Exploring the Anemia Ecology: A New Approach to an Old Problem

A webinar on behalf of the U.S. Global Nutrition Coordination Plan Ecology of Parent, Infant, and Child (EPIC) Nutrition Subgroup
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USAID Advancing Nutrition
Anemia Task Force

An Ecological Approach to
Addressing an Intractable
(and perhaps misunderstood)
Global Challenge

Daniel J. Raiten, Ph.D.
Program Director- Nutrition
NICHD/NIH
What’s the Problem?
This logic is limited because it ignores the biological and environmental realities of health and disease. CONTEXT MATTERS!
Context Matters

Why “one-size-fits-all” doesn’t!

The need for an ecological approach

Ecology:
“the set of relationships existing between any complex system and its surroundings or environment.”
(Dictionary.Com)
The “Environment” - A holistic view

The Environment

HOME
COMMUNITY

NATURAL
(land, water, climate)

BIOLOGICAL
Nutrition, Life stage, Health/
Genetics

SOCIAL/
ECONOMIC/
POLITICAL
A Complex Health Context:
it’s not just about too much or too little!

Environment

Under-nutrition  Malnutrition ("Double-Burden")

Infectious Diseases  Nutrition Transition  Microbiome Inflammation

Non-communicable Disease

(DOHaD)

Birth  Death
GB of Anemia

- There were a total of 1.93 billion people with anemia in 2013
- 950 million cases of mild anemia,
- 906 million cases of moderate anemia, and,
- 75.6 million cases of severe anemia.
- The total global number of YLDs also changed very little, decreasing from 62,023,831 (95% UI, 41,591,487–89,266,761) to 61,525,570 (95% UI, 41,020,763–88,730,696) for both sexes

(Kassebaum, 2016)

Note: most of this information comes from DHS's and similar population surveys. There is a growing belief that those figures are grossly overestimates. Moreover, in the case of children younger than 5 years of age, the WHO current recommendation of using a single threshold value to diagnose anemia may be incorrect, especially for children younger than 24 months of age.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron-deficiency anemia (IDA)</td>
<td>1,208,360.1</td>
<td>62.57</td>
</tr>
<tr>
<td>Thalassemia trait</td>
<td>104,232.6</td>
<td>5.40</td>
</tr>
<tr>
<td>Malaria</td>
<td>80,602.4</td>
<td>4.17</td>
</tr>
<tr>
<td>Gastritis and duodenitis</td>
<td>63,222.9</td>
<td>3.27</td>
</tr>
<tr>
<td>Other neglected tropical diseases</td>
<td>59,728.3</td>
<td>3.09</td>
</tr>
<tr>
<td>Other hemoglobinopathies and hemolytic anemias</td>
<td>55,804.0</td>
<td>2.89</td>
</tr>
<tr>
<td>Other infectious diseases</td>
<td>49,771.4</td>
<td>2.58</td>
</tr>
<tr>
<td>Endocrine, metabolic, blood immune disorders</td>
<td>49,327.8</td>
<td>2.55</td>
</tr>
<tr>
<td>Sickle cell trait</td>
<td>43,353.9</td>
<td>2.24</td>
</tr>
<tr>
<td>Uterine fibroids (females only)</td>
<td>36,833.7</td>
<td>1.91</td>
</tr>
<tr>
<td>Hookworm disease</td>
<td>34,579.6</td>
<td>1.79</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>32,726.7</td>
<td>1.69</td>
</tr>
<tr>
<td>Chronic kidney disease owing to other causes</td>
<td>26,007.2</td>
<td>1.35</td>
</tr>
</tbody>
</table>
Summary: Kassebaum (2016)

- “IDA is the dominant cause of anemia in most countries and populations.”
- “If we include those conditions such as hookworm, schistosomiasis, and gastrointestinal and gynecologic conditions that also manifest as IDA, its importance grows even more apparent.”
- “Despite its continued dominance, a decrease in IDA has been the primary driver of reduced global anemia burden since 1990.”
- “The improvements have been partially offset, however, by increases in anemia owing to
  - chronic kidney diseases (CKDs),
  - hemoglobinopathies,
  - malaria, and
  - schistosomiasis.
  “Most of the increase in these latter conditions is related to population aging (for CKD) and population growth in endemic areas.”
Challenges: the Complexity of Anemia

