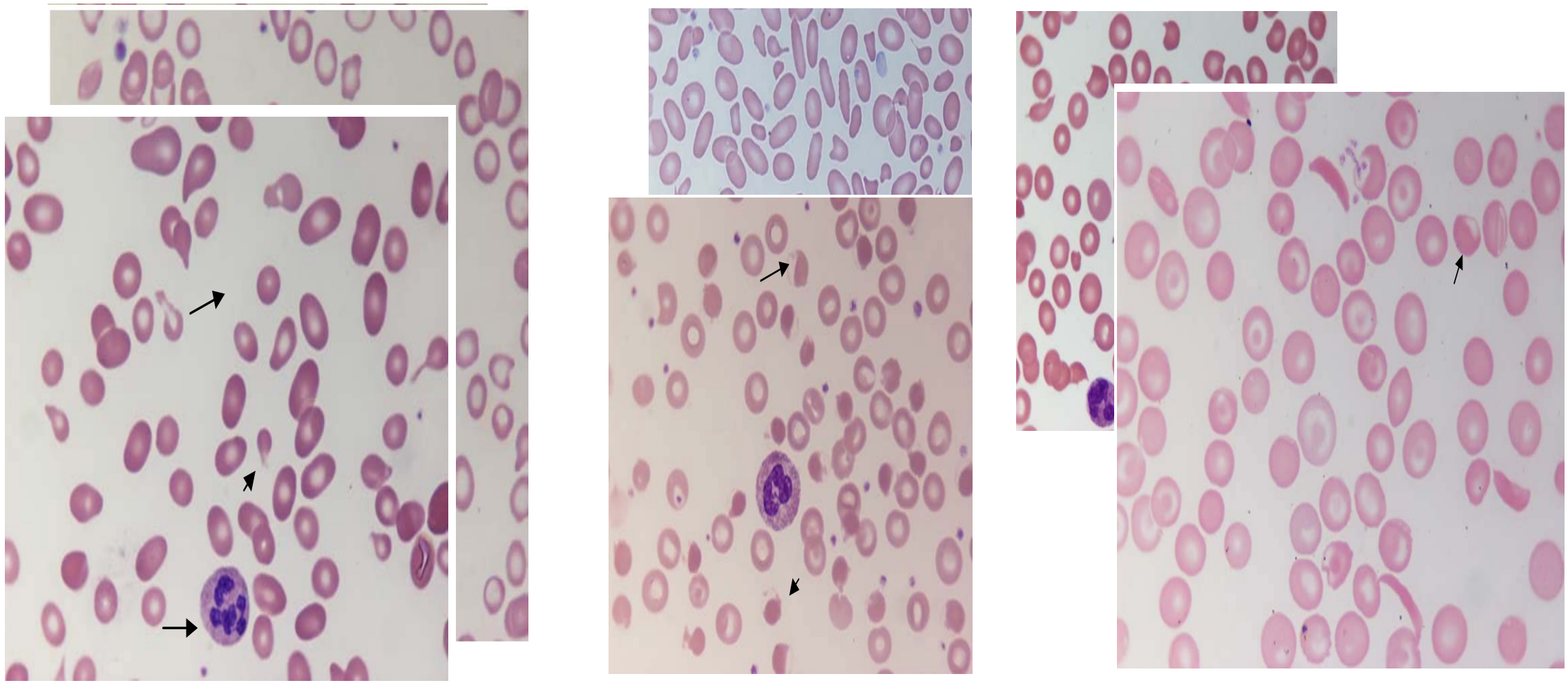
Reduced Red Cell Production

- Iron Deficiency Anaemia
- Anaemia of chronic disease (inflammation)
- Reduced erythropoietin production (renal disease)
- Bone marrow failure:
  - Aplastic anaemia (primary or due to drugs, irradiation etc.)
  - Leukaemia
  - Replacement by cancer, tuberculosis etc.
- Inadequate red cell maturation/ dyserythropoiesis
  - B12/ folate deficiency
  - Myelodysplasia
  - Thalassaemia
  - Congenital dyserythropoietic anaemia

Increased Red Cell Destruction

- Haemolysis
  - Inherited Conditions:
    - Red cell membrane (spherocytosis, elliptocytosis)
    - Red cell enzymes (G6PD Deficiency)
    - Haemoglobinopathies (sickle cell, thalassaemia)
  - Acquired conditions
    - Warm immune haemolysis
    - Microangiopathic haemolytic anaemia
    - Malaria
    - Mechanical
- Hypersplenism
- Bleeding
  - Acute
  - Chronic – anaemia likely mediated via iron deficiency

Detection of anaemia is a critical step for many clinical diagnoses



Neame PB, 2006: Diagnostic images in hematology, BloodMed.com

Adaptions to anaemia

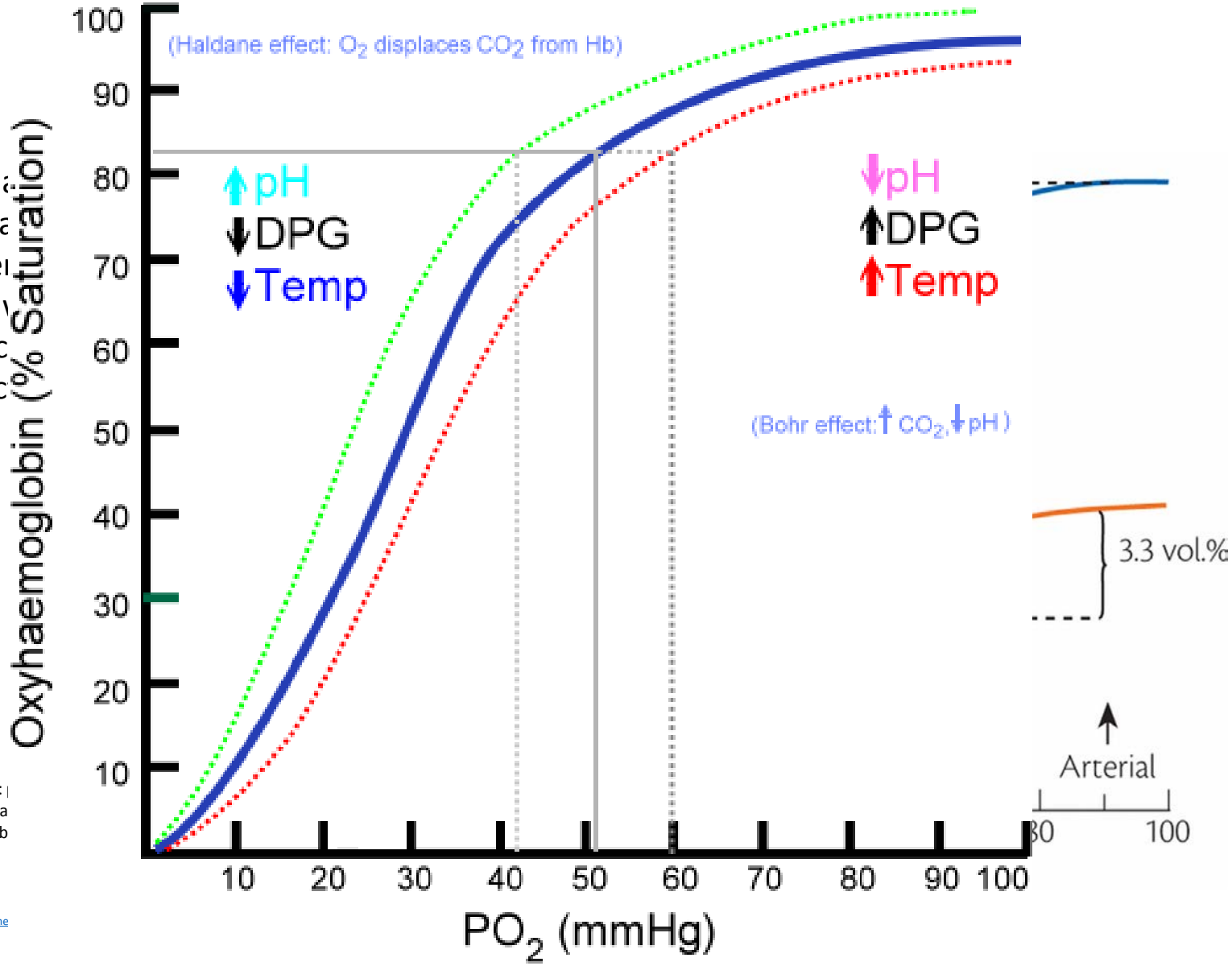


Fig. 22.5.2.1 Enha
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Chapter: Anaemia:
Author(s): D.J. Wea
From: Oxford Textb

Anaemia is evident in many complex medical conditions

- Sign of severity / prognosis in many conditions e.g.:
  - Renal Failure (Epo deficiency, inflammation)
  - Liver Failure (haemolysis, damage to red cell membrane, renal failure)
  - Inflammatory conditions (hepcidin, direct toxicity to bone marrow)
  - Cardiac Failure (cause and effect)
  - Cancer (inflammation, bone marrow replacement)
  - Ageing (?)
- (Cause and effect less certain – directly treating/ over treating anaemia can be harmful e.g. in cancer)

Why do we need to be able to diagnose anaemia?

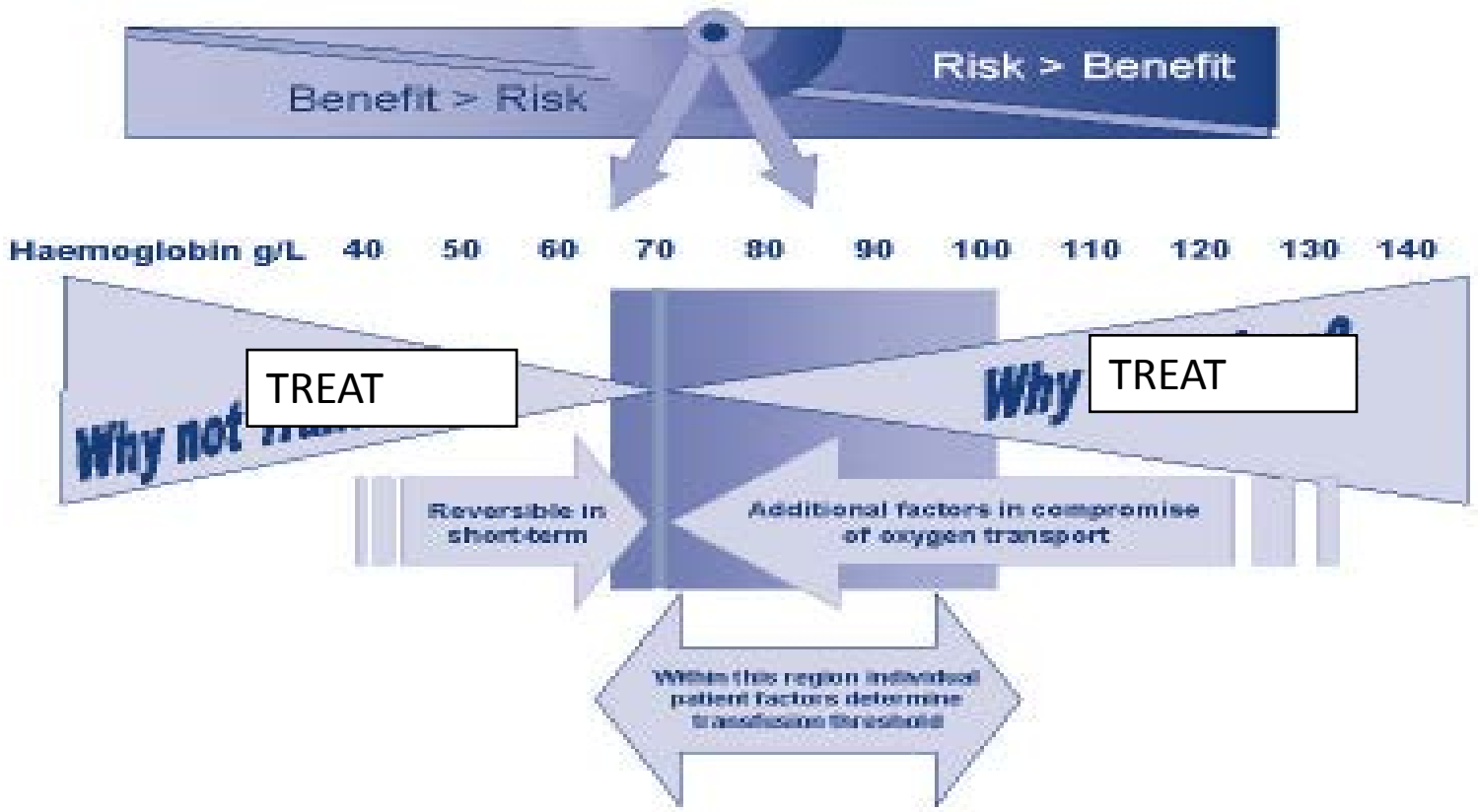
Clinical

- Diagnostic:
  - Clinically suspect an underlying disease.
  - Clinically stage severity of an underlying disease.
- Guide treatment:
  - Improve patient wellbeing
  - Improve clinical outcomes (e.g. rehabilitation, wound healing.)

