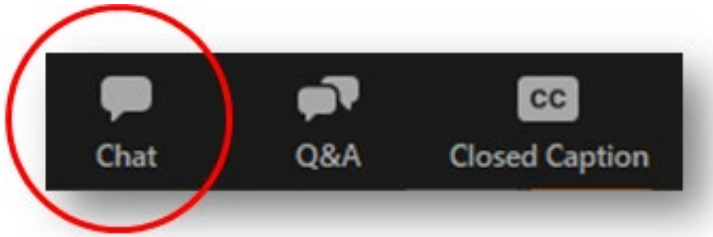
In Search of Better Anemia Estimates:

USAID Advancing Nutrition's HEmoglobin MEasurement (HEME) Project

May 17, 2023
9:00-10:00 AM EDT (GMT-4)

Zoom Webinar Reminders

- If at any point during today's webinar you are unable to hear the speakers, please make sure you've connected your audio by selecting the headphones icon.



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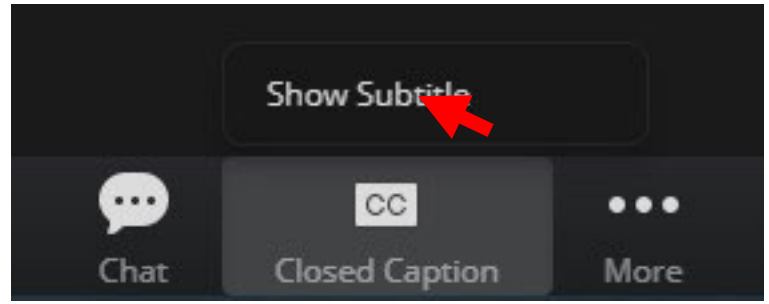
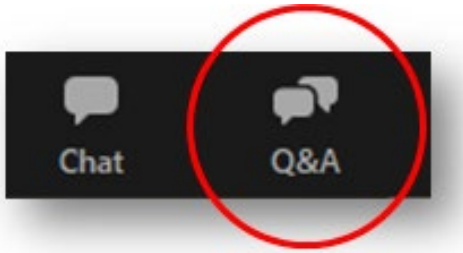


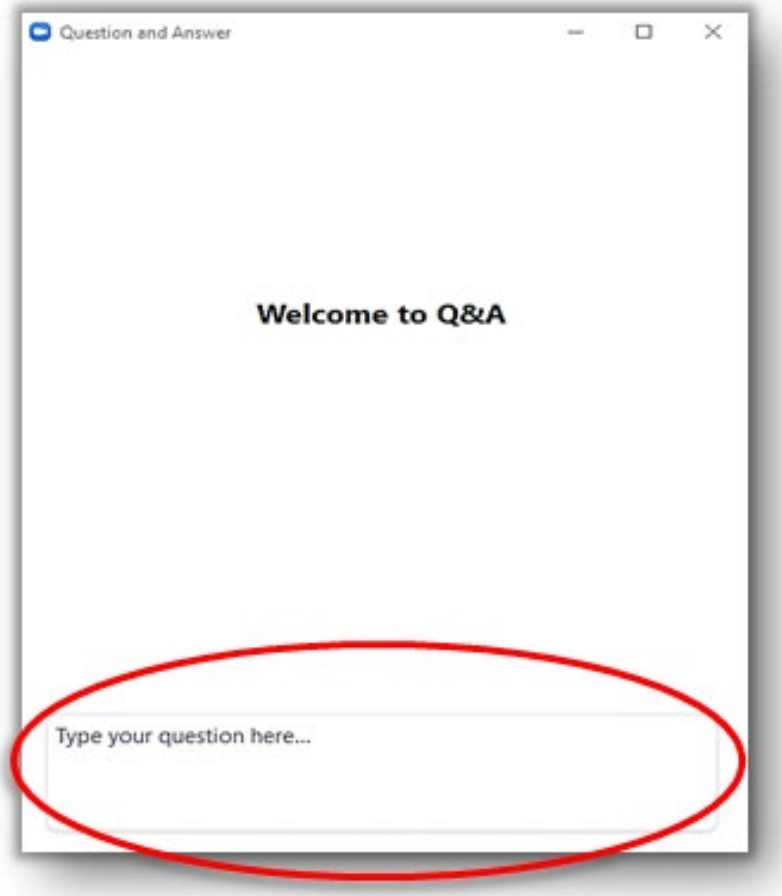
- Finally, please note that this meeting is being recorded and live streamed.

Zoom Webinar Reminders

Please submit your questions for the panelists in the Q&A box.



Panelists will either reply back to you via text in the Q&A box or will answer your question during the QA discussion portion of the webinar.