- Nutrition
- Macro-Micro-nutrient
- Health
- Infection/inflammation
- Genetics

ANEMIA
The Ecology of Anemia:

- Environments
  - Physical/
  - Climate/Economic/
  - Social/Behavioral

- Diet & Nutrition
  - Nutrient Exposition/Status
  - Food Systems

- Health
  - Life stage
  - Clinical/Population
  - Inflammation/
  - Genetics/Disease

Ecology of Anemia
ANATF
Goals and Objectives
So, what are we talking about?

Challenge: the current vernacular perpetuates

1. the perception about the predominance of iron deficiency, and
2. conflates nutritional iron Deficiency (NID) with impaired iron physiology due to a myriad of causes.

Questions:

✔ How do we distinguish between the contribution of NID, and more broadly, nutrient responsive anemia (NRA) involving other nutrients?
✔ How do we account for the multiple factors that contribute to anemia in a population?
✔ How can we improve precision of assessment to support context-specific, safe, effective and equitable interventions?
USAID’s Response

● Constituted the USAID Advancing Nutrition Anemia Task Force (ANATF)

What is the ANATF?

It’s a 4-year project with the following overarching objectives:

- Advise USAID-AN in all areas of anemia reduction from a public health perspective, and
- Serve as a research advisory body and translate state-of-the-art evidence in micronutrient nutrition for distribution through USAID-AN and its dissemination platforms.
ANATF Conceptual Approach

Assessment

intervention

Biology
ANATF: Process and Deliverables

**Process:**

- **Step 1** Develop a Technical Report to be:
  - ✔ Delivered to USAID
  - ✔ Disseminated to relevant stakeholder groups/agencies/organizations
  - ✔ Published in appropriate peer-reviewed journal (TBD) delivered to USAID

- **Step 2:** Work with USAID/AN to
  - ✔ identify relevant resources and platforms to implement a research strategy to address key elements outlined in the Technical Report.
  - ✔ Provide advice to USAID as needed.

**Deliverables**

- Technical Report
- Redesign of the USAID Anemia Toolkit
- Quarterly updates on progress of USAID Advancing Nutrition Task Force activities
Thank You!
Biology of Anemia: A Public Health Perspective

Gary Brittenham, Gemma Moir-Meyer, Kelvin Mokaya Abuga, Ananya Datta Mitra, Carla Cerami, Ralph Green, Sant-Rayn Pasricha, Sarah Atkinson
Disclosure of Financial Interests: 2022

- **Research support:**
  - **National Institutes of Health:**
    - R01DK115449-01-05; R01FD006372-01-04, R01DK116126 -01-05
  - **Bill and Melinda Gates Foundation:**
    - INV-036845, INV-039533

- **Consultant:** European Food Safety Authority (EFSA): Tolerable upper intake level (UL) for iron.

- **Medical Advisory Board:** Tesseract Health, Inc. Guilford CT. Advise on development of therapeutic and diagnostic products.

- **Intellectual Property:** Inventor on Columbia University patent US 20190110718A1 for "Apparatus and method for noninvasive measurement of a fluorescent analyte using alternating wavelengths for tissue excitation."
Assessment and interventions for anemia rely on recognizing the roles of:

• absolute and functional iron deficiency
• other nutrient deficiencies (folate, vitamin A, B\textsubscript{12})
• infections (malaria, helminths, Tb, other)
• genetics (hemoglobinopathies)
Red Blood Cell (RBC) Production

- Kidney
- Erythropoietin
- Bone Marrow (Iron, B_{12}, Folate)

RBC
Red Blood Cell (RBC) Production and Loss

**Normal:**

RBC Production

= 

RBC Loss
Red Blood Cell (RBC) Production and Loss

**Normal:**
RBC Production = RBC Loss

**Anemia:**
RBC Production < RBC Loss

- **External** (Bleeding)
- **Internal** (Hemolysis)
Hepcidin controls iron entry into plasma
Body Iron Supply and Storage

