

Case Study Summary

Title: Evidence Mapping as a Tool for Acknowledging and Weighing Benefits and Risks for Controversial Issues Subject to Misinformation: Examples for Loss of Benefits with Pasteurizing Human Donor Breastmilk and Milk from Pastured Cows

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Introduction: This is an atypical case study for panel peer-review for the Alliance for Risk Assessment based largely on issues raised in the 2009 National Academies report (Science and Decisions: Advancing Risk Assessment). This case study addresses both benefits and risks of foodborne microbes in milks, including pathogens that can pose human health risks, rather than typical case studies addressing chemical risks.

The case study is not intended to advocate for or oppose access to fresh unprocessed (raw) breastmilk and bovine milk. Rather, it provides a structured, systematic, and transparent method for acknowledging and weighing studies on benefits and risks to inform evidence-based decision-making in light of advances in the recent decade of knowledge of the raw milk ecosystem. This case study addresses gaps in knowledge about the role of the natural milk microbiota of mammals (Appendix Figure A-1 from Oikonomou et al., 2020) in ‘seeding and feeding’ the gut. Raw milk bioactives including the milk microbiota (see Appendix Table A-1 from Coleman, 2025) are known to promote innate immune health via mechanisms protecting against infectious diseases and chronic non-communicable diseases or NCDs (Buey et al., 2023; Phillip et al., 2023; Xu et al., 2025). Regarding the dense and diverse microbes in milk (milk microbiota hereafter), scientific advances documenting protective effects of microbes continue to illuminate the ‘microbiome revolution’ (Blaser, 2014) and roles of microbes as our partners in health (Dietert, 2016).

The case study also addresses key issues raised by Aven and Thekdi (2022) for characterizing and confronting misinformation in risk contexts. The importance of opening multi-way dialogue with diverse stakeholders as a key to addressing misinformation about raw milks cannot be overstated. For example, the case study addresses common assumptions about raw milk that are inconsistent with the current body of evidence. For example, misinformation includes claims that: i) raw milks are inherently dangerous; ii) risks exceed benefits for raw breast milk and raw cow milk; and iii) no benefits exist for raw cow milk.

Pasteurization is required by human donor milk bank policy in the US and many countries around the world; pasteurization is required by federal law (21 CFR § 1240.61) for inter-state distribution of cow milk in the US. The current US policy and law prohibiting access to raw donor milk and raw cow milk do not acknowledge ‘downsides’ to pasteurization or integrate advances in knowledge of the protective effects of the milk microbiota and other bioactive components damaged or destroyed by heating. This case study addresses that knowledge gap that is not informed by available evidence.

Commercial pasteurization for donor breastmilk is typically 63°C (145°F) for 30 minutes, while cow milk may be heat-treated at 57°C to 140 °C (135°F to 284°F). See Appendix Table 2 for explicit time-temperature ranges for various pasteurization processes providing at least a 5-log

kill based on a 1957 challenge study using high levels of the highly heat-resistant pathogen *Coxiella burnetii*.

Heat impacts bacterial survival and function and inactivates many other bioactive components of raw milks. Heating milk to 72°C (162°F) inactivated ~90% of the milk microbiota (Quigley et al., 2013). Heating milk to 80°C (176°F) or less denatures many bioactive components and proteins, the latter contributing to asthma and milk allergy outcomes in children and mice fed pasteurized, not raw, milk (Abbring et al., 2017, 2019). Further, many key bioactive milk components degrade with heating. For example, over 80% of the antimicrobial and immune-modulator lactoferrin was inactivated by Holder pasteurization of donor milk (Davis et al., 2025), and the whey protein beta lactoglobulin (BLG) in raw cow milk was degraded when heated at pasteurization temperatures between 50°C and 90°C (122°F to 194°F) to a state with higher immunoreactivity and allergenicity compared to unheated milk (Evrendilek and Güven, 2026). Loss or degradation of raw milk bioactives, including nearly all milk proteins (Lin et al., 2022; see also Appendix Table A-1), have potential to decrease benefits to gut health and increase risks of milk allergy, intolerance, and acute and chronic disease.

Although raw cow milk sales are prohibited across state lines in the US, states have legal authority to allow access to raw cow milk within their borders¹ (see map in Appendix Figure A-2). US states determine the type and frequency of inspections and testing. Some states monitor raw milk for microbial indicators of hygiene and for foodborne pathogens (Dietert et al., 2022, Table 1).

Various models exist for managing risks associated with raw milks around the world. In Norway, officials screen mothers and donor milk and distribute raw donor milk to infants needing it. At least 6 European countries (Italy, France, Slovenia, Switzerland, Austria and The Netherlands) permit farms to distribute raw cow milk directly to consumers from vending machines on their farms and conduct monitoring. England/Wales and Germany permit retail sale of sealed bottles of raw milk and conduct monitoring.