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Director, Measurement
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Omar Dary
Health Science Specialist (Nutrition)
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USAID Addresses Anemia
USAID Advancing Nutrition- HeMe Project

Omar Dary, Ph.D.
USAID/Bureau for Global Health

May 17th, 2023

Global-endorsed goals for anemia reduction

By the year 2025: **Extended in 2020 to 2030 as an U.N.SDG**

"Achieve a 50% reduction in **anemia** in women of reproductive age [of the figures of 2012]"

Source: 2012-WHA Nutrition Targets

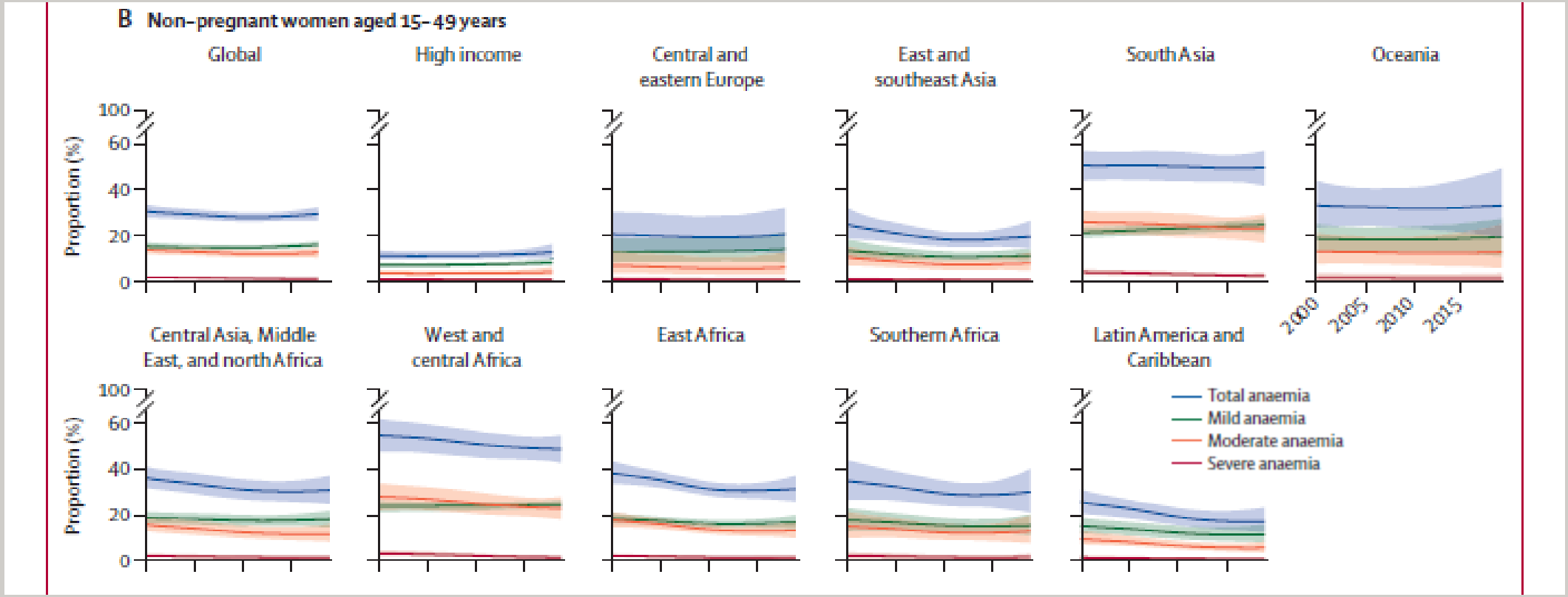
Is this type of commitment new?

By the year 2000:

"Reduction of ***iron deficiency*** **anemia** in women by one third of the 1990 levels"

Source: UNICEF, World Summit for Children, 1990. https://www.unicef.org/wsc/goals.htm#Nutrition

Anemia tendence of women of child-bearing age per region



Reference: Stevens GA, Paciorek CJ, Flores-Urrutia, MC, Borghi E, Namaste S, Wirth JP, Suchdev PS, Ezzati M, Rohner F, Flaxman ST, Roger LM. National, regional, and global estimates of anaemia by severity in women and children for 2000–19: a pooled analysis of population-representative data. *Lancet Glob Health* 2022; **10**: e627–39

Questions:

- Were the hemoglobinopathies taken in consideration for making adjustments?
- Do the geographic regions have similar environmental and health conditions?
- What about the methods to determine Hb in each one of these regions?

