New Evidence on the Importance of Maternal Nutrition in Lactation for Milk Quality (Micronutrients)

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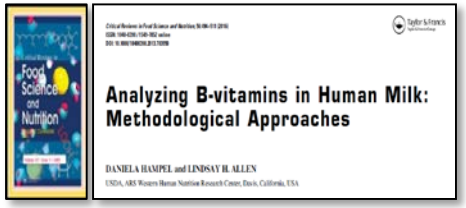
Importance of measuring milk MN

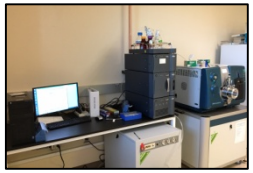
- Lack of information on maternal nutritional status in lactation, and on nutrients in milk.
- Milk is sole source of MN for 6 mo, important for 24 mo.
- Milk concentrations are used to set recommended MN intakes for infants, young children and lactating women.
- Used to estimate MN gaps in complementary feeding; Requirement – amount from milk = gap
- Prevalence of low/inadequate milk MN concentrations in populations? *How do we define low?*
- Effects of low milk levels on infant status, growth, development?
- Need multiple MN supplements? In pregnancy *and* lactation?
- Are milk MN concentrations a population MN status biomarker?

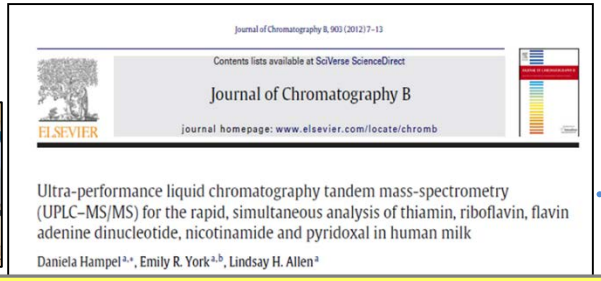
MN groups in lactation (Allen 1994, revised 2019)

Group I	Group II
Milk MN ∝ to maternal status, infant depleted. Supplements can ↑ MN in milk.	Milk MN independent of maternal status, mother depleted. Supplements no effect on milk.
B-1, B-2, B-6, B-12, C **A, D, E, K** **Choline** **Iodine** **Selenium**	**Folate** **Calcium** **Iron, copper, zinc**

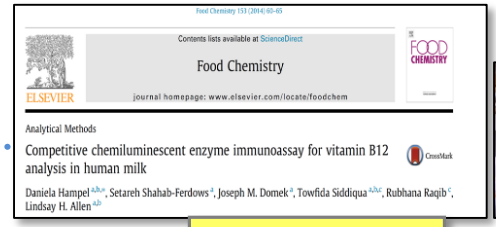
Development of analytical methods





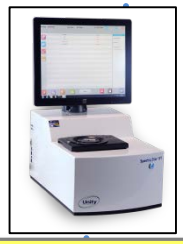


Free thiamin, riboflavin, FAD, nicotinamide, pyridoxal, pyridoxine, biotin, pantothenic acid via UPLC-MS/MS



B12 via CPBA

Iron, copper, zinc, calcium, potassium, magnesium, phosphorus, sodium via ICP-AES

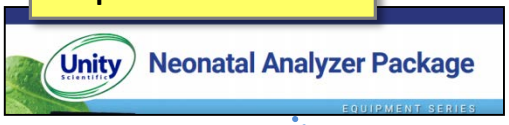


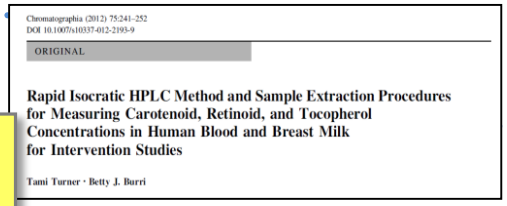
Carbohydrates, fat, protein via NIRS

5 platforms

6 methodological approaches

≈1 mL of milk





Vitamin A and E via HPLC-DAD

Total thiamin via HPLC-FLD

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SUPPLEMENT

AN Advances in Nutrition
AN INTERNATIONAL REVIEW JOURNAL

Current Knowledge on Micronutrients in Human Milk: Adequacy, Analysis and Need for Research