A review of data from the US, Canada, and Germany concluded that ‘Raw milk can be produced with a high level of hygiene and safety’ (Berge and Baars, 2020). Yet, US consumers are rightly confused about the quality and safety of raw milk available in their states, and about what is misinformation inconsistent with current evidence. Further, stakeholders including consumers have not had the opportunity to participate in risk analysis processes regarding decisions to pasteurize milks.

The intent of this case study is to promote open public discourse about benefits and risks of raw milks so that families can make informed decisions and regulatory officials can develop evidence-based policies about access to raw milks.

1. Provide a few sentences summarizing the method illustrated by the case study.

The team chose to apply evidence mapping (Wiedemann et al. 2011; Khalil et al. 2025) as a visual and analytical technique to conduct structured, systematic, and transparent reviews of the available basis of knowledge and convey a simplified overview of the complex evidence

¹ States permitting: retail access, AK, AR, AZ, CA, CT, DE, ID, ME, NH, NM, OR, PA, SC, WA, WY, UT; on-farm access, GA, KA, IL, KS, MA, MN, MO, MS, MT, ND, NE, NY, OK, SD, VT, WI, WV; herdshare/cowshare, CO, MI, NC, OH, TN; no law prohibiting herdshare/cowshare, IN, KY, VA; pet milk, AL, FL, LA, MD, NJ; prohibited, DC, HI, NV, RI.

landscapes associated with benefits and risks of pasteurizing milks over short- and long-term periods.

The evidence maps provided below for human donor breastmilk (donor milk hereafter; (Coleman et al. 2021)) and bovine milk (cow milk hereafter; (Dietert et al. 2022)) provide visual representation of the available bodies of evidence supporting benefits and risk, with identification of gaps and uncertainties. These evidence maps were designed to facilitate open public discourse in areas subject to misinformation and to inform decision-making that weighs current evidence for benefits and risks.

The Evidence Basis sections (darker green text boxes in the upper right portions of Figures 1 and 2) include human cohort studies and randomized trials, some large longitudinal prospective cohorts. Other study types include: benefit–risk assessment; quantitative microbial risk assessment (QMRAs); meta-analyses; reviews; systematic reviews; and observational data from epidemiologic investigations.

Major studies from the Basis of Evidence form the Pro-Arguments on benefits and Contra-Arguments on risks in the blue text boxes in the center of Figures 1 and 2 below. Narrative descriptions are provided for each of the major studies in the manuscripts for breastmilk (Coleman et al., 2021) and for bovine milk (Dietert et al., 2022). The Evidence Basis also includes supporting and attenuating studies that modify the Pro- and Contra- Arguments. Studies demonstrating plausible mechanisms for protection or susceptibility/risk are listed in lighter green text boxes on the left portion of Figures 1 and 2, with study summaries listed in the Supplementary Materials sections of the manuscripts.

Conclusions are listed in yellow-gold text boxes on the right of the figures. Remaining uncertainties intended as researchable questions are listed in light yellow text boxes on the lower right of the figures.