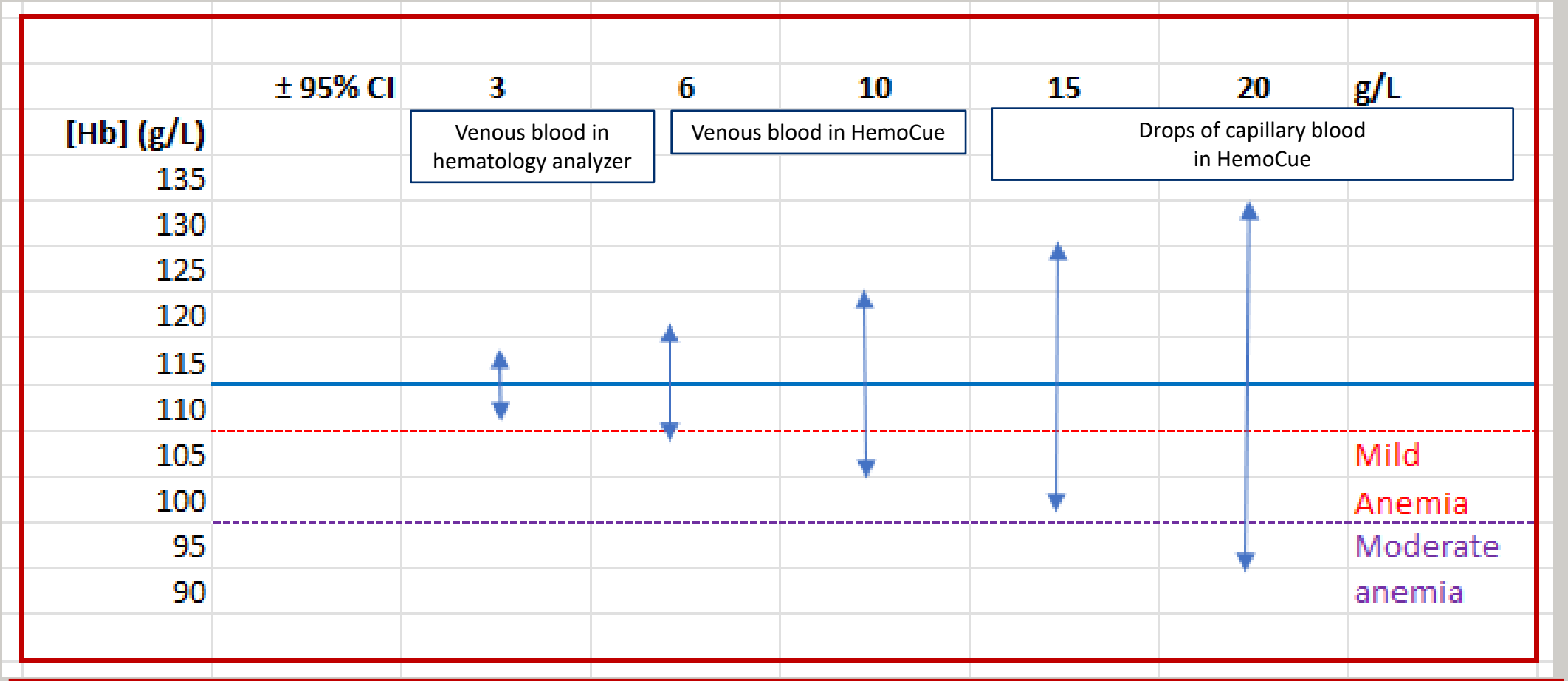
Justification: Large differences between population surveys

Difference of anemia prevalence in preschoolers between two types of surveys

Country	DHS* Capillary drop HemoCue 201+	MNS** Venous/capillary pool HemoCue 301	DHS/ MNS	Change in prevalence	** Reference
Malawi-2015/2016	63 %	30 %	2.1	Severe to Moderate	Malawi NSO, Nutr, and HIV/AID in collaboration with CDC/IMMPaCt, 2016
Ethiopia-2016	57 %	34 %	1.7	Severe to Moderate	Ethiopia Public Health Institute, 2016
Uganda 2016/2018	53%	32 %	1.7	Severe to Moderate	Uganda Panel Survey UBOS/CDC-IMMPaCt,2022
Bangladesh-2011/2012	51 %	33 %	1.5	Severe to Moderate	Icddrb, et al. 2013
Guatemala-2014/2015	32 %	12 %	2.7	Moderate to Mild	SESAN-Guatemala, in collaboration with INCAP, and CDC/IMMPaCt, 2015

Source: * Plus DHS's Reports: Country partner plus ICF; and in Guatemala, ENSMI, Ministry of Public Health, 2014

Implications of lack of precision of the Hb determination for the diagnosis of anemia in individuals and populations