Public Health

- Improvement of population health outcomes:
  - Maternal (mortality, birthweight, gestation duration).
  - Childhood (development)
  - Physical exercise performance
  - Wellbeing (all populations)
  - Economic productivity/ potential

Should I try to treat the anaemia?



Australian Red Cross Blood Service 2009

How should I treat the anaemia?

- Therapeutic options:
  - Treat the underlying cause, e.g.
    - Antibiotics
    - Immunosuppression
    - Chemotherapy
    - Surgery
  - Erythropoiesis stimulating agents (ESAs)
  - Iron (intravenous or oral)
  - Blood transfusion

Identification of anaemia is crucial to public health interventions

Potential BENEFITS

- Anaemia
- Wellbeing
- Pregnancy outcomes
- Cognitive development

Potential RISKS

- Infection
  - Malaria
  - Diarrhoea
  - Pneumonia

Consider:

Prevalence of anaemia

Incidence of malaria, diarrhoea, pneumonia

Malaria prevention

Is it worth giving iron?

What do we mean when we say ‘anaemia’?

- ‘A state in which the circulating red-cell mass is insufficient to meet the oxygen requirements of the tissues’. (Weatherall, Oxford Textbook of Medicine 5th Edition).
- ‘A reduced absolute number of circulating red blood cells’ (Schrier, UpToDate)
- ‘A condition in which the number of red blood cells (and consequently their oxygen-carrying capacity) is insufficient to meet the body’s physiologic needs.’ (World Health Organization)

- **Statistical Definitions**
- **Physiologic Definitions**
- **Red cells? Haemoglobin?**

Approaches to definitions of anaemia

- How should we base our approach to defining haemoglobin thresholds to define anaemia?
  - Statistical – haemoglobin concentration below which 2.5% or 5% of the healthy population falls.
  - Symptomatic – haemoglobin concentration below which symptoms of anaemia emerge (e.g. fatigue, lethargy).
  - Prognostic – haemoglobin concentration below which worse health outcomes exist e.g. for the mother and fetus.
  - Diagnostic – haemoglobin concentration below which underlying diseases need to be considered and identified (e.g. cancer).

Ontogeny of WHO Hb thresholds

2. Haematological Values for Detection of Anaemias

To detect and evaluate the anaemia problem of a community, it is necessary to have standards of reference, even if they be somewhat arbitrary, so that not only the severe cases, but also the less obvious ones, may be discovered. Such standards are also of considerable importance for the comparison of surveys done in different parts of the world. The Group reviewed the large body of haematological data derived from studies of apparently normal persons throughout the world, and from these data and the personal observations of the Group members, haemoglobin values, which can be considered as the lower limits of normal for the purpose of determining the presence or absence of anaemia in nutritional surveys, have been selected (see Table I). They are intended to act as general standards of reference for the investigator and to indicate that lower values than these are suggestive of anaemia. In individuals, however, higher

TABLE I. HAEMOGLOBIN VALUES BELOW WHICH ANAEMIA CAN BE CONSIDERED TO EXIST, AND ASSOCIATED HAEMATOLOGICAL VALUES

Years	Sex	Hb g/100 ml		RBC M/mm³	PCV %	MCH mm³	MCHC %
0.6- 4		10.8	11.5	4.1	32	79	33
5- 9		11.5		4.1	33	80	34
10-14		12.5		4.5	37	82	34
Adults	Male	14		4.7	42	87	34
	Female	12		4.0	35	87	34

WHO Technical Report Series No 182, 1959

Nutritional Anaemias: Report of a WHO Scientific Group, 1968

3. CRITERIA FOR THE DIAGNOSIS OF ANAEMIA

In detecting and evaluating an anaemia problem in a community, reference standards are necessary, even though they may be somewhat arbitrary. The report [2] of the 1958 WHO Study Group recommended haemoglobin values below which anaemia could be considered to exist. These figures were chosen arbitrarily and it is still not possible to define normality precisely.[3] However, more recent data [4] indicate that the values given previously should be modified. It is recommended that, in future studies, anaemia should be considered to exist in those whose haemoglobin levels are lower than the figures given below (the values given are in g/100 ml of venous blood of persons residing at sea level) :

children aged 6 months to 6 years :	11
children aged 6–14 years :	12
adult males :	13
adult females, nonpregnant :	12
adult females, pregnant :	11

At all ages the normal mean corpuscular haemoglobin concentration should be 34. Consequently, the haematocrit values corresponding to the haemoglobin concentrations given above may be obtained by multiplying

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[1] International Committee for Standardization in Haematology (1967) *Brit. J. Haemat.*, **13** (Suppl.), 71.

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1959, No. 182, p. 4.

[3] Wintrobe, M. M. (1967) *Clinical hematology*, 6th ed., Philadelphia, Pa., Lea & Febiger.

[4] Natvig, K. (1966) *Acta med. scand.*, **180**, 613 ; Tibblin, G., unpublished observations ; Kilpatrick, G. S. & Hardisty, R. M. (1961) *Brit. med. J.*, **1**, 778 ; De Leeuw, N. K. M., Lowenstein, L. & Hsiek, Y. S. (1966) *Medicine (Baltimore)*, **45**, 291 ; Sturgeon, P. (1959) *Brit. J. Haemat.*, **5**, 31.

Studies incorporated in 1968 consultation

Study	Country	Population	N	Consideration of iron status
Natvig *et al*, Acta Medica Scandinavica 1968	Norway	Males 15-21 employed at iron/ engineering enterprises.	312	No measurement of iron indices. Excluded if blood donor, haemorrhage, iron therapy, severe sweating.
Kilpatrick *et al*, BMJ 1961	UK	Mining community. Recruitment of males stratified by age and mining employment status. All women 55-64y.	723 (543 men, 180 women)	Serum iron measured but not accounted for in analysis.
Leeuw N *et al* Medicine, 1966	Canada	Antenatal women from low-income area.	66	Self allocated to control, oral or intramuscular iron.
Sturgeon Brit J Haem 1959	USA	Women from higher income settings	149	Self allocated to control, oral or intramuscular iron.
Tibblin E, (unpublished at time of guideline)	Sweden	Women aged 38, 46, 50, 54 and 60; quasi-randomised sampling via Revenue Office register	1462	None. Sub-analysis for smokers, and for 'infection in the last month' presented.

Limitations

- Epidemiologic design
- Laboratory methodology:
  - Haematology
  - Iron biochemistry
  - Other biochemistry
- Statistical analysis
- Populations considered:
  - Ethnicity
  - Geography
  - Age range (children, elderly)
  - Pregnancy status
  - Altitude

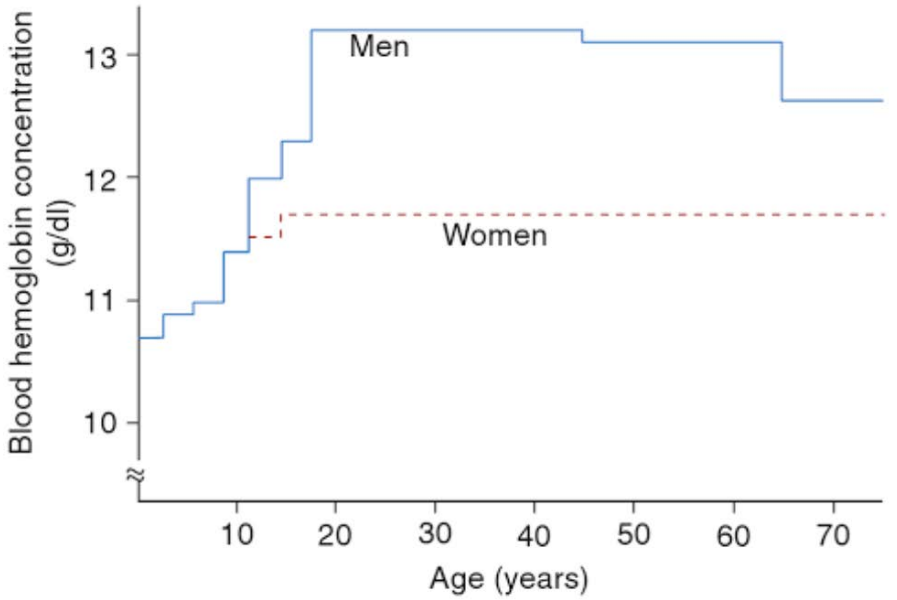

FIGURE 22.1. The lower limit of normal blood hemoglobin concentration in men and women of various ages. Values were calculated from a sample of 11,547 subjects selected to represent the population of the United States. Subjects with iron deficiency, pregnancy, or an abnormal hemoglobin value were excluded from the sample. (Data from Dallman PR, Yip R, Johnson C. Prevalence and causes of anemia in the United States, 1976 to 1980. Am J Clin Nutr 1984;39(3):437–445.)

Wintrobe's Haematology

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Iron Deficiency Anaemia: a guide for programme managers (red book) WHO/UNU/UNICEF 2001

7.1.1 Criteria of anaemia

It is well known that normal haemoglobin distributions vary with age and gender, at different stages of pregnancy, and with altitude and smoking *(86,87)*. There is also evidence of a genetic influence. In the United States, for

Haemoglobin concentrations for the diagnosis if anaemia and assessment of severity (WHO 2011)

Table 1
Haemoglobin levels to diagnose anaemia at sea level (g/l)±

Population	Non -Anaemia*	Anaemia*		
		Mild[a]	Moderate	Severe
Children 6 - 59 months of age	110 or higher	100-109	70-99	lower than 70
Children 5 - 11 years of age	115 or higher	110-114	80-109	lower than 80
Children 12 - 14 years of age	120 or higher	110-119	80-109	lower than 80
Non-pregnant women (15 years of age and above)	120 or higher	110-119	80-109	lower than 80
Pregnant women	110 or higher	100-109	70-99	lower than 70
Men (15 years of age and above)	130 or higher	110-129	80-109	lower than 80

± Adapted from references 5 and 6
* Haemoglobin in grams per litre
a "Mild" is a misnomer: iron deficiency is already advanced by the time anaemia is detected. The deficiency has consequences even when no anaemia is clinically apparent.

below

Pregnant women	110	8.07	0.39
Men (above 15 years of age)	130		

[a] Conventional conversion factors: 100 g haemoglobin = 6.2 mmol haemoglobin = 0.30 l/l haematocrit.
Adapted from reference *(89)*, by splitting the age group for children 5-14 years and applying a haemoglobin cut-off level for those 5-11 years which has been lowered by 5 g/l to reflect the findings in the USA (cf. Table A1 in Annex 3).

Variation in cutoffs

Table 1. Anemia envelope definitions, anemia DWs, and cause-specific attribution strategy

Region	Age-Adjusted Prevalence		Prevalence by age range (per 100,000 population)						Age-Adjusted Prevalence		Prevalence by age range (per 100,000 population)					
Country	1990	2010	Neonatal	Post-neonatal	1-4 years	5-14 years	15-59 years	60+ years	1990	2010	Neonatal	Post-neonatal	1-4 years	5-14 years	15-59 years	60+ years
Iceland	14,427 (8,758-37,580)	14,315 (8,462-26,445)	48 (35-67)	74,948 (1,070-241,585)	57,079 (475-204,928)	34,881 (25,267-41,898)	2,720 (2,412-3,064)	11,710 (9,882-13,813)	18,312 (10,208-31,904)	18,207 (10,240-35,651)	1 (1-1)	74,792 (1,019-475,930)	64,107 (556-172,989)	17,072 (7,130-33,395)	12,937 (11,156-14,983)	12,165 (10,145-14,645)
Ireland	14,432 (8,775-37,825)	14,287 (8,286-22,943)	48 (37-62)	74,973 (1,116-1,976)	57,064 (486-195,515)	35,164 (26,451-42,431)	2,651 (2,354-3,021)	11,217 (8,837-14,504)	18,284 (9,949-31,966)	18,183 (9,564-37,920)	1 (1-1)	74,789 (1,052-565,088)	64,095 (558-172,467)	17,162 (7,209-33,056)	13,065 (10,970-15,650)	12,084 (9,218-15,982)
Israel	14,406 (8,972-20,837)	14,305 (9,585-20,674)	48 (42-54)	74,886 (1,375-337,242)	57,058 (22,250-82,183)	35,386 (21,580-47,689)	2,672 (2,313-3,122)	11,614 (9,342-14,968)	18,633 (14,651-22,323)	18,482 (14,317-22,300)	1 (1-1)	74,778 (2,838-133,852)	64,087 (31,575-88,770)	17,254 (14,584-20,081)	13,483 (12,200-15,079)	12,043 (9,214-16,077)
Italy	14,250 (8,238-26,206)	14,175 (9,323-24,892)	48 (42-54)	74,789 (17,084-120,087)	56,919 (40,687-87,429)	34,824 (18,521-92,807)	2,683 (2,343-2,972)	11,572 (9,994-13,475)	17,757 (13,759-24,259)	17,712 (12,426-26,938)	1 (1-1)	74,677 (43,504-97,617)	63,943 (16,243-175,293)	17,036 (13,021-20,690)	12,298 (10,925-13,769)	11,797 (10,171-13,695)
Luxembourg	14,388 (8,078-40,673)	14,321 (8,195-53,732)	48 (36-65)	78,158 (1,081-1,963)	57,025 (434-638,680)	34,704 (29,989-38,250)	2,716 (2,386-3,121)	11,535 (8,628-15,911)	18,072 (8,571-48,870)	17,999 (9,119-49,526)	1 (1-1)	74,814 (981-845,717)	64,055 (469-411,406)	16,972 (8,726-32,638)	12,660 (9,586-16,634)	12,221 (8,819-17,015)

95% UI	0.0030-0.0062	0.0453-0.0727

Kassebaum 2014

Severity definitions and corresponding DWs (from IHME Disability Weights Survey) used to calculate GBD 2010 anemia envelope. We calculated anemia as a total "envelope" and hierarchically divided the envelope among contributing etiologies in mutually exclusive fashion for each country, age group, sex, and year. HgB thresholds for 5 different groups were the same as those used in GBD 2000 and adapted from WHO guideline definitions of anemia.[21,22] DWs with uncertainty intervals for each severity of anemia were obtained via the IHME Disability Weights Survey.[24]

HgB, hemoglobin B; UI, uncertainty interval.

