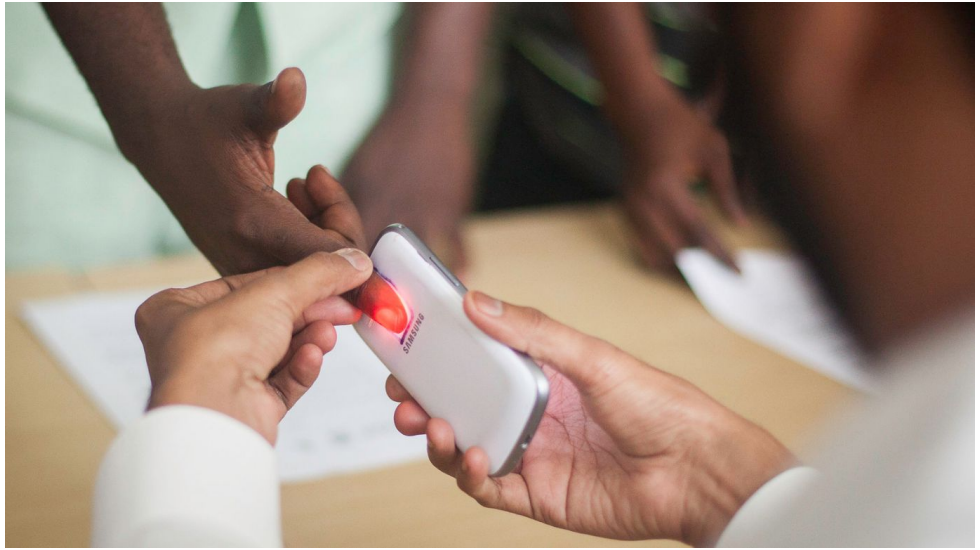
Exploring the Anemia Ecology: A New Approach to an Old Problem

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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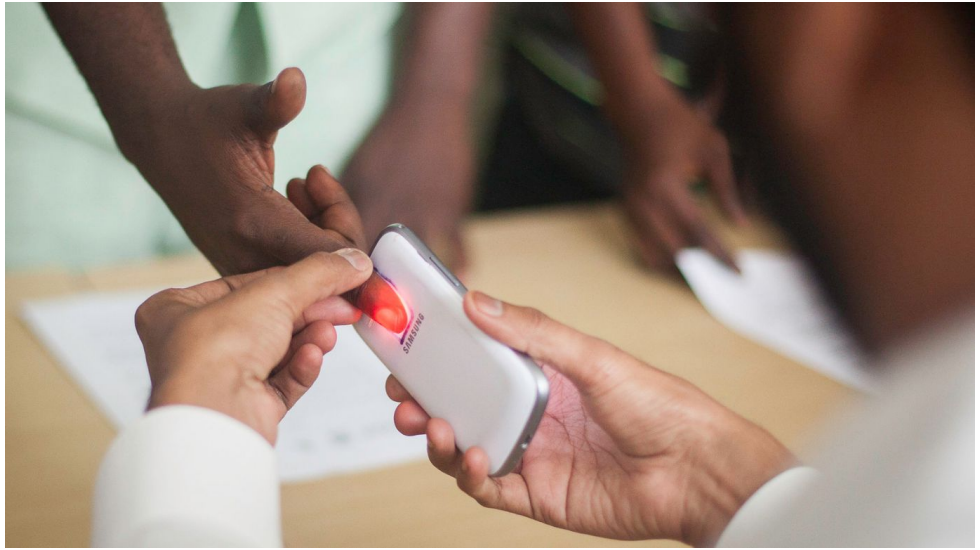


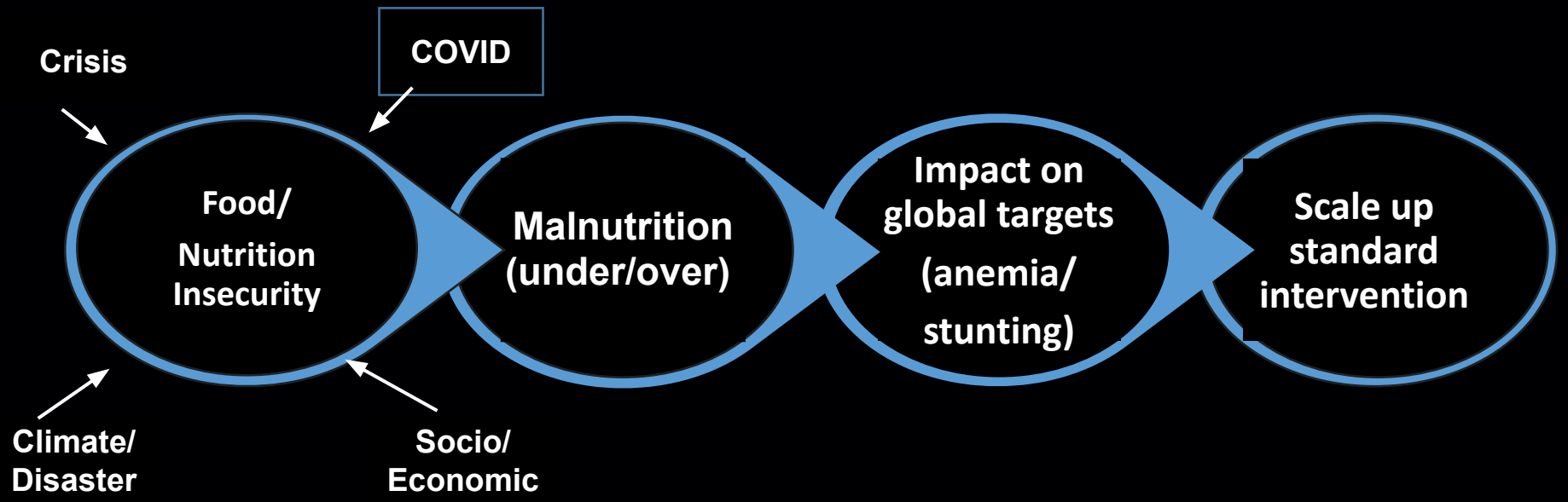
USAID Advancing Nutrition Anemia Task Force

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?

The Linear Logic:
Response to Global Health/Nutrition Challenges



This logic is limited because it ignores the biological and environmental realities of health and disease.

CONTEXT MATTERS!

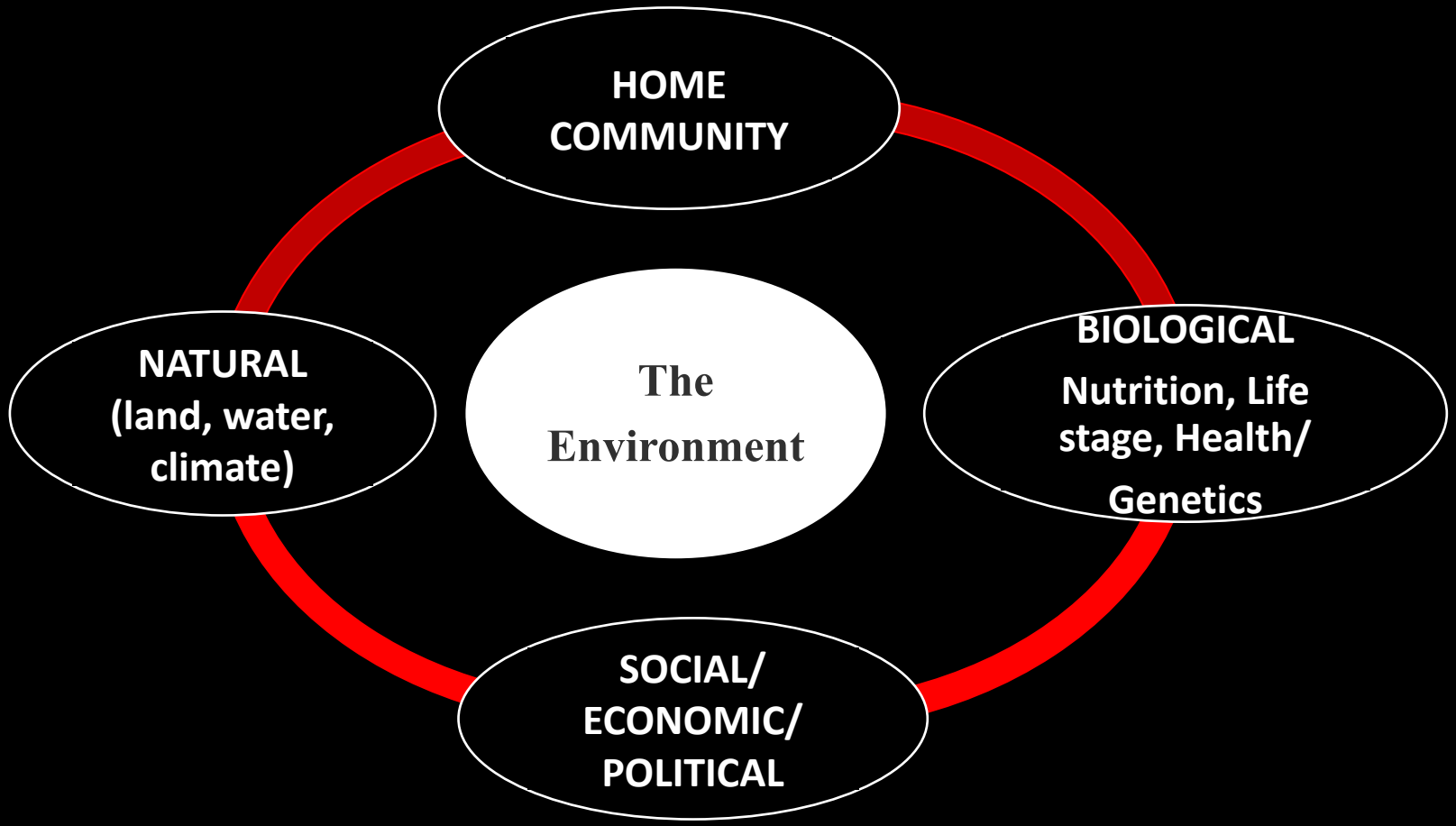
Context Matters

Why “one-size-fits- all” doesn’t!

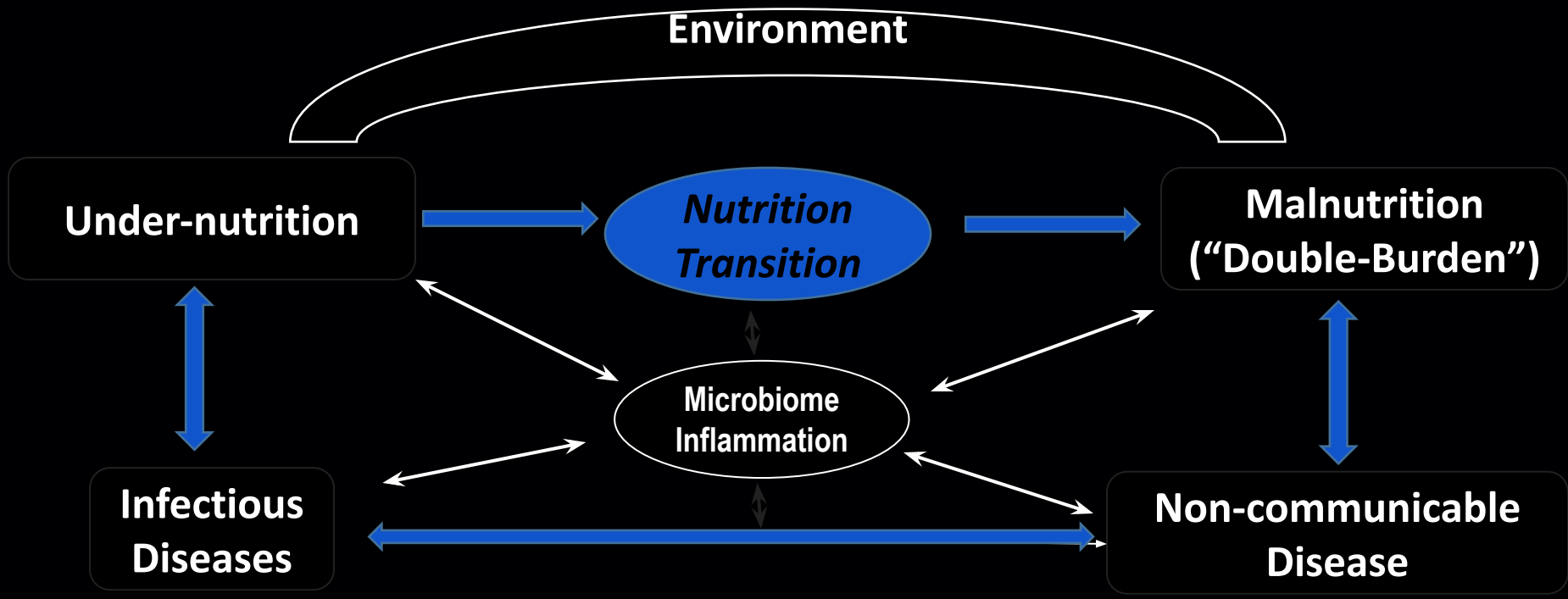
The need for an ecological approach

Ecology:
“the set of relationships existing between any complex system and its surroundings or environment.”
(Dictionary.Com)

The "Environment"- A holistic view



A Complex Health Context:
it's not just about too much or too little!