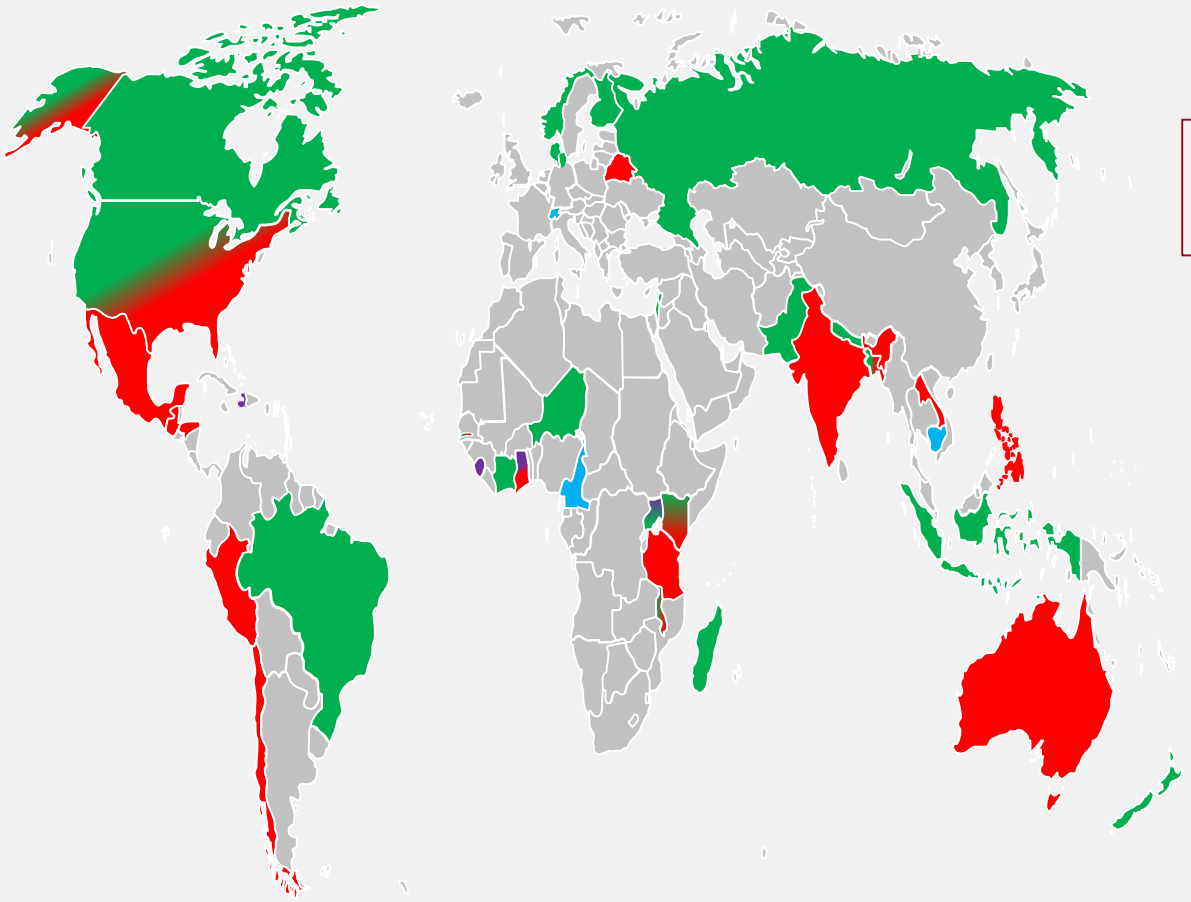
Supplement Coordinators:

Lindsay H Allen and Daphna K Dror
US Department of Agriculture, Agricultural Research Service, Western Human Nutrition Research Center

Published as a Supplement to Advances in Nutrition

- Introduction to Current Knowledge on Micronutrients in Human Milk: Adequacy, Analysis, and Need for Research.
- Overview of Nutrients in Human Milk.
- Limitations of the Evidence Base Used to Set Recommended Nutrient Intakes for Infants and Lactating Women.
- Micronutrients in Human Milk: Analytical Methods.
- Retinol-to-Fat Ratio and Retinol Concentration in Human Milk Show Similar Time Trends and Associations with Maternal Factors at the Population Level: A Systematic Review and Meta-Analysis.
- Iodine in Human Milk: A Systematic Review.
- Vitamin B-12 in Human Milk: A Systematic Review.