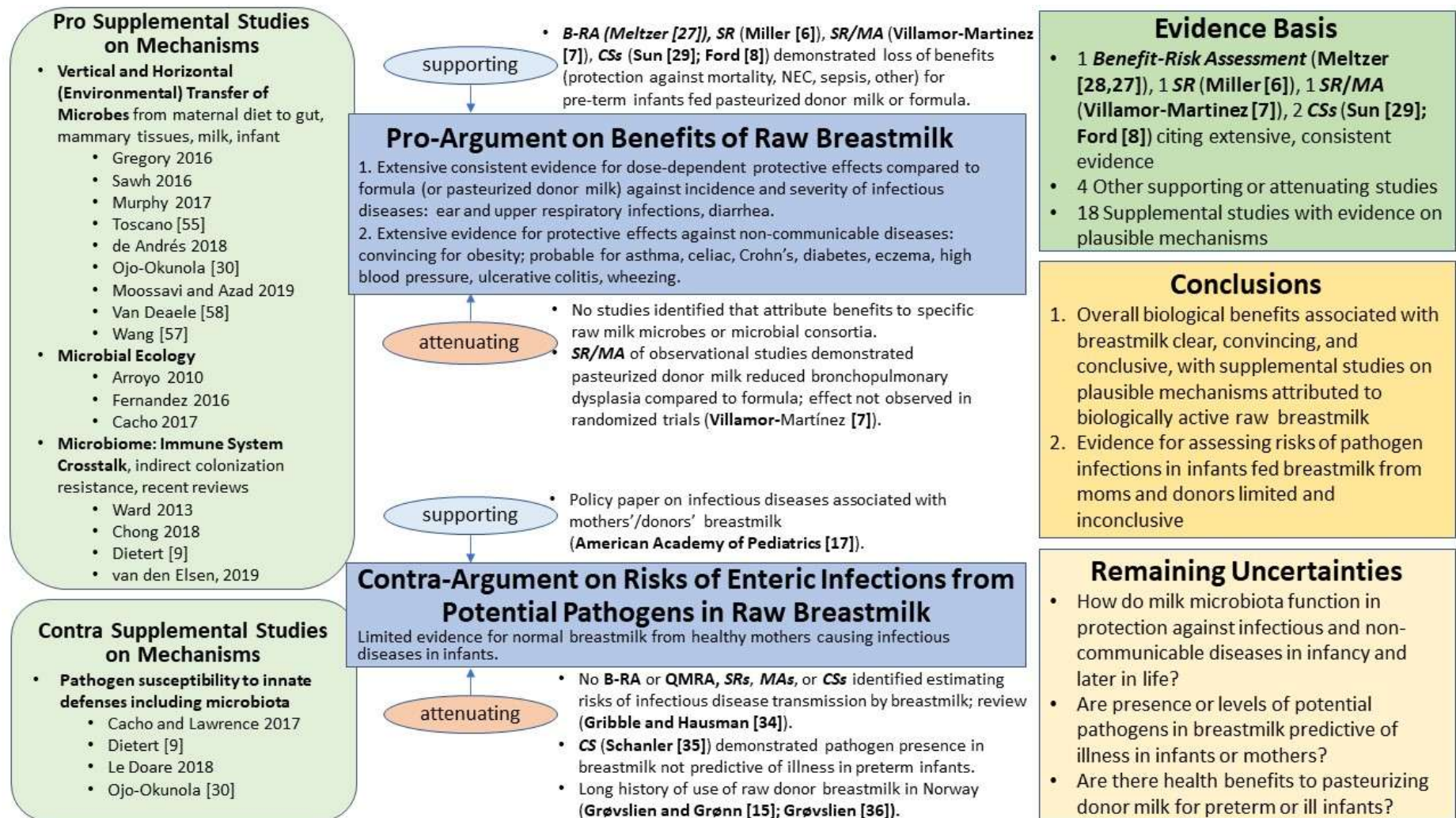


Figure 1. Evidence map for breastmilk ecosystem (Coleman et al., 2021). B-RA = Benefit–Risk Assessment; QMRA = Quantitative Microbial Risk Assessment; CS = human cohort study; MA = meta-analysis; R = review; RT = randomized trial; SR = systematic review; and NEC = necrotizing enterocolitis.