(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.

Primary Causes of Anemia: 2013

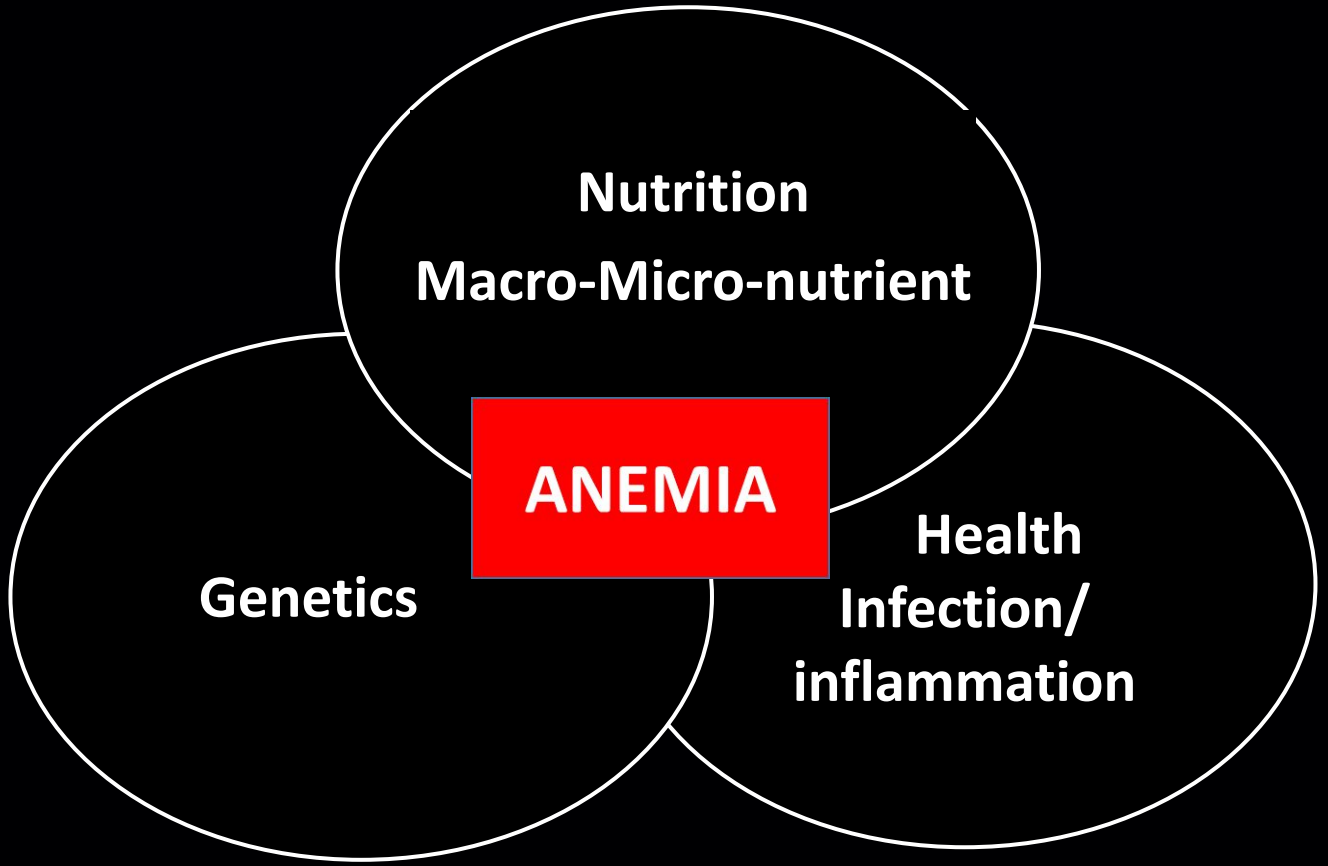
Iron-deficiency anemia (IDA)	1,208,360.1 (62.57)
Thalassemia trait	104,232.6 (5.40)
Malaria	80,602.4 (4.17)
Gastritis and duodenitis	63,222.9 (3.27)
Other neglected tropical diseases	59,728.3 (3.09)
Other hemoglobinopathies and hemolytic anemias	55,804.0 (2.89)
Other infectious diseases	49,771.4 (2.58)
Endocrine, metabolic, blood immune disorders	49,327.8 (2.55)
Sickle cell trait	43,353.9 (2.24)
Uterine fibroids (females only)	36,833.7 (1.91)
Hookworm disease	34,579.6 (1.79)
Peptic ulcer disease	32,726.7 (1.69)
Chronic kidney disease owing to other causes	26,007.2 (1.35)

Summary: Kassebaum (2016)

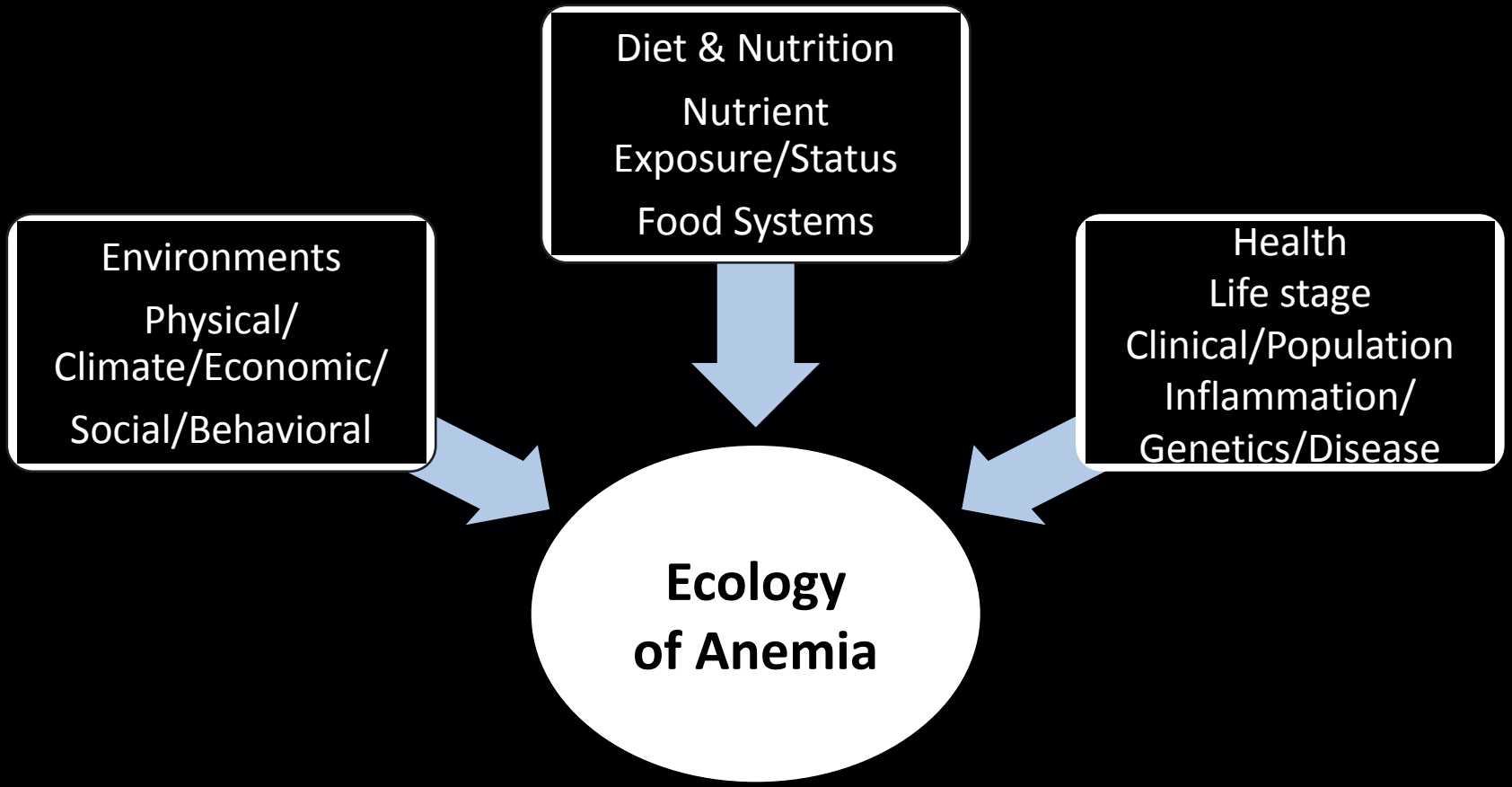
- “IDA is the dominant cause of anemia in most countries and populations.”
- “ If we include those conditions such as hookworm, schistosomiasis, and gastrointestinal and gynecologic conditions that also manifest as IDA, its importance grows even more apparent.“
- “Despite its continued dominance, a decrease 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



The 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

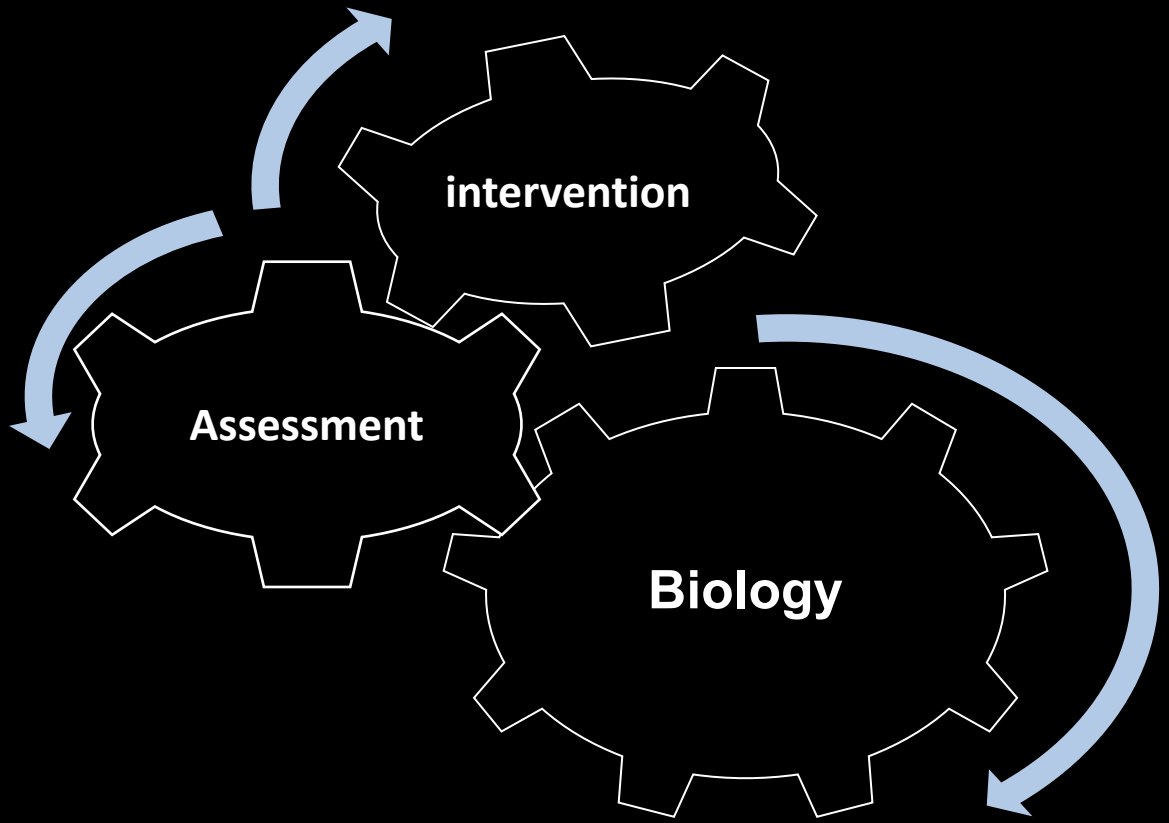
- **Constituted the USAID Advancing Nutrition Anemia Task Force (ANATF)**

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



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

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  Bill and Melinda Gates Foundation:

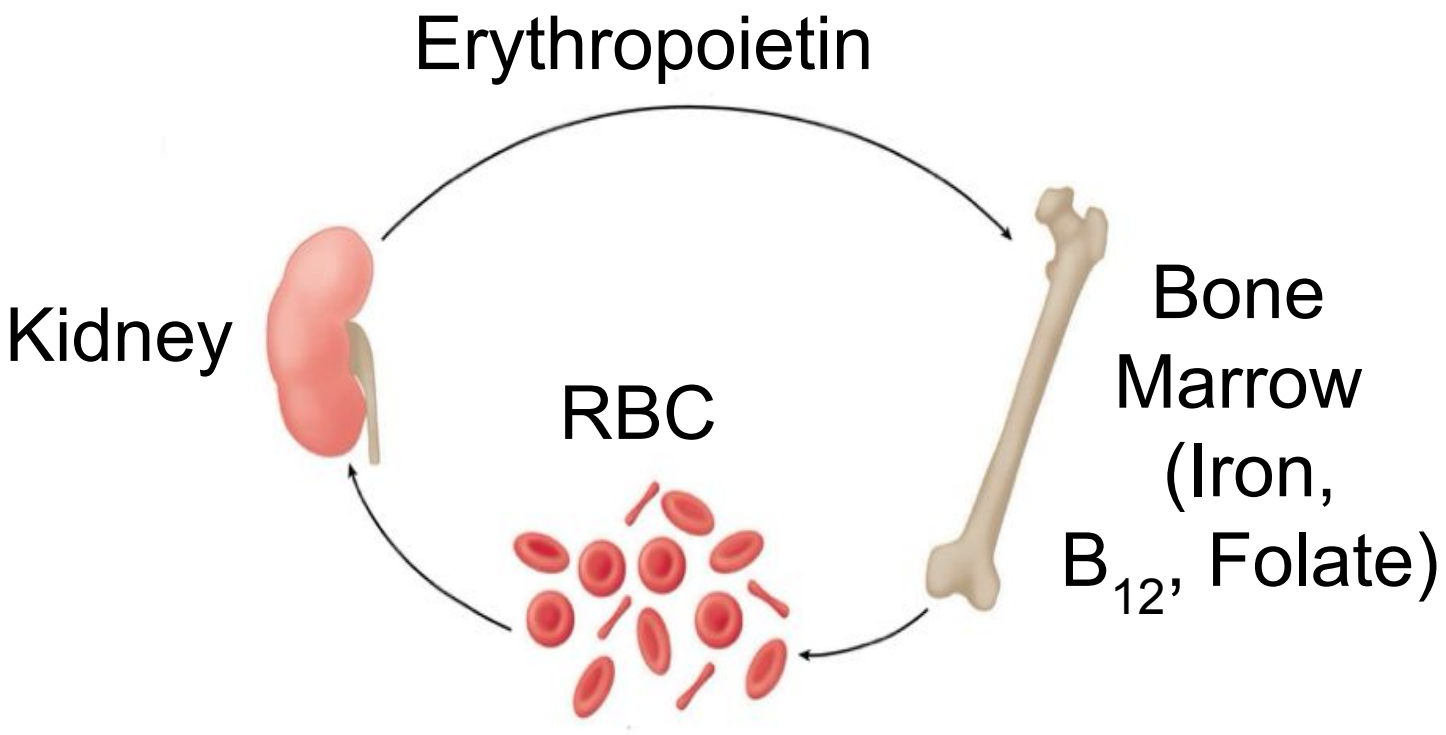
  INV-036845, INV-039533

- **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_{12})
- infections (malaria, helminths, Tb, other)
- genetics (hemoglobinopathies)

Red Blood Cell (RBC) Production



Red Blood Cell (RBC) Production and Loss

<u>Normal:</u>

RBC Production

=

RBC Loss

Red Blood Cell (RBC) Production and Loss

Normal:

RBC Production

=

RBC Loss

Anemia:

RBC Production

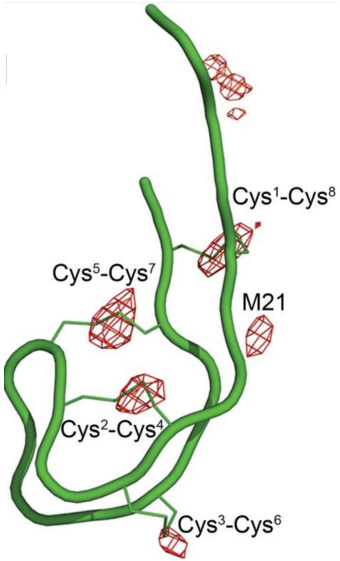
<

RBC Loss

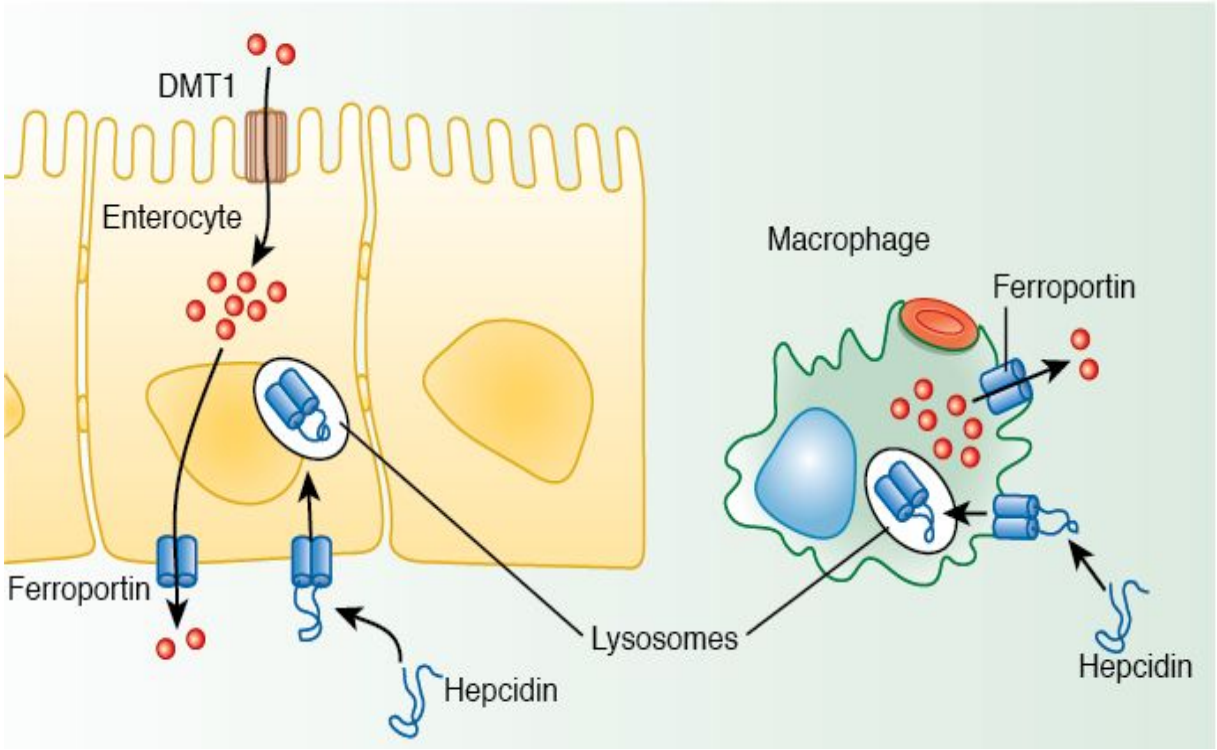
External (Bleeding)

Internal (Hemolysis)

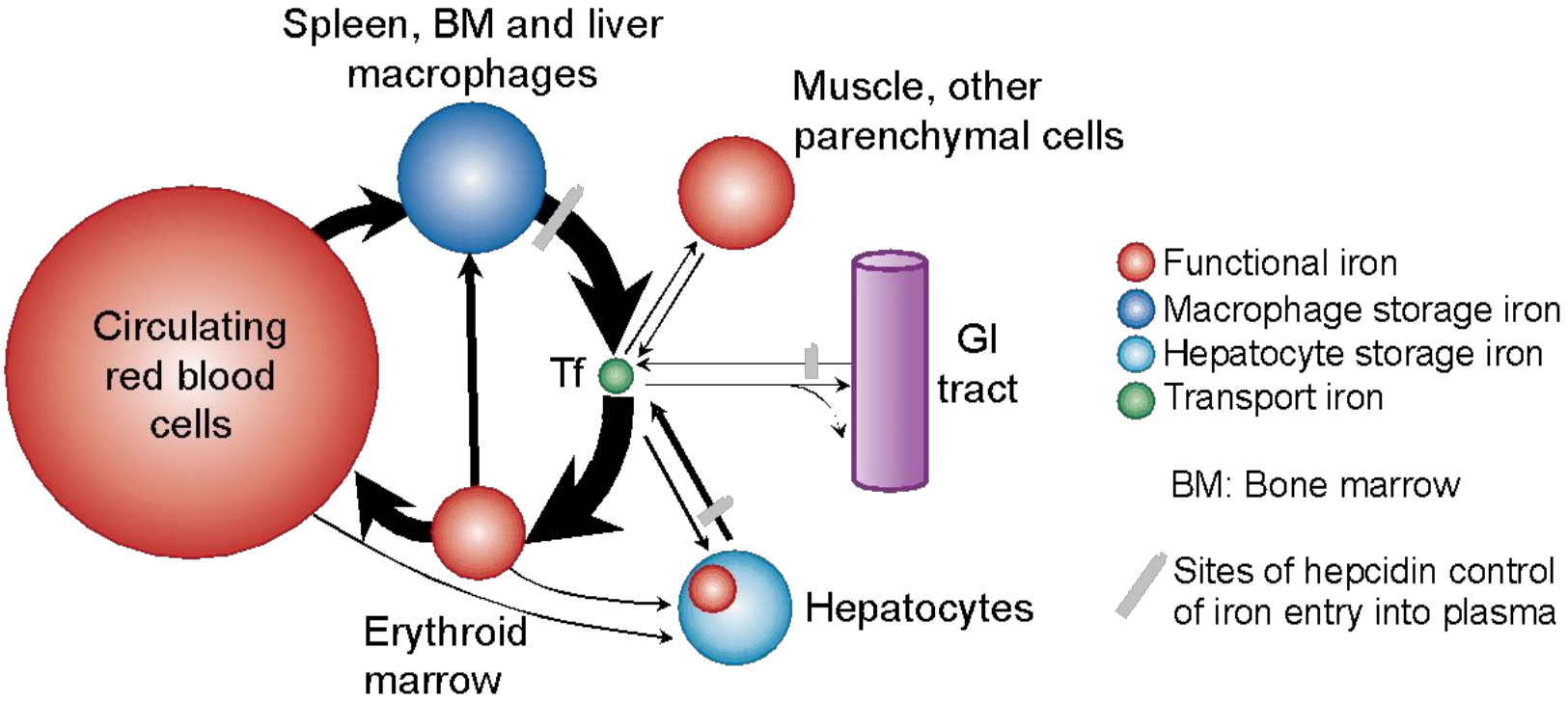
Hepcidin controls iron entry into plasma