Hb difference between 90 and 95 centiles, and between 95 and 97 centiles**: 2 g/L**

Hb adjustment between 1,000 to 1,500 m over the sea level: **3 g/L**

Laura Hackl
Consultant
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HEME Project and Preliminary Results of the Multi-Country Study

Laura Hackl

USAID Advancing Nutrition

Measuring hemoglobin

Automated hematology analyzers

- Appropriate standard for hemoglobin measurement used with venous blood

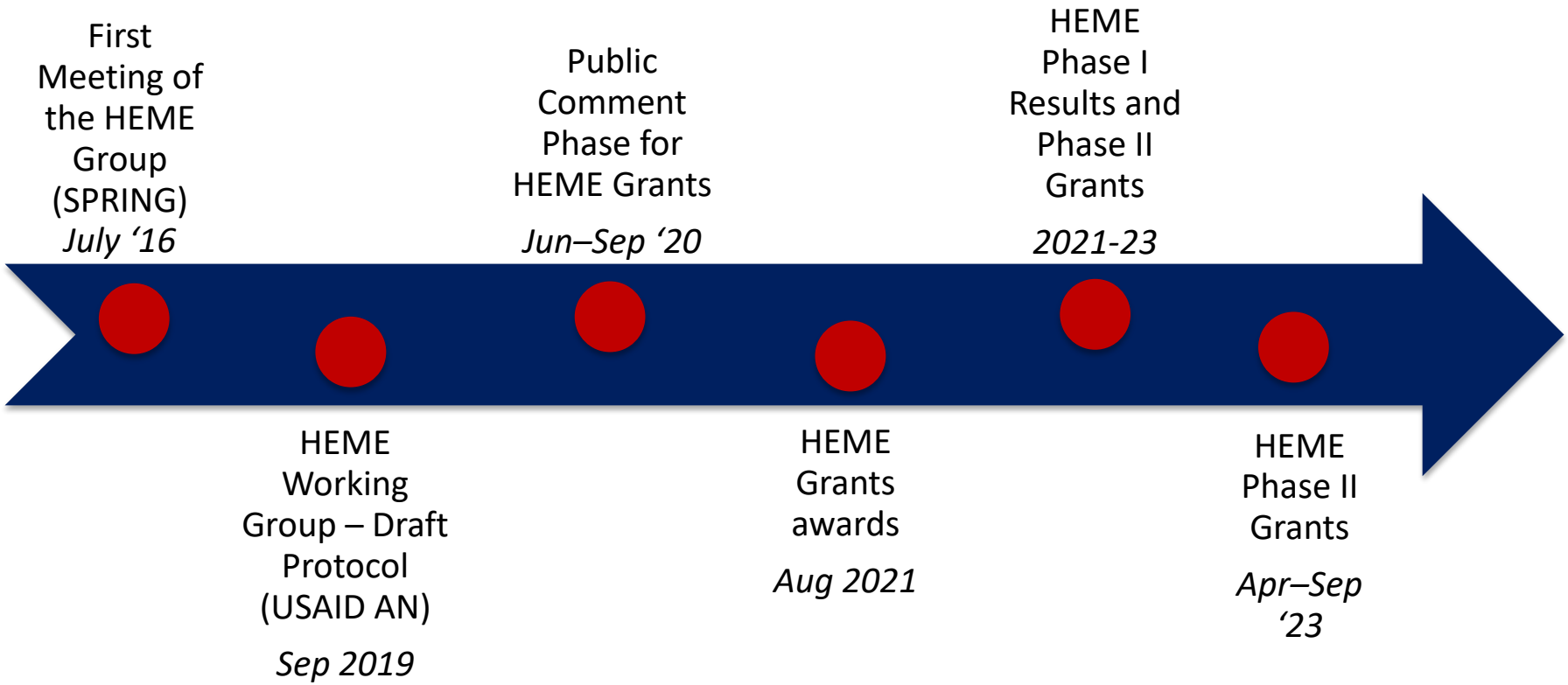
Portable devices

- Most commonly used: HemoCue® (HC) device (HemoCue®, Angelholm, Sweden)
- Usually used with capillary blood samples
  - Single drop of capillary blood from a finger prick, or
  - Pooled capillary blood

Various factors at different stages of blood collection can affect measurement

  - Venous or capillary blood collection
  - Measurement device
  - Sample storage and analysis conditions
  - Environmental factors (e.g., temperature, humidity)

HEmoglobin MEasurement (HEME) Project - SPRING & USAID Advancing Nutrition



HEmoglobin MEasurement Phase I Grants

Objective

- To identify the best procedures/methods for determining hemoglobin concentration/anemia prevalence in population-based surveys

Specifically—

- to assess the performance of three HemoCue® models (201+, 301, and 801) in comparison to a certified hemoglobin autoanalyzer
- using venous, pooled capillary, and single-drop capillary blood samples.

