Recent Evidence for Benefit-Risk Analysis of Raw and Pasteurized Milks

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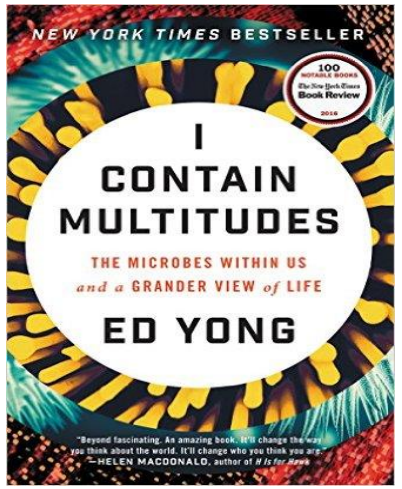
21 October 2021

International Society of Microbiota

8th World Congress on Targeting Microbiota 2021

Milk: A Mammalian Innovation

200 Million-Year-Old 'Superfood' (Yong, 2016)



Human milk

- Emphasis on human milk waxed and waned over recent centuries, but now **maternal milk** recommended from birth and for two years or more
- Wet nursing ancient practice in many cultures (Code of Hammurabi from 2250 BC)

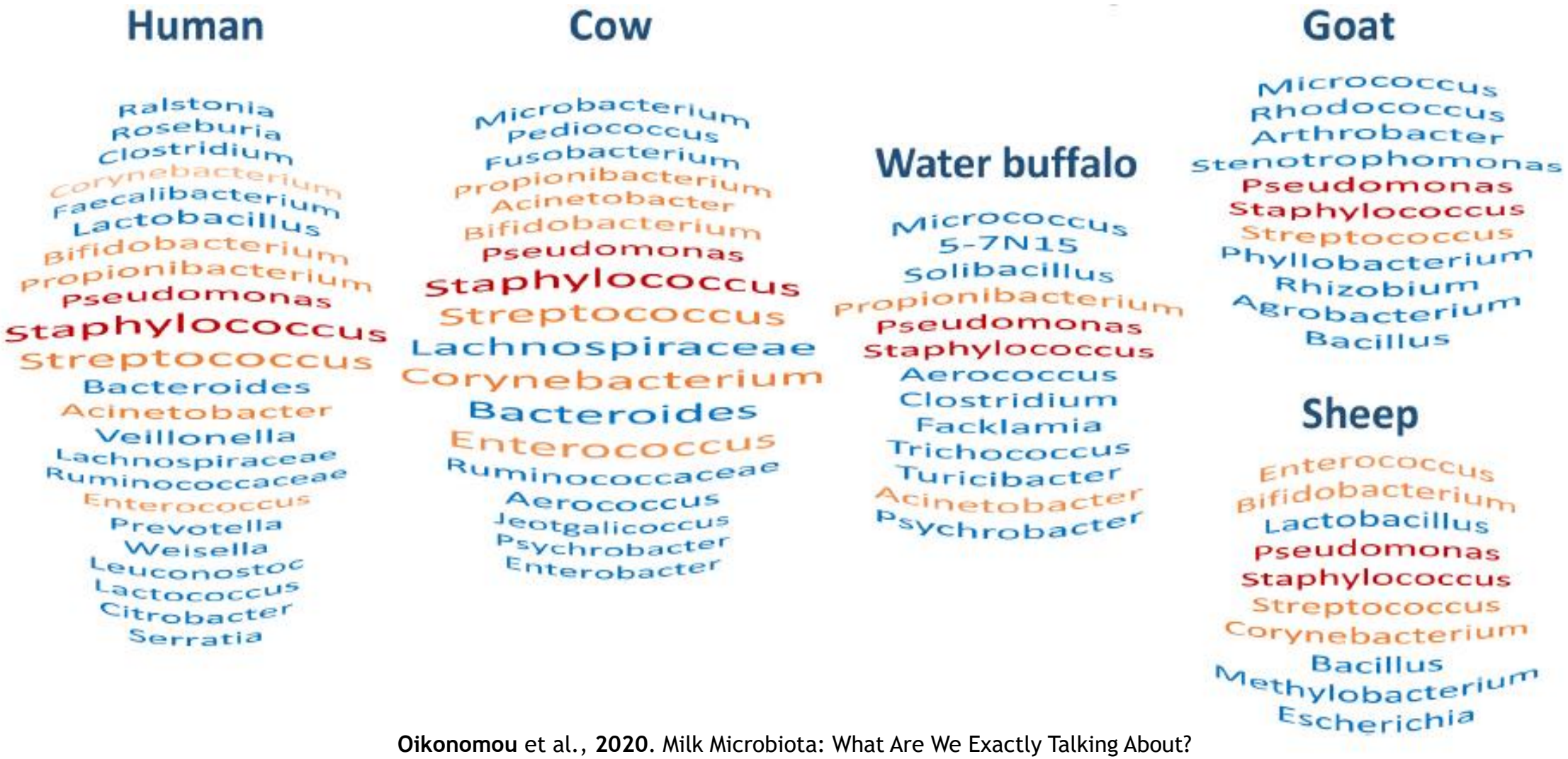
World Health Organization recommends exclusive breastfeeding for first 6 months of life (WHO, UNICEF, 2003)