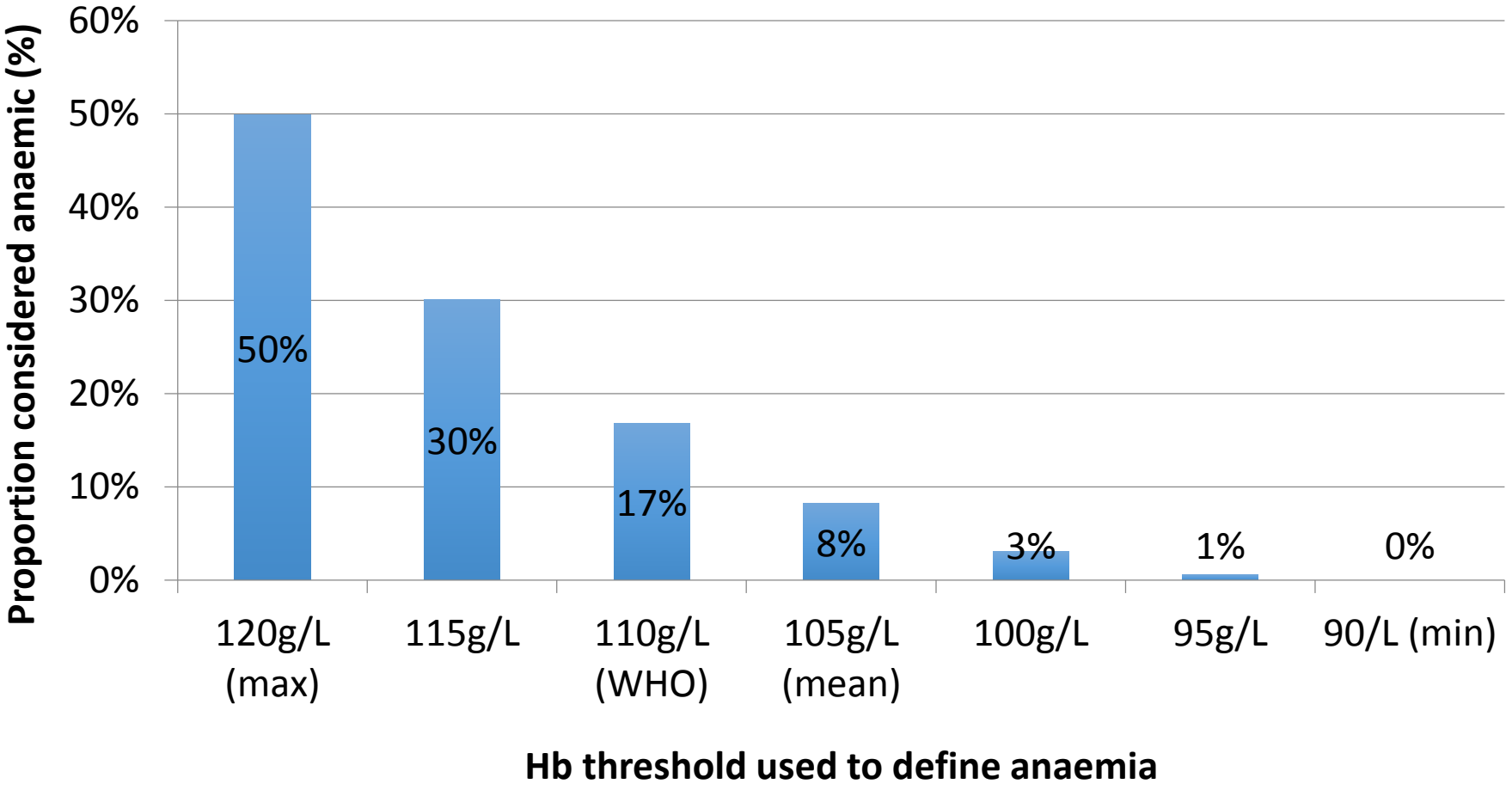
Tietz[8] ded

Hoffman et al[9] ded

Beutler and Waalen, Blood 2006

Modelling different Hb thresholds and implications for anaemia prevalence

Assumptions: Mean 120g/L, SD 10g/L, n=1000



Current recommendations for Hb thresholds used to define anaemia

Source	Males	Females	Children	Children	Pregnancy		
			<5 years	6-12 years	First Trimester (0-12 weeks' gestation)	Second Trimester (13-27 weeks' gestation)	Third Trimester (28 weeks until delivery)
WHO[2]	<130	<120	<110	<115	<110	<110	<110
CDC[70]	<133 if 15-<18years <135 if ≥18years	<120	<110 if 1-<2years	<115 if 5-<8years <119 if 8-12years	<110	<105	<110
			<111 if 2-5years				
Dacie and Lewis Practical Haematology 2011[11]	<130	<120	<110	<115	<124	<110	<106
Harrison's Principles of Internal Medicine 2015[71]	<140	<110 (pre-menopause) <120 (post-menopause)	<120	<130	<100	<100	<100
Williams Haematology 2015[72,73]	<120-137	<102-120	<112	<114-118	<110	<105	<110
Davidson's Principles and Practices of Medicine 2014[74,75]	<130	<115	-	-	<115	<106 (at 28 weeks)	-
UpToDate 2010[76,77]	<130*	<120*	<110*	<115*	<116	<97	<95
BMJ Best Practice[78]	<140	<120	-	-	<110	<110	<110
British Committee for Standards in Haematology (BCSH)[51]	-	-	-	-	<110	<105	<105
National Institute for Health Care and Excellence (NICE) guidelines 2008[79,80]	"See laboratory for local reference range"				<110	<105	<105
Royal College of Pathologists of Australia (RCPA) 2015[81]	"Below normal range for age and gender"						

Key: - = no range for that subgroup

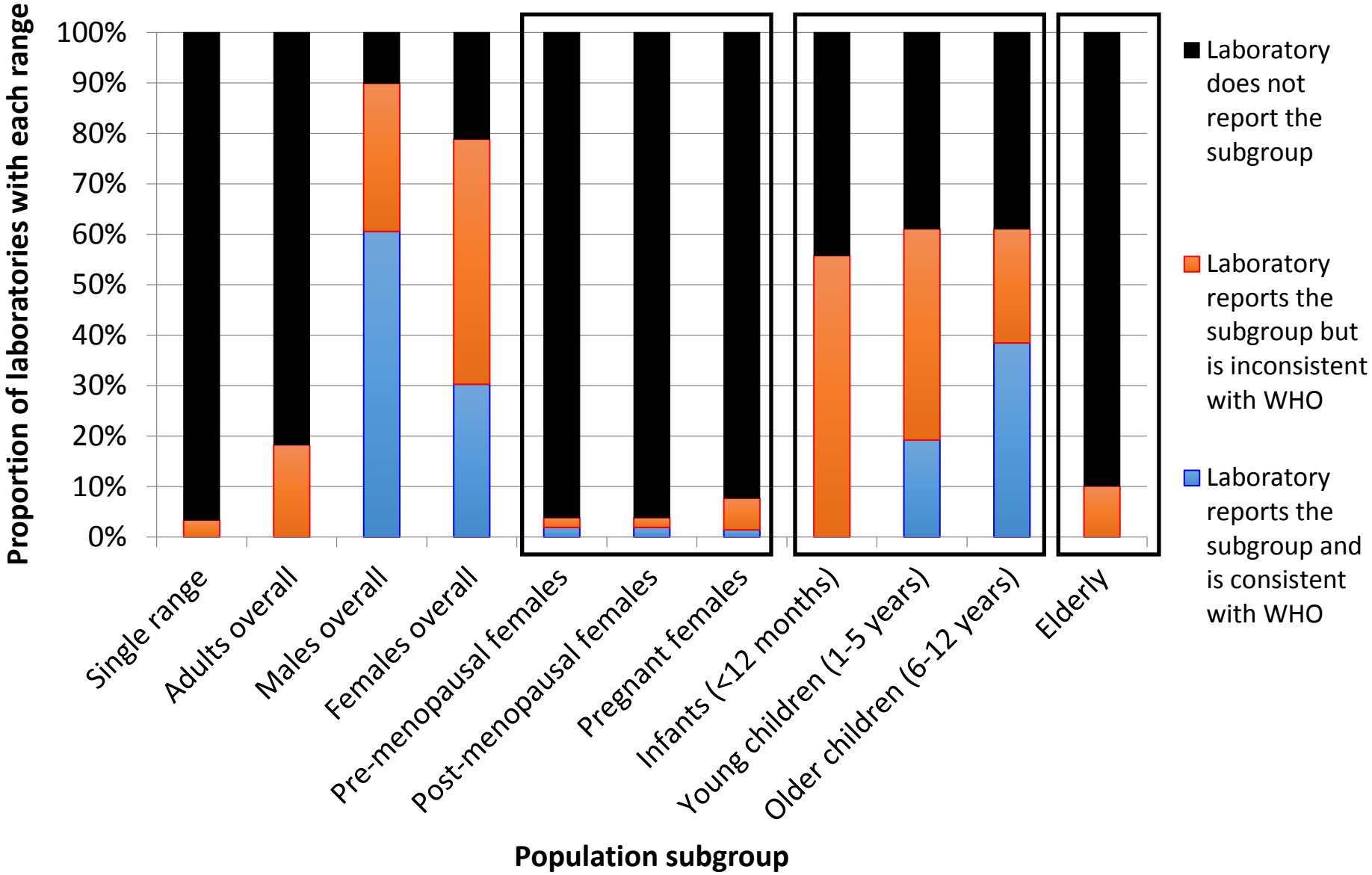
* = references WHO's recommended Hb ranges to define anaemia

How is anaemia being defined in clinical practice?

