Reviewing haemoglobin thresholds for the determination of anaemia

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University of Oxford
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

WHA Global Nutrition Targets 2025: Anaemia Policy Brief

TARGET: 50% reduction of anaemia in women of reproductive age
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 Enhancement of oxygen loading by decreased red-cell oxygen affinity in a patient with anaemia. An anaemic patient with a 50% reduction in haemoglobin concentration has only a 27% reduction in oxygen unloading.

Chapter: Anaemia: pathophysiology, classification, and clinical features
Author(s): D.J. Weatherall and Chris Hatton
From: Oxford Textbook of Medicine (5 ed.)
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>
<thead>
<tr>
<th>TABLE I: HAEMOGLOBIN VALUES BELOW WHICH ANAEMIA CAN BE CONSIDERED TO EXIST, AND ASSOCIATED HAEMATOLOGICAL VALUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>0.6- 4</td>
</tr>
<tr>
<td>5- 9</td>
</tr>
<tr>
<td>10-14</td>
</tr>
<tr>
<td>Adults</td>
</tr>
</tbody>
</table>

WHO Technical Report Series No 182, 1959
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 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. However, more recent data 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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### Studies incorporated in 1968 consultation

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

- Epidemiologic design
- Laboratory methodology:
  - Haematology
  - Iron biochemistry
  - Other biochemistry
- Statistical analysis
- Populations considered:
  - Ethnicity
  - Geography
  - Age range (children, elderly)
  - Pregnancy status
  - Altitude
Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity (WHO 2011)

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

<table>
<thead>
<tr>
<th>Population</th>
<th>Non-A anaemia</th>
<th>Mild*</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood 6 - 59 months of age</td>
<td>110 or higher</td>
<td>100-109</td>
<td>70-99</td>
<td>Lower than 70</td>
</tr>
<tr>
<td>Childhood 5 - 11 years of age</td>
<td>115 or higher</td>
<td>110-114</td>
<td>80-109</td>
<td>Lower than 80</td>
</tr>
<tr>
<td>Children 12 - 14 years of age</td>
<td>120 or higher</td>
<td>110-119</td>
<td>80-109</td>
<td>Lower than 80</td>
</tr>
<tr>
<td>Non-pregnant Women (15 years of age and above)</td>
<td>120 or higher</td>
<td>110-119</td>
<td>80-109</td>
<td>Lower than 80</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>110 or higher</td>
<td>100-109</td>
<td>70-99</td>
<td>Lower than 70</td>
</tr>
<tr>
<td>Men (15 years of age and above)</td>
<td>130 or higher</td>
<td>110-129</td>
<td>80-109</td>
<td>Lower than 80</td>
</tr>
</tbody>
</table>

* Adopted from references 5 and 6
* Haemoglobin in grams per litre
a "Mild" is a manoeum. Iron deficiency is already advanced by the time anaemia is detected. The deficiency has consequences even when no anaemia is clinically apparent.
Variation in cutoffs

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

<table>
<thead>
<tr>
<th>Country</th>
<th>Age-Adjusted Prevalence</th>
<th>Prevalence by age range (per 100,000 population)</th>
<th>Age-Adjusted Prevalence</th>
<th>Prevalence by age range (per 100,000 population)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1990</td>
<td>2010</td>
<td>Neonatal</td>
<td>Post-natal</td>
</tr>
<tr>
<td></td>
<td>95% UI</td>
<td>0.0030-0.0062</td>
<td>0.0453-0.0727</td>
<td></td>
</tr>
</tbody>
</table>

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.
Modelling different Hb thresholds and implications for anaemia prevalence

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

<table>
<thead>
<tr>
<th>Hb threshold used to define anaemia</th>
<th>Proportion considered anaemic (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120g/L (max)</td>
<td>50%</td>
</tr>
<tr>
<td>115g/L (WHO)</td>
<td>30%</td>
</tr>
<tr>
<td>110g/L (mean)</td>
<td>17%</td>
</tr>
<tr>
<td>105g/L (mean)</td>
<td>8%</td>
</tr>
<tr>
<td>100g/L</td>
<td>3%</td>
</tr>
<tr>
<td>95g/L</td>
<td>1%</td>
</tr>
<tr>
<td>90g/L (min)</td>
<td>0%</td>
</tr>
</tbody>
</table>
### Current recommendations for Hb thresholds used to define anaemia