Study Implementation - HEME Phase I

Multi-Country Project

- 16 submissions, 6 grantees (5 USAID AN + 1 external funding)
  - American University of Beirut (AUB), Lebanon
  - eHealth Africa, Nigeria
  - Instituto de Nutrición de Centro América y Panamá, Guatemala
  - National Institute of Medical Research Mwanza, Tanzania
  - University of British Columbia, Canada; in collaboration with HKI, Cambodia
  - Haramaya University, Ethiopia (funded by Nutrition International)

Study participants

- women of reproductive age (15-49 years)
- children 12 to 59 months of age in a LMIC

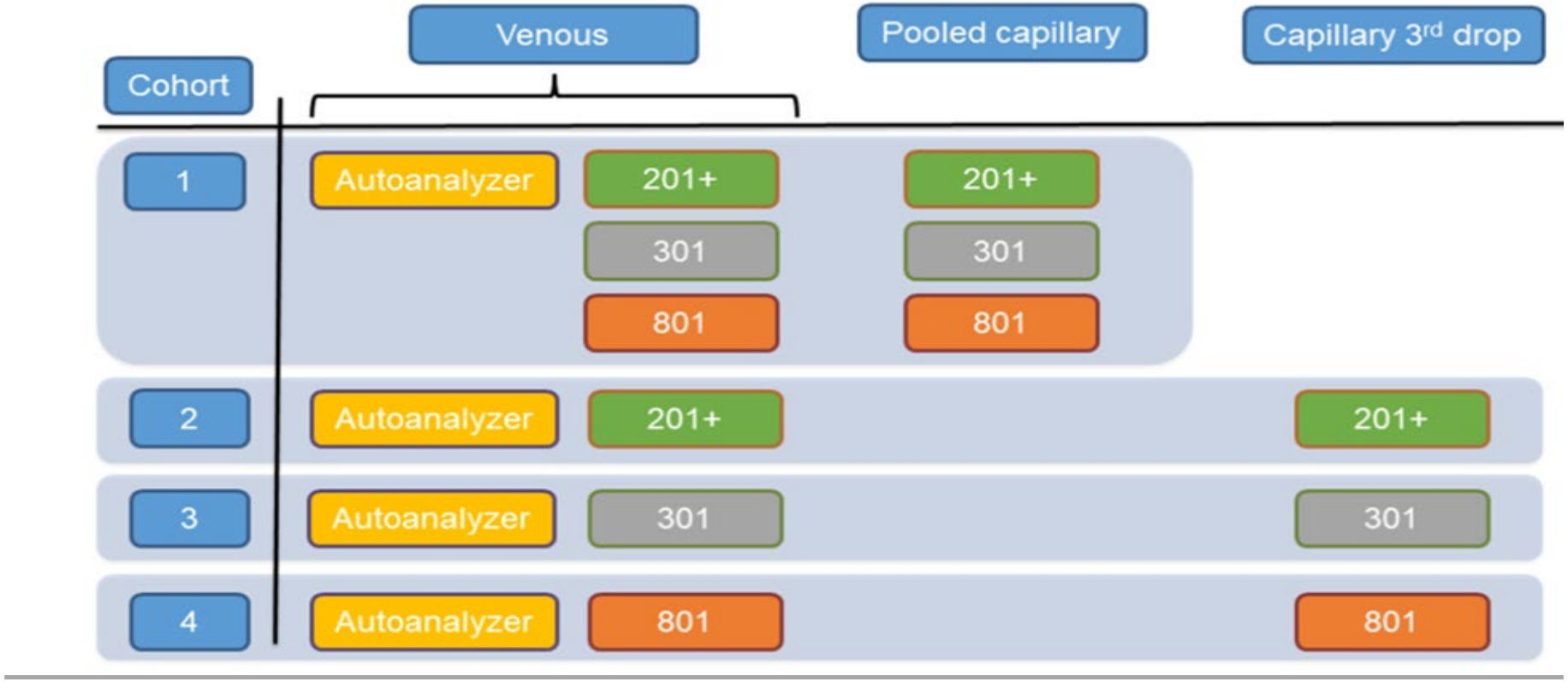
HEME Protocol Questions

1) What is the **accuracy and precision** of three HC device models (**201+, 301 and 801**) in a controlled laboratory setting **compared to** a certified **hematology autoanalyzer** when measuring Hb concentration **using venous blood** from women of reproductive age (WRA) and children 12-59 months of age?