Spleen, BM and liver macrophages

Muscle, other parenchymal cells

Circulating red blood cells

Erythroid marrow

Hepatocytes

GI tract

Functional iron
Macroage storage iron
Hepatocyte storage iron
Transport iron

BM: Bone marrow

Sites of hepcidin control of iron entry into plasma
Normal iron stores

IRON STORES ↔ IRON USAGE

Normal hepcidin

IRON HOMEOSTASIS
Absolute iron deficiency

Iron stores < iron demand

Absolute iron deficiency
Functional iron deficiency anemia

IRON AVAILABILITY < IRON DEMAND
↑ Hepcidin

FUNCTIONAL IRON DEFICIENCY
Absolute iron deficiency: the most vulnerable
Other nutrients: Vitamin B$_{12}$ and folate cause anemia by limiting DNA synthesis
Vitamin A deficiency disorders

- Keratomalacia
- Corneal ulceration
- Night blindness
- Metaplasia, impaired immunity, morbidity, anemia, poor growth
- Systemic effects
- Alteration in genetic and metabolic function
- Tissue and plasma "depletion"
- Chronic dietary deficit

Mortality risk
Vitamin A deficiency in preschool children
## Global Prevalence of Selected Infections by Age in Millions

<table>
<thead>
<tr>
<th>Infection</th>
<th>All Ages (95% CI)</th>
<th>Young Children ≤5 Years (95% CI)</th>
<th>School-age Children, 5–14 Years (95% CI)</th>
<th>Adolescents and Adults ≥14 Years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>228 (206–258)</td>
<td>23.8*</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Hookworm</td>
<td>451 (425–479)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>190 (180–200)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS)</td>
<td>38 (31.6–44.5)</td>
<td>1.8 (1.3–2.2)</td>
<td></td>
<td>36.2 (30.2–42.5)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>10.0 (8.99–11.1)</td>
<td>1.12 (0.98–1.25)</td>
<td></td>
<td>8.9 (7.85–9.94)</td>
</tr>
<tr>
<td>Non-typhoidal Salmonellae (NTS)</td>
<td>0.54 (0.41–0.71)</td>
<td>0.22 (0.16–0.37)</td>
<td>0.12 (0.07–0.18)</td>
<td>180.3†</td>
</tr>
</tbody>
</table>
# Mechanisms of anemia in infectious diseases

<table>
<thead>
<tr>
<th>Anemia Etiology</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia of inflammation</td>
<td>Chronic infections</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>Malaria, schistosomiasis, HIV, bacterial hemolysins</td>
</tr>
<tr>
<td>Blood loss</td>
<td>Hookworm, schistosomiasis, HIV/AIDS</td>
</tr>
<tr>
<td>Ineffective RBC production</td>
<td>Malaria, HIV</td>
</tr>
<tr>
<td>Nutrient malabsorption</td>
<td>Hookworm, Helicobacter pylori, gut microbiome*</td>
</tr>
<tr>
<td>Hypersplenism</td>
<td>Malaria, hepatitis C virus (HCV), tuberculosis, schistosomiasis</td>
</tr>
<tr>
<td>Drug treatment*</td>
<td>HCV, HIV, tuberculosis, bacterial infections</td>
</tr>
</tbody>
</table>
Life Cycle of *Plasmodium falciparum*
Malaria and anemia: effects on iron
Historical global map of malaria endemicity
Distribution of origins of the thalassemias

α-thalassemias

β-thalassemias
Assessment and interventions for anemia rely on recognizing the roles of

- absolute and functional iron deficiency
- other nutrients (folate, vitamins A, B\textsubscript{12})
- infections (malaria, helminths, Tb, other)
- genetics (hemoglobinopathies)
IMPROVING ANEMIA ASSESSMENT IN CLINICAL AND PUBLIC HEALTH SETTINGS

ANNE WILLIAMS, KENNETH BROWN, LINDSAY ALLEN, OMAR DARY, RAHUL RAWAT, DENISH MOORTHY, PARMJ SUCHDEV

Medical Epidemiologist, CDC Central America Regional Office
Professor of Pediatrics and Global Health, Emory University
September 13, 2022
Disclosures

I receive grant support for nutrition research and surveillance from the Centers for Disease Control & Prevention and Bill and Melinda Gates Foundation.