**How is anaemia being defined in clinical practice?**

<table>
<thead>
<tr>
<th>Source</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
<th>0-1 years</th>
<th>1-2 years</th>
<th>3-4 years</th>
<th>5 years &amp; older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>&lt; 13</td>
<td>&lt; 10</td>
<td>&lt; 8</td>
<td>&lt; 11</td>
<td>&lt; 11</td>
<td>&lt; 13</td>
<td>&lt; 13</td>
</tr>
<tr>
<td>WHO</td>
<td>&lt; 13</td>
<td>&lt; 11</td>
<td>&lt; 8</td>
<td>&lt; 12</td>
<td>&lt; 12</td>
<td>&lt; 13</td>
<td>&lt; 13</td>
</tr>
<tr>
<td>NHGRI</td>
<td>&lt; 13</td>
<td>&lt; 11</td>
<td>&lt; 8</td>
<td>&lt; 12</td>
<td>&lt; 12</td>
<td>&lt; 13</td>
<td>&lt; 13</td>
</tr>
</tbody>
</table>

**Key**
- *Hb*: haemoglobin
- *WHO*: World Health Organization
- *NHGRI*: National Heart, Lung, and Blood Institute
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
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

Times of Hb variation

**Infancy**

**TABLE 22.1**

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

**Elderly**

Wintrobe’s Hematology
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

<table>
<thead>
<tr>
<th></th>
<th>Scripps-Kaiser</th>
<th>NHANES-III</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>2.5% actual</td>
<td>2.5% normal distribution</td>
<td>5% actual</td>
<td>5% normal distribution</td>
<td>No.</td>
</tr>
<tr>
<td>White men, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-59</td>
<td>6709</td>
<td>13.4</td>
<td>13.4</td>
<td>13.7</td>
<td>13.7</td>
<td>1456</td>
</tr>
<tr>
<td>60+</td>
<td>5515</td>
<td>12.8</td>
<td>12.8</td>
<td>13.2</td>
<td>13.2</td>
<td>934</td>
</tr>
<tr>
<td>White women, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-49</td>
<td>2966</td>
<td>11.9</td>
<td>11.9</td>
<td>12.2</td>
<td>12.2</td>
<td>1045</td>
</tr>
<tr>
<td>50+</td>
<td>8313</td>
<td>11.9</td>
<td>11.9</td>
<td>12.2</td>
<td>12.2</td>
<td>1395</td>
</tr>
<tr>
<td>Black men, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-59</td>
<td>434</td>
<td>12.6</td>
<td>12.5</td>
<td>12.9</td>
<td>12.9</td>
<td>1253</td>
</tr>
<tr>
<td>60+</td>
<td>135</td>
<td>—</td>
<td>12.4</td>
<td>—</td>
<td>12.7</td>
<td>235</td>
</tr>
<tr>
<td>Black women, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-49</td>
<td>205</td>
<td>11.2</td>
<td>11.2</td>
<td>11.5</td>
<td>11.5</td>
<td>904</td>
</tr>
<tr>
<td>50+</td>
<td>255</td>
<td>11.2</td>
<td>11.2</td>
<td>11.5</td>
<td>11.5</td>
<td>442</td>
</tr>
</tbody>
</table>

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
(From the Department of Physiological Chemistry and the John Herr Musser Department of Research Medicine, School of Medicine, University of Pennsylvania, Philadelphia)

(Received for publication, June 10, 1935)

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 HbO₂, Hb, HbCO, MHB-CN, 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 eg 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** (eg NATA).
External Quality assurance
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 policymakers, 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

1. Establishment of the WHO steering committee
   Determining the scope of the guideline

2. Identifying the guideline development group
   Identifying the external review group

3. Obtaining disclosures of interests and manage conflicts of interest

4. Formulating questions for the evidence reviews in PICOCT format (Population, Intervention/Exposure, Comparator, Outcome, Timing)
   Choosing important outcomes

5. Formulation of recommendations and determination of their strength
   Plans for updating

6. Evidence retrieval, assessment, and synthesis

7. Peer review of draft guideline by external review group

8. Publication, dissemination, adaptation

9. Evaluation
Scoping Exercise

Step 1:
- Create reference group!
- Questionnaire I! 123 experts proposed 553 questions!

Step 2:
- 553 questions considered!
- Duplicates
- Out of scope
- Consolidation of similar questions
- 48 consolidated questions considered for scoring!