Survey of current practices

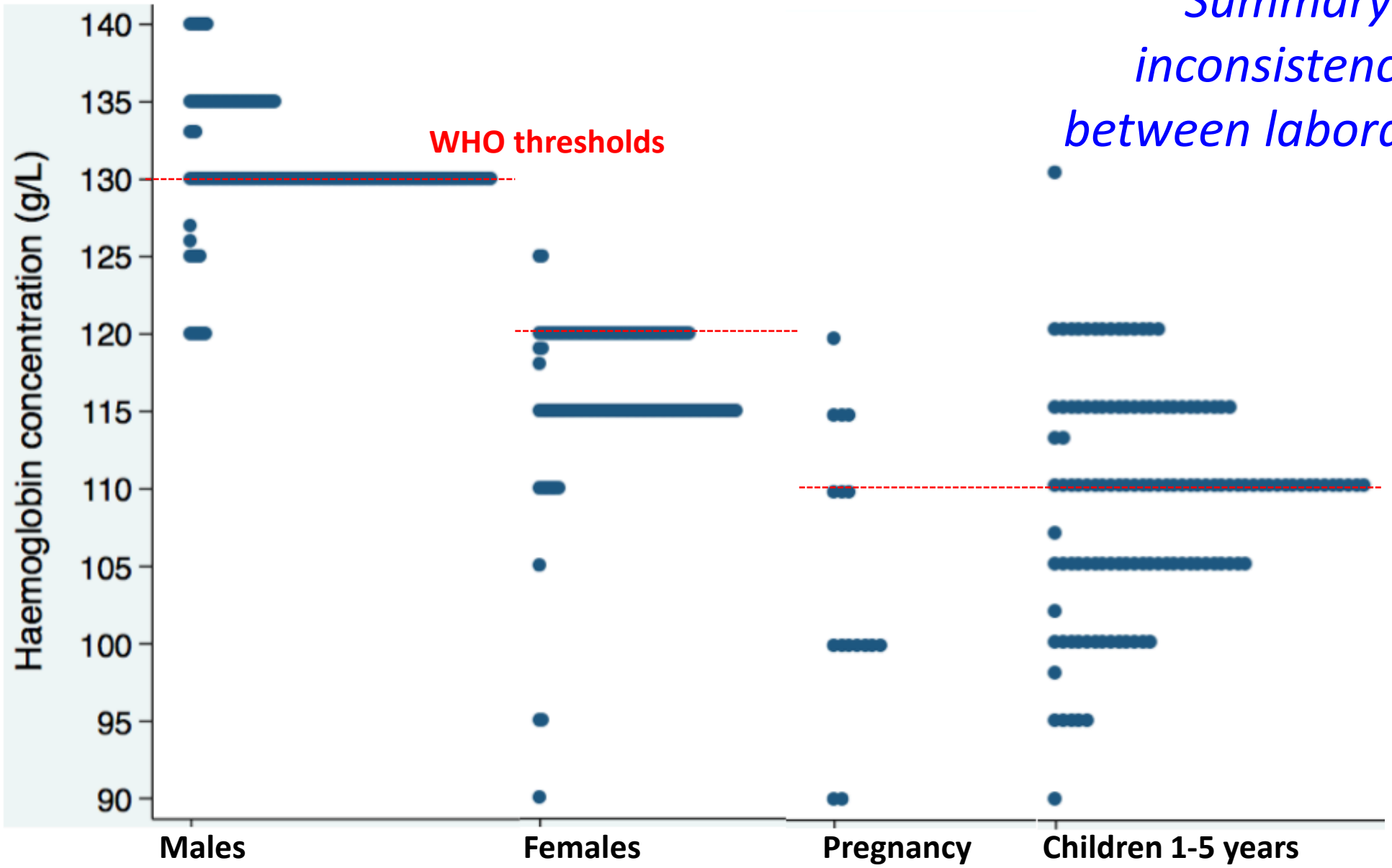
- NEQAS: National External Quality Assessment Service
  - Voluntary quality assessment and control
- Participants
  - Sent to 606 laboratories
  - Responses from 208 laboratories from 14 countries
    - 67% UK
    - 96% European
    - Median 4000 Hb assays / week

Population subgroups with individualised ranges

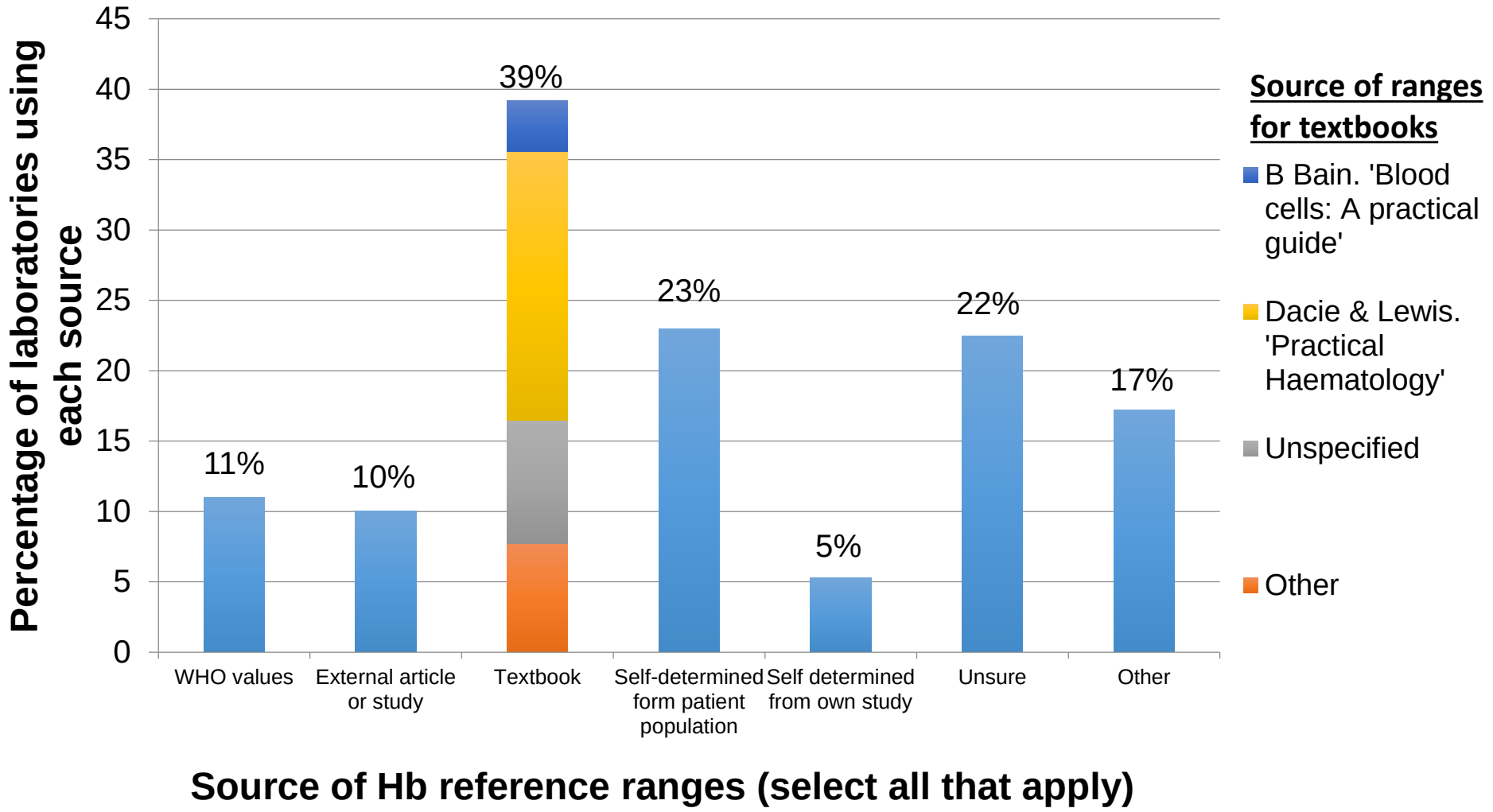


Hb thresholds used in males and females in NEQAS laboratories

Summary: inconsistencies between laboratories



Source of Hb ranges



Summary: Many different sources, WHO recommendations not commonly used

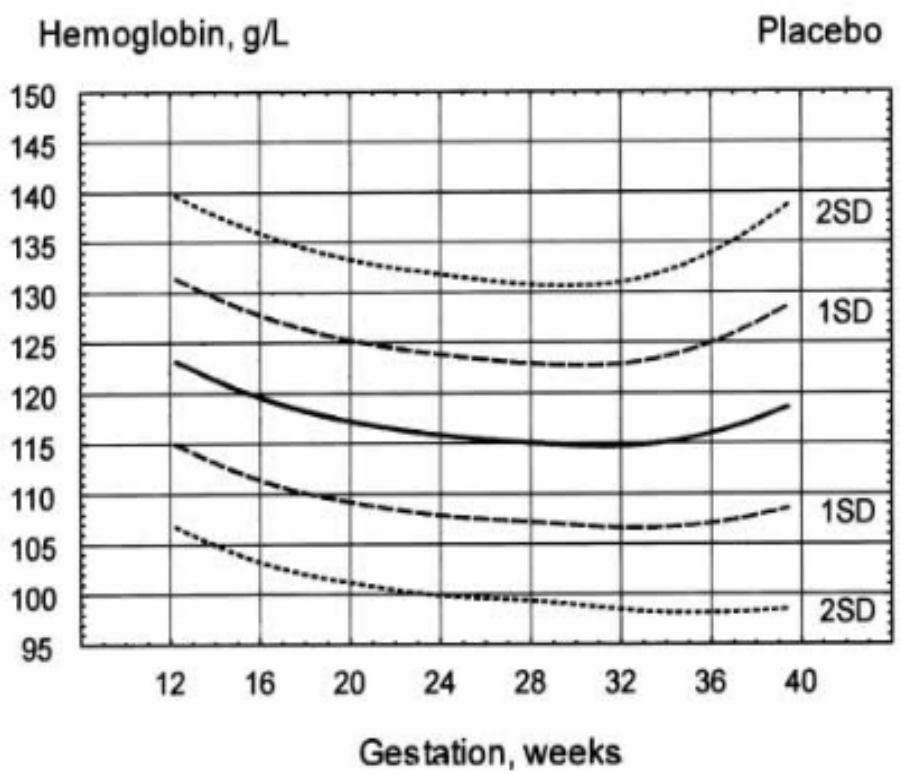
Summary of NEQAS Survey

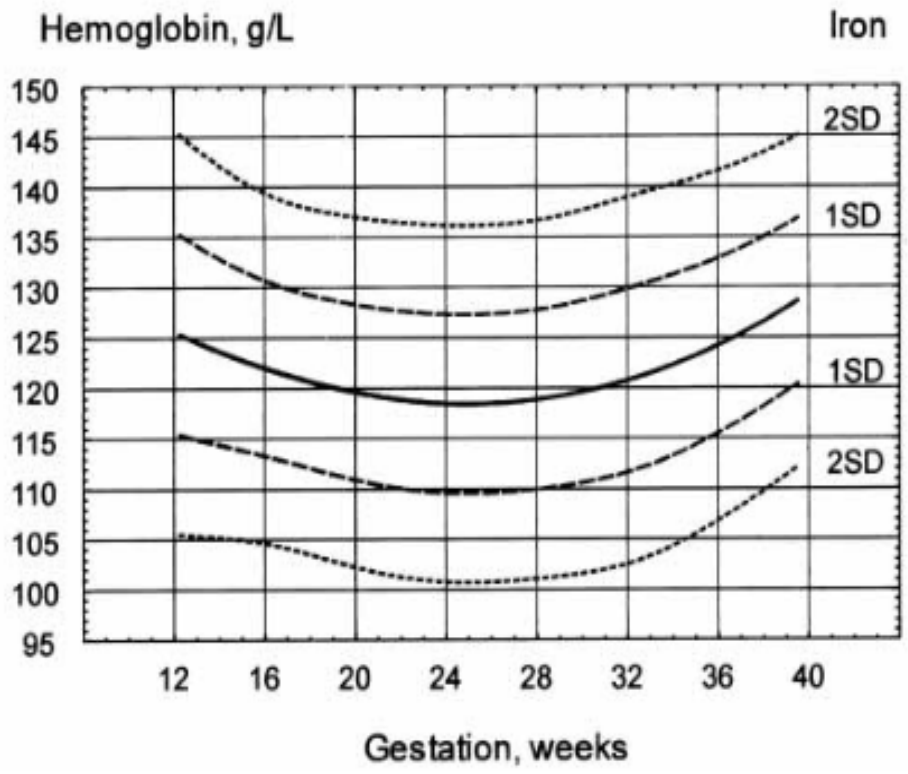
- UK/ European laboratories are not using WHO thresholds
- Likewise, many discordant international recommendations.
- Patients can have different diagnoses in different hospitals in the same county/ country.
- This is not due to different assays/ instruments.

Other limitations of WHO Hb thresholds

1. Value in pregnancy
2. Value in the first months of life?
3. Adjustments in individuals of different ethnicity.

Haemoglobin (mean + SD) during normal pregnancy in placebo and iron-supplemented women





Source: Milman N, Byg K-E, Ole Agger A. Hemoglobin and erythrocyte indices during normal pregnancy and postpartum in 206 women with and without iron supplementation. Acta Obstet Gynecol Scand 2000;79:89-98.