I have no financial or commercial conflict of interest related to this presentation.

"The findings and conclusions in this presentation have not been formally disseminated by the Centers for Disease Control and Prevention and should not be construed to represent any agency determination or policy."
USAID Advancing Nutrition Anemia Task Force

The Assessment working group will provide a practical approach to assessment of anemia in public health settings, with a focus on evaluating the etiology.

www.advancingnutrition.org/what-we-do/monitoring-evaluation-and-learning/anemia-task-force
“If you cannot measure it, you cannot improve it”

-Lord Kelvin
Time for a Zoom poll

How likely are we to meet the 2025 World Health Assembly target for 50% anemia reduction in women of reproductive age?

a) 80%
b) 50%
c) 20%
d) 3%
Progress of Reducing Anemia by 50% in Women is Slow and Uneven

- Slow decline of only 0.3 percentage point (pp) per year
- Only 2 countries (Guatemala & Philippines) on track to meet target
Objective of assessment group

1. Review how to **assess anemia** based on low hemoglobin
2. Review assessment of **anemia causes** in different settings
3. Propose a **decision tree** to systematically approach anemia assessment in surveys
4. Discuss **research gaps and priorities** related to anemia assessment
Diagnosing Anemia

• Anemia diagnosed by
  ✔ Low Hemoglobin (g/dL or g/L)
  ✔ Low Hematocrit (packed cell volume, %)

• Clinical signs are not reliable
Multiple approaches to measure hemoglobin

Fingerstick

Phlebotomy

Non-invasive
Factors Affecting Hemoglobin Testing

- Adjust for altitude and smoking
- Cut-offs based on age, sex, pregnancy status
- Inflammation and infection
- Extreme climate
- Poor infrastructure
- Source of blood collection (venous vs. capillary)*
- Cost, time, ethics
- Standardized training
- Accuracy
- Reproducibility
- Quality control

*www.researchsquare.com/article/rs-1875378/v1
Hemoglobin cutoffs based on lowest 5% of hemoglobin in “healthy”* children

<table>
<thead>
<tr>
<th>Survey</th>
<th>Sample size</th>
<th>Hb 5th percentile, g/dL (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pakistan 2011</td>
<td>1119</td>
<td>7.90 (7.54-8.26)</td>
</tr>
<tr>
<td>Côte d’Ivoire 2007</td>
<td>147</td>
<td>7.94 (6.62-9.26)</td>
</tr>
<tr>
<td>Bangladesh 2010</td>
<td>777</td>
<td>8.40 (8.23-8.56)</td>
</tr>
<tr>
<td>Kenya 2010</td>
<td>167</td>
<td>8.73 (7.79-9.68)</td>
</tr>
<tr>
<td>Afghanistan 2013</td>
<td>205</td>
<td>8.82 (8.20-9.45)</td>
</tr>
<tr>
<td>Cambodia 2014</td>
<td>198</td>
<td>8.89 (8.51-9.28)</td>
</tr>
<tr>
<td>Laos 2006</td>
<td>216</td>
<td>9.06 (8.55-9.57)</td>
</tr>
<tr>
<td>Liberia 2011</td>
<td>341</td>
<td>9.15 (8.79-9.51)</td>
</tr>
<tr>
<td>Philippines 2011</td>
<td>906</td>
<td>9.53 (9.28-9.77)</td>
</tr>
<tr>
<td>Kenya 2007</td>
<td>116</td>
<td>9.62 (8.45-10.70)</td>
</tr>
<tr>
<td>Cameroon 2009</td>
<td>232</td>
<td>9.76 (9.30-10.22)</td>
</tr>
<tr>
<td>Mexico 2006</td>
<td>1015</td>
<td>9.80 (9.60-9.99)</td>
</tr>
<tr>
<td>Azerbaijan 2013</td>
<td>579</td>
<td>9.82 (9.55-10.10)</td>
</tr>
<tr>
<td>Rwanda 2010</td>
<td>367</td>
<td>10.07 (9.81-10.33)</td>
</tr>
<tr>
<td>Mexico 2012</td>
<td>1471</td>
<td>10.08 (9.95-10.20)</td>
</tr>
<tr>
<td>Bangladesh 2012</td>
<td>218</td>
<td>10.15 (9.81-10.49)</td>
</tr>
<tr>
<td>Ecuador 2012</td>
<td>1339</td>
<td>10.20 (10.12-10.28)</td>
</tr>
<tr>
<td>Colombia 2010</td>
<td>2115</td>
<td>10.27 (10.17-10.37)</td>
</tr>
<tr>
<td>Malawi 2016</td>
<td>291</td>
<td>10.33 (9.97-10.68)</td>
</tr>
<tr>
<td>Nicaragua 2005</td>
<td>440</td>
<td>10.52 (10.40-10.65)</td>
</tr>
<tr>
<td>Vietnam 2010</td>
<td>249</td>
<td>10.96 (10.63-11.30)</td>
</tr>
<tr>
<td>US 2006</td>
<td>937</td>
<td>11.23 (11.14-11.33)</td>
</tr>
<tr>
<td>Pooled estimate</td>
<td></td>
<td>9.65 (9.26-10.04)</td>
</tr>
</tbody>
</table>