Step 3:
- Questionnaire II! 195 experts scored 48 questions!
- RPS calculated
- Highest 15 questions considered as top research priorities
- Results compared between questionnaires I and II!

Step 4:
- Ranked priority questions!
<table>
<thead>
<tr>
<th>Stakeholder Map</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increase CREDIBILITY of the program</strong></td>
</tr>
<tr>
<td>□ WHO</td>
</tr>
<tr>
<td>□ WHO units e.g. Blood Transfusion Safety Unit, Department of Nutrition / Health and Development, Department of Essential Health Technologies</td>
</tr>
<tr>
<td>□ United Nations Children’s Emergency Fund (UNICEF)</td>
</tr>
<tr>
<td>□ CDC</td>
</tr>
<tr>
<td>□ Experts publishing ≥7 papers between 2011-16 (n=500)</td>
</tr>
</tbody>
</table>

| **IMPLEMENT the interventions that are central to this effort** |
| □ Clinicians: e.g. haematologists, paediatricians, obstetricians. |
| □ Blood banks |
| □ Research institutes |
| □ Clinical laboratories |

| **ADVOCATE for changes to make this effort sustainable** |
| □ Haematology societies: e.g. American Society of Haematology, European Haematology Association |
| □ International Federation of Blood transfusion societies |
| □ 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 |

| **FUND/AUTHORIZE the continuing or expanding this effort** |
| □ Donors |
| □ Bill & Melinda Gates Foundation |
| □ Governments and Ministries of Health |
| □ Micronutrient Initiative |
| □ Global alliance for Improved Nutrition |
Online consultation to identify priority questions for revising WHO haemoglobin concentrations for the diagnosis of anaemia and assessment of severity

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
Scoring of questions

Table 4.4 – Scoring criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition / explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Answerability</strong></td>
<td>Can this question be achievably answered either through existing evidence by undertaking new research?</td>
</tr>
<tr>
<td><strong>Effectiveness</strong></td>
<td>Will answering this question lead to useful information that would inform definition of haemoglobin thresholds to diagnose anaemia?</td>
</tr>
<tr>
<td><strong>Impact</strong></td>
<td>Would the information obtained by answering this question lead to changes the haemoglobin thresholds to define anaemia or their interpretation in a way that would make a meaningful difference to clinical and/or public health?</td>
</tr>
<tr>
<td><strong>Equity and Public Health</strong></td>
<td>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?</td>
</tr>
</tbody>
</table>
## Top Ranked Questions

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

<table>
<thead>
<tr>
<th>Requirement</th>
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<tbody>
<tr>
<td>No health, environmental or economic constraints on growth</td>
</tr>
<tr>
<td>Mother willing to follow feeding recommendations</td>
</tr>
<tr>
<td>Term birth: gestational age ≥ 37 completed weeks</td>
</tr>
<tr>
<td>(259 days) and &lt; 42 completed weeks (294 days)</td>
</tr>
<tr>
<td>Single birth</td>
</tr>
<tr>
<td>Absence of significant morbidity</td>
</tr>
<tr>
<td>Nonsmoking mother (before and after delivery)</td>
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</tbody>
</table>

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

Epigenetics
- DNA
- RNA

Protein
- Metabolites
- Serum lipids
- Inflammatory
- Hematology
- Iron/anemia
- Infectious
- Questionnaire
- Clinic

Disease risk factors
- NMR panel
- DIHRMS
- Metabolon

Disease
- eHealth records

Serial and multivariate molecular phenotypes
- Recall by genotype

Nicole Soranzo, Willem Ouwehand, John Danesh, Dave Roberts
Randomised Trials

9m EPI vaccine → Randomise

- Iron + dummy → Follow up
- Placebo (double dummy) → Follow up
- MMPs + dummy → Follow up

AGE:
- 9m: Intensive Visits: Cognitive, wellbeing, anthropometry, labs
- 13m: Weekly visits: Adherence, infection, Clinic attendance/hospitalisation
- 24m: Monthly visits: Infection, clinic attendance/hospitalisation

Biggs, Pasricha NHMRC 2015
Final guideline meeting

Population based statistical considerations

Physiologic considerations

Measurement of anaemia

Clinical considerations (acute and primary care medicine)

Functional consequences (clinical and population)
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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