Breastfeeding reduces **frequency** AND **duration** of **respiratory** and **diarrheal** illness in infants <6 months age (Lopez-Alarcon et al., 1997)

Exclusive breastfeeding protects against common infections during infancy and lessens the **frequency** AND **severity** of infectious episodes (Ladomenou et al., 2010)

Recent Milk Microbiota Study

UK Colleague George Oikonomou



Oikonomou et al., **2020**. Milk Microbiota: What Are We Exactly Talking About?
Frontiers in Microbiology

Graphical Abstract: *Applied Microbiology* Paper

Coleman et al., 2021a. Examining Evidence of Benefits and Risks for Pasteurizing Donor Breastmilk

Benefits and Risks of Raw and Pasteurized Breastmilk

Raw Breastmilk

photo by Kyle Nieber on Unsplash

- ↑ diversity of gut microbiota
- ↑ colonization resistance
- ↓ infectious and noninfectious diseases
- ↓ risk of childhood and maternal obesity
- ↑ developing nervous system
- ↑ cognitive development
- ↓ chronic disease

Pasteurized Donor Milk

photo by Lucy Wolski on Unsplash

- ↓ diversity gut microbiota
- ↑ dysbiosis
- ↓ colonization resistance
- ↓ weight gain and growth
- ↑ risk of necrotizing enterocolitis
- ↑ risk of mortality
- ↑ risk of infectious and noninfectious diseases
- ↑ cost
- ↓ cognitive development
- ↑ chronic disease

General View for Human Milk Bank Policies

- Rigorous donor screening methods similar to blood donation
- Some screen donor milk for other potential pathogens and indicators of contamination
- Some limits for pathogens/indicators (counts per mL) in donor milks (Omarsdottir et al., 2008)
  - <100,000 *Staphylococcus aureus*
  - <100 Enterobacteriaceae
  - 0 (below limit of detection) for potential pathogens

    Listeria monocytogenes, Salmonella, Group B/α-hemolytic *Streptococcus*, coagulase-negative *Staphylococcus*
- Most **pasteurize** donor milk (NOT Germany, Japan, Norway)

Assumption: *Pasteurization Minimizes Risks for NICU Infants*

Benefits AND Risks for Vulnerable Population

Human Milk Banks

provide **pasteurized** human donor milk to hospitalized preterm infants and sick/high risk infants