*Excluded those with iron deficiency, vit A deficiency, inflammation, malaria

Cutoff confirmed using physiological measure of erythropoiesis
## Common causes of anemia

Anemia itself is not a disease

<table>
<thead>
<tr>
<th>Non-nutritional causes of anemia</th>
<th>Nutrition-specific causes of anemia*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood loss</strong></td>
<td><strong>Microcytic</strong></td>
</tr>
<tr>
<td>Postpartum hemorrhage</td>
<td>Iron deficiency*</td>
</tr>
<tr>
<td>Heavy menstrual bleeding*</td>
<td>Folate deficiency*</td>
</tr>
<tr>
<td>Gastrointestinal blood loss*</td>
<td>Vitamin B12 deficiency*</td>
</tr>
<tr>
<td>Urinary blood loss*</td>
<td></td>
</tr>
<tr>
<td><strong>Increased hemolysis</strong></td>
<td><strong>Normocytic</strong></td>
</tr>
<tr>
<td>Infection (malaria)*</td>
<td>Anemia of inflammation*</td>
</tr>
<tr>
<td>Hemoglobin disorders (SCD, thalassemias)</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Enzymopathies (G6PD deficiency)</td>
<td>Bone marrow failure</td>
</tr>
<tr>
<td>Immune-mediated</td>
<td></td>
</tr>
<tr>
<td>Hypersplenism</td>
<td></td>
</tr>
<tr>
<td><strong>Deficient erythropoiesis</strong></td>
<td><strong>Microcytosis</strong></td>
</tr>
<tr>
<td>Anemia of inflammation*</td>
<td>· Iron deficiency*</td>
</tr>
<tr>
<td>Thalassemias</td>
<td>· Vitamin A deficiency*</td>
</tr>
<tr>
<td><strong>Macrocytosis</strong></td>
<td>· Riboflavin deficiency*</td>
</tr>
<tr>
<td><em>Can be caused by insufficient dietary intake, impaired absorption or increased losses</em></td>
<td></td>
</tr>
</tbody>
</table>
| *Preventable or treatable*
Application of an Ecological Approach to Anemia Assessment

- Individuals in clinical settings
- Population-based surveys
Clinical assessment of anemia in *individuals*

- **Examination of CBC and peripheral blood smear**
  - **MCV < 80**
    - Microcytic anemia
      - Serum iron studies
        - Low ferritin with high TIBC
        - Iron deficiency anemia
          - Mentzer index (MCV/RBC) < 13
            - Thalassemia
  - **MCV 80–100**
    - Normocytic anemia
      - Reticulocyte count
        - < 2% (hypoproliferative)
        - > 2% (hyperproliferative)
          - Leukemias
          - Aplastic anemia
          - Anemia of inflammation
          - Other marrow failure syndromes
          - Hemorrhage
          - Hemolytic anemias
          - Gastrointestinal or urinary blood loss
          - C6GFD deficiency
          - Infection (malaria)
  - **MCV > 100**
    - Macrocytic anemia
      - Megalocytes and segmented neutrophils on peripheral smears
        - Present: megaloblastic
        - Absent: non-megaloblastic
          - Vitamin B12 and/or folate deficiency
          - Drug-Induced
          - Alcohol abuse
          - Myelodysplastic syndrome
          - Liver disease
          - Congenital bone marrow failure syndromes