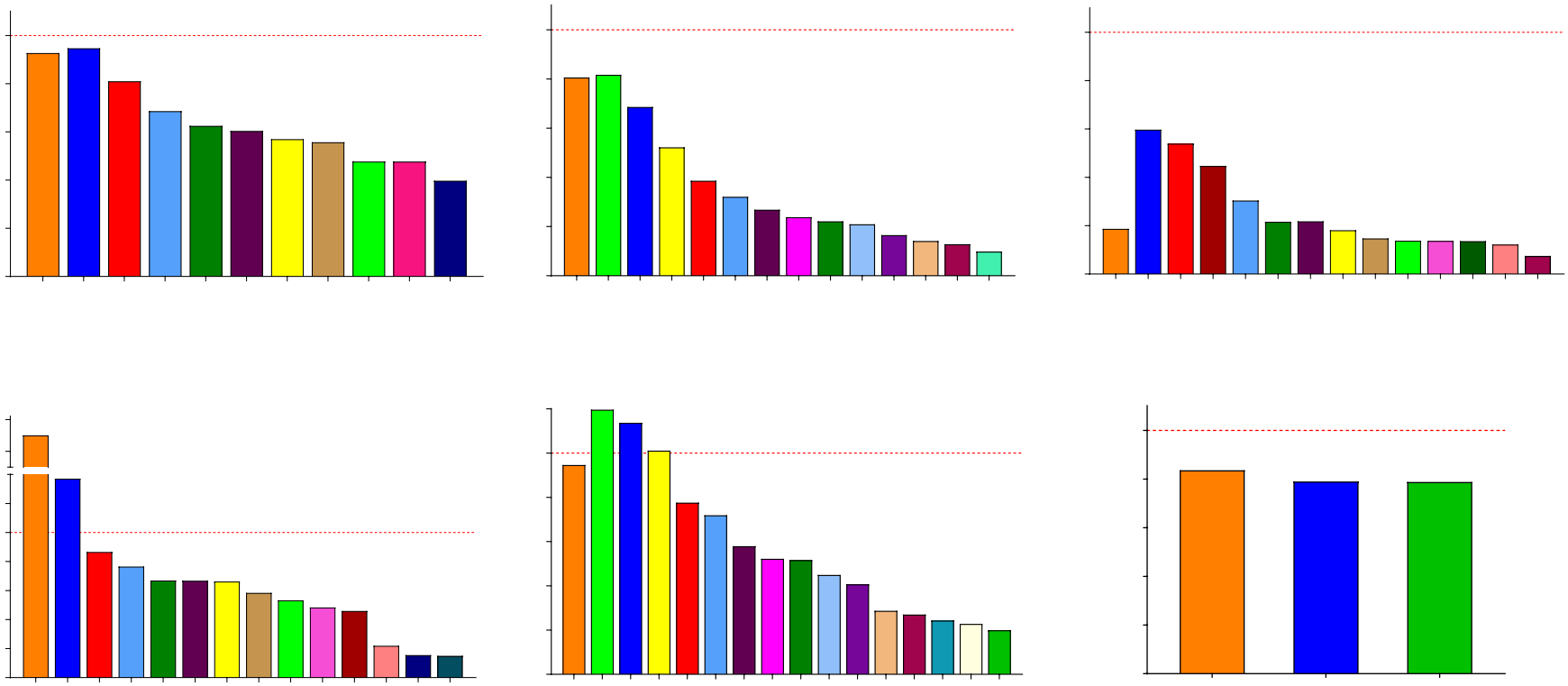
World map of Allen lab's milk composition studies