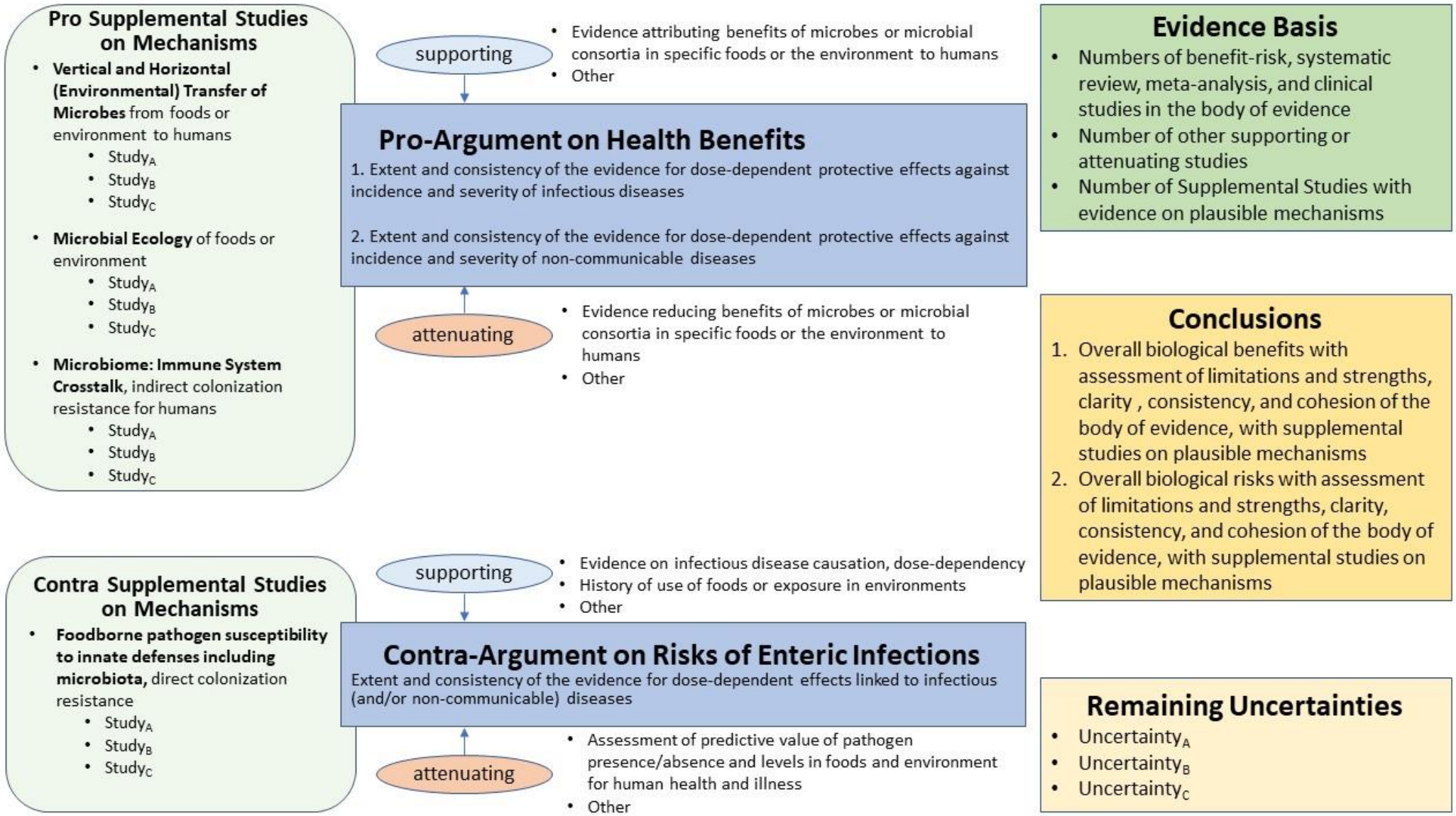
Holder pasteurization (heating to 62.5°C for 30 minutes) is required due to **perception**: possible presence of potential pathogens perceived as **'risky'**

Yet Loss of Benefits for Pasteurized Milks in Clinical Studies around the World!