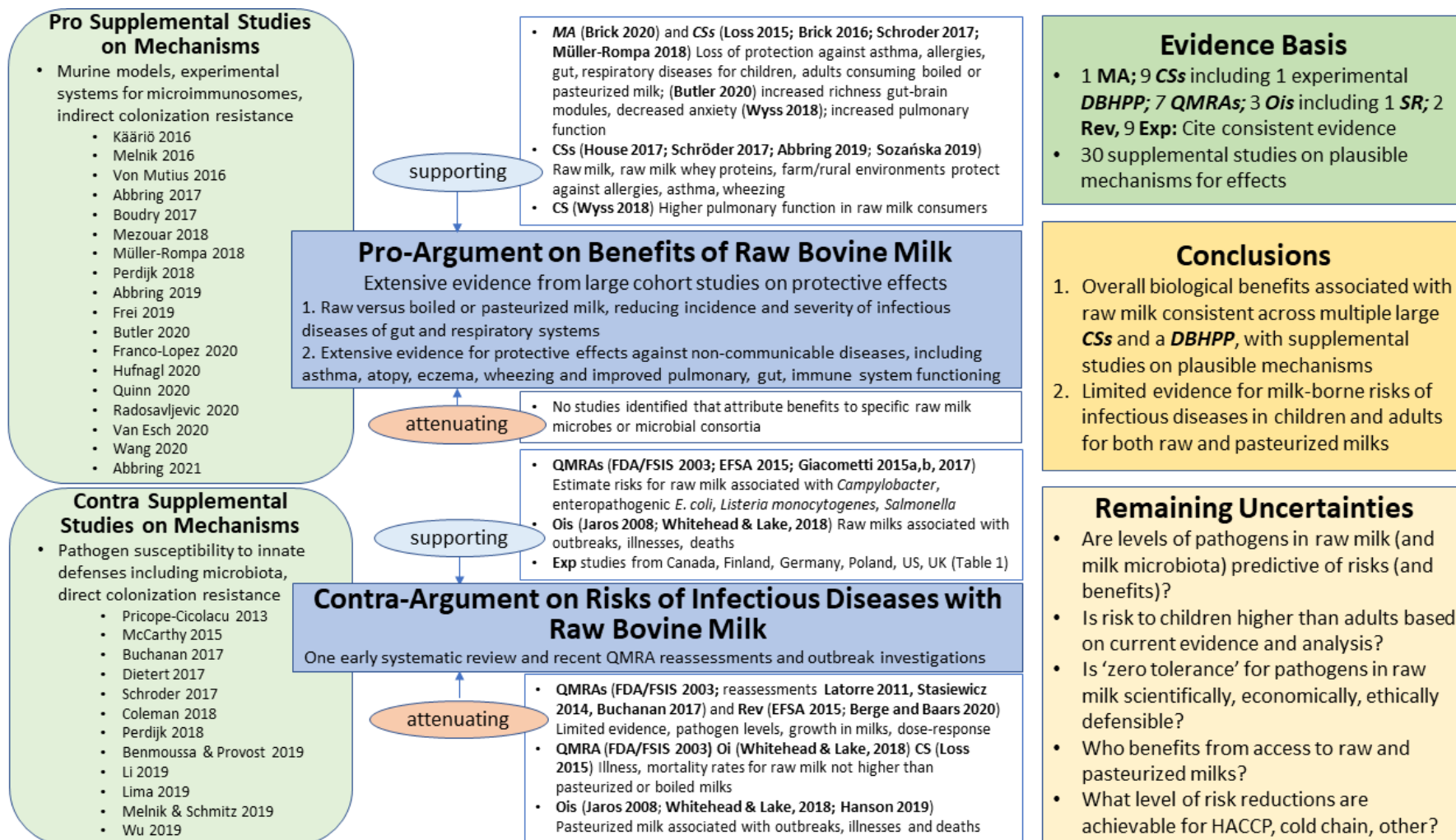


Figure 2 . Evidence map for bovine milk ecosystem (Dietert et al., 2022). CS = human cohort study; DBHPP = double-blinded randomized human provocation pilot; MA = meta analysis; Oi = Outbreak investigation; QMRA = Quantitative Microbial Risk Assessment; Rev = recent review; Exp = exposure study on prevalence of major foodborne pathogens from routine monitoring of licensed raw milk farms; SR = systematic review.

2. Describe the problem formulation(s) the case study is designed to address. How is the method described in the case useful for addressing the problem formulation?

For donor milk, the population at risk from ingestion of contaminated milk is infants, often in Neonatal Intensive Care Units (NICU) due to illness or pre-term or low-birth-weight. Clinical studies including random trials and cohort studies with preterm and low-birth-weight infants conducted in NICUs around the world were included in the Evidence Basis.

For cow milk, the populations at risk from ingestion of contaminated milk include infants, children, and adults. Clinical studies of small and large cohorts of infants, children, and adults were included in the Basis of Evidence.

The evidence on ‘downsides’ of pasteurization, data gaps, extrapolations, and assumptions that might normally be explored and deliberated in Problem Formulation have been largely excluded from public discourse. In our view, no discussion of milkborne risks is complete without addressing both acute infectious diseases and the more recent and more devastating epidemic of chronic NCDs, often linked to diets enriched in highly processed foods, including pasteurized milk.

As introduced above, the key mechanism associated with increased allergenicity of pasteurized milk is heat causing denaturation and allergenicity of milk components. An estimated 15 million people suffer from chronic milk allergy and intolerance (Warren et al., 2022, 2024), and 46% experience food-induced anaphylaxis that can be life-threatening. Milk allergy and intolerance may be linked with allergic co-morbidities including atopic dermatitis, asthma, and allergic rhinitis. Nocerino and colleagues (2025) documented \$52.5 million in economic burden of health care costs for cow milk protein allergy for the US in 2022, the highest costs of the ten countries with data available. Since 2005, the National Food Death Allergy Registry has reported 15 fatalities in the US related to milk allergy (11 in children from age 3-17; 4 in adults age 20-42).

No evidence exists, to our knowledge, linking raw milk to milk allergy. In fact, a peer-reviewed double-blinded provocation pilot study determined that all 11 children suffering milk allergy recruited for the study tolerated the maximum volume of raw milk tested (50 mL) without any symptoms, but suffered symptoms after consuming an average volume of 8.6 mL of the same milk following pasteurization (Abbring et al., 2019). The advances of the ‘microbiome revolution’ (Blaser 2014) challenge outdated policies that may be influenced by our current culture of germophobia, excluding insights about our microbiota as our partners in health (Dietert 2016; Dietert 2018; Dietert and Dietert 2021; Dietert 2023).

Evidence map methodology is useful to acknowledge and expand the basis of evidence behind policies on pasteurization and access to raw milks to include the most recent decade of advances in understanding the function of milkborne bioactives, including microbes, in developing and maintaining healthy gut, immune, neural, and respiratory systems.

3. Comment on whether the method is general enough to be used directly, or if it can be extrapolated, for application to other chemicals and/or problem formulations. Please explain why or why not.

Evidence maps have been used in risk communication and decision-making for diverse societal issues, particularly where scientists, risk practitioners, and stakeholders might

disagree about benefits or risks to public or environmental health. The published literature applying evidence maps cited herein address diverse societal problems, including the efficacy of traditional Eastern and Western medicine and alternative therapeutics by systematic and transparent visualizations of current knowledge and gaps (Afonso et al. 2024; Bero et al. 2023; Chukwu et al. 2024; Holliman and Saunders 2025; Kano and Hayashi 2021; Khalil et al. 2025; Kwon 2025; Mo et al. 2024; O’Shea et al. 2022; South and Rodgers 2023; Strong et al. 2025; Yang et al. 2025).