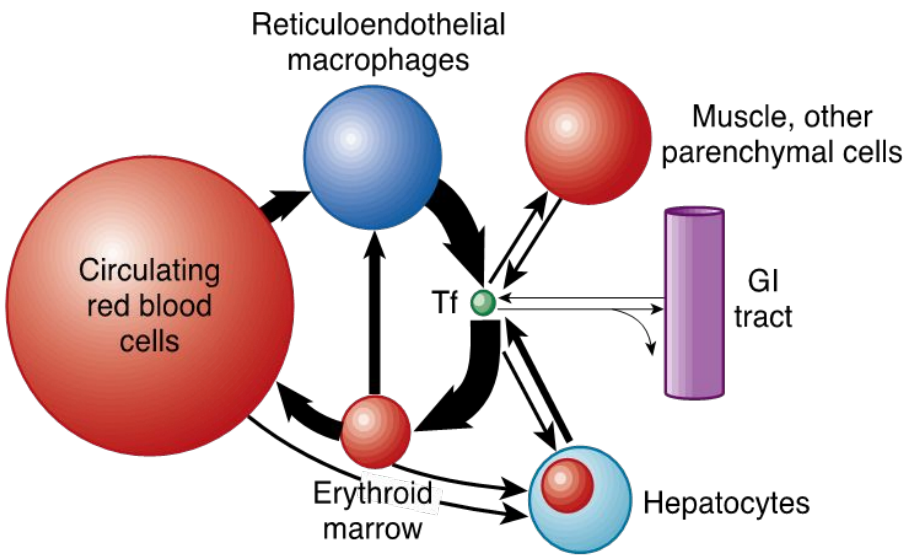
Hepcidin

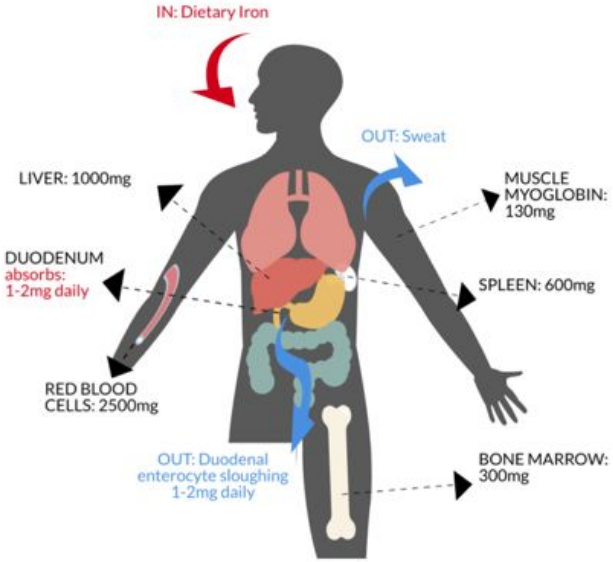


Body Iron Supply and Storage



Normal iron stores



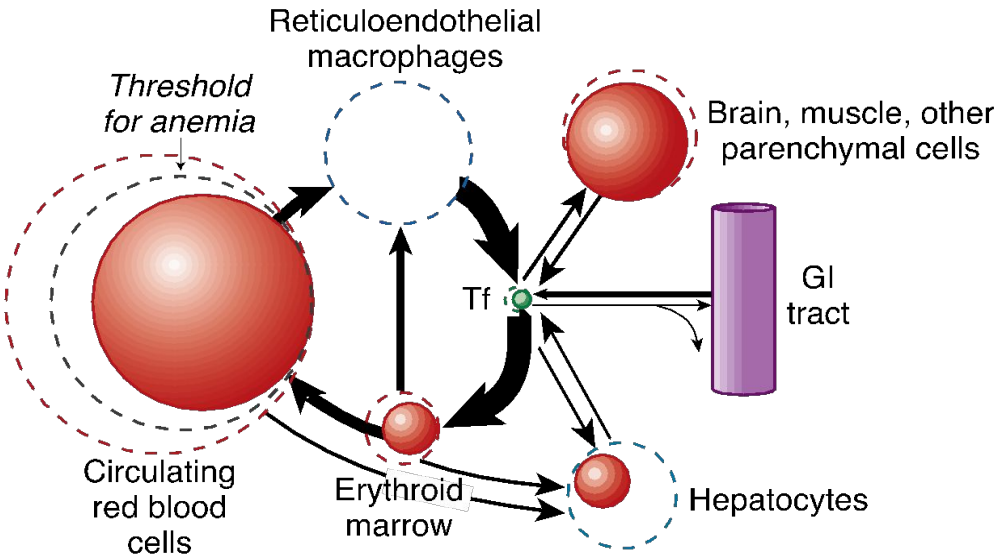


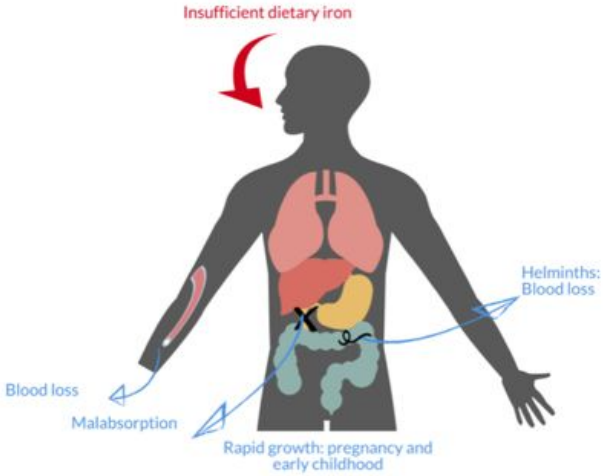
IRON STORES ⇄ IRON USAGE

Normal hepcidin

IRON HOMEOSTASIS

Absolute iron deficiency



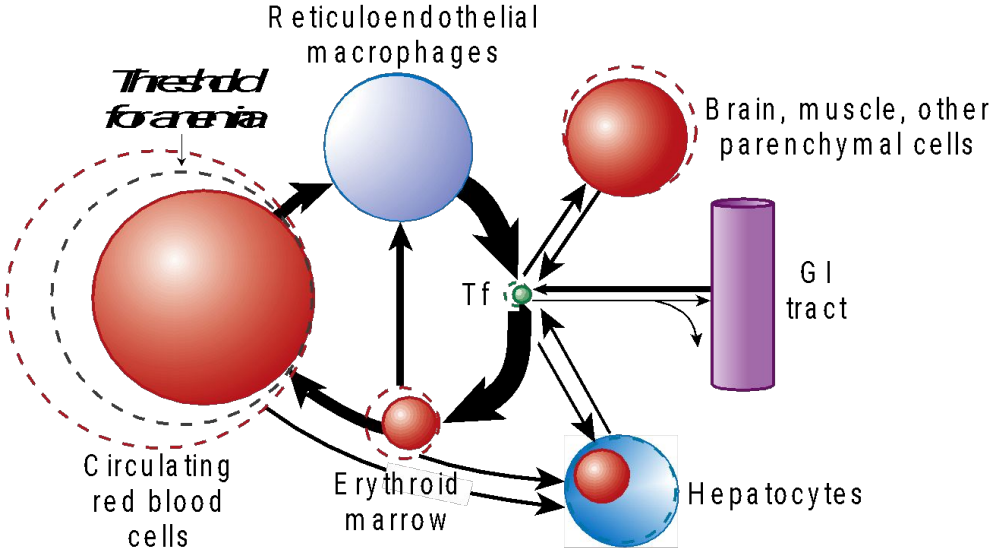


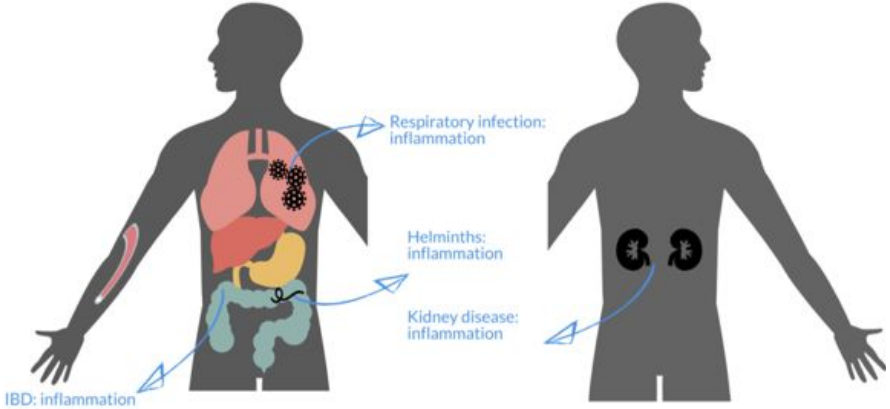
IRON STORES < IRON DEMAND

↓ Hepcidin

ABSOLUTE IRON DEFICIENCY

Functional iron deficiency anemia



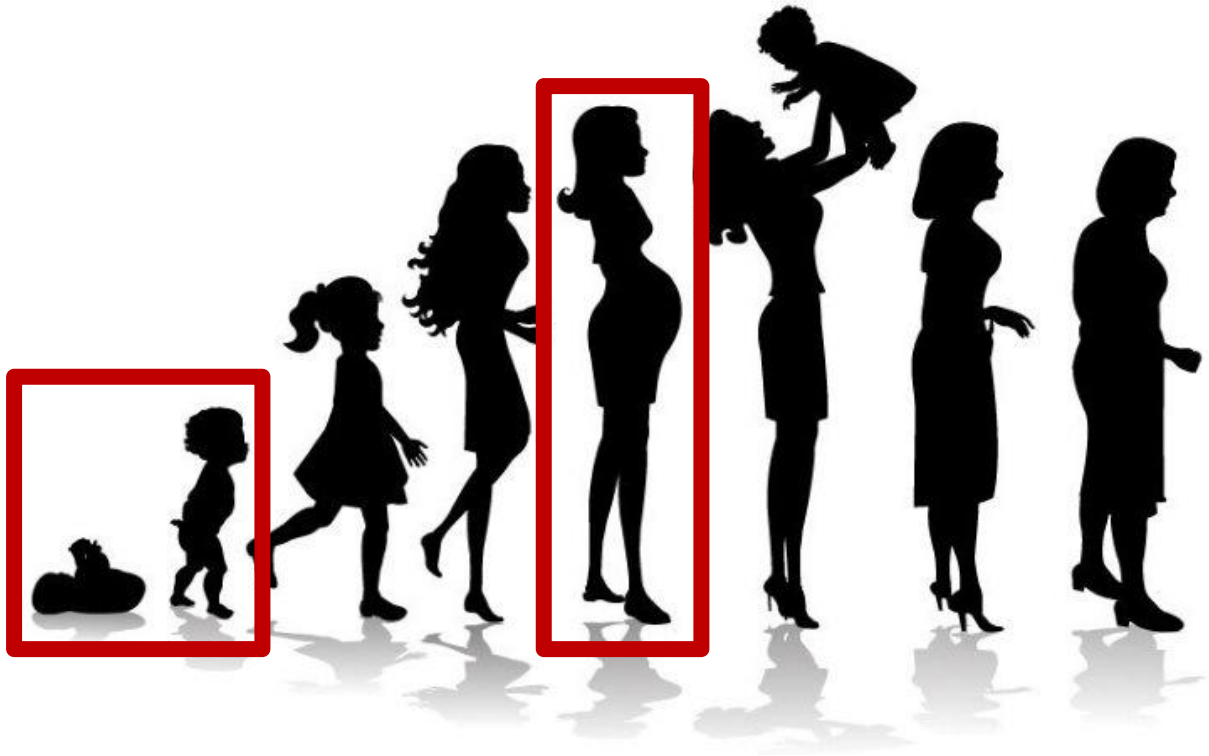


IRON AVAILABILITY < IRON DEMAND

↑ Hepcidin

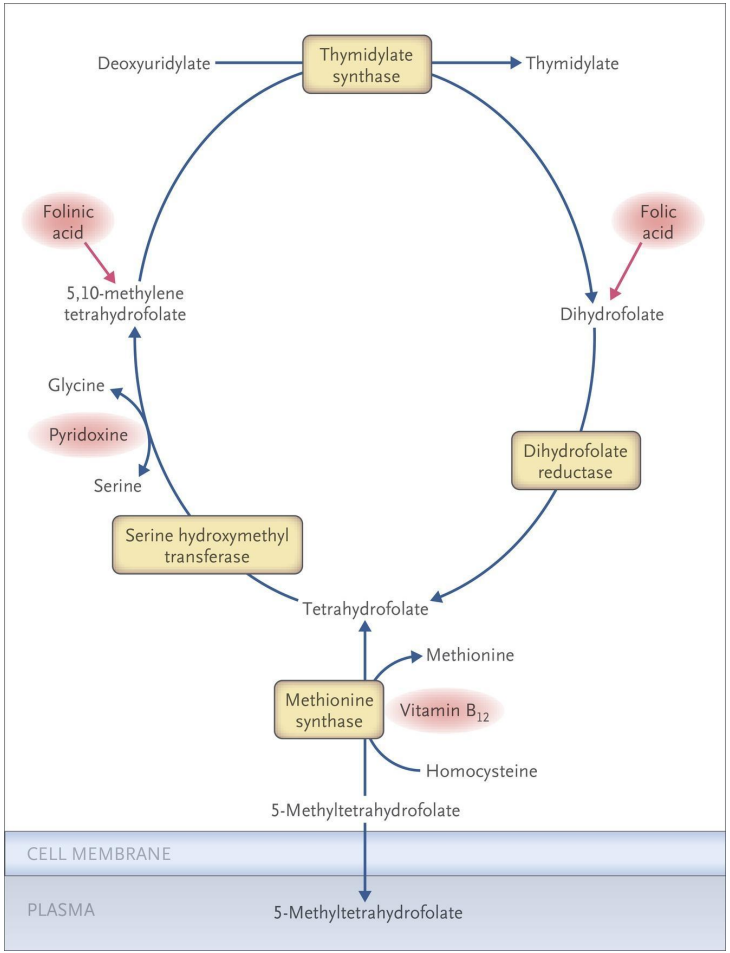
FUNCTIONAL IRON DEFICIENCY

Absolute iron deficiency: the most vulnerable

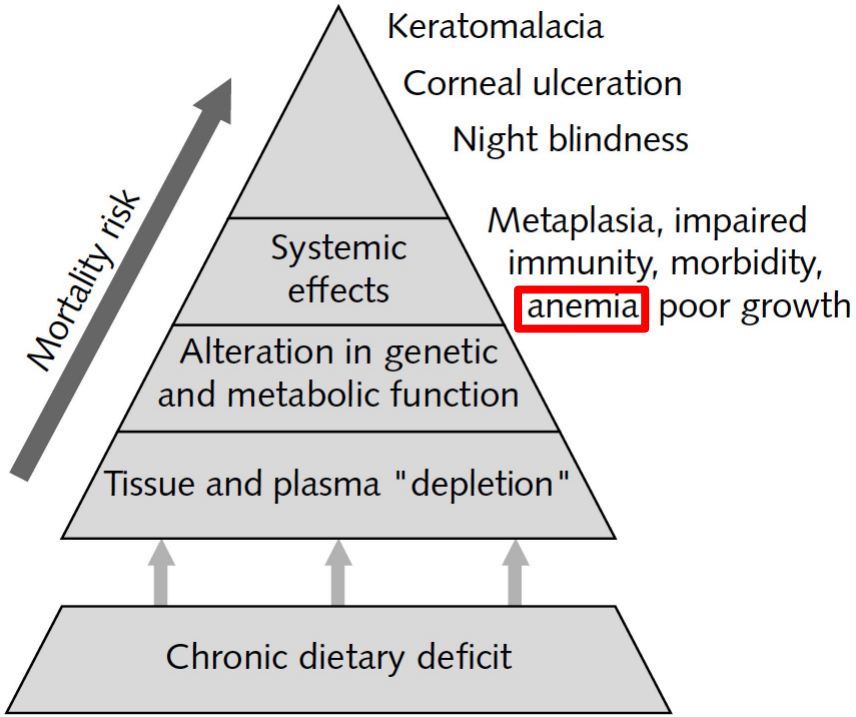


Other nutrients:

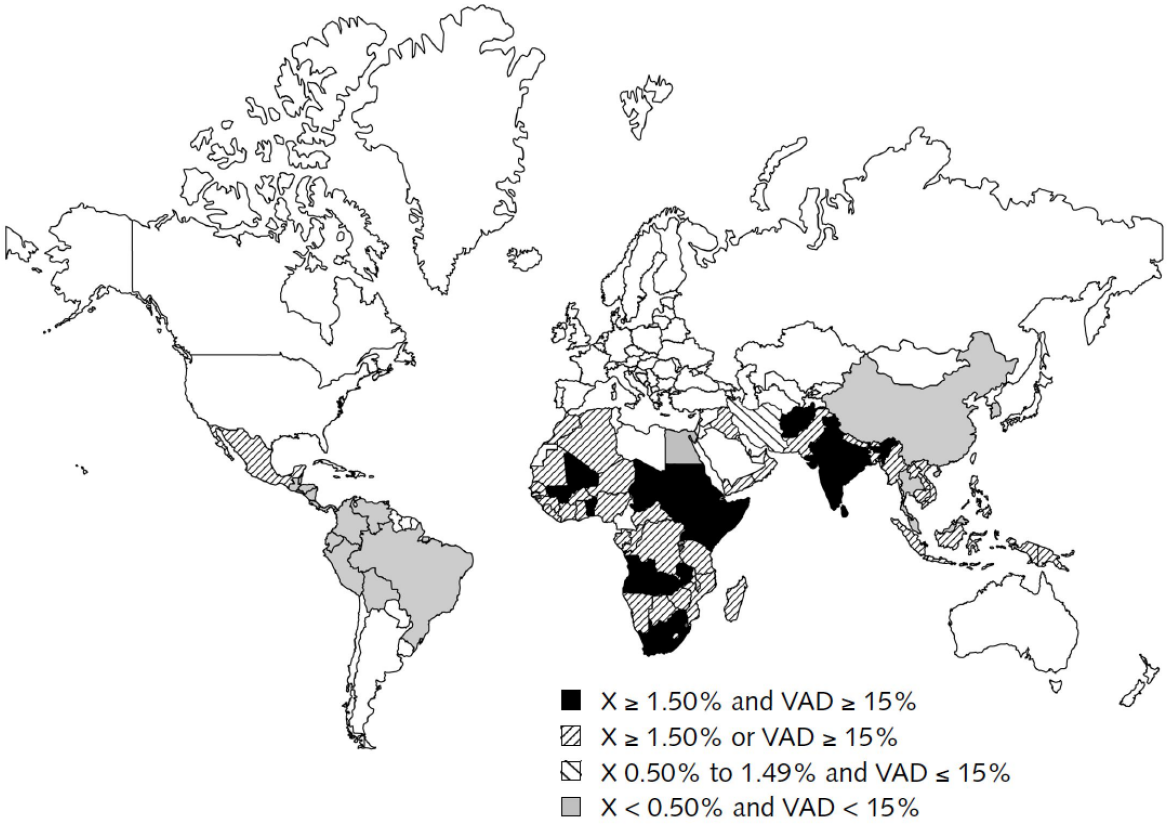
Vitamin B_{12} and folate cause anemia by limiting DNA synthesis



Vitamin A deficiency disorders



Vitamin A deficiency in preschool children



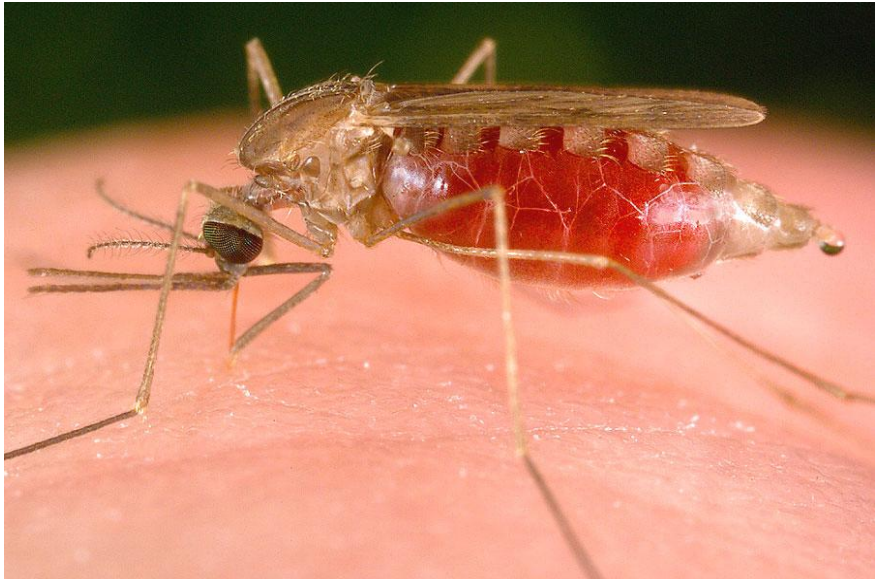
Global Prevalence of Selected Infections by Age in Millions

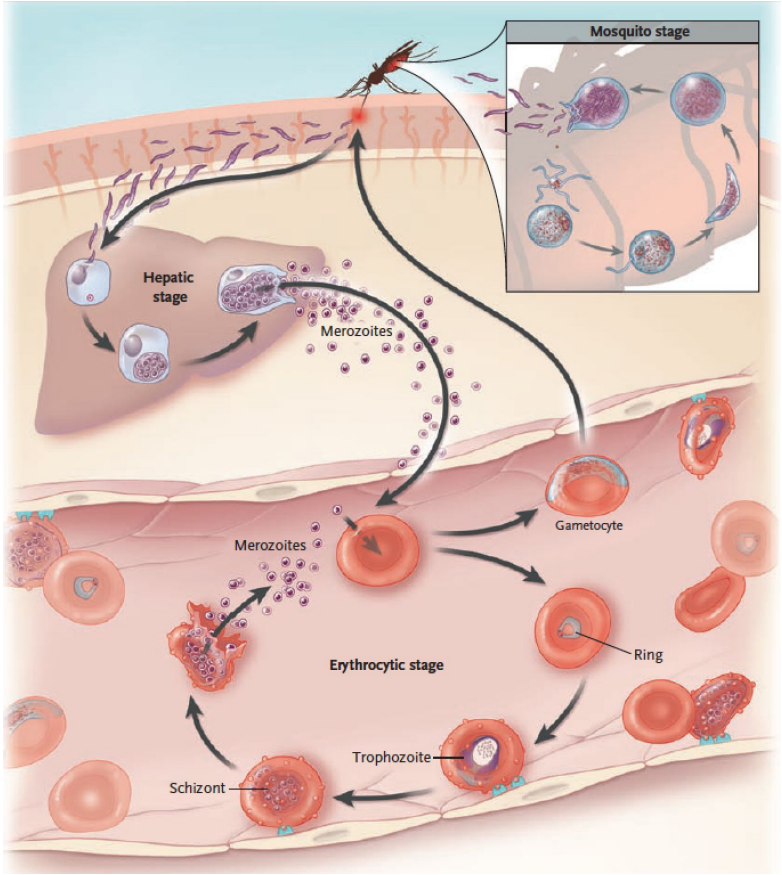
Infection	All Ages (95% CI)	Young Children ≤5 Years (95% CI)	School-age Children, 5–14 Years (95% CI)	Adolescents and Adults ≥14 Years (95% CI)
Malaria	228 (206–258)	23.8*	N/A	N/A
Hookworm	451 (425–479)	N/A	N/A	N/A
Schistosomiasis	190 (180–200)	N/A	N/A	N/A
Human immunodeficiency virus (HIV)/acquired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

Mechanisms of anemia in infectious diseases

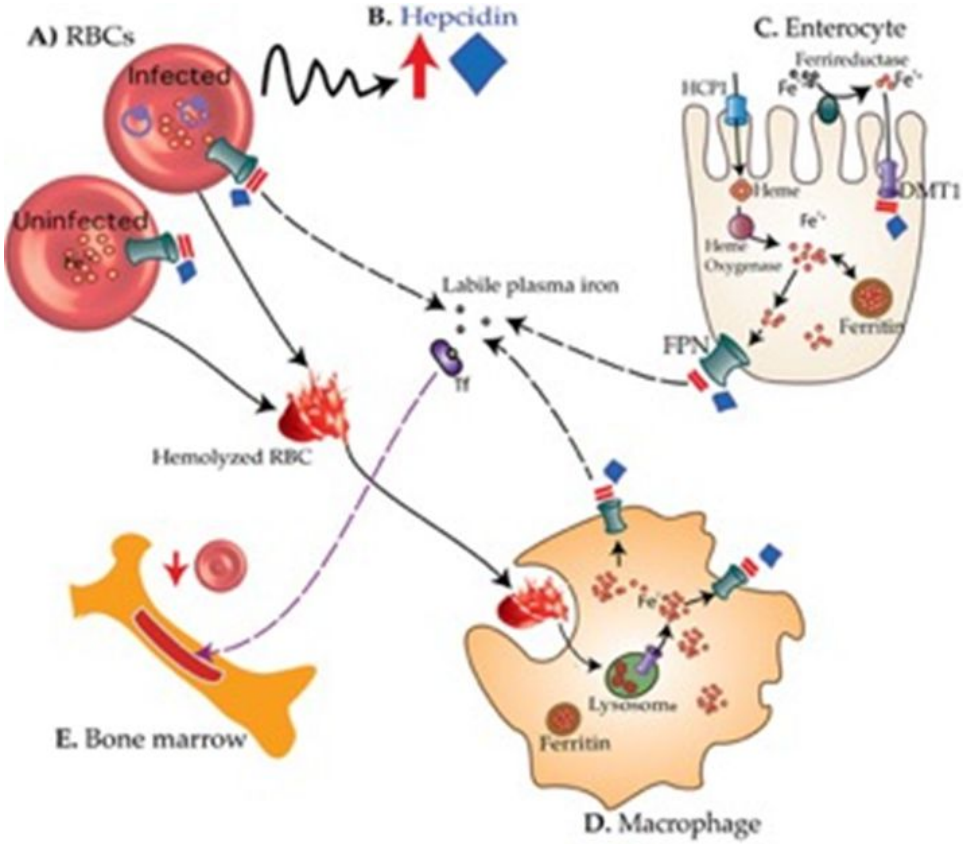
Anemia Etiology	Infection
Anemia of inflammation	Chronic infections
Hemolysis	Malaria, schistosomiasis, HIV, bacterial hemolysins
Blood loss	Hookworm, schistosomiasis, HIV/AIDS
Ineffective RBC production	Malaria, HIV
Nutrient malabsorption	Hookworm, Helicobacter pylori, gut microbiome¶
Hypersplenism	Malaria, hepatitis C virus (HCV), tuberculosis, schistosomiasis
Drug treatment*	HCV, HIV, tuberculosis, bacterial infections