- **Ford et al., 2019:** 74 preterm infants raw, 43 past donor (US, TX)
- **Sun et al., 2019:** 98 very preterm infants raw, 109 past donor (China)
- **Squires, 2017**: 302 low birth weight infants (US, WA)
- **Cossey** et al., **2013**: 303 very low birth weight infants (Belgium)
- **Strand** et al., **2012**: 335 infants and toddlers (Nepal)
- **Montjaux-Regis** et al., **2011**: 55 premature infants (France)
- **Schanler** et al., **2005**: 243 extremely low birth weight infants (US, TX)
- **Narayanan** et al., **1984**: 226 high risk, low birth weight infants (India)

Evidence Map Template

(motivated by Wiedemann et al., 2011)



Evidence Map for Breastmilk Ecosystem

Pro Supplemental Studies on Mechanisms

- **Vertical and Horizontal (Environmental) Transfer of Microbes** from maternal diet to gut, mammary tissues, milk, infant
  - Gregory 2016
  - Sawh 2016
  - Murphy 2017
  - Toscano 2017
  - de Andrés 2018
  - Ojo-Okunola 2018
  - Moossavi and Azad 2019
  - Van Deaele 2019
  - Wang 2020
- **Microbial Ecology**
  - Arroyo 2010
  - Fernandez 2016
  - Cacho 2017
- **Microbiome: Immune System Crosstalk**, indirect colonization resistance, recent reviews
  - Ward 2013
  - Chong 2018
  - Dietert 2018
  - van den Elsen, 2019

Contra Supplemental Studies on Mechanisms

- **Pathogen susceptibility to innate defenses including microbiota**
  - Cacho and Lawrence 2017
  - Dietert 2018
  - Le Doare 2018
  - Ojo-Okunola 2018

supporting

- ***B-RA (Meltzer 2016), SR*** **(Miller 2018)**, ***SR/MA*** **(Villamor-Martinez 2018)**, ***CSs*** **(Sun 2019; Ford 2019)** demonstrated loss of benefits (protection against mortality, NEC, sepsis, other) for pre-term infants fed pasteurized donor milk or formula.

Pro-Argument on Benefits of Raw Breastmilk

1. Extensive consistent evidence for dose-dependent protective effects compared to formula (or pasteurized donor milk) against incidence and severity of infectious diseases: ear and upper respiratory infections, diarrhea.
2. Extensive evidence for protective effects against non-communicable diseases: convincing for obesity; probable for asthma, celiac, Crohn's, diabetes, eczema, high blood pressure, ulcerative colitis, wheezing.

attenuating

- No studies identified that attribute benefits to specific raw milk microbes or microbial consortia.
- ***SR/MA*** of observational studies demonstrated pasteurized donor milk reduced bronchopulmonary dysplasia compared to formula; effect not observed in randomized trials (**Villamor-**Martínez **2018**).

supporting

- **CS (Bapistella 2019)** demonstrated lower CMV infection rates for mother's own breastmilk treated with short-term pasteurization than historical controls fed raw breastmilk.
- Policy paper on infectious diseases associated with mothers' & donors' breastmilk (**American Academy of Pediatrics, 2017**).

Contra-Argument on Risks of Enteric Infections from Potential Pathogens in Raw Breastmilk

Limited evidence for normal breastmilk from healthy mothers causing infectious diseases in infants.

attenuating

- No **B-RA** or **QMRA, *SRs*, *MAs*,** or ***CSs*** identified estimating risks of infectious disease transmission by breastmilk; review (**Gribble and Hausman, 2012**).
- ***CS*** **(Schanler, 2011)** demonstrated pathogen presence in breastmilk not predictive of illness in preterm infants.
- Long history of use of raw donor breastmilk in Norway **(Grøvslien and Grønn, 2009; Grøvslien 2020).**