Our evidence map studies are the first, to our knowledge, intended for use in risk communication and decision-making about balancing benefits and risks of microbes in foods (donor breast milk and cow milk). The methodology is general and adaptable to other microbial and chemical risk scenarios.

4. Discuss the overall strengths and weaknesses of the method.

Strengths of evidence maps include providing user-friendly, visual overviews or qualitative narratives about what is known and gaps in knowledge for complex research landscapes. Evidence maps can support deliberations with stakeholders, decision-makers, and researchers and generate a synthesis of evidence-based medical or public health research. Further, a living evidence map developed by Kwon used simultaneous collaborations between automated (artificial intelligence) and expert reviews (Kwon 2025) to create a practical tool for real-time updating of an evidence map for prioritization of research gaps on a unique Korean medicine treatment (pharmacopuncture).

Similarly, the major strength of our published evidence maps is inclusion of studies depicting both acute infectious (communicable) and chronic NCDs potentially associated with raw and pasteurized milks. The structured methodology assessed the evidence basis broadly, including benefit-risk assessment, quantitative microbial risk assessment, human cohort studies and random trials, human observational studies from CDC outbreak evidence, and systematic reviews and meta-analyses. Pro- and contra-arguments were structured from the evidence basis, with attenuating and supporting studies and supplemental studies on mechanisms. Characteristics indicating the quality of the studies (see Appendix Table A-3) and representativeness of the data for extrapolation to benefit-risk assessment were considered, as well as uncertainties. Remaining uncertainties phrased as researchable questions and conclusions based on available evidence were provided in the evidence maps.

A weakness for our published evidence maps is that each map represents knowledge at a static point in time, imposing a burden of periodic or continuous monitoring of literature that might inform future updates. Another weakness of our study was reliance on English language studies, potentially resulting in linguistic bias. Also, a single expert evaluated the full studies and supplementary information and developed draft evidence maps, while one or two other authors undertook review of the evidence maps. Therefore, the generalizability of the results may be limited.

5. Outline the minimum data requirements and describe the types of data sets that are needed.

The beauty of evidence maps is that complex bodies of evidence are structured visually using a framework that is flexible enough to accommodate both qualitative and quantitative studies. The published literature was searched for studies including: benefit–risk assessment;

epidemiologic investigations; human cohort studies; Quantitative Microbial Risk Assessments (QMRAs); meta-analyses; reviews; randomized trials; and systematic reviews. Also included were mechanistic data from *in vitro* and *in vivo* studies, the latter including murine models consistent with observed human effects.

We note that most studies were descriptive and observational, thus correlative, some with plausible evidence of mechanisms. The following study designs were considered descriptive and inappropriate for evaluating associations and potential causality: outbreak investigations without a denominator (i.e., total numbers exposed, including healthy and asymptomatic individuals); surveys of disease frequency or distribution; case series; and case reports (Jaros et al., 2008; Appendix Table A-3). The same study ranked the following study types for utility in assessing causal associations: experimental human studies, very high; cohort studies, high; case-control studies, moderate; cross-sectional and outbreak investigations with a denominator, low.

For breastmilk and donor milk, experimental studies including randomized controlled trials were cited in a systematic review (Miller et al., 2018) and a systematic review/meta-analysis (Villamor-Martinez, 2018). No simulation studies estimating risk were identified for breastmilk or donor milk.

The Miller study cited 6 random controlled trials representing 1,472 infants, and concluded that raw breastmilk provided clear or possible protective effects against many diseases of prematurity, while benefits for pasteurized donor milk were inconclusive. The Villamor-Martinez study included 18 studies (7 randomized and 11 observational) and concluded that raw breastmilk provided a significant reduction in bronchopulmonary dysplasia compared to pasteurized donor milk from two random trials. The authors also noted that raw breastmilk is more effective in reducing risk of multiple morbidities than pasteurized donor milk. A benefit-risk assessment (Meltzer et al., 2013, 2016) reported

- (i) convincing evidence of beneficial effects of breastmilk on neurodevelopment;
- (ii) convincing evidence for a protective effect of breastmilk on infections (acute otitis, and gastrointestinal and respiratory infections), immune response-associated diseases (celiac disease, Crohn's disease, inflammatory bowel disease, and ulcerative colitis), and type 1 diabetes; and
- (iii) convincing evidence of a protective effect of breastmilk on growth abnormalities (overweight and obesity in childhood).

Overall, the 2016 Meltzer study concluded that:

‘the benefits of breastmilk clearly outweigh the possible risks from contaminants’ for neurodevelopment, defense against infections, and growth abnormalities. Probable beneficial effects later in life were noted for type 1 and type 2 diabetes, as well as high blood pressure. No conclusions were drawn regarding other diseases of the immune system (allergy, asthma and wheezing, atopic dermatitis) due to ‘inconclusive results on the benefit side and few and disperse studies on the risk side’.