Life Cycle of *Plasmodium falciparum*

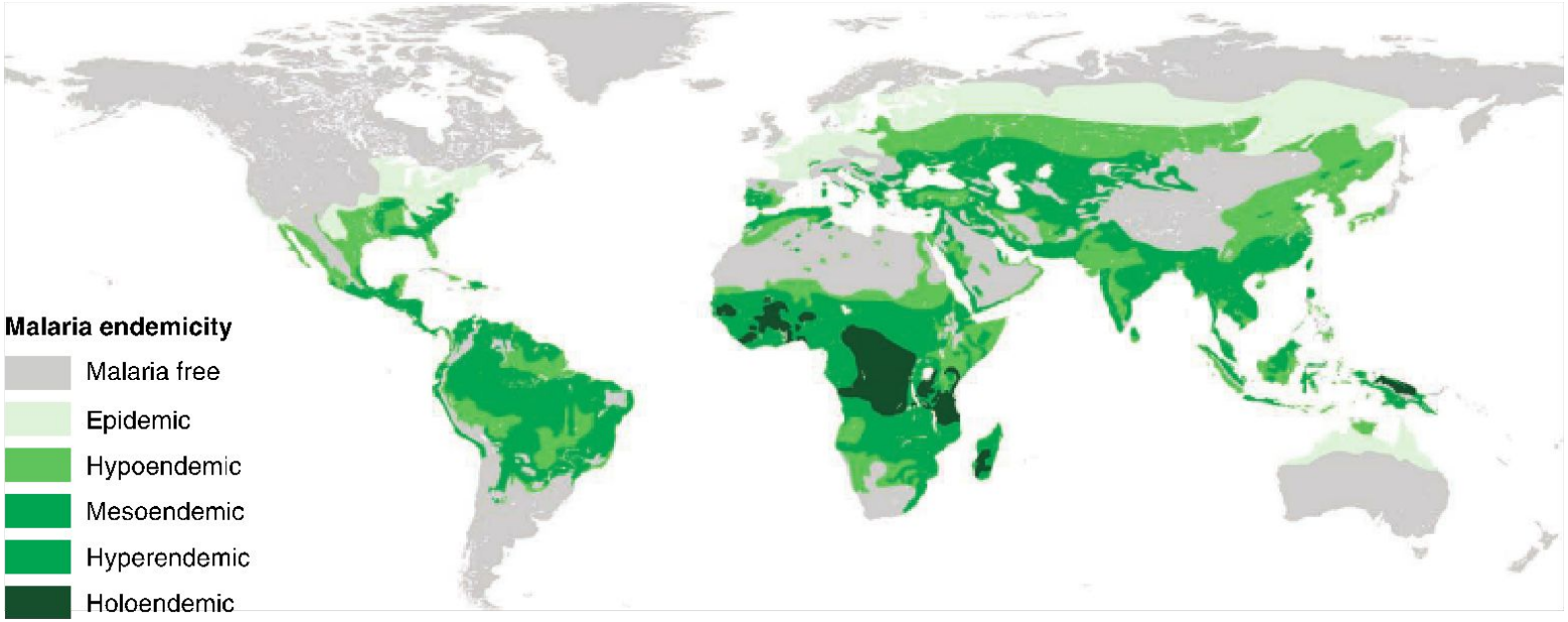




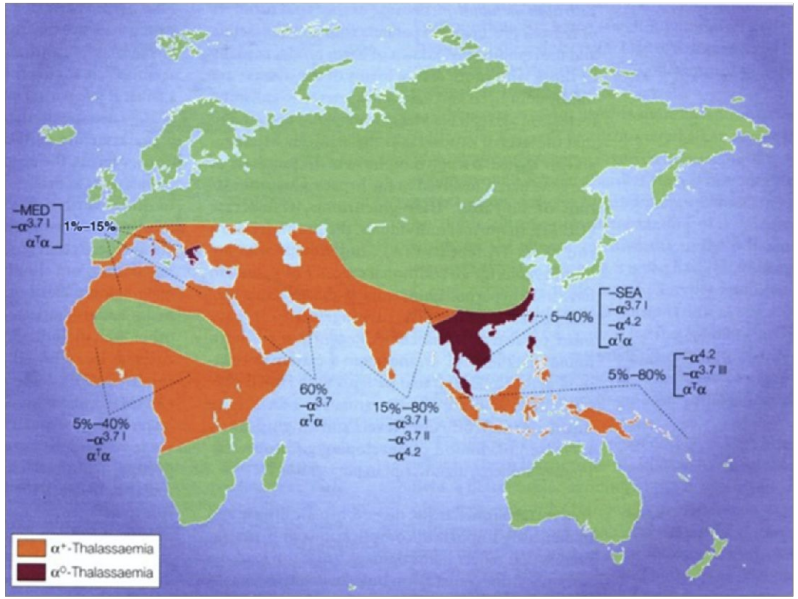
Malaria and anemia: effects on iron



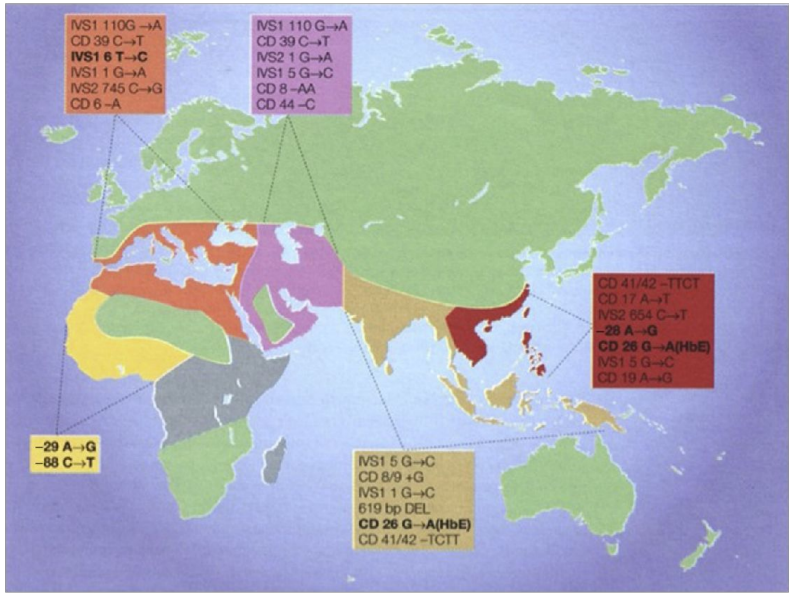
Historical global map of malaria endemicity



Distribution of origins of the thalassemias



α−thalassemias

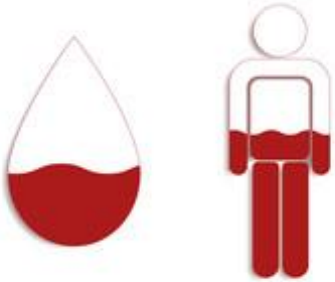


β−thalassemias

Assessment and interventions for anemia rely on recognizing the roles of

- absolute and functional iron deficiency
- other nutrients (folate, vitamins A, B_{12})
- infections (malaria, helminths, Tb, other)
- genetics (hemoglobinopathies)

IMPROVING ANEMIA ASSESSMENT IN CLINICAL AND PUBLIC HEALTH SETTINGS



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September 13. 2022

CDC
Centers for Disease Control and Prevention

Children's
Healthcare of Atlanta

Emory University School of Medicine
Global Health and Equity Office

Disclosures

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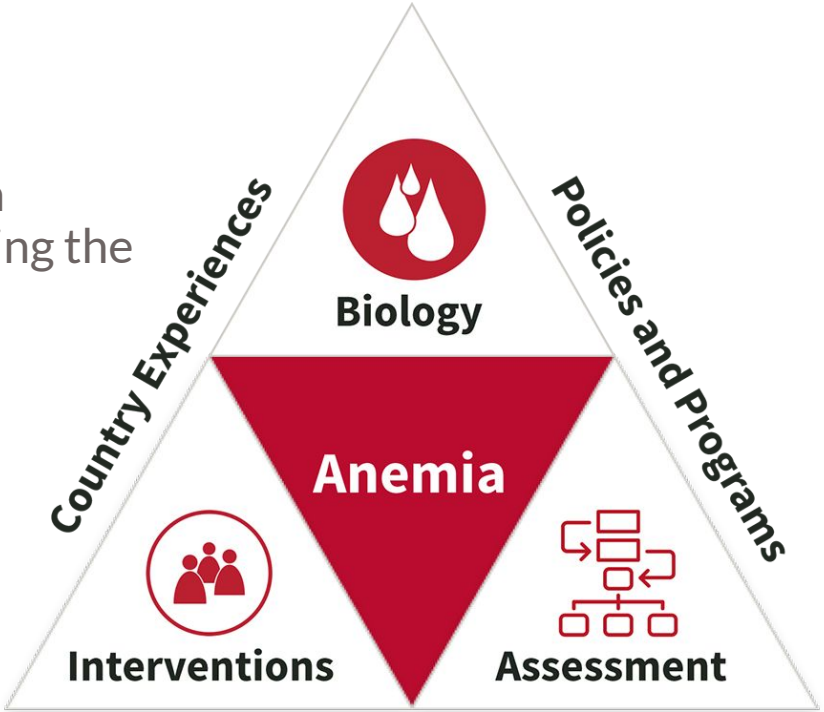
I have no financial or commercial conflict of interest related to this presentation.

"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.

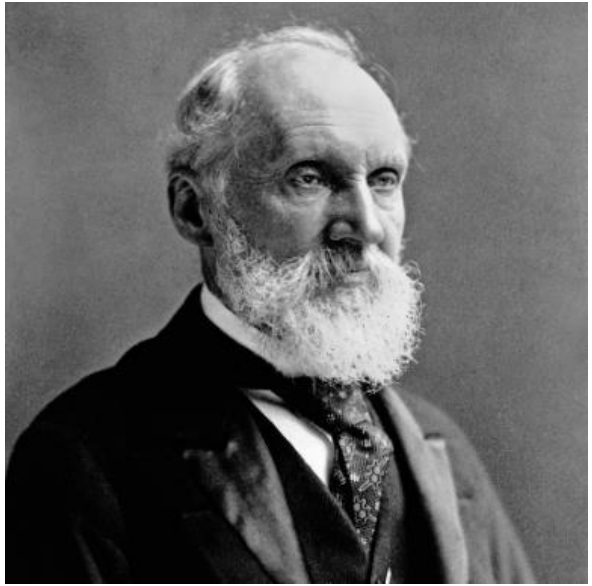


USAID
FROM THE AMERICAN PEOPLE

www.advancingnutrition.org/what-we-do/monitoring-evaluation-and-learning/anemia-task-force

“If you cannot measure it, you cannot improve it”