Evidence Basis

- 1 ***Benefit-Risk Assessment*** **(Meltzer 2013/16)**, 1 ***SR*** **(Miller 2018)**, 1 ***SR/MA*** **(Villamor-Martinez 2018)**, 2 ***CSs*** **(Sun 2019; Ford 2019)** citing extensive, consistent evidence
- 5 Other supporting or attenuating studies
- 18 Supplemental studies with evidence on plausible mechanisms

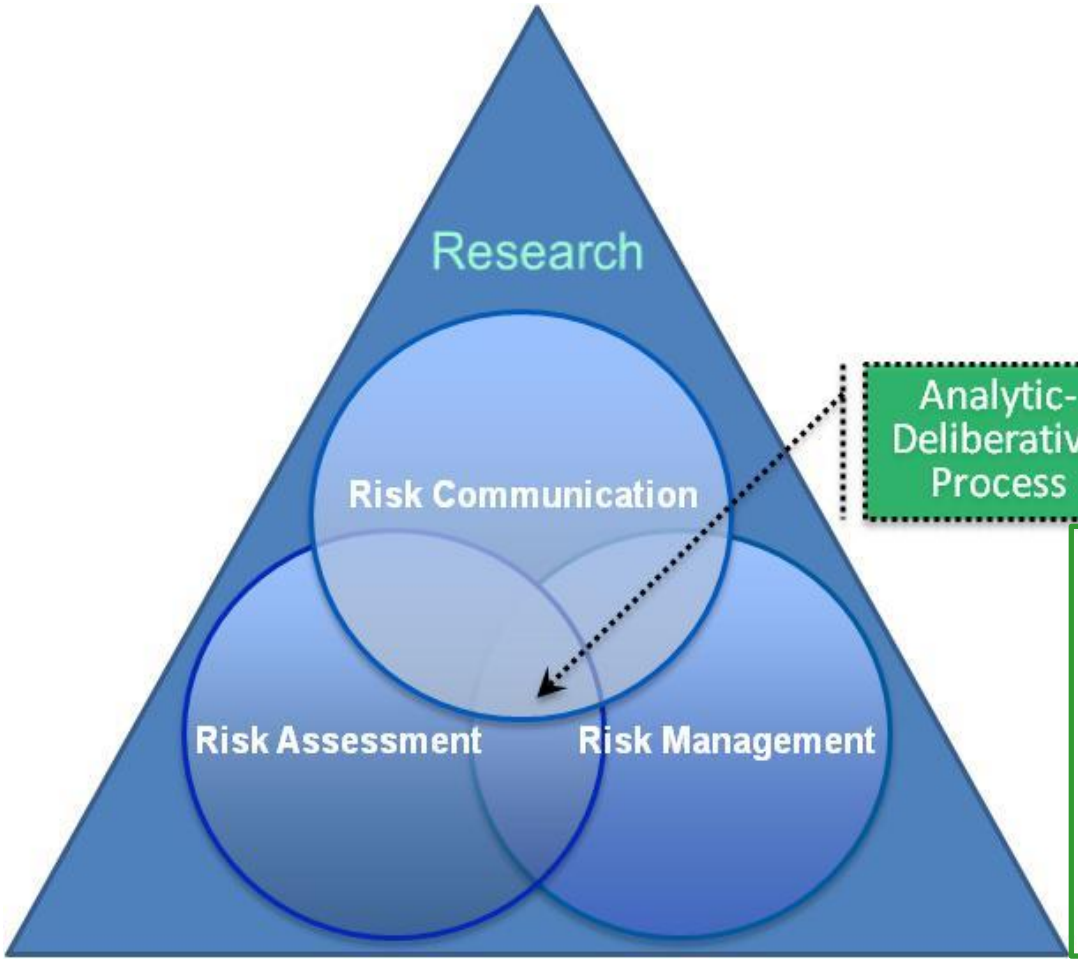
Conclusions

1. Overall biological benefits associated with breastmilk clear, convincing, and conclusive, with supplemental studies on plausible mechanisms attributed to biologically active raw breastmilk
2. Evidence for assessing risks of pathogen infections in infants fed breastmilk from moms and donors limited and inconclusive