One clinical study (Schanler et al., 2011) documented that presence of potentially pathogenic bacteria in breastmilk was not predictive of transmission of disease to neonates, as cited in the 2021 evidence map.

Subsequent studies addressed the influence of breastmilk on acute and chronic disease including NCDs (McCormick et al., 2022; Yeo et al., 2022; Vassilopoulou et al., 2024; Capra et al., 2025; Ganbold et al., 2025; Kariyawasam et al., 2025).

For cow milk, no random clinical trials were identified, although large and small cohort studies were included, as well as simulation studies estimating risk.

In addition to studies demonstrating benefits of raw cow milk for children and adults included in the evidence maps, subsequently published studies on longitudinal cohorts and epidemiologic analyses strengthen the basis of evidence and conclusions. Subsequent studies addressing both risks and benefits are highlighted below, with key findings noted. Additional information from these studies will be addressed in our presentations to the panel.

For cow milk, the basis of evidence included a meta-analysis, 9 cohort studies, a double-blinded, randomized human provocation trial, 3 outbreak investigations without denominators, including a systematic review, 2 reviews, 7 risk assessments for diarrheal endpoints, and 9 experimental studies.

Extensive evidence exists for raw milk protections against infectious diseases of the respiratory system as well as the gut, compared to feeding pasteurized or boiled milk. Extensive evidence exists for raw milk protections against NCDs including asthma, atopy, eczema, wheezing and improved gut, immune, and pulmonary system functioning, including double-blinded provocation trial in a small cohort of 11 children with milk allergy. All 11 children tolerated the maximum volume of raw milk (50 mL) without allergic reactions, but all suffered allergy symptoms at an average of 8.6 mL pasteurized milk (Abbring et al., 2019), consistent with murine studies. Limited evidence was available on pathogen presence, levels, and growth in raw milk, dose-response, and burden of disease for raw and pasteurized milks from epidemiologic investigations. Denominators were not available for US CDC outbreak datasets, thus providing correlative, not causal, evidence.

Overall biological benefits of unpasteurized bovine milk were consistent across multiple cohort studies controlling for potential confounding effects, including both studies cited in the evidence maps and subsequent studies, including those tabulated below. Raw cow milk feeding of infants, compared to heated milks, provided the highest level of protection against respiratory and ear infections in a large prospective cohort study (983 infants), comparable to breastfeeding (Loss et al., 2015). Diarrhea was not associated with raw milk feeding to infants in this or a subsequent study that documented results for the diarrheal endpoint (Järvinen et al. 2022), comparable to breastfeeding.

For bovine milk regulated at the state level, CDC data on numbers and rates of outbreaks, illnesses, hospitalizations, and deaths were not increasing by state or nationally (Whitehead and Lake, 2018; Stephenson et al., 2024). For the period from years 2005-2020 included in the latter study, raw milk contributed to less than 1% of the burden of infectious disease in the US over this 16-year period: 0.4% outbreaks, 0.1% illnesses, 0.5% hospitalizations). State-level data on hospitalization rates is provided in Appendix Figure A-3.

CDC data on deaths (1 confirmed for raw milk, 4 confirmed for pasteurized milk in the 16-year period) were too sparse for reliable prediction of future milkborne mortality.

Table 1. Findings relevant to evidence map studies from subsequently published studies, including **two bolded studies on breastmilk**

Subsequent study findings	Reference, supported studies
• Single-center, randomized, double-blind placebo-controlled proof of concept study documented a unifying mechanism for ‘farm effect’ and ‘raw milk effect’ in protecting against allergic rhinitis in a small cohort • Major whey protein beta lactoglobulin (BLG, notably denatured by heat to ‘alo’ form, associated with allergenicity for pasteurized milk) formulated into holoBLG (chelated BLG) lozenge significantly improved clinical allergy symptoms, modulated innate immune system functioning, re-balanced immune cells, and established and maintained immune homeostasis or immune resilience	Bartosik et al., 2022 ² , builds on Abbring et al., 2019
• Early allergic manifestations of food allergy and atopic dermatitis were robust in urban infants fed pasteurized milk compared to lower rates in rural Mennonite infants fed raw milk though differences were not statistically significant at 2 years of age • No differences were reported in diarrheal outcomes for infants and children fed raw and pasteurized milks, consistent with Loss study in infants	Järvinen et al. 2022 ³ , consistent with Loss et al. 2015
• Pasteurized dairy was associated with significantly higher outbreaks, hospitalizations, and deaths compared to raw dairy, as well as 20 cases of stillbirth, miscarriage, or premature delivery, none reported in raw milk	Sebastianski et al., 2022 ⁴
• Allergy and intolerance to heated/pasteurized milk based on a nationally representative survey of >78,000 individuals affected approximately 5% of the US population • Milk allergy affected 37% of a cohort of 5,587 people with food allergy, with 46% experience food-induced anaphylaxis, with allergic co-morbidities including atopic dermatitis, asthma, and allergic rhinitis	Warren et al., 2022, 2024 ⁵ , consistent with Abbring et al., 2019
• Strongest protective effect against hay fever was continuous consumption of raw milk from infancy up to school age in latest study for Protection against Allergy-Study in Rural Environments (PASTURE) longitudinal birth cohort • Evidence of dose-response effect with inverse association of raw milk consumption and hay fever; daily consumption of pasteurized milk positively associated with hay fever • 18.4% of the total multifactorial protective effect of raw milk on hay fever was mediated by gut microbiome richness, suggesting the mechanism of protection involves the interactions of the gut microbiota with the	Pechlivanis et al., 2023 ⁶ , builds on PASTURE studies, Loss et al., 2015, Brick et al., 2016, Schröder et al., 2017