CBC—complete blood count; MCV—mean corpuscle volume; TIBC—total iron binding capacity; RBC—red blood cell count
Decision tree for prioritizing biomarkers to measure causes of anemia in population surveys

**STEP 1**—Review anemia situation at national and sub-national levels. Engage with anemia stakeholders to assess data availability and gaps.

**STEP 2**—Are data available to estimate the proportion of anemia that is iron deficiency anemia?

- **NO**
  - MEASURE CHARACTERISTICS TO ESTIMATE IDA:
    - Iron (ferritin)
    - Inflammation (C-reactive protein, alpha-1-acid glycoprotein)

- **YES**
  - MEASURE CHARACTERISTICS TO BE ABLE TO ESTIMATE HOW RESPONSIVE A POPULATION MAY BE TO IRON INTERVENTION:
    - Iron program data
    - Infections (parasitic—malaria; bacterial; viral)
    - Inherited blood disorders

**STEP 3**—Are data available to contextualize IDA data to determine why iron interventions may have been (or have not been) successful? For example—

- Does iron program intervention data suggest challenges faced with supply, distribution, acceptability, or uptake?
- What is known about the populations’ underlying infection burden or inflammation status (specifically malaria)?
- Are inherited blood disorders common in the population?

- **NO**
  - MEASURE COMMON CAUSES OF BLOOD LOSS WITHIN THE POPULATION:
    - Hookworm and schistosomiasis infections
    - Uterine fibroids and heavy menses among women

- **YES**
  - MEASURE OTHER NUTRITIONAL CAUSES OF ANEMIA:
    - Additional micronutrients (vitamin A, folate, vitamin B12, riboflavin)
    - Cooking or consumption patterns that influence micronutrient absorption

**STEP 4**—Are data available to estimate the proportion of anemia due to blood loss (e.g., helminths or heavy menses among women)?

- **NO**
- **YES**

**STEP 5**—Are data available to characterize non-iron micronutrient (e.g., vitamin A) or nutrition-specific (e.g., phytate-rich diet) causes of anemia?

- **NO**

**YES**! With these available data, program planners will be equipped to determine what are the most likely underlying causes of anemia within their populations and respond accordingly.
## Important Considerations for Anemia Assessment

### Assessment and interpretation of hemoglobin

1. Utilize venous (or pooled capillary) blood and automated analyzer or point-of-care Hemocue device
2. Apply updated adjustments for altitude and smoking
3. Apply global, age and sex-specific, and physiologically-validated cutoffs to define anemia

### Assessment and interpretation of anemia causes

1. Assess all relevant causes of anemia in surveys, surveillance or program monitoring (e.g., infections, inflammation, blood loss, inherited blood disorders, micronutrient deficiencies)
2. Apply analytical methods to measure the relative contributions of multiple anemia causes in the population to inform anemia interventions
## Research Needs

<table>
<thead>
<tr>
<th>Assess hemoglobin and anemia etiology</th>
<th>Population anemia etiology assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Non-invasive methods to measure Hb</td>
<td>1. Statistical approaches to assess anemia etiologies using cross-sectional data</td>
</tr>
<tr>
<td>2. Point-of-care assessment of ferritin, hepcidin and erythropoietin</td>
<td>2. Cost and logistical implications of stepwise algorithm vs broad-based screening</td>
</tr>
<tr>
<td>3. Role of multiple micronutrient deficiencies in anemia</td>
<td></td>
</tr>
<tr>
<td>4. Re-evaluation of Hb thresholds to define anemia</td>
<td></td>
</tr>
</tbody>
</table>
Time for a Zoom poll

Which research need would you prioritize?

a) Non-invasive methods to measure Hb
b) Point-of-care assessment of ferritin, hepcidin and erythropoietin
c) Role of multiple micronutrient deficiencies in anemia
d) Re-evaluation of Hb thresholds to define anemia
e) Statistical approaches to assess anemia etiologies using cross-sectional data
f) Cost and logistical implications of stepwise algorithm vs broad-based screening
Take Home Points

- Anemia is itself not a disease, but a condition reflective of its diverse and overlapping causes.