37 articles + 7 in progress

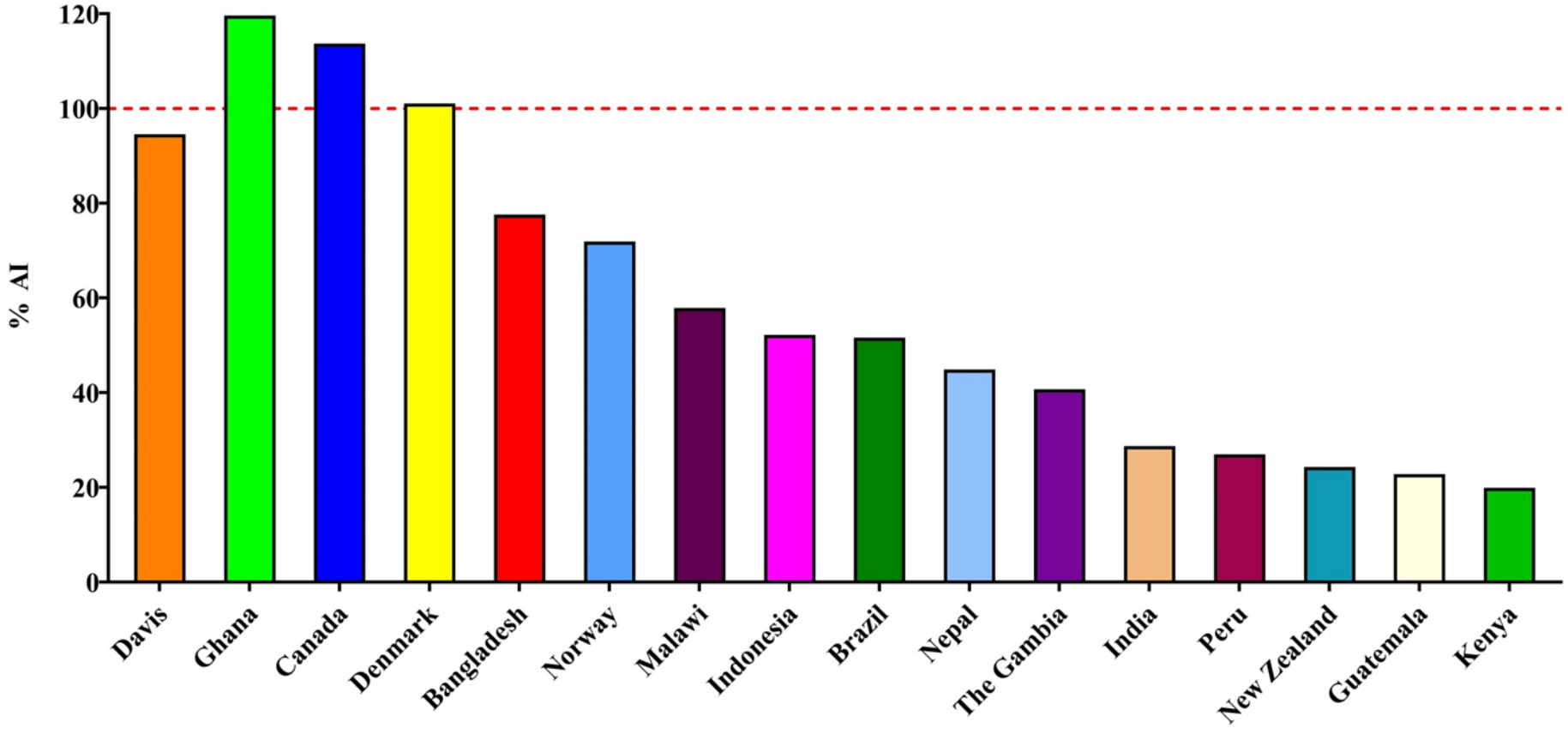
Cross-sectional Intervention
Fortification Survey