² Bartosik, 2022. Ameliorating Atopy by Compensating Micronutritional Deficiencies in Immune Cells: A Double-Blind Placebo-Controlled Pilot Study

³ Järvinen et al. 2022. Biomarkers of development of immunity and allergic diseases in farming and non-farming lifestyle infants: design, methods and 1 year outcomes in the “Zooming in to Old Order Mennonites” Birth Cohort Study

⁴ Sebastianski et al., 2022. Disease outbreaks linked to pasteurized and unpasteurized dairy products in Canada and the United States: a systematic review

⁵ Warren et al, 2022, 2024. The US population-level burden of cow's milk allergy, The clinical burden of food allergies: Insights from the Food Allergy Research & Education (FARE) Patient Registry

⁶ Pechlivanis et al., 2023. Continuous rather than solely early farm exposure protects from hay fever development

Subsequent study findings	Reference, supported studies
immune system	
• No increasing trends for numbers or rates of outbreaks, illnesses, hospitalizations, or deaths for raw cow milk based on CDC data for 2005-2020	Stephenson, et al., 2024 ⁷ , Whitehead and Lake, 2018.
• Systematic review of non-randomized cohort studies found distinctly different clustering of gut microbiota in infants fed mothers own milk or pasteurized donor milk • Gut microbiota differences by feeding are linked to adverse health outcomes (late onset sepsis, necrotizing enterocolitis, neurodevelopmental delay beyond infancy, intestinal inflammation) suggesting deviance from healthy infant gut microbiomes with donor milk feeding of preterm infants • Feeding type contributed more to differences in alpha and beta diversity than any other factor • Feeding donor milk contributed to decreased abundance of key gut microbes (<i>Bifidobacterium</i> genus, Bacteroidetes phylum)	Chen et al., 2025⁸ , builds on Villamor-Martinez et al., 2018
• Feeding raw breastmilk (mothers own milk or MOM) significantly lowered rates of one disease of prematurity (retinopathy of prematurity) compared to pasteurized donor milk • No significant differences for other diseases of prematurity • Diet (MOM, Holder-pasteurized/Retort-pasteurized donor milk) significant effects on infant gut microbiota	Ocampo-Chih et al., 2025⁹ , builds on Villamor-Martinez et al., 2018
• Raw dairy products associated with approximately 29, 75, and 14-fold greater risks of illness, hospitalization, and death, respectively, than pasteurized dairy products	Hsu and Wu, 2026 ¹⁰ , attenuates Whitehead and Lake, 2018
• No increasing frequency or severity of illness associated with increasing access to raw milk • No increasing trends in severe illness (hospitalization numbers or rates) associated with raw milk in US, accounting for state-level differences • Maintaining state-level data structure essential to drawing inferences on mode of access, burdens of illness	Stephenson et al, 2026 ¹¹ , builds on Whitehead and Lake, 2018

⁷ Stephenson et al., 2024. Trends in Burdens of Disease by Transmission Source (USA, 2005–2020) and Hazard Identification for Foods: Focus on Milkborne Disease

⁸ Chen et al., 2024. Impact of mother’s own milk vs. donor human milk on gut microbiota colonization in preterm infants: a systematic review

⁹ Ocampo-Chih et al., 2025. Impact of donor human milk pasteurization methods on the gut microbiome of preterm infants

¹⁰ Hsu and Wu, 2026. The Unseen Risks of Dairyborne Disease: Disease Burden, Economic Impact, and Regulatory Trends in Raw Milk and Cheese in the US, 2000-2020.

¹¹ Stephenson et al., 2026. Further Analysis for Trends in Burdens of Foodborne Disease: Leafy Greens and Raw Milk

Pasteurizing milk did not prevent 4,313 acute infectious illnesses, 343 hospitalizations, and 26 deaths for dairy-borne infectious disease over this period. Pasteurized milk was also associated with NCDs, intolerance, and sometimes fatal allergies. Pasteurized dairy was associated with significantly higher outbreaks, hospitalizations, and deaths compared to raw dairy, as well as 20 cases of stillbirth, miscarriage, or premature delivery, while none reported for raw milk in a subsequent systematic review (Sebastianski et al. 2022).