Times of Hb variation

Infancy

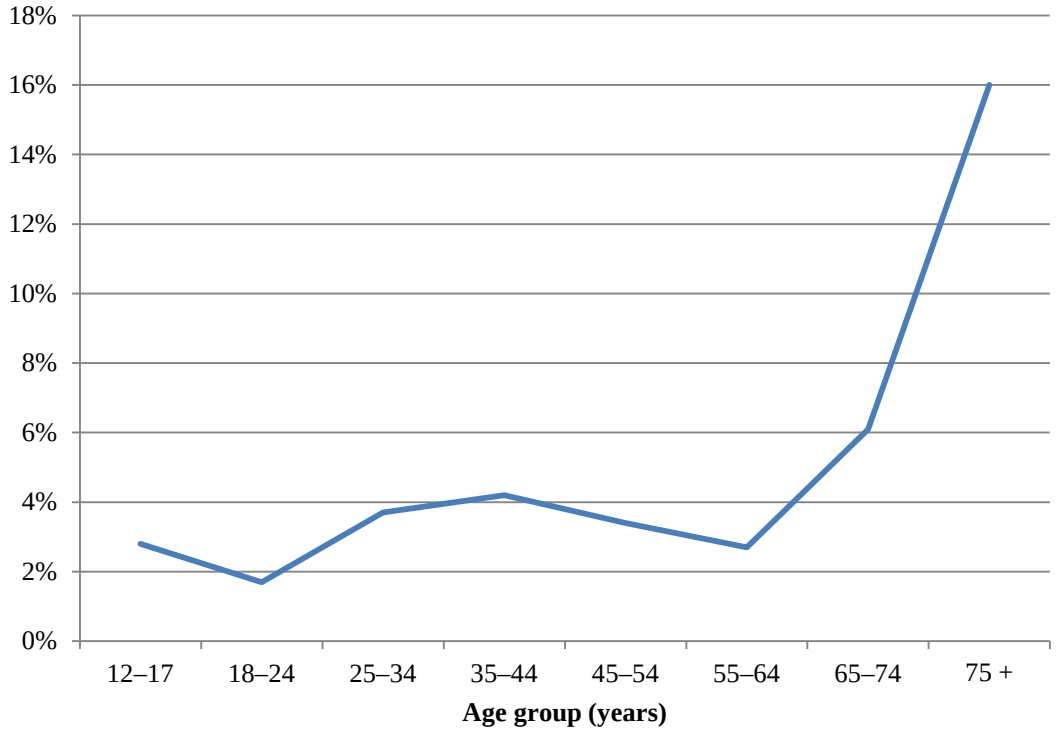
TABLE 22.1

RED BLOOD CELL CHARACTERISTICS IN CHILDHOOD

Age	Lowest Normal Hb (g/dl)	Normal Red Blood Cell Size Mean Corpuscular Volume (fl)	Fetal Hb (%)
Birth	14.0	100–130	55–90
1 mo	12.0	90–110	50–80
2 mo	10.5	80–100	30–55
3–6 mo	10.5	75–90	5–25
6 mo–1 y	11.0	70–85	<5
1–4 y	11.0	70–85	<2
4 y–puberty	11.5	75–90	<2
Adult female	12.0	80–95	<2
Adult male	14.0	80–95	<2

Wintrobe's Hematology

Elderly



Evidence of ethnic variation in thresholds

Table 3. Lower limits of normal for hemoglobin concentration of the blood in g/dL of younger (age 20-59 for men; 20-49 for women) and older white and black adults

	Scripps-Kaiser					NHANES-III				
	No.	2.5% actual	2.5% normal distribution	5% actual	5% normal distribution	No.	2.5% actual	2.5% normal distribution	5% actual	5% normal distribution
White men, y										
20-59	6709	13.4	13.4	13.7	13.7	1456	13.4	13.4	13.8	13.7
60+	5515	12.8	12.8	13.2	13.2	934	12.2	12.4	12.8	12.7
White women, y										
20-49	2966	11.9	11.9	12.2	12.2	1045	12.0	11.9	12.2	12.1
50+	8313	11.9	11.9	12.2	12.2	1395	11.5	11.6	12.0	11.9
Black men, y										
20-59	434	12.6	12.5	12.9	12.9	1253	12.3	12.4	12.8	12.8
60+	135	—	12.4	—	12.7	235	11.4	11.9	11.8	12.2
Black women, y										
20-49	205	11.2	11.2	11.5	11.5	904	10.9	10.8	11.3	11.1
50+	255	11.2	11.2	11.5	11.5	442	11.0	10.9	11.3	11.2

To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
— indicates insufficient numbers to determine.

Beutler and Waalen, Blood 2006

Laboratory considerations for Hb measurement

- How do pathologists consider ‘things going wrong’ when measuring biomarkers?
  - Pre-analytic
    - Sample (venous vs capillary)
    - Tube
    - Storage
    - Labeling
  - Analytic
    - Instrument
    - Laboratory vs point of care
    - Calibration
  - Post-analytic
    - Hb thresholds used to define anaemia!
    - Reporting
- ’Quality’ of laboratory should encompass all of these considerations.

Measurement of haemoglobin

- Spectrophotometry
  - Blood lysed in solution of potassium cyanide and potassium ferricyanide
  - Methaemoglobin and cyanmethaemoglobin (HICN)
  - HICN read at 540nM against a reference standard solution.

SPECTROPHOTOMETRIC STUDIES

II. PREPARATIONS FROM WASHED BLOOD CELLS; NITRIC OXIDE HEMOGLOBIN AND SULFHEMOGLOBIN

By DAVID L. DRABKIN and J. HAROLD AUSTIN

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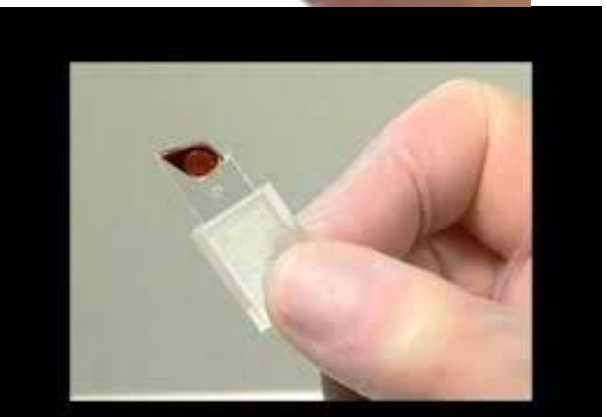
In this paper evidence will be presented which indicates that spectrophotometric constants are more precisely reproducible with solutions prepared from washed erythrocytes than from hemolyzed whole blood, used in our earlier analyses (1). The data, obtained under standard conditions which will be defined, include the absorption curves of HbO_2, Hb, HbCO, MHbCN, HbNO (nitric oxide hemoglobin), and SHb (sulfhemoglobin). The two latter pigments were the main subjects of the investigation.

Laboratory Instruments

- Multichamber instruments:
  - Lyse red cells, measures haemoglobin via spectrophotometry - cyanmethaemoglobin method (Coulter), or non-cyanide methods (Sysmex).
  - Absorbance measured at 525-540nm.
  - Counts and sizes red cells, white cells and platelets using coulter principle.
- Comprehensive daily, routine and continuous quality control.
- Several different manufacturers, many instruments on the market.

Field methods



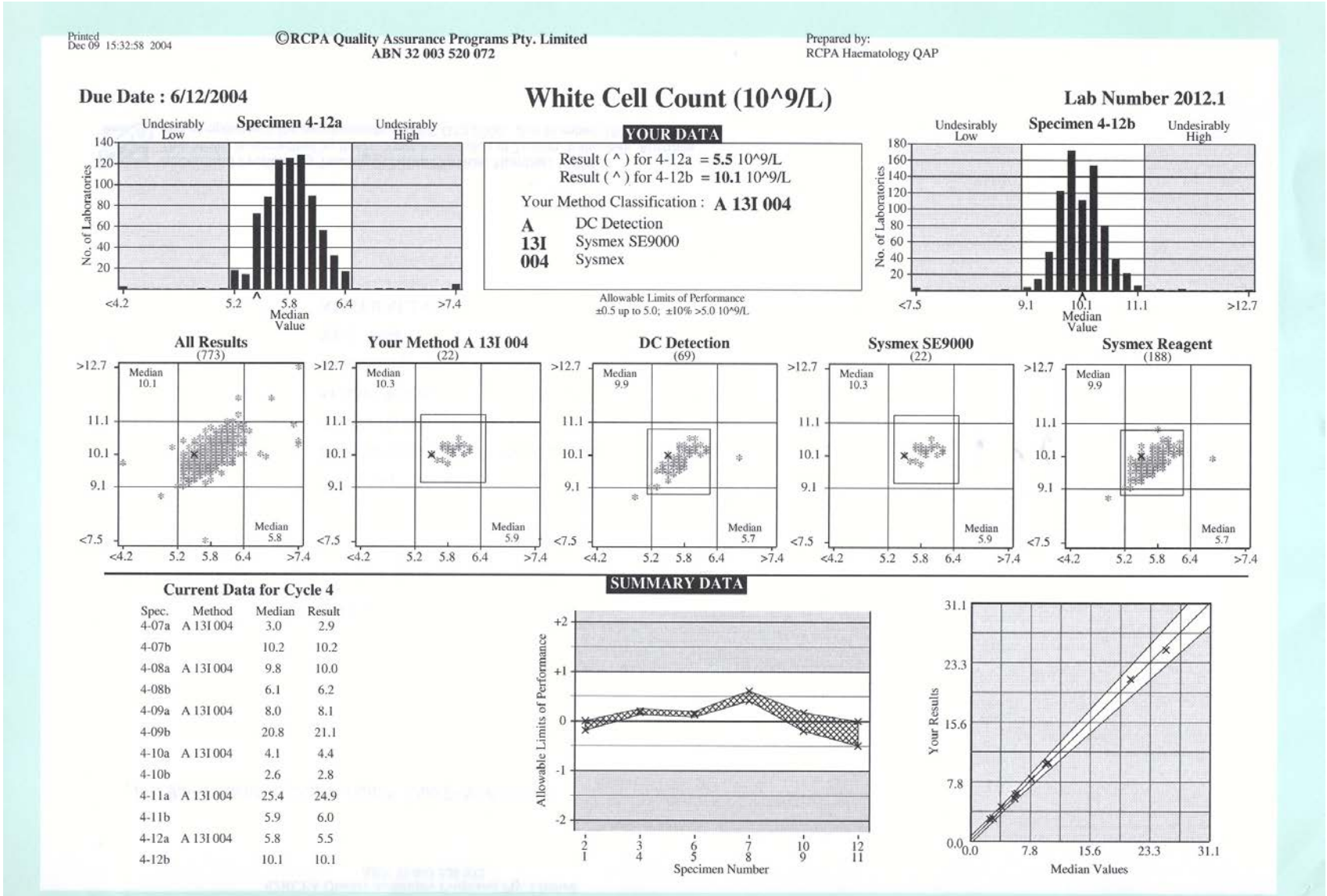
- HemoCue:
  - Cuvette contains reagents to lyse erythrocytes
  - Chemical conversion to azidemethemoglobin.
  - Concentration measured spectrophotometrically at two wavelengths.

- Spectrophotometry:
  - Clinical measurement in the field.
  - Depends on quality control.

Laboratory Quality Control

- **Quality control** = internal steps taken on a daily basis to ensure results are appropriate.
- **External Quality Assurance** = measurement of third party samples to ensure results in this lab reflect those of other labs (e.g. RCPA QAP, NEQAS, etc.).
- **Certification/ accreditation** = process of accrediting labs to ensure the above (as well as staff training, etc.) is happening well. Measured against international standards egg ISO15189) Generally, if a lab is accredited you need not worry about anything else and you can just trust them. **It is extremely hard work to get accredited** (egg NATA)**.**