-Lord Kelvin



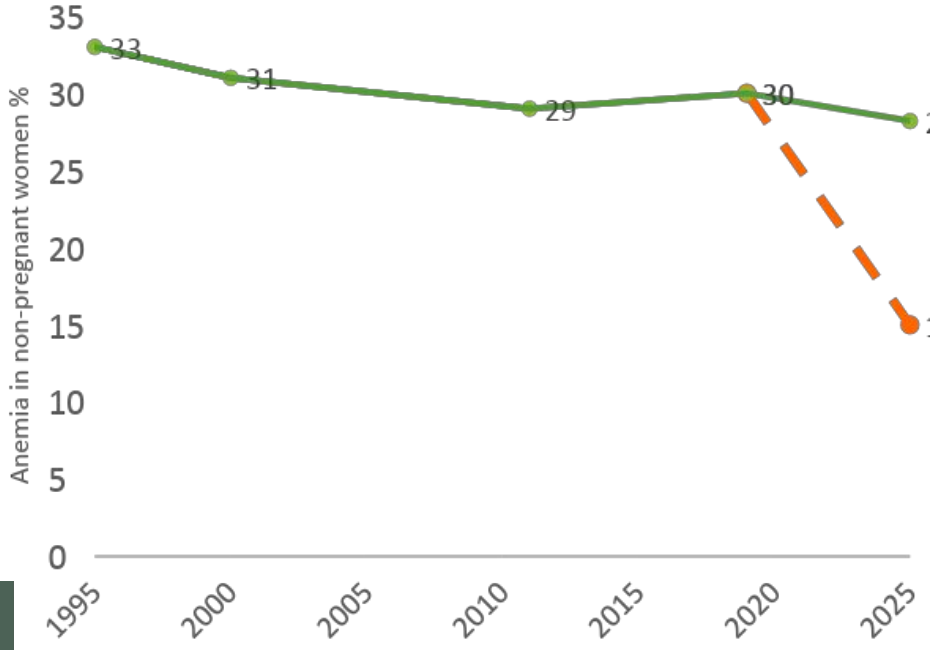
Time for a Zoom poll

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



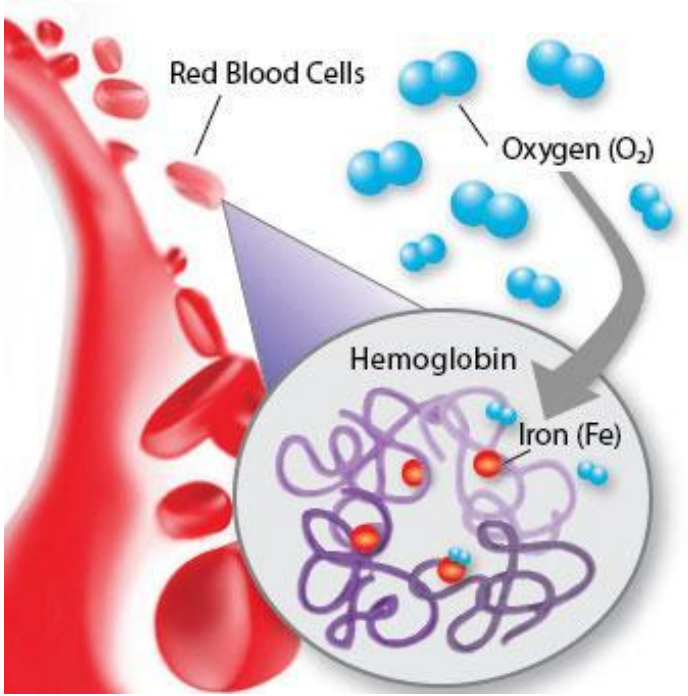
Lancet Glob Health 2022

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

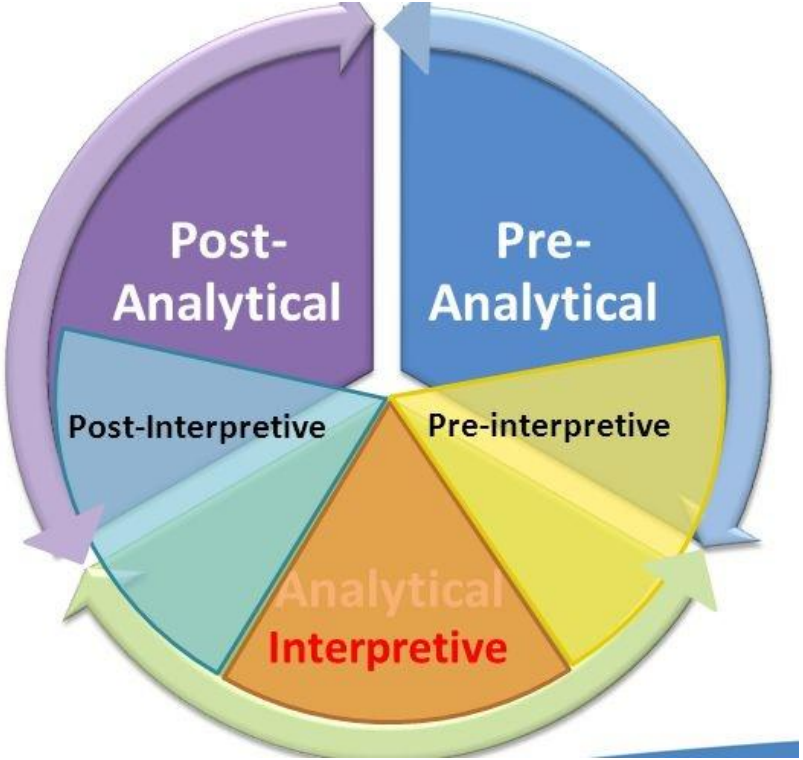
Phlebotomy

Fingerstick

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

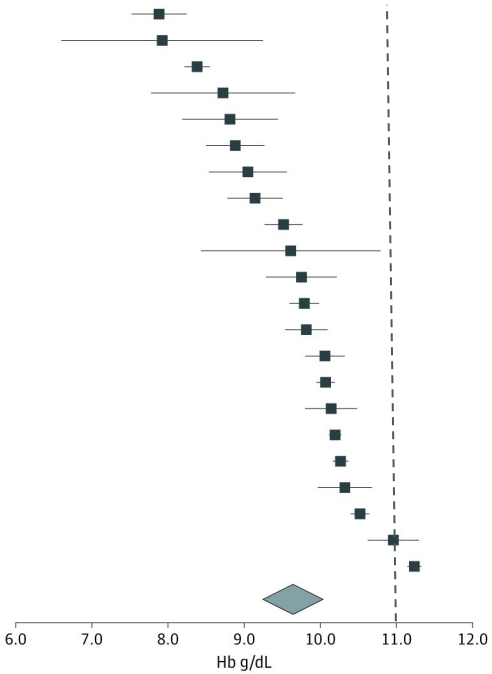
- Accuracy
- Reproducibility
- Quality control

*www.researchsquare.com/article/rs-1875378/v1

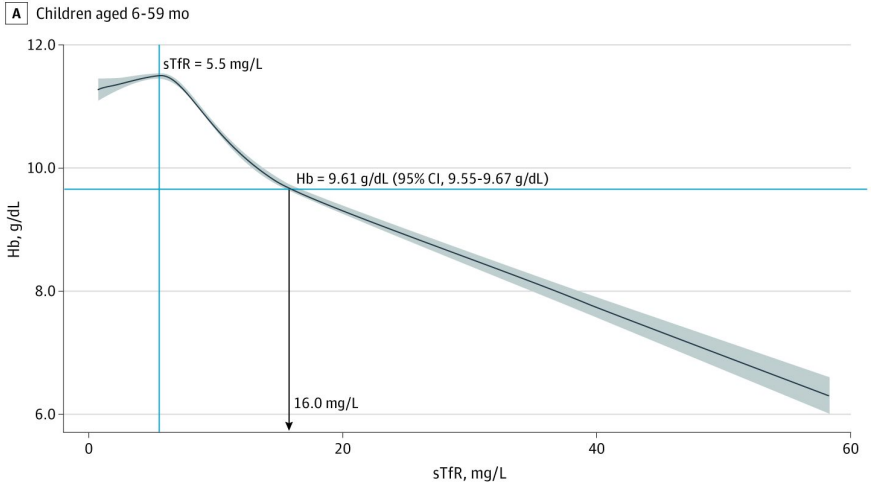
Hemoglobin cutoffs based on lowest 5% of hemoglobin in "healthy"* children

A Children aged 6-59 mo

Survey	Sample size	Hb 5th percentile, g/dL (95% CI)
Pakistan 2011	1119	7.90 (7.54-8.26)
Côte d'Ivoire 2007	147	7.94 (6.62-9.26)
Bangladesh 2010	777	8.40 (8.23-8.56)
Kenya 2010	167	8.73 (7.79-9.68)
Afghanistan 2013	205	8.82 (8.20-9.45)
Cambodia 2014	198	8.89 (8.51-9.28)
Laos 2006	216	9.06 (8.55-9.57)
Liberia 2011	341	9.15 (8.79-9.51)
Philippines 2011	906	9.53 (9.28-9.77)
Kenya 2007	116	9.62 (8.45-10.79)
Cameroon 2009	232	9.76 (9.30-10.22)
Mexico 2006	1015	9.80 (9.60-9.99)
Azerbaijan 2013	579	9.82 (9.55-10.10)
Rwanda 2010	367	10.07 (9.81-10.33)
Mexico 2012	1471	10.08 (9.95-10.20)
Bangladesh 2012	218	10.15 (9.81-10.49)
Ecuador 2012	1339	10.20 (10.12-10.28)
Colombia 2010	2115	10.27 (10.17-10.37)
Malawi 2016	291	10.33 (9.97-10.68)
Nicaragua 2005	440	10.52 (10.40-10.65)
Vietnam 2010	249	10.96 (10.63-11.30)
US 2006	937	11.23 (11.14-11.33)
Pooled estimate (Q/*df* = 21; *P* < .001; *t* = 0.85 g/dL)		**9.65 (9.26-10.04)**



Cutoff confirmed using physiological measure of erythropoiesis



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

BRINDA, *JAMA Network Open*, 2021

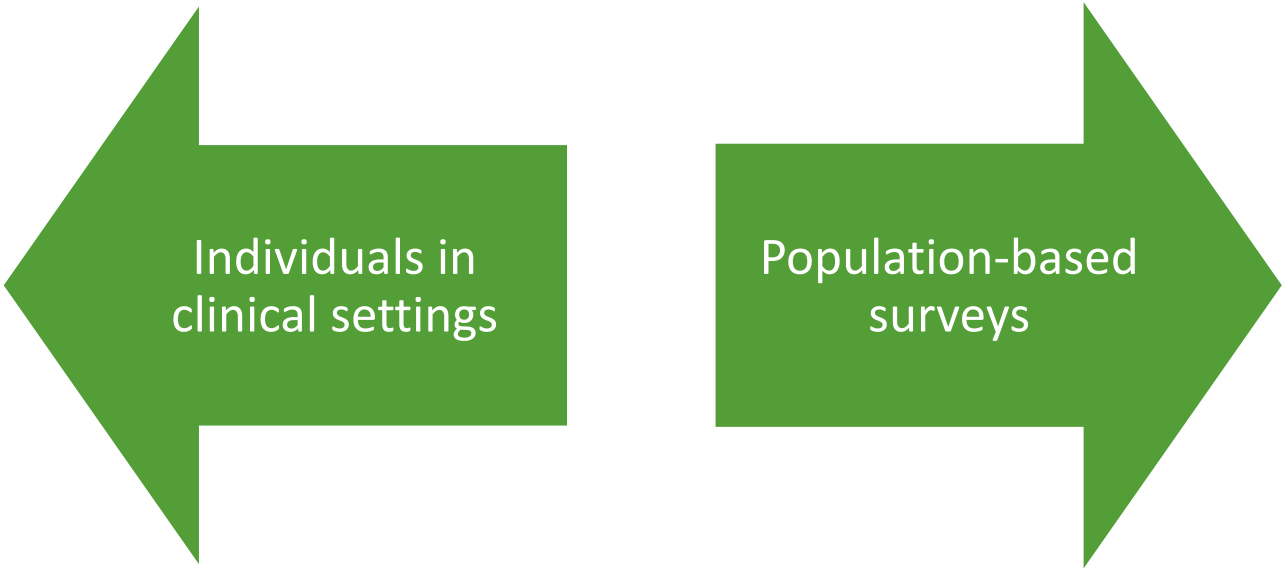
Common causes of anemia

Non-nutritional causes of anemia				Nutrition-specific causes of anemia[+]	
Blood loss	**Increased hemolysis**	**Deficient erythropoiesis**		**Microcytosis**	**Macrocytosis**
		Microcytic	*Normocytic*		
• Postpartum hemorrhage • Heavy menstrual bleeding* • Gastrointestinal blood loss[*] • Urinary blood loss[*]	• Infection (malaria)[*] • Hemoglobin disorders (SCD, thalassemias) • Enzymopathies (G6PD deficiency) • Immune-mediated • Hypersplenism	• Anemia of inflammation[*] • Thalassemias	• Anemia of inflammation[*] • Renal failure • Bone marrow failure	• Iron deficiency[*] • Vitamin A deficiency[*] • Riboflavin deficiency[*]	• Folate deficiency[*] • Vitamin B12 deficiency[*]

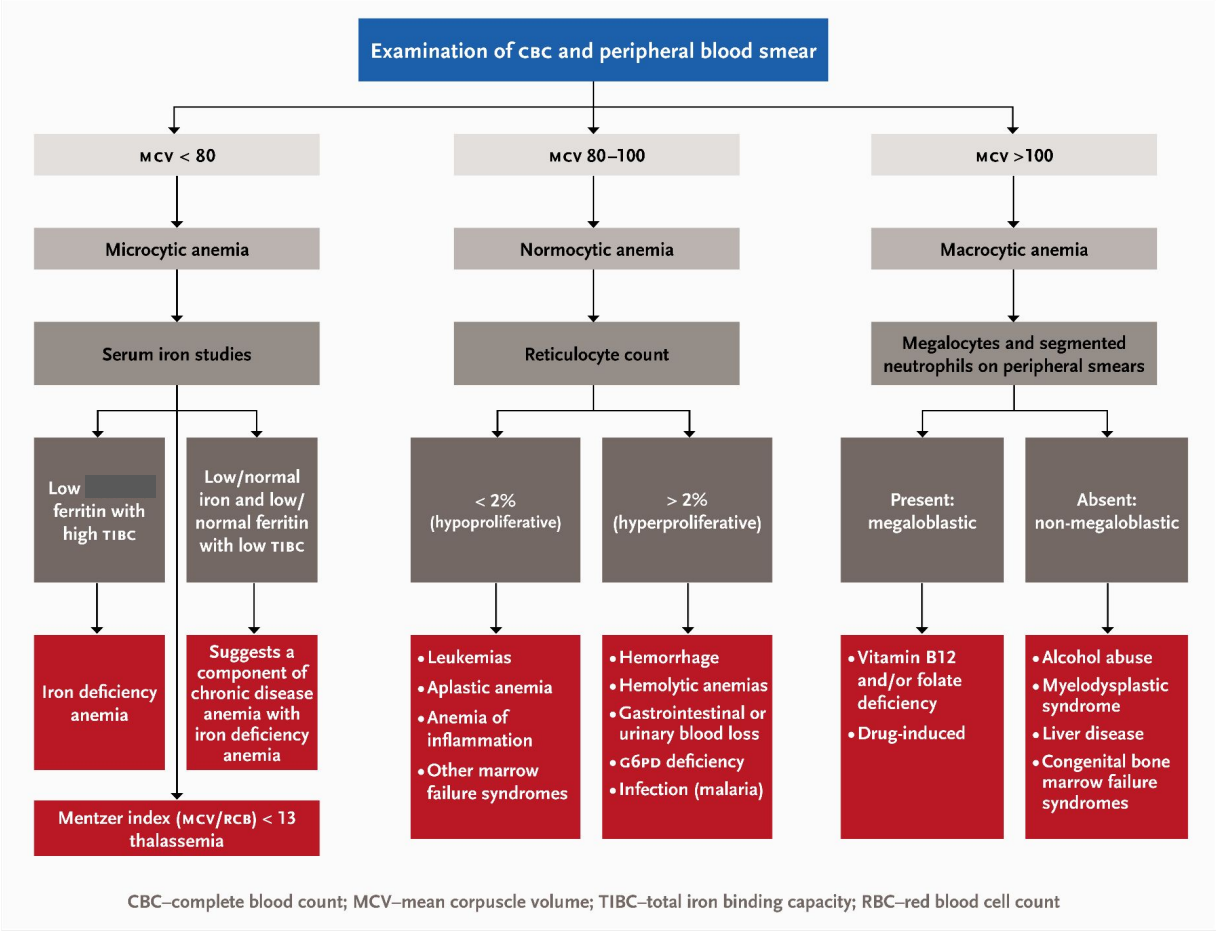
[+]Can be caused by insufficient dietary intake, impaired absorption or increased losses
[*]Preventable or treatable