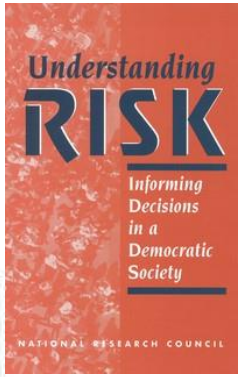
Remaining Uncertainties

- How do milk microbiota function in protection against infectious and non-communicable diseases in infancy and later in life?
- Are presence or levels of potential pathogens in breastmilk predictive of illness in infants or mothers?
- Are there health benefits to pasteurizing donor milk for preterm or ill infants?

Dogmas from 20th Century Science, Risk Analysis, and the 'Microbiome Revolution'



Analytic-Deliberative Process



Free download at National Academies Press https://www.nap.edu/catalog/5138/understanding-risk-informing-decisions-in-a-democratic-society

Builds in cycles of **research, analysis**, **deliberation**, and **interpretation** with stakeholders on

- **what goes in** (data, assumptions)

AND

- **what comes out** of risk models (**estimates of risk, uncertainty**).

Dogmas (assumptions, opinions, or perceptions) about risks that don't match up with scientific evidence warrant analytic-deliberative process.

Highlights of Ongoing Project on Milk Microbiota Benefits and Risks

Joint Project, Upstate NY Society for Risk Analysis (SRA), partners in **Australia/New Zealand, New England,** and **UK** on the **Natural Microbiota of Raw Milks** of human, bovine superorganisms

- **2017**: **SRA webinar series**, beginning with record-setting webinar by Rod Dietert, ***Protecting the Human Superorganism***, closing with ***Preparing to Deliberate the Evidence on Benefits and Risks*** by collaborators Warner North & Peg Coleman

- **2017-2019**: SRA round table panel symposia, presentations on evidence, data/analysis, pasteurization policies for human donor breastmilk and bovine milk

- **2019-2021**: prepared companion manuscripts on epidemiology, immunology, microbiology, and decision science for breastmilk and bovine milk

- **2021:** preparing invited manuscripts for special collection in *Applied Microbiology*

- **2022**: seeking partners for developing international workshops to deliberate evidence/knowledge gaps for **BENEFITS and RISKS** of raw milks

Questions? Comments? Interested Partners?

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21 October 2021, International Society of Microbiota, 8th World Congress on Targeting Microbiota 2021

Backup Slides

Suggested Reading

Margaret E. (Peg) Coleman, D. Warner North, and Colleagues, Risk Analysis

- 1996: National Research Council (NRC) Understanding Risk: Informing Decisions in a Democratic Society.
- 1998: Marks, H.M.; Coleman, M.E.; Lin, C.T.J. Topics in Microbial Risk Assessment: Dynamic Flow Tree Process. Risk Anal. 18, 309–328.
- 2011: Wiedemann, P.; Schütz, H.; Spangenberg, A.; Krug, H.F. Evidence Maps: Communicating Risk Assessments in Societal Controversies: The Case of Engineered Nanoparticles. Risk Anal. 31, 1770–1783.
- 2018: Coleman, M.; Elkins, C.; Gutting, B.; Mongodin, E.; Solano-Aguilar, G.; Walls, I. Microbiota and Dose Response: Evolving Paradigm of Health Triangle. Risk Anal. 38, 2013–2028.
- 2019: North, D.W.; Cox, L.A.; Popken, D.A. Mega-Review: Causality Books. Causal Analytics for Applied Risk Analysis. Risk Anal. 39, 1647–1654.
- 2020: North, D.W. Risk Analysis, Decision analysis, causal analysis, and economics: A personal perspective from more than 40 years experience. Risk Anal. 40, 2178–2190.
- 2021a: Coleman, M.E.; North, D.W., Dietert, R.R.; Stephenson, M.M. Examining Evidence of Benefits and Risks for Pasteurizing Donor Breastmilk. Accepted for publication in the December issue of Applied Microbiology.
- 2021b: Coleman, M.E.; Dietert, R.R.; North, D.W., Stephenson, M.M. Enhancing Human Superorganism Ecosystem Resilience by Holistically ‘Managing Our Microbes’. Accepted for publication in the December issue of Applied Microbiology.