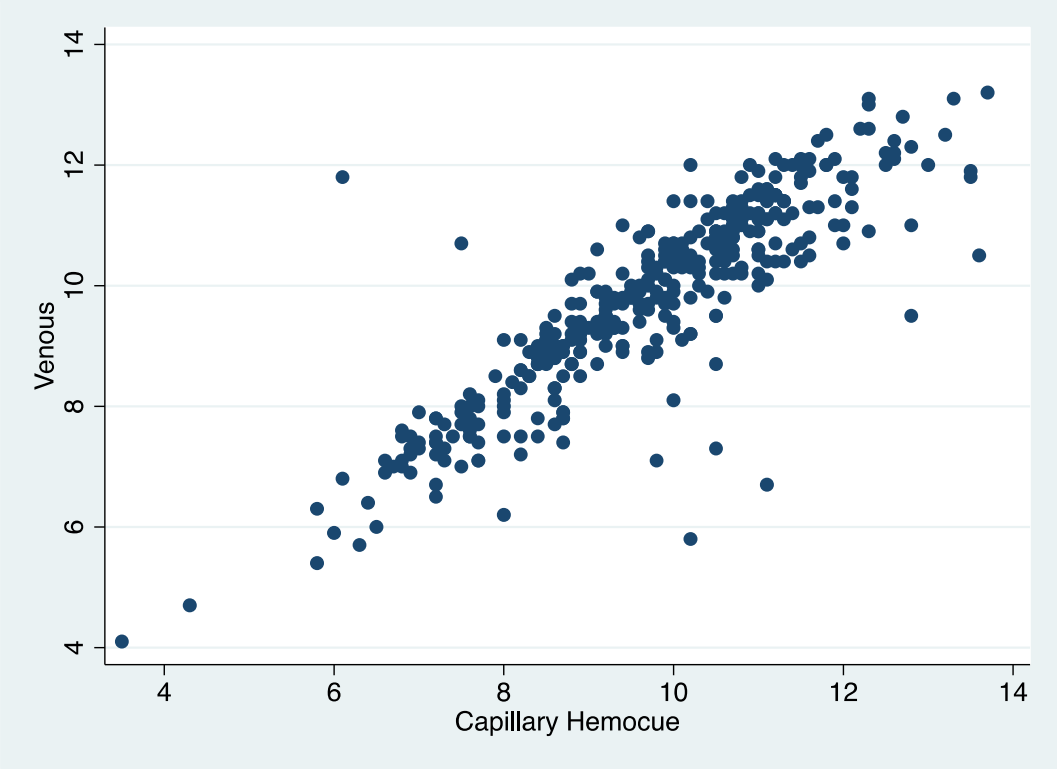
External Quality assurance



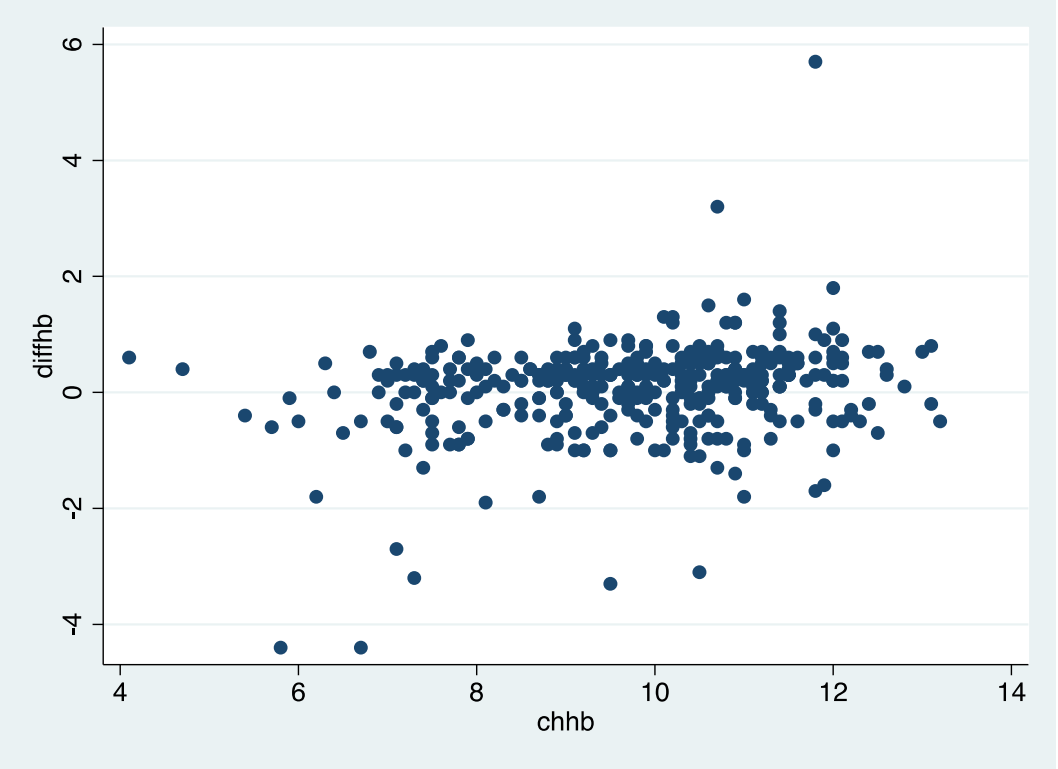
RCPA QAP

Comparing methods or sample sources

Venous vs Capillary Hb



Bland Altman



Mean Hb: Venous 9.75 vs Capillary 9.70, P=0.204

World Health Organization program

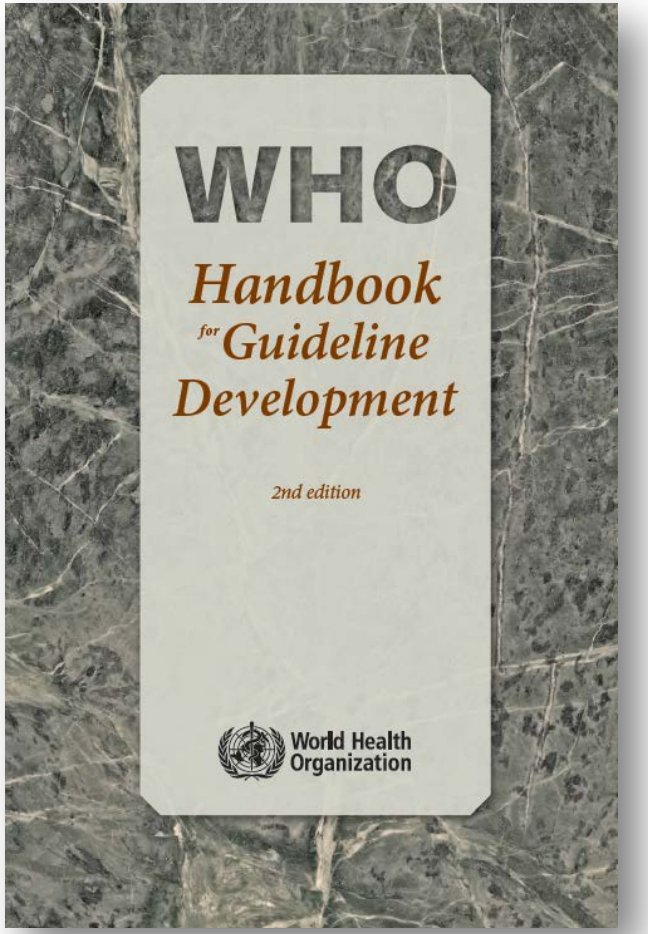
- **Use and interpretation of haemoglobin concentrations for assessing anaemia status in individuals and populations**
  - WHO Department of Nutrition for Health and Development
  - Centers for Disease Control and Prevention
  - Walter & Eliza Hall Institute of Medical Research, Melbourne, Australia

A WHO guideline

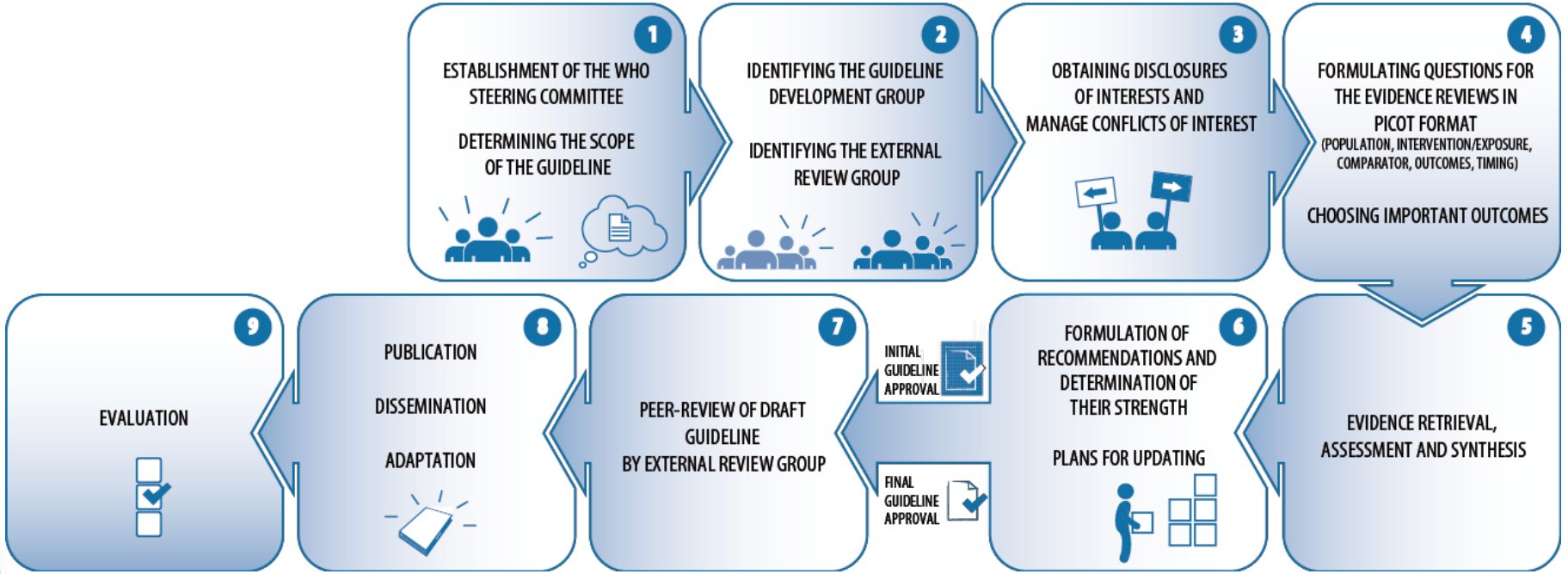
- Any document, whatever its title, containing WHO recommendations about health interventions, whether they be clinical, public health or policy interventions.
- A recommendation provides information about what policy-makers, health-care providers or patients should do. It implies a choice between different options 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.

WHO evidence-informed guideline development process

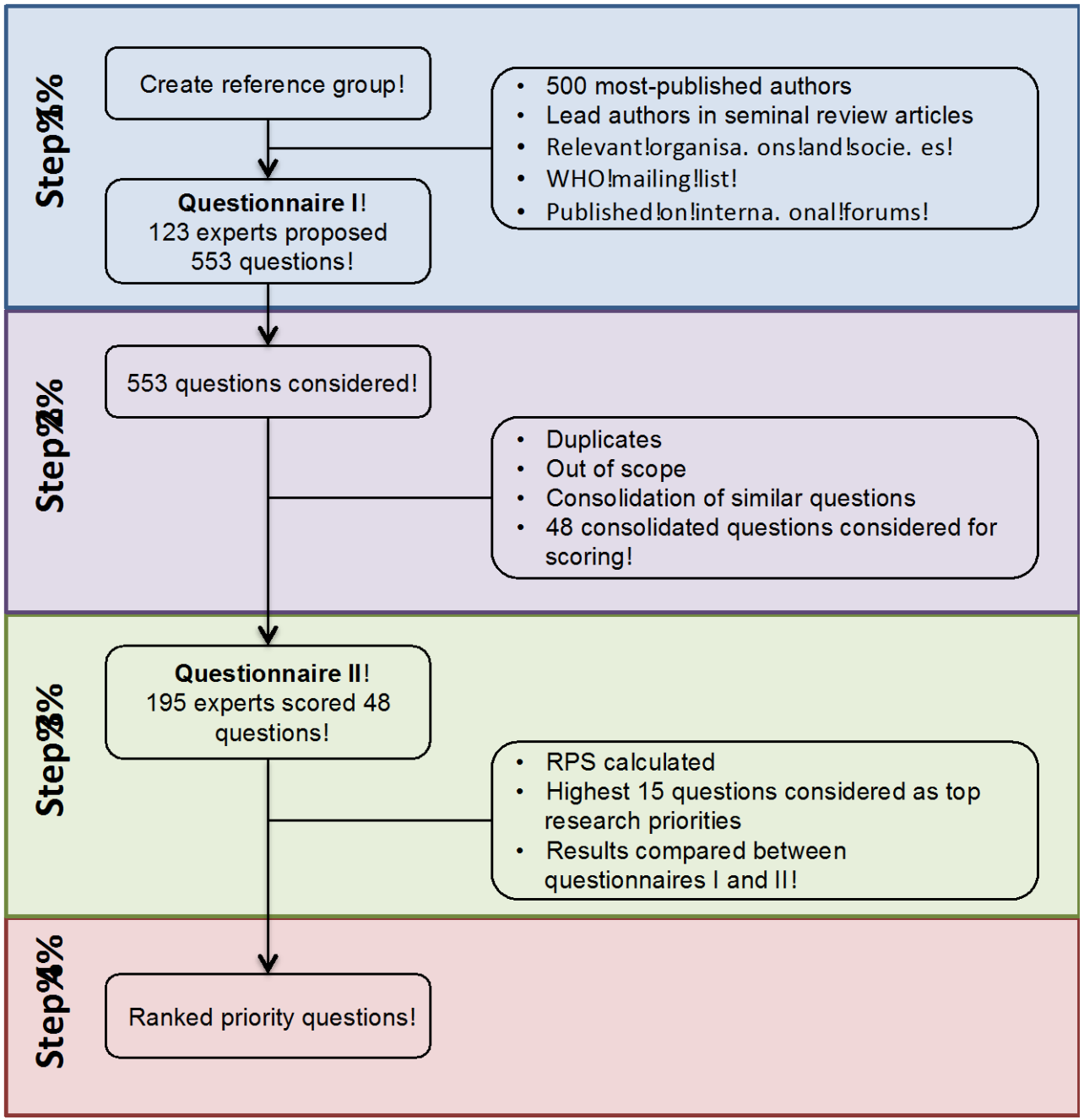
- New WHO guideline development process adopted in 2009
- 2nd edition of WHO Handbook for guideline development released in December 2014
  - Provides guidance on the development of documents or publications containing WHO recommendations
  - Sets out procedures to follow



WHO evidence-informed guideline development process



Scoping Exercise



Stakeholder Map

Increase CREDIBILITY of the program	IMPLEMENT the interventions that are central to this effort	ADVOCATE for changes to make this effort sustainable	FUND/AUTHORIZE the continuing or expanding this effort
□ WHO □ WHO units e.g. Blood Transfusion Safety Unit, Department of Nutrition / Health and Development, Department of Essential Health Technologies □ United Nations Children's Emergency Fund (UNICEF) □ CDC □ Experts publishing ≥7 papers between 2011-16 (n=500)	□ Clinicians: e.g. haematologists, paediatricians, obstetricians. □ Blood banks □ Research institutes □ Clinical laboratories	□ Haematology societies: e.g. American Society of Haematology, European Haematology Association □ International BioIron society □ Nutrition societies: e.g. African Nutrition Society, Latinoamericano de Nutrición □ Pathology societies: e.g. RCPA □ Blood transfusion societies: e.g. International Society of Blood Transfusion, Blood Banks	□ Donors □ Bill & Melinda Gates Foundation □ Governments and Ministries of Health □ Micronutrient Initiative □ Global alliance for Improved Nutrition

Scoping process

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Online consultation to identify priority questions for revising WHO haemoglobin concentrations for the diagnosis of anaemia and assessment of severity

Share Print

Deadline: 15 July 2016

The World Health Organization (WHO) is planning to review its global guidelines for haemoglobin thresholds used to define anaemia at the individual and population level. We would like to seek your input through this online consultation.