Anemia itself is not a disease

Application of an Ecological Approach to Anemia Assessment

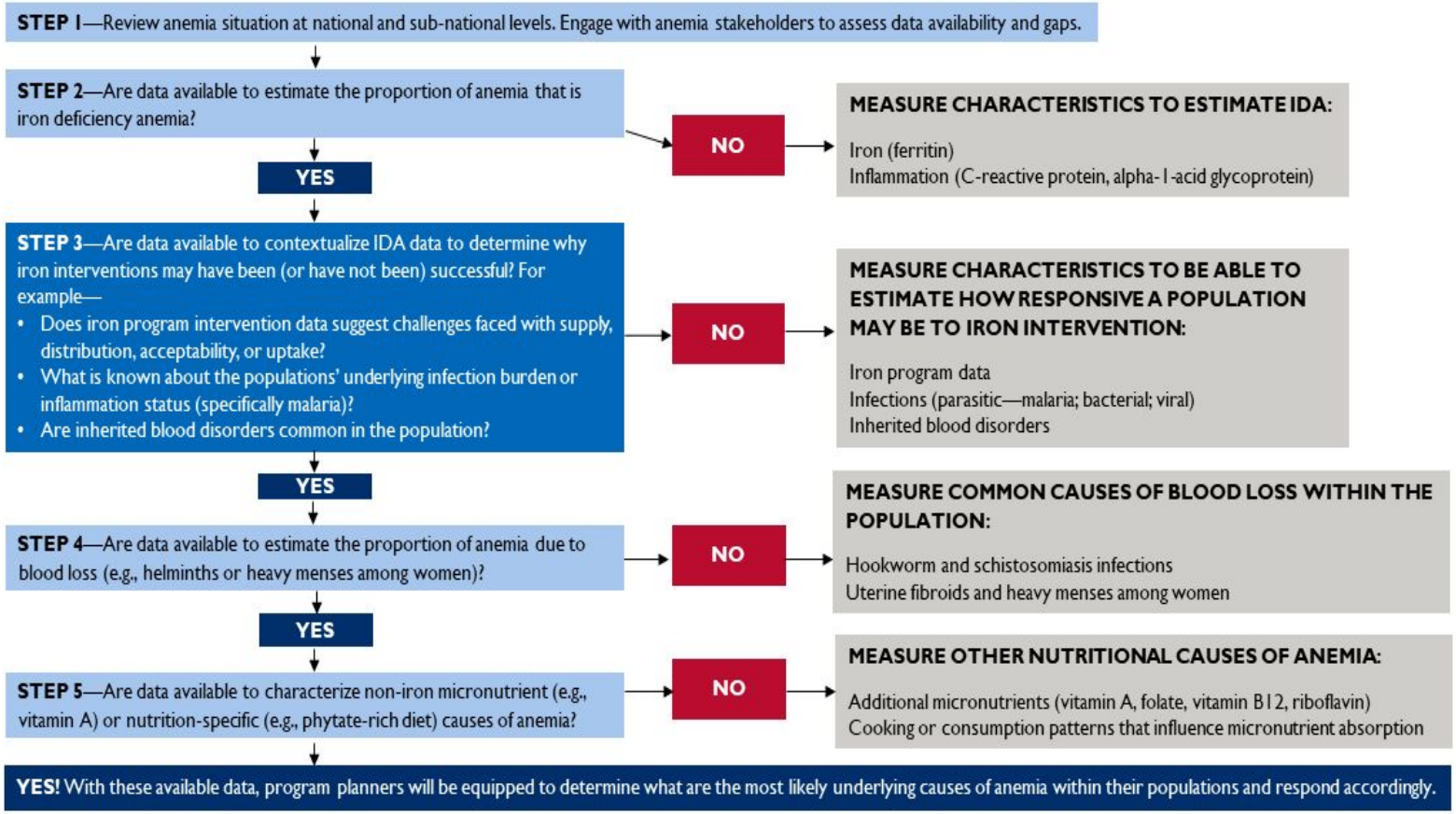


Clinical assessment of anemia in *individuals*



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*



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

Assess hemoglobin and anemia etiology	Population anemia etiology assessment
1. Non-invasive methods to measure Hb 2. Point-of-care assessment of ferritin, hepcidin and erythropoietin 3. Role of multiple micronutrient deficiencies in anemia 4. Re-evaluation of Hb thresholds to define anemia	1. Statistical approaches to assess anemia etiologies using cross-sectional data 2. Cost and logistical implications of stepwise algorithm vs broad-based screening

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.

USAID
Advancing Nutrition

THANK YOU

CHAMPS

BRINDA
Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia

brinda-nutrition.org/

champshealth.org/

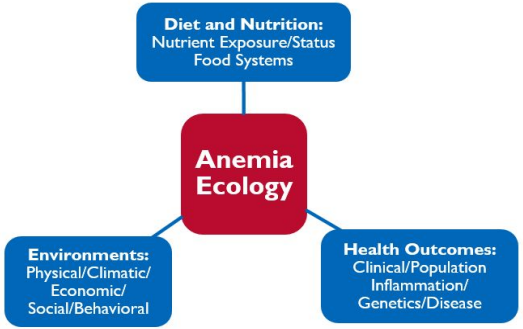
Approaches to Address Anemia

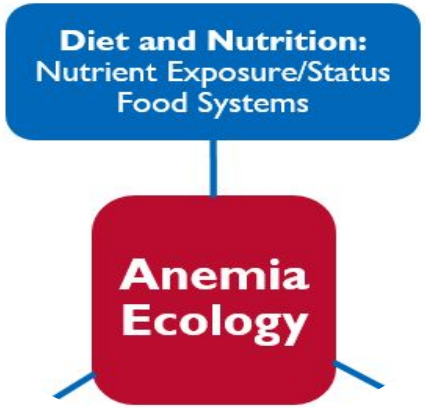
Working Group 'Translation and Implementation'

Cornelia Loechl, Ananya Datta Mitra, Lindy Fenlason, Ralph Green, Laura Hackl, Laura Itzkowitz, Marion Koso-Thomas, Denish Moorthy, Victor Owino, Helena Pachón, Nicole Stoffel, Michael Zimmerman, Daniel Raiten

*No conflict of interest to disclose

Anemia Ecology: Food Systems



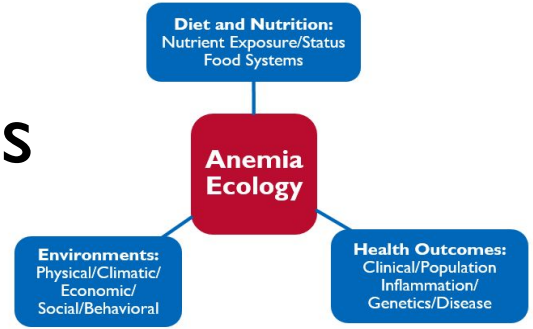


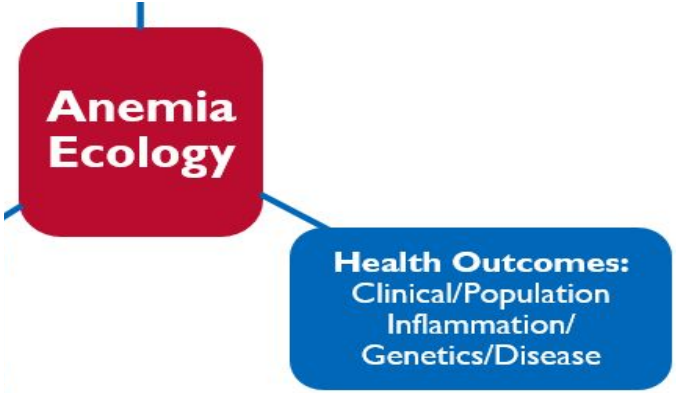
Ecology of traditional food systems

- 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

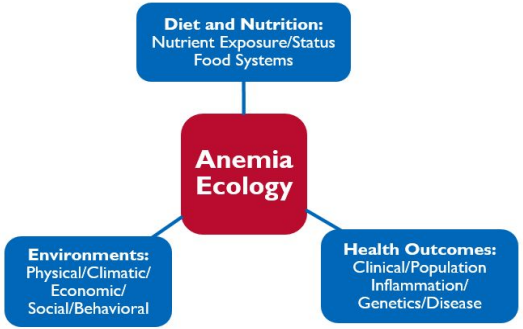


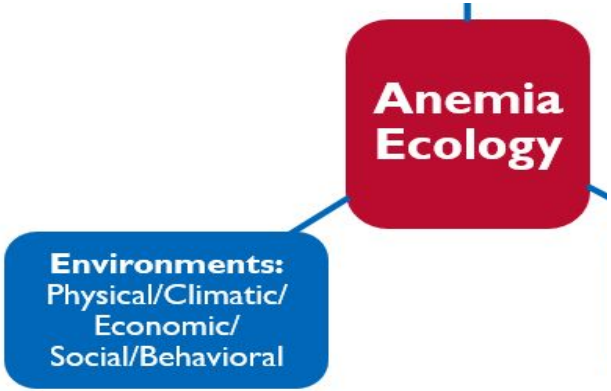


Non-dietary interventions for anemia prevention/treatment

- 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

Anemia Ecology: Environments





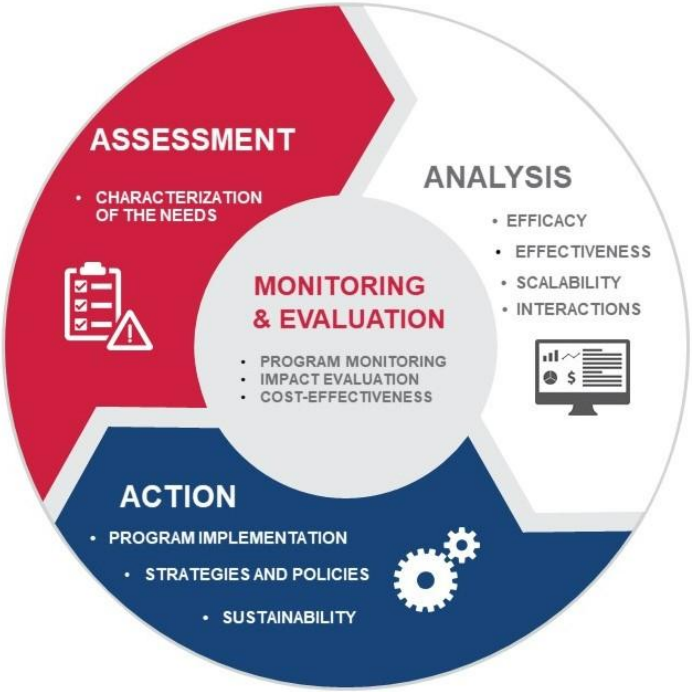
Climate change

- 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

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

Other clinical conditions

- Acute loss due to postpartum hemorrhage
- Chronic loss due to menstruation
- Inherited red blood cell disorders

Non-Dietary Interventions - Evidence

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

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

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

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

Intervention	Efficacy	Proven Effectiveness	Scalability
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—

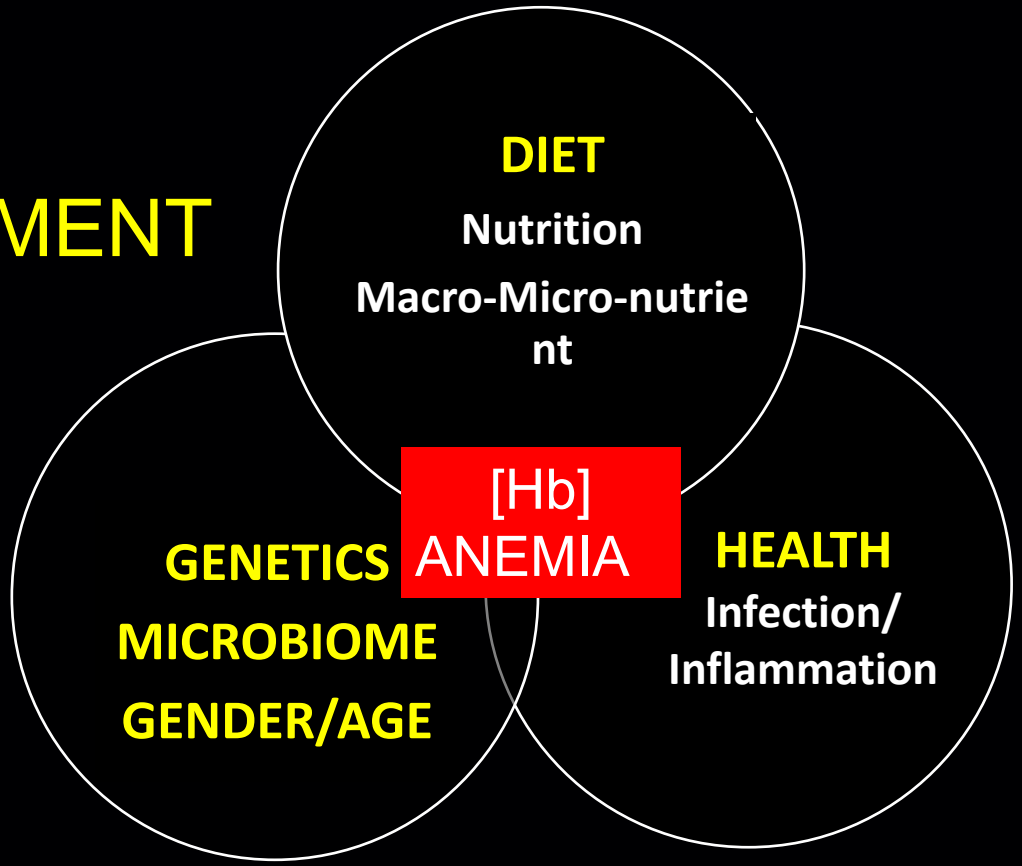
- Impact of climate change on biological pathways related to iron nutrition/anemia
- Value of traditional food processing techniques for improving nutrient status
- Traditional food processing techniques (e.g., germination) and pathogen contamination
- Appropriate food vehicles for targeted fortification
- 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



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.