B-vitamin concentrations in milk vs. Adequate Intake (AI) value

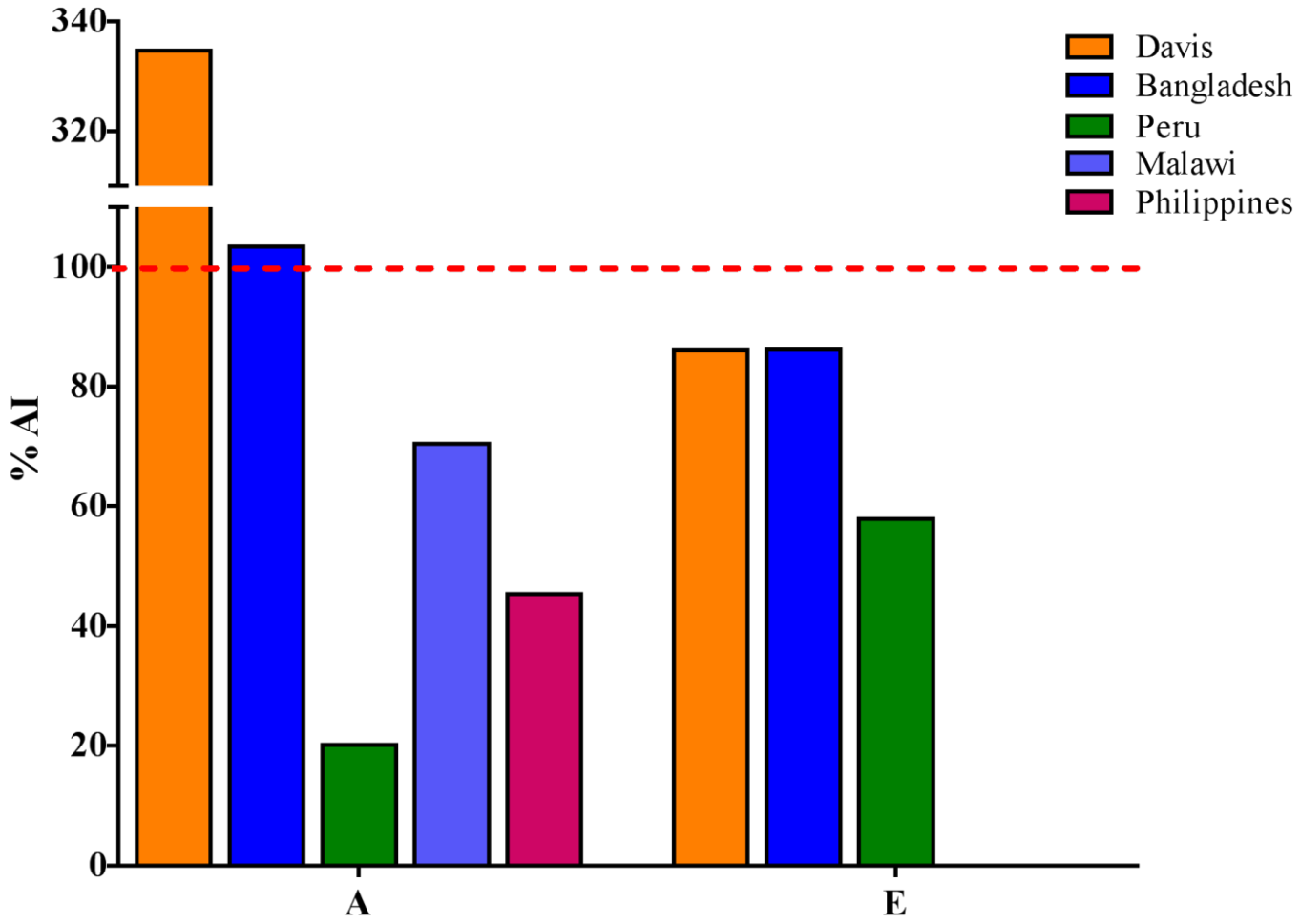


- Our recent measurements of milk vitamin concentrations globally show median levels below current recommendations

Global values for milk B12: analyses from the Allen lab
Median values as % of Adequate Intake value



Relative median concentrations of vitamin A and E in milk as % of Adequate Intake value