Rodney R. Dietert, Collaborator and Emeritus Professor of Immunotoxicology, Cornell University

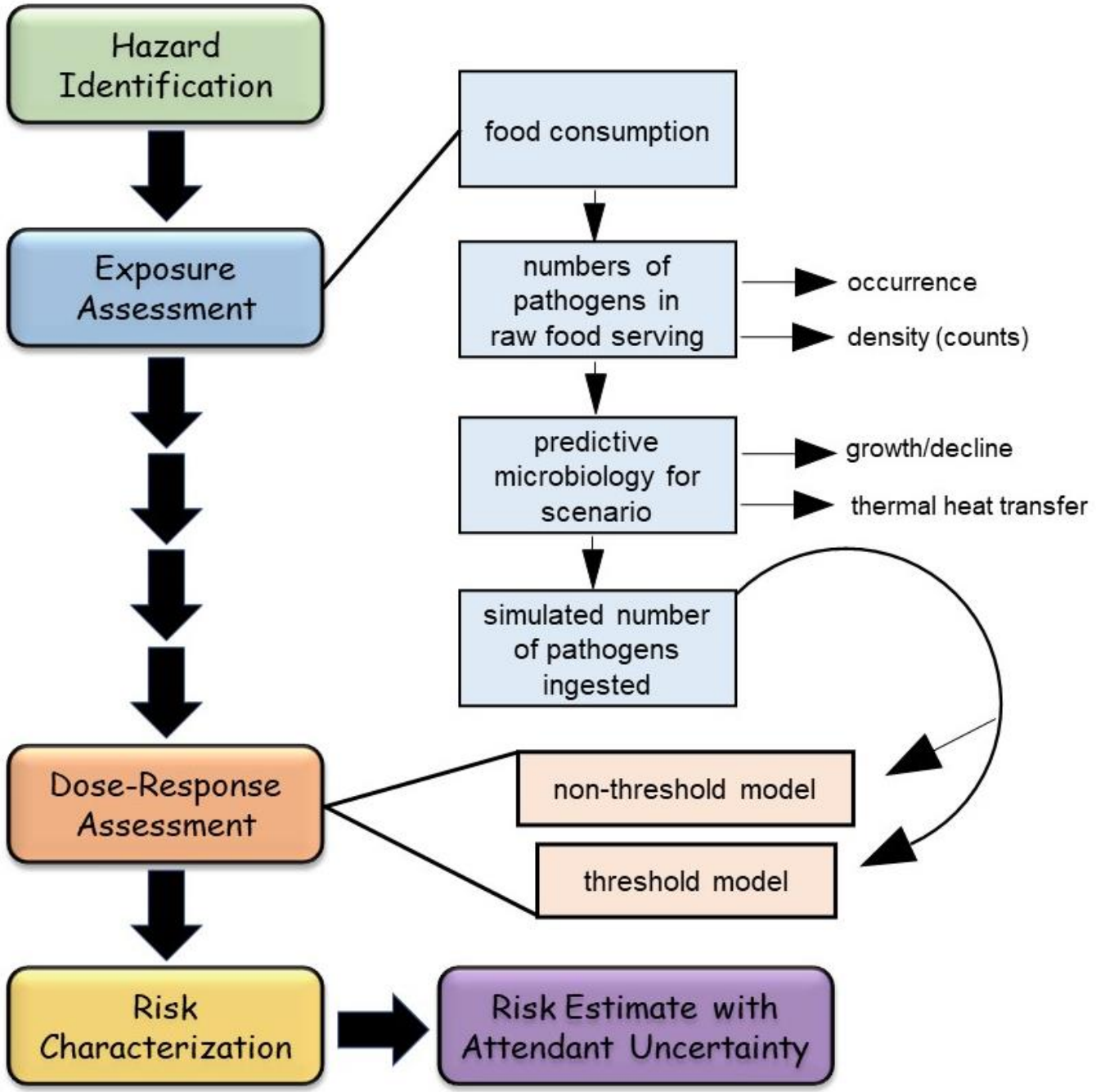
- 2016: Dietert, R.R. The Human Superorganism: How the Microbiome Is Revolutionizing the Pursuit of a Healthy Life; Dutton: New York, New York.
- 2015: Dietert, R.R.; Silbergeld, E.K. Biomarkers for the 21st Century: Listening to the Microbiome. Toxicol. Sci. Off. J. Soc. Toxicol. 144, 208–216.
- 2017: Dietert, R.R. Safety and Risk Assessment for the Human Superorganism. Hum. Ecol. Risk Assess. 23, 1819–1829.
- 2018: Dietert, R.R. A Focus on Microbiome Completeness and Optimized Colonization Resistance in Neonatology. NeoReviews 19, 78–88.
- 2021: Dietert, R.R.; Dietert, J.M. Twentieth Century Dogmas Prevent Sustainable Healthcare. Am. J. Biomed. Sci. Res. 13, 409–417.