As the first step, we need to understand the key information and knowledge that would enable appropriate definition of haemoglobin thresholds, in the form of a prioritized list of scoping questions.

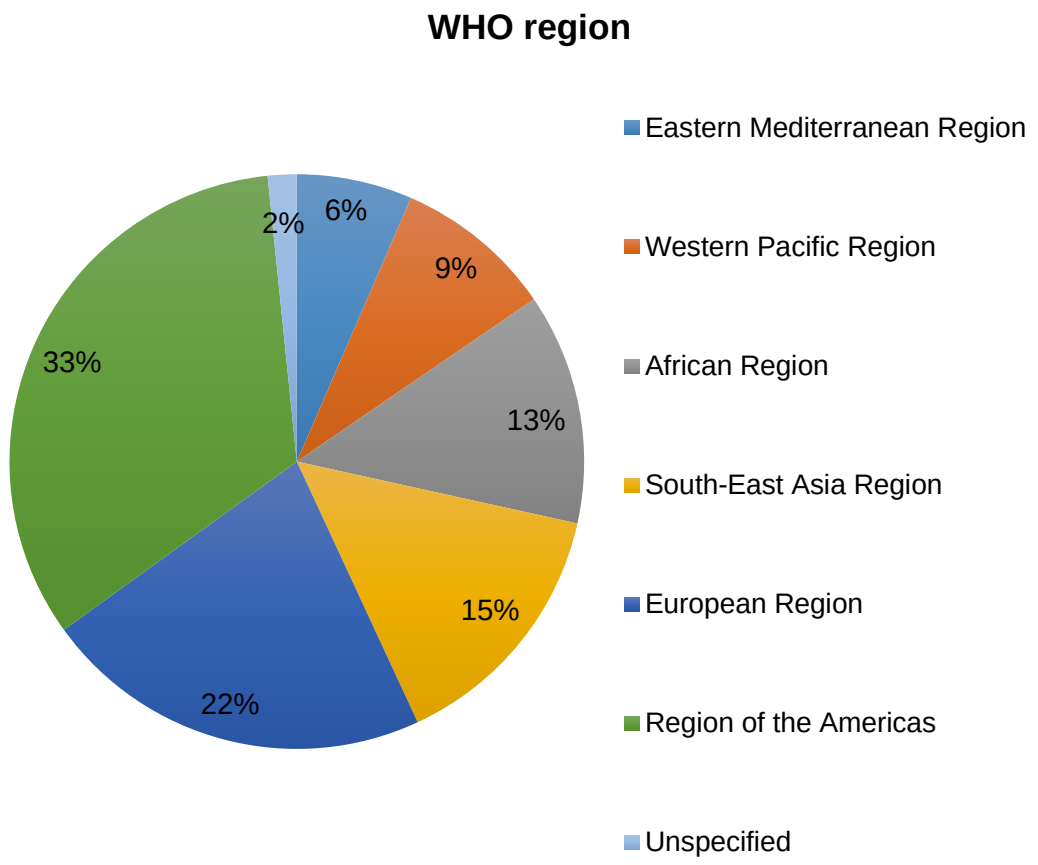
We would like you to propose a **list of priority questions for WHO guidance**.

The questions should be targeted towards identifying information and/or knowledge gaps that would assist with definition of haemoglobin reference ranges by clinicians and policy makers. Please feel free to propose questions regardless of whether data or evidence presently exists to provide an answer, as the questions will be used to guide evidence gathering or future primary research. Please draw on your own expertise and experience in devising these questions.

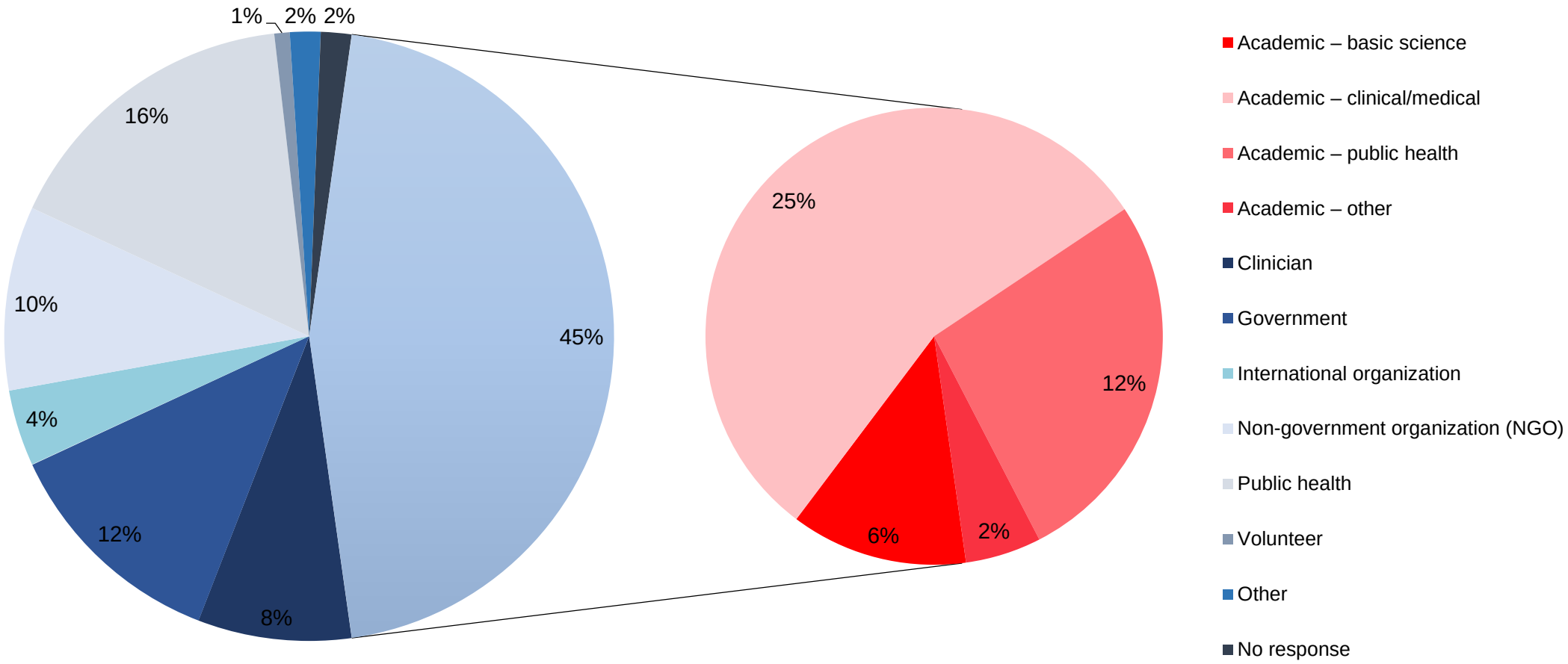
We will produce a list with your research questions and those submitted by other

Initial Scoping Exercise

- Initial Online Consultation:
  - Participants asked to pose questions (free form text).
  - 123 respondents
  - 553 questions proposed
- Questions rationalised to 58 questions arranged into six themes:
  - Physiology of anaemia
  - Hb thresholds for different population groups
  - Definition of anaemia across clinical and environmental contexts
  - Approach to developing anaemia thresholds
  - Laboratory and diagnostic considerations
  - Management of WHO's Hb threshold guidelines



Initial Scoping Exercise



Scoring of questions

Table 4.4 – Scoring criteria	
Criteria	**Definition / explanation**
Answerability	Can this question be achievably answered either through existing evidence by undertaking new research?
Effectiveness	Will answering this question lead to useful information that would inform definition of haemoglobin thresholds to diagnose anaemia?
Impact	Would the information obtained by answering this question lead to changes the haemoglobin thresholds to define anaemia or their interpretation in a wa that would make a meaningful difference to clinical and/or public health?
Equity and Public Health	Would the information obtained by answering the question reduce inequity (i.e. will it help improve the health and wellbeing of both vulnerable groups and the more advantaged) and help improve public healthcare?

Top Ranked Questions

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

Key topics

- Definition of anaemia severity in clinical and public health
- Definitions of anaemia in males/ females
- Definition of anaemia across the lifecycle.
- Effects of different micronutrient deficiencies on Hb concentrations.
- Adjustment of Hb for altitude
- Effects of Hb concentration on functional outcomes:
  - pregnancy / fetal outcomes,
  - Infant and child growth and development.
- Laboratory measurement of Hb.

Call for authors

World Health Organization

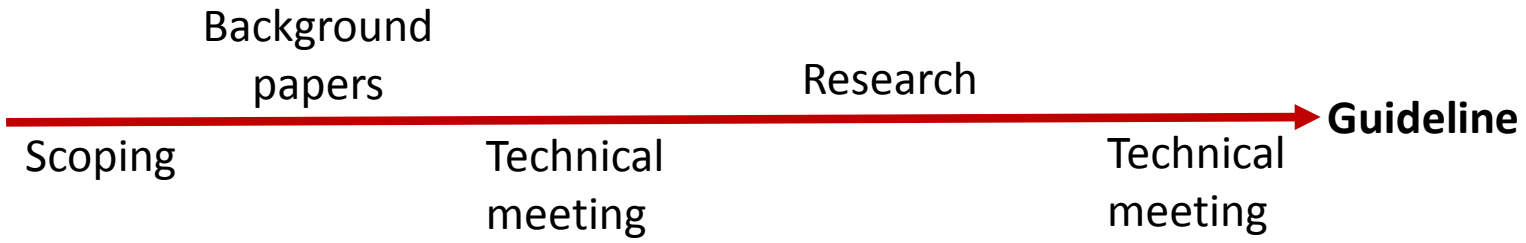
Use and interpretation of haemoglobin concentrations for assessing anaemia status in individuals and populations

CALL FOR AUTHORS

Anaemia is an important global health problem, considered to affect about a quarter of the world's population. Controlling the global burden of anaemia is a strategic public health nutrition objective. The 2025 Global Nutrition Targets include a 50% reduction in the prevalence of anaemia among women[1]. The 2030 Sustainable Development Goals 2 (End hunger, achieve food security and improved nutrition and promote sustainable agriculture) and 3 (Ensure healthy lives and promote well-being for all at all ages) encompass control of anaemia[2]. Clinically, diagnosis and management of anaemia and identification of its underlying causes is a common, everyday problem for primary

Next Steps

- WHO Technical Consultation
  - Late November 2017
  - To consolidate knowledge/ identify evidence gaps.
- To plan research agenda over 2018-2019.
  - Systematic reviews
  - New research
    - Prospective
    - Banked samples
    - Databases



Key stakeholder groups

- Clinical
  - Haematology
    - Laboratory
    - Clinical
    - Transfusion
  - Other subspecialties (obstetrics, internal medicine, paediatrics)
- Public Health
  - Nutrition
  - Global Burden of Disease
- Government/ non governmental agencies, including laboratories and health departments
- Donors and aid organisations involved in nutrition sensitive/ specific interventions

What sort of research might we need?