Randomized controlled trials

The Journal of Nutrition
Community and International Nutrition

Vitamin B-12 Supplementation during Pregnancy and Early Lactation Increases Maternal, Breast Milk, and Infant Measures of Vitamin B-12 Status[1,2]

Christopher Duggan,[3,6,11]* Krishnamachari Srinivasan,[4] Tinku Thomas,[5] Tinu Samuel,[3] Ramya Rajendran,[4] Sumithra Muthayya,[3] Julia L. Finkelstein,[9] Ammu Lukose,[4] Wafaie Fawzi,[6,7] Lindsay H. Allen,[10] Ronald J. Bosch,[8] and Anura V. Kurpad[3]

Antiretroviral therapy provided to HIV-infected Malawian women in a randomized trial diminishes the positive effects of lipid-based nutrient supplements on breast-milk B vitamins[1–3]

Lindsay H Allen,[4,5] Daniela Hampel,[4,5] Setareh Shahab-Ferdows,[4] Emily R York,[4,5] Linda S Adair,[6] Valerie L Flax,[6] Gerald Tegha,[8] Charles S Chasela,[8,9] Debbie Kamwendo,[8] Denise J Jamieson,[7] and Margaret E Bentley[6]*

RESEARCH ARTICLE

Thiamin and Riboflavin in Human Milk: Effects of Lipid-Based Nutrient Supplementation and Stage of Lactation on Vitamer Secretion and Contributions to Total Vitamin Content

PLOS ONE

Daniela Hampel[1,2]*, Setareh Shahab-Ferdows[1], Linda S. Adair[3], Margaret E. Bentley[3], Valerie L. Flax[3], Denise J. Jamieson[4], Sascha R. Ellington[4], Gerald Tegha[5], Charles S. Chasela[5,6], Debbie Kamwendo[5], Lindsay H. Allen[1,2]

Perinatal Consumption of Thiamine-Fortified Fish Sauce in Rural Cambodia A Randomized Clinical Trial.

Kyly C. Whitfield, Crystal D. Karakochuk, Hou Kroeun, Daniela Hampel et al.

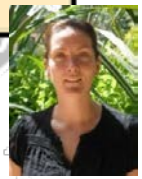
JAMA Pediatr. 2016

Locations and Co-Investigators: Mothers, Infants, Lactation Quality (MILQ) Study

PI: Prof Kim F. Michaelsen

PI: Dr Lindsay Allen

PI: Dr Sophie Moore



PI: Dr Munir Islam

PI: Prof Gilberto Kac

Measurement schedule (n=250 dyads x 4 sites)

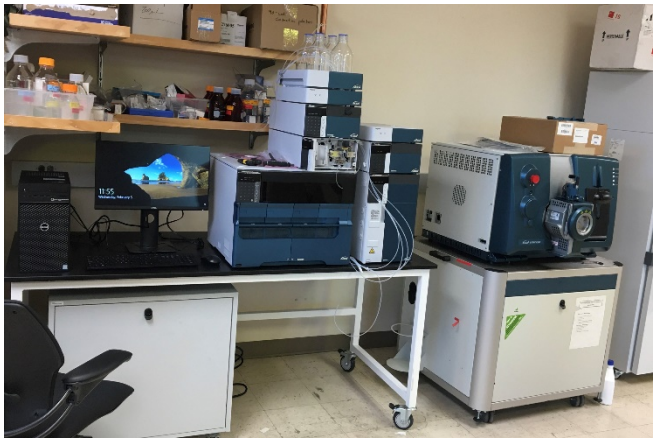
	Pregnancy	Birth	1 – 3.49 m	3.5 – 5.99 m	6 – 8.49 m
Screen/enroll	X			X	
Colostrum/milk		X	X	X	X
Milk volume, D2O			X	X	X
Blood mother			X	X	X
Blood infant			X	X (50%)	X (50%)
Dried blood infant			X	X (50%)	X (50%)
Urine mother/infant			X	X	X
Anthrop. mother	X	X	X	X	X
Anthrop. infant		X	X	X	X
Development				X	X
Diet mother (2 d)		X	X	X	X
Diet infant (2 d)		X	X	X	X
Feces mother/infant			X	X	X