2) What is the **accuracy and precision** of Hb concentration determinations using **venous** blood or **pooled capillary** or **single-drop** capillary (third drop), from WRA and children 12-59 months of age, analyzed in three HC device models (**201+, 301 and 801**) against **venous blood** analyzed in a certified **hematology autoanalyzer** ?

Study setup

Each study site had up to 4 cohorts



Data analysis

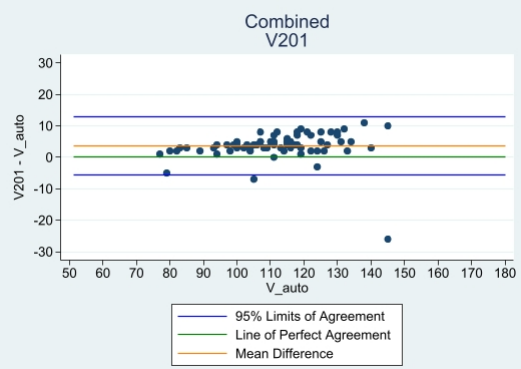
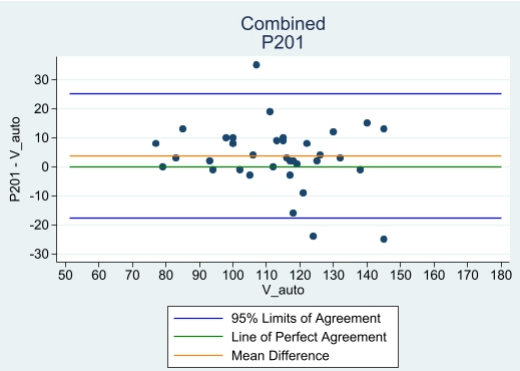
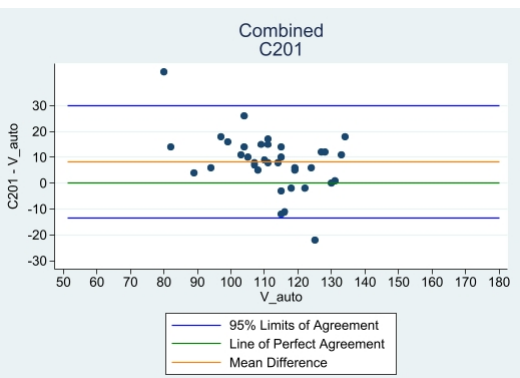
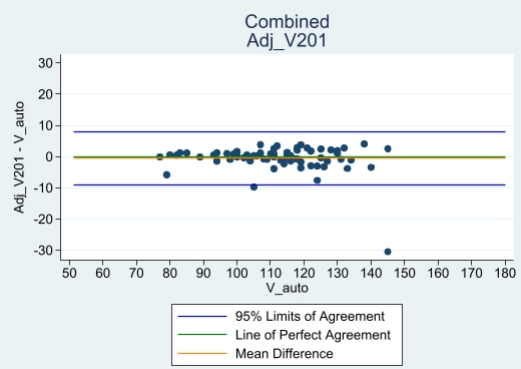
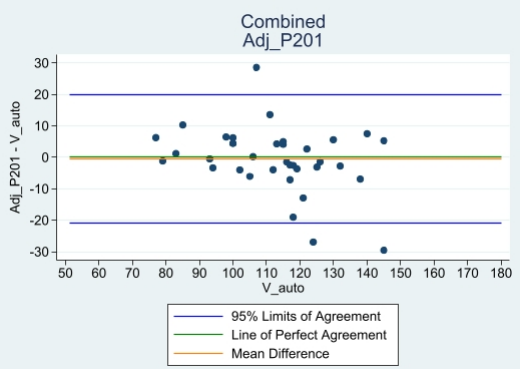
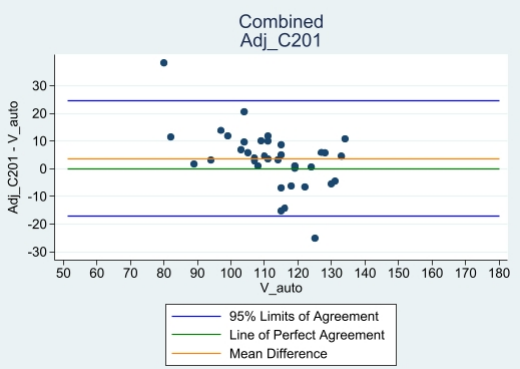
1. Graphing differences - Hb in HemoCue vs. auto-analyzer
   - Accuracy: Difference of the mean from the "zero" identity (no difference)
   - Precision: 95% limits of agreement (LOA) width (i.e., dispersion of values)
2. Accuracy improvement - Adjustment of machine bias / systematic error
   - HemoCue Hb values adjusted by regression calibration
   - Bland-Altman adjustment (data not presented): Subtraction of average difference between Hb from venous blood in HemoCue vs. hematology analyzer