- Broadening the focus from predominantly iron to a better understanding of nutritional and non-nutritional anemia determinants would inform clinical care and anemia control programs.

- Adopting a practical, systematic approach to anemia assessment is essential to address data gaps.
THANK YOU
Approaches
to Address Anemia

Working Group ‘Translation and Implementation’

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*No conflict of interest to disclose
Anemia Ecology: Food Systems

Ecology of traditional food systems
- Production and consumption patterns
- Social, behavioral, cultural, and economic factors
- Anti-nutrient compounds in plant-based diets

=> Considerations for nutrition-specific interventions
Anemia Ecology: Health Outcomes

Non-dietary interventions for anemia prevention/treatment

• Include a broad range of approaches to apply to an individual or at the population level
• Can be a single clinical intervention or broader public health programs
Climate change
- Is profoundly impacting food systems, dietary diversity, diet quality and health
- Limits food availability via severe weather events, drought/water shortages, and reductions in arable land

Greenhouse gas emissions impact
- Food quantity: ↓ Crop yields
- Food quality: Changed nutrient composition, ↓ Essential nutrients
Triple A: Assessment – Analysis – Action

Adapted from UNICEF 1990, 17.
Non-Dietary Interventions

Can be applied at individual or population levels

<table>
<thead>
<tr>
<th>Cause</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>use of intermittent preventive chemoprophylaxis; insecticide-treated nets</td>
</tr>
<tr>
<td>Intestinal Parasites</td>
<td>mass drug administration, targeted chemotherapy, selective therapy</td>
</tr>
<tr>
<td>Tuberculosis/HIV</td>
<td>differentiation between nutritional (incl. iron deficiency) and genetic causes</td>
</tr>
</tbody>
</table>

Other clinical conditions
- Acute loss due to postpartum hemorrhage
- Chronic loss due to menstruation
- Inherited red blood cell disorders
Non-Dietary Interventions - Evidence

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Efficacy</th>
<th>Proven Effectiveness</th>
<th>Scalability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Malaria treatment</td>
<td>Proven</td>
<td>Proven</td>
<td>Already scaled up</td>
</tr>
<tr>
<td>Helminthiasis</td>
<td>Proven</td>
<td>Confounded by interactions Proven at community level in combination with WASH and iron and vitamin A supplementation programs</td>
<td>Programs are scaled up</td>
</tr>
<tr>
<td>Delayed cord clamping</td>
<td>Proven</td>
<td>Proven and used widely</td>
<td>Scaled up</td>
</tr>
<tr>
<td>Management of Tuberculosis and HIV</td>
<td>Proven—when addressing underlying cause</td>
<td>Proven—anemia improves with treatment of tuberculosis and HIV</td>
<td>Programs are scaled up</td>
</tr>
<tr>
<td>Management of acute blood loss</td>
<td>Proven—when addressing underlying cause</td>
<td>Implementation challenges in health facilities</td>
<td>Even with facility resources, low uptake</td>
</tr>
<tr>
<td>Management of chronic blood loss</td>
<td>Evidence quality is low</td>
<td>Implementation challenges</td>
<td>Even with facility resources, low uptake</td>
</tr>
<tr>
<td>Management of inherited blood disorders</td>
<td>Supportive and palliative care</td>
<td>More research needed</td>
<td>More research needed</td>
</tr>
</tbody>
</table>
Research Needs – Non-dietary Interventions

To improve our understanding of—

- Drug resistance/interactions
- Benefit of malaria vaccination
- Compliance of large-scale deworming programs
- Frequency of delayed cord clamping and benefit to scale-up
- Broad approach to reduction of inflammation