Some planned analyses

Analytes	# Assays	# Samples	Methods
Milk vitamins (18)	5	3000	HPLC, LC-MS/MS
Milk minerals (10)	2	3000	ICP-AES, MS
Milk metabolomics, proteomics	2	3000	LC-TOF-MS, LC-CHIP Q-TOF, LC-MS/MS
Macronutrients (3)	1	3000	IR-Spectroscopy
Milk volume	1	15,750	FTIR
Infant vitamins (13)	2	2000	HPLC, LC-FLD, e411, LC-MS/MS
Infant minerals (3)	1	2000	ICP-AES
Infant thyroid /iodine	2	5000	ELISA, GSP, Colorimetric
Infant metabolomics	1	800	Biocrates
Infant inflammation	6	2000	Integra
Fecal, milk microbiomes		2000	
Mothers……		3000	Diet, MN status, genetics …….

MILQ metabolomics

- New MxP® Quant 500 kit for analyzing ~630 metabolites



Sciex ExionLC couples to Sciex 6500+ QTRAP MS

Small Molecules

- Alkaloids (1)
- Amine oxides (1)
- ★ Amino acids (20)
- Amino acid related (30)
- Bile acids (14)
- ★ Biogenic amines (9)
- Carbohydrates and related (1)
- Carboxylic acids (7)
- Cresols (1)
- Fatty acids (12)
- Hormones (4)
- Indoles and derivatives (4)
- Nucleobases and related (2)
- Vitamins and cofactors (1)

Lipids

- ★ Acylcarnitines (40)
- ★ Phosphatidylcholines (76)
- ★ Lysophosphatidylcholines (14)
- ★ Sphingomyelins (15)
- Ceramides (28)
- Dihydroceramides (8)
- Hexosylceramides (19)
- Dihexosylceramides (9)
- Trihexosylceramides (6)
- Cholesteryl esters (22)
- Diglycerides (44)
- Triglycerides (242)

https://www.biocrates.com/products/research-products/mxp-quant-500

Novel aspects of the study

- Reference values: nutrients in milk, maternal and infant biomarkers.
- Revise nutrient requirements, mothers/infants.
- Enables global comparisons.
- Population nutritional status biomarker?
- Milk biology; new vitamers, metabolites, HMOs, antibodies…….
- Nutrient intake data

- Maternal genomics
- Milk cell….
- Early MILQ

Policy implications

- Need to raise awareness of prevalence of low milk MN – without causing alarm. Should focus on mother's nutrition during lactation.
- Multiple MN supplementation is not (yet) recommended by WHO for pregnant women to improve maternal and perinatal outcomes. But might be needed to improve milk MN.
- If maternal supplements not effective enough, need infant supplements in some situations?
- More accurate intake recommendations may change estimates of nutrient gaps, and formulation of complementary foods, for infants, young children.

Collaborators in milk research

WHNRC:

Setti Shahab-Ferdows

Daniela Hampel

Julianne Saracha

Juliana Haber

Janet Peerson

USDA Agricultural Research Service

Bangladesh: M. Islam, R. Raqib, T. Siddiqua

Brazil: G. Kac, E. Barros, D. Farias

Cambodia: K. Whitfield

Cameroon: R. Engle-Stone, K. Brown

Canada: T. Green, P. Chebaya

Denmark: E. Nexo, D. Lildballe, K. Michaelsen, K. Eriksen, S. Hilario Christensen

Gambia: S. Moore, A. Doel

Ghana: K. Dewey, iLiNS team

Guatemala: M. Ramirez, N. Solomons

India: C. Duggan, A. Kurpad

Indonesia: L. Houghton, R. Gibson

Kenya: A. Williams, C. Stewart. C. Chantry

Malawi: P. Bentley, L. Adair, V. Flax, K. Dewey, P. Ashorn

New Zealand: T. Green

Norway: T. Strand, S. Henjum

Peru: T. Gyorkos, L. Mofid

Philippines: M. Haskell

Tanzania: W. Fawzi

USA: M. Perrin, R. Pawlak, J. Smilowitz

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MILQ Mothers, Infants and Lactation Quality