- Use of large epidemiologic datasets from low and middle income countries to define anaemia thresholds statistically is unlikely to be useful.
  - High prevalence of underlying disease, inflammation and nutritional deficiency and anaemia will be hard to account for.
  - Major efforts to optimise physiological norms have generally not repurposed epidemiologic studies.
  - Some very well selected datasets may be useful.

Intergrowth-21 Study

- To develop scientifically robust clinical tools to assess fetal growth and the nutritional status of newborn infants.
- Eight geographically diverse populations will participate, covering North and South America (USA, Brazil), Europe (Italy), Africa (Kenya), Western Asia (China) and the Indian Subcontinent (India).
- ‘Well populations’
  - Nutritionally adequate.
  - No socioeconomic constraints likely to affect fetal growth.
  - Absence of pollution/ smoke etc.
  - No anaemia during the pregnancy
- Screened 59,000 -> recruited 20,500 (i.e. most women failed inclusion criteria).

WHO Multicentre Growth Reference Study

- Collected primary growth data and related information from approximately 8500 children from widely different ethnic backgrounds and cultural settings (Brazil, Ghana, India, Norway, Oman and the USA).

No health, environmental or economic constraints on growth
Mother willing to follow feeding recommendations
Term birth: gestational age ≥ 37 completed weeks (259 days) and < 42 completed weeks (294 days)
Single birth
Absence of significant morbidity
Nonsmoking mother (before and after delivery)

De Onis et al 2014

Who would have an optimal Hb?

- Micronutrient replete (received fortified foods and/ or iron supplementation)
- No clinical or laboratory evidence of inflammation
- No underlying medical condition
- Also consider:
  - Nutritionally replete (growth/ BMI)
  - Underlying genotype (Hb AA?)
  - Environmental exposures (smoking, air pollution)
  - Socioeconomic status (independent predictor of Hb in some studies)
  - Parity
  - Normal birth weight and gestation duration
  - Healthy ageing
  - Medications
- Relatively easily done in Western country (just use NHANES, Biobank etc). More challenging in LMIC – but needed to account for population variations.

Other approaches to defining Hb thresholds

- What can we learn from other markers – e.g. Vitamin D?
  - Deficiency – bone disease (osteomalacia, rickets)
  - Deficiency is considered widespread.
  - Thresholds are controversial
- Approaches taken include:
  - Population norms using a Gaussian distribution
  - Levels at which a feedback hormone (parathyroid hormone) is suppressed.
  - Levels associated with risk of bone disease (bone mineral density, serum ALP) etc.
- Parallels with Hb:
  - Erythropoietin is a feedback hormone, suppressed when Hb is ‘normal’.
  - Clinical outcomes for anaemia *may* be detectable though correlation may be indistinct.

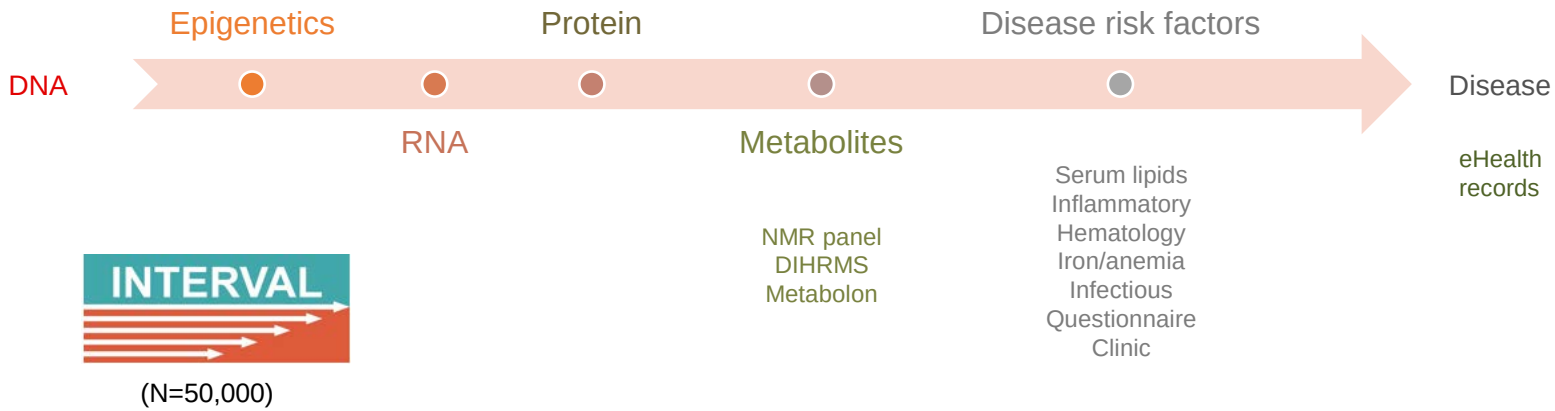
Exploiting powerful population resources

Large scale population resources

- Multivariate phenotypes
- Environmental exposures

biobank UK

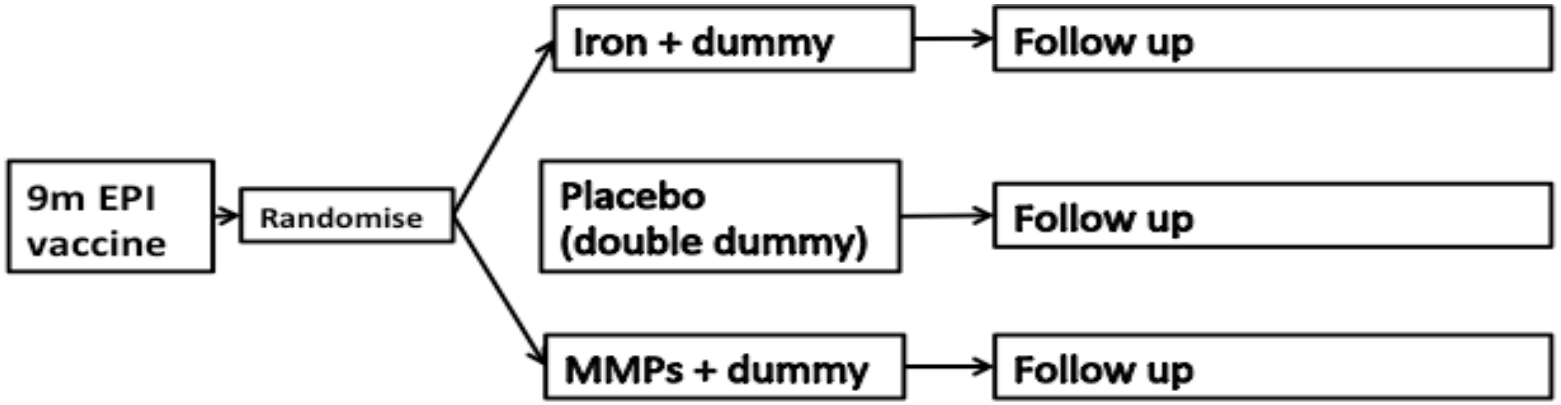
(N=500,000)

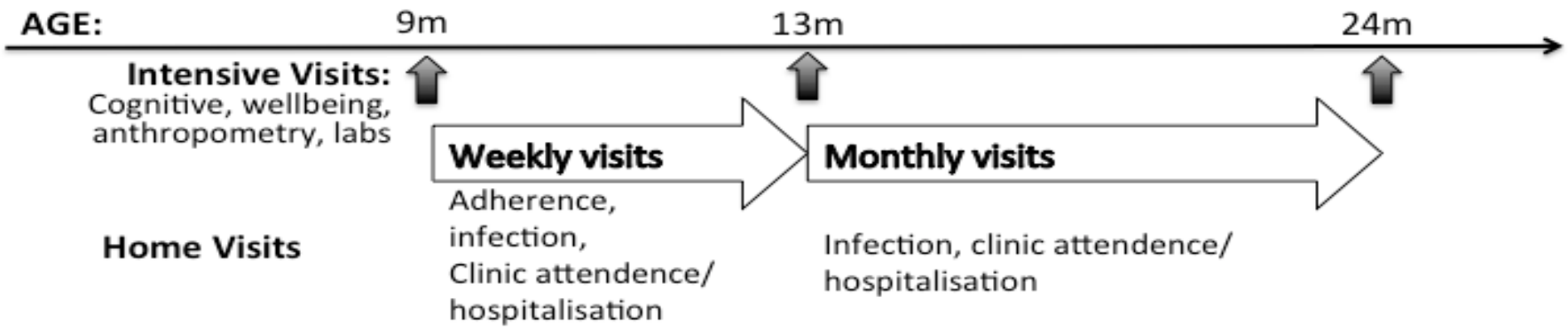


- Serial and multivariate molecular phenotypes
- Recall by genotype

Nicole Soranzo, Willem Ouwehand, John Danesh, Dave Roberts

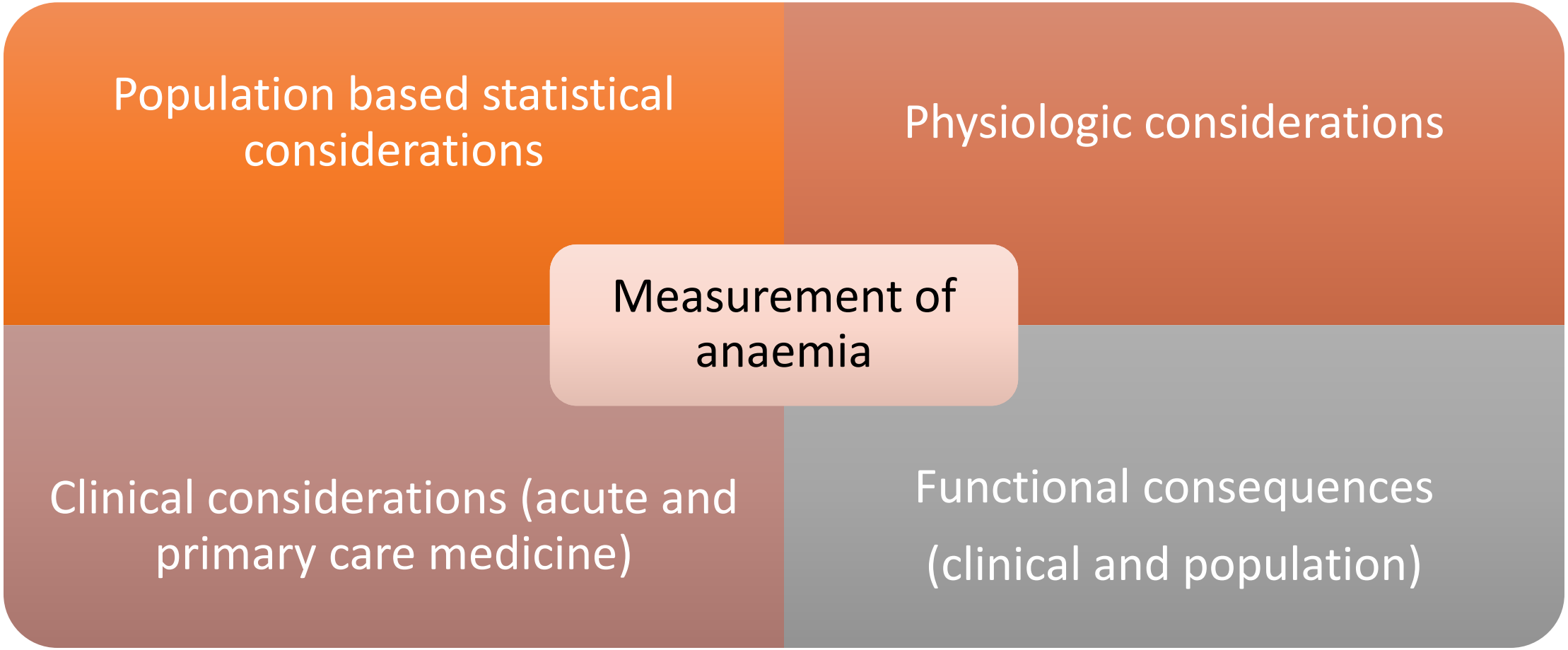
Randomised Trials





Biggs, Pasricha NHMRC 2015

Final guideline meeting



Outcomes of this programme

- Change in Hb thresholds?
  - Not necessarily (but perhaps)
  - Instead:
    - Refinement of thresholds in critical population subgroups (young, pregnancy, elderly)
    - Understanding of implications of an anaemia diagnosis
      - Statistical (sensitivity/ specificity etc.)
      - Physiologic and clinical
- Harmonisation of definitions of anaemia
  - Nationally
  - Internationally
  - Clinical and public health (difficult to separate these)
- Summary of the functional burden of global disease caused by anaemia.
- Summary of most appropriate approaches to measure Hb.

We need your help!

- Advice
- Ideas
- Datasets
- Banked samples
- Reviewers for papers
- Reviewers for grants
- Other stakeholders we haven't thought of
- Spread the word through your networks
- (Looking for team members)

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