Precision - Random error or dispersion

- Not affected by the adjustment → cannot be corrected

Particularly important bc. anemia is interpreted through the proportion of samples below Hb threshold

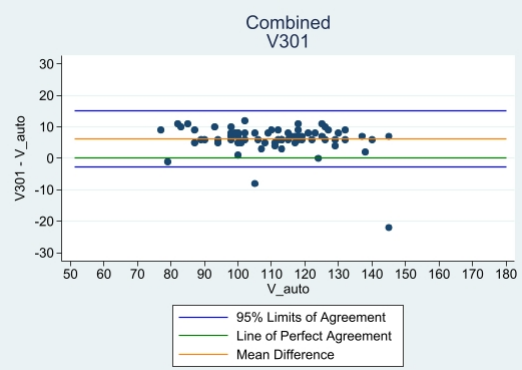
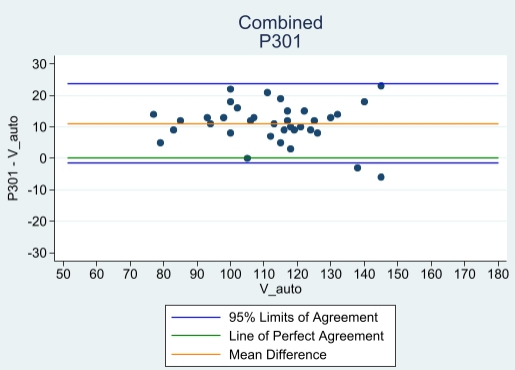
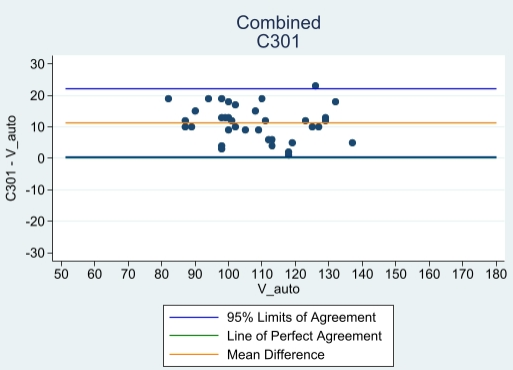
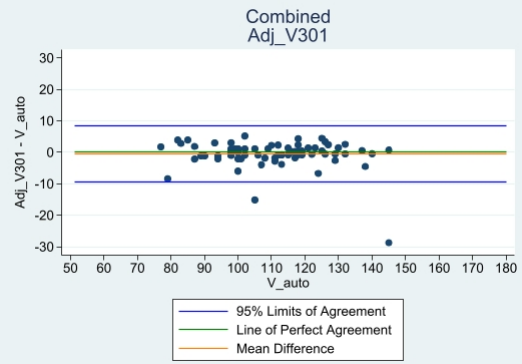
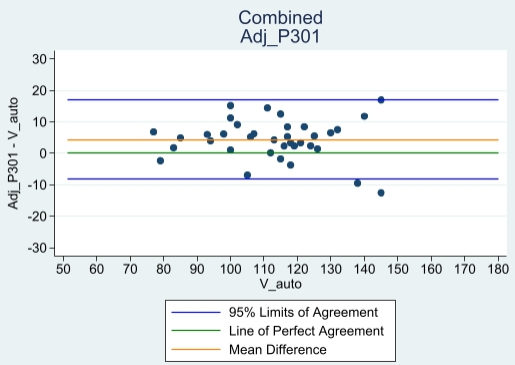
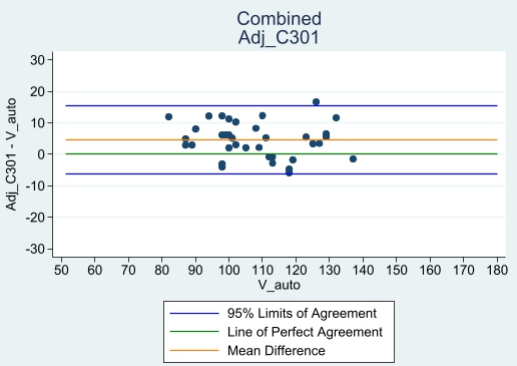
201+ B-A Differences – Tanzania Women + Children

	Venous	Pooled	Single-Drop
UnAdj			
Adj			

Finding:

1) Adjustment by regression reduced average difference (systematic error due to the machine bias) & increased accuracy for venous & pooled blood, not for single-drop samples
2) Dispersion/precision (i.e. random error) w/ pooled & single-drop capillary >2X than w/ venous

301 B-A Differences – Tanzania Women + Children

	Venous	Pooled	Single-Drop
UnAdj			
Adj			

Finding:

1) **Accuracy** without adjustment: worse than when using HemoCue 201+
2) **Dispersion/precision** w/ pooled and single drop capillary 1.5X than w/ venous blood

Accuracy

Country	HemoCue model	Venous Blood	
		Unadjusted	Adjusted
Guatemala	201+		
	301		
	801		
Cambodia	201+		
	301		
	801		
Tanzania	201+		
	301		
Lebanon	201+		
	301		
	801		
Ethiopia	201+		
	301		
	801		
Nigeria	201+		
	301		

Absolute difference (g/L)

- ± 1
- 1.1 - 2
- 2.1 - 4
- > 4

Adjustment

- Necessary in most cases to improve accuracy to < 1 g/L w/ venous blood

Dispersion/Precision

Based on 95% LOA

Country	HemoCue model	Venous	Pooled	Single-Drop
Guatemala	201+			
	301			
	801			
Cambodia	201+			
	301			
	801			
Tanzania	201+			
	301			
Lebanon	201+			
	301			
	801			
Ethiopia	201+			
	301			
	801			
Nigeria	201+			
	301			

Dispersion in g/L

- ≤ 10
- 10.1 -15
- 15.1-20
- > 20

Venous blood: Least dispersion (5-15.1 g/L), different across sites
→ Training for blood collection & instrument use

Capillary blood: Dispersion >10 g/L in all sites (and > 20 g/L in some sites)

Conclusions

- Systematic error is device and model specific and main source of error is the variability associated with blood sampling technique
  - Machine verification - regression calibration adjustment for machine bias
- Which HemoCue?
  - **W/ systematic bias adjustment, use any of the models**
  - **W/ unadjusted values, use 201+**
- Which Blood Sample?
  - **Venous sample are precise and accurate when compared to pooled and single-drop samples**
  - Precision of Hb measurements in pooled similar to single-drop samples
- **Ensure rigor in sample collection**, eg. pooled sample collection errors not corrected by regression

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Panel

Experiences in Implementation of the HEME study

Principal Investigators from Guatemala, Lebanon, Tanzania, Nigeria, Ethiopia

Researcher, INCAP, Guatemala

PhD Student, American University of Beirut, Lebanon

Clinical Research Scientist, Mwanza Research Centre, Tanzania

Medical and Scientific Director, eHealth Africa, Nigeria

Associate Professor, Haramaya University, Ethiopia

Denish Moorthy
Senior Technical Advisor
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What's Next for HEME?

Denish Moorthy

USAID Advancing Nutrition

Issues Identified in HEME I

- Venous blood is the sample of choice BUT pooled capillary blood may still be useful if we can reduce heterogeneity of the Hb results

- Preanalytical factors that influence precision in pooled capillary blood sampling
  - Blood collection procedures
  - Environmental factors
- Venous blood in field-like conditions
  - Impact of storage and transport
  - Stability of biomarkers

Second Phase HEME Studies

3 sites

- American University of Beirut (AUB), Lebanon
- Instituto de Nutrición de Centro América y Panamá, Guatemala
- National Institute of Medical Research Mwanza, Tanzania
- Haramaya University, Ethiopia (funded by Nutrition International)

Study participants

- Women of reproductive age (15-49 years)
- Children 12 to 59 months of age in a LMIC

Implementation period: April – September 2023

Factors being Studied in Second Phase HEME studies

INCAP Guatemala

- Pooled capillary
  - Microcuvette loading for po
  - Ratio of volume of blood to anticoagulant
  - Temperature and time on Hb
- Venous
  - Aliquot volume
  - Delayed blood processing and biomarkers

NIMR, Tanzania

- Pooled Capillary
  - Delayed reading of microcuvette
  - Microcuvette loading
  - Positional effects (sitting vs supine)

AUB Lebanon

- Pooled Capillary
  - Use of an automated vacuum-assisted fingertip blood micro-collection device (Haiim)
- Venous
  - Delayed blood processing and biomarkers

Haramaya University, Ethiopia

- Pooled Capillary
  - Lancet type
  - Volume of anticoagulant
- Venous
  - Delayed blood processing and biomarkers

HEME at SPRING Project
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Ralph Whitehead Jr
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Laura Hackl
Veronica Varela
Silvia Alayon

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Understanding Infant and Young Child Feeding Measurement: A Comparative Analysis of Data Collection Methods for Dietary Data
May 31st from 9-10:30 AM EST

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