Traditional Framework for Microbial Risk Assessment

(Marks et al., 1998; Coleman et al., 2021b)

Perceptions in Food Safety

- 20th century: manage presence or detection of pathogens (genera including pathogens)
- 21st century: account for effects of natural microbiota in milk and healthy gut microbiota driving resistance to low doses of pathogens
  - Evidence for thresholds challenges past default assumption that single pathogen cell causes disease in healthy humans



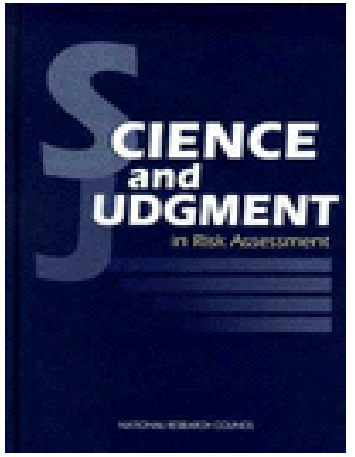
Science? Outdated Dogma?

Fact?

Fiction?

Possibility?

Judgment?



Evidence from 21st century science challenges outdated dogma and misinformation

- **Presence** of bacteria alone **insufficient** to predict **responses** (**beneficial OR adverse**)
- **Doses** (amounts) of **beneficial AND pathogenic** bacteria ingested matter
  - **Dose - Response** curves **simulate** foodborne illness
  - **Effects** (**beneficial** and **adverse**) increase with increasing doses (**natural milk microbiota** and **pathogens**)
- **Microbiota** matters, protects against pathogens (**colonization resistance**)

Is Pasteurizing Human Donor and Cow Milks Beneficial to Health?

- **Human donor milk banks** pasteurize breast milk from donors because of the assumption that pathogens may be present.
- Similarly, some fear **fresh unprocessed (raw) cow milk** because pathogens may be present.
- However, **natural, beneficial microbes** (microbiota) dominate milk from cows as well as humans.
- Large numbers of the natural microbiota **outcompete pathogens, protect against illness** (provide colonization resistance), and **contribute to healthy gut, immune, neural, and respiratory systems**. **Benefits** are **lost** with **pasteurization**!

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