Suggested Actions

- Improve, develop, and enhance sero-surveillance of malaria in pregnancy.
- Develop empiric guidelines for duration of delayed cord clamping.
- Identify and develop strategies to address new and emerging parasitic infections.
Nutrition-Specific Approaches to Address Anemia

• Food-based Approaches
  □ Improving Dietary Diversity
  □ Biofortification
  □ Addition of Animal-Source Foods
  □ Food Processing
  □ Food Fortification

• Supplementation
Food-Based Approaches to Address Anemia

- **Dietary Diversity**: defined as the number of individual food items or food groups consumed over a given period of time

- **Biofortification**: increases the micronutrient content or bioavailability of commonly consumed crops via breeding or modification

- **Animal-Source Foods**: to improve nutrient absorption
# Food-Based Approaches - Evidence I

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Efficacy</th>
<th>Proven Effectiveness</th>
<th>Scalability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improving dietary diversity and adding animal sources of iron to foods to</td>
<td>Mixed effects, not conclusive</td>
<td>Not yet</td>
<td>More research needed</td>
</tr>
<tr>
<td>enhance iron intake and absorption</td>
<td>• Systematic review shows benefit of</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>dietary diversity and animal source</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>food consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• More evidence needed on dose-response</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>relationship</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Larger randomized trials needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biofortification</td>
<td>Proven</td>
<td>Increasing</td>
<td>Integration into agricultural value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>chains and food systems</td>
</tr>
</tbody>
</table>


Food-Based Approaches to Address Anemia ctd’

- **Food Processing:** Traditional household-level food preparation techniques: dehulling, peeling, soaking, germination, fermentation, drying

- **Food Fortification:** Addition of one or more essential nutrients to an industry-produced food, requires well-developed and centralized industries
  - *Mass fortification:* addition of vitamins and minerals to commonly consumed food vehicles
  - *Targeted fortification:* addition of micronutrients to foods consumed by specific population or age groups
    - *Ready-to-Use Therapeutic Foods*
    - *Ready to Use Supplementary Foods*
# Food-Based Approaches - Evidence II

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Efficacy</th>
<th>Proven Effectiveness</th>
<th>Scalability</th>
</tr>
</thead>
</table>
| Food processing to improve iron bioavailability  | • Limited information from small studies  
• Mixed effects  
• Greatest potential shown in dehulling, phytase enzyme, and extrusion cooking | Not yet                 | • Limited scalability  
• Opportunity cost due to labor intensive traditional processing techniques  
• More research needed |
| Mass food fortification                           | Proven                                                                   | Proven, but not sufficient | Scaled up                                                      |
| Targeted food fortification                       | Proven                                                                   | Proven in specific contexts | Not widely used                                                 |
Supplementation

- **Direct oral** supplementation
- Consuming micronutrient **supplements combined with foods**

- Oral iron supplementation
  - First line treatment for iron deficiency and iron deficiency anemia in women
  - WHO recommends daily oral iron and folic acid supplementation
    - Multiple micronutrient supplementation for pregnant women in rigorous research context

- Scant evidence to support supplementation of vitamin A, folate, vitamin $B_{12}$
Research Needs - Nutrition-specific Approaches

To **improve our understanding** of—

- Impact of climate change on biological pathways related to iron nutrition/anemia
- Value of traditional food processing techniques for improving nutrient status
- Traditional food processing techniques (e.g., germination) and pathogen contamination
- Appropriate food vehicles for targeted fortification
- Integration of biofortified crops into food value chains
- Benefits and risks of iron supplementation during pregnancy and in NCDs

**Suggested Actions**

- Conduct systematic review on home-based dietary enhancement strategies.
- Model impact of fortification concurrently with other interventions.
- Develop safer formulations of oral iron supplements and iron-containing MNPs and optimized protocols to reduce side effects.
[Hemoglobin] (i.e., anemia prevalence) depends on the context

ENVIRONMENT

DIET
Nutrition
Macro-Micro-nutrient

GENETICS

MICROBIOME

GENDER/AGE

HEALTH
Infection/Inflammation

[ANEMIA]

Modified from D. Raiten, 2022
Thank you for joining us.

A recording of today’s webinar will be share with you via email in a few days.