No national data on numbers of raw milk consumers in the US is available. Data available for rates of illness per serving for millions of annual retail raw milk servings produced by one raw dairy in Appendix Figure A-4 will be discussed further in our presentations to the panel regarding common assumptions that 2-5% of US milk drinkers consume raw milk and raw milk is inherently dangerous.

6. This case study does not address typical aspects of toxicology and quantitative risk assessment in the case study framework provided: dose-response relationships; human variability and sensitive populations; background exposures or responses; extrapolations; calculation of risk. It does address the following.

A. Address incorporation of existing biological understanding of the likely mode of action?

Yes, this case study combines biological understanding of modes of disease transmission and biological mechanisms causing adverse or beneficial effects including protection from infections and NCDs. The case study will address similarities between modes and mechanisms demonstrated in both breastmilk and cow milk, as well as differences.

A common mechanism of protection for raw breastmilk and cow milk is ‘seeding and feeding’ the gut microbiota, with microbe-rich milks contributing to gut health via colonization resistance (Dietert, 2018; Dietert et al., 2022), as well as healthy immune, neural, and respiratory systems consistent with cohort studies (Loss et al., 2015, Järvinen et al. 2022). Subsequent studies including mother-infant dyads document data on gut microbiota assembly and mechanisms of colonization resistance, suggesting that the gut microbiota differ by diet and infectious disease outcomes, with feeding pasteurized milks associated with higher rates of adverse outcomes (Caballero-Flores et al., 2023; Mangalea et al., 2024; Shao et al., 2024; Woelfel et al., 2024; Chen et al., 2025; Dinleyici and Cagri, 2025).

A unique mechanism of protection for cow milk is linked to functional activity of chelated β -lactoglobulin (holoBLG), a heat-sensitive bioactive component present in raw cow milk and in cow urine that protected against multiple adult allergies in a randomized, double-blind, placebo-controlled human study (Bartosik et al., 2022). The multifactorial protections against allergy include both ingestion of raw milk and farm exposures to pregnant women, infants, children, and adults in multiple cohort studies in the evidence map for cow milk and subsequent studies documented in Table 1.

Advances in understanding the diverse functions of the milk microbiota over the past decade emphasize likely health benefits linked to the consumption dairy foods with high levels of live microorganisms. Researchers are questioning whether it's time to consider setting Recommended Daily Allowances for Microbes (RDA_M) (Hill, 2018; Marco et al., 2020), akin to those RDAs established for many vitamins.

Studies suggest that intake of foods enriched in microbes can lead to improvements in various aspects of health, including gut function, cognitive abilities, and protection against many chronic diseases. Living microbe counts vary significantly across dairy foods: i) pasteurized milk having low levels of predominantly dead microbes; ii) raw milk from humans and cows having medium levels of living microbes; and iii) fermented dairy products like kefir and yogurt exhibiting high levels of living microbes. Both medium- and high-level foods are linked to numerous health benefits, despite wide variability in microbes and their levels in different types and brands of dairy foods (see Appendix Table A-4 for references).

Indeed, recent studies, built on a framework using US National Health and Nutrition Examination Survey (NHANES) data (Marco et al., 2022), link consumption of foods containing medium and high levels of live microorganisms (10,000 to 10 million and greater than 10 million colony forming units per gram, respectively) to health improvements, including gut and cognitive function and protection from cardiovascular disease, constipation, depression, diabetes, inflammation, osteoporosis, and loss of frailty, muscle mass, and strength (see Appendix Table A-4 for references).

B. Address uncertainty?

Yes. Both evidence maps relied predominantly on cohort studies that are correlative, with limited supplemental studies on mechanisms to establish causality for either benefits or risks. Both evidence maps include a section on Remaining Uncertainties that raised uncertainties that are still unresolved in 2026.

The following uncertainties remain for breastmilk.

1. How do milk microbiota function in protection against infectious and non-communicable diseases in infancy and later in life?
2. Are presence or levels of potential pathogens in breastmilk predictive of illness in infants or mothers?
3. Are there health benefits to pasteurizing donor milk for preterm or ill infants?
4. An additional question: Have the roles of the microbiome, interactions among communities of bacteria, and colonization resistance been considered?

The following uncertainties remain for cow milk.

1. Are levels of pathogens in raw milk (and milk microbiota) predictive of risks (and benefits)?
2. Is risk to children higher than adults based on current evidence and analysis?
3. Is ‘zero tolerance’ for pathogens in raw milk scientifically, economically, ethically defensible?
4. Who benefits from access to raw and pasteurized milks?
5. What level of risk reductions are achievable for Hazard Analysis and Critical Control Points systems, cold chain management, interventions in addition to pasteurization?

6. Additional question: Is 'zero tolerance' compatible with the present scientific understanding of microbiome-driven colonization resistance?

C. Work practically? If the method still requires development, how close is it to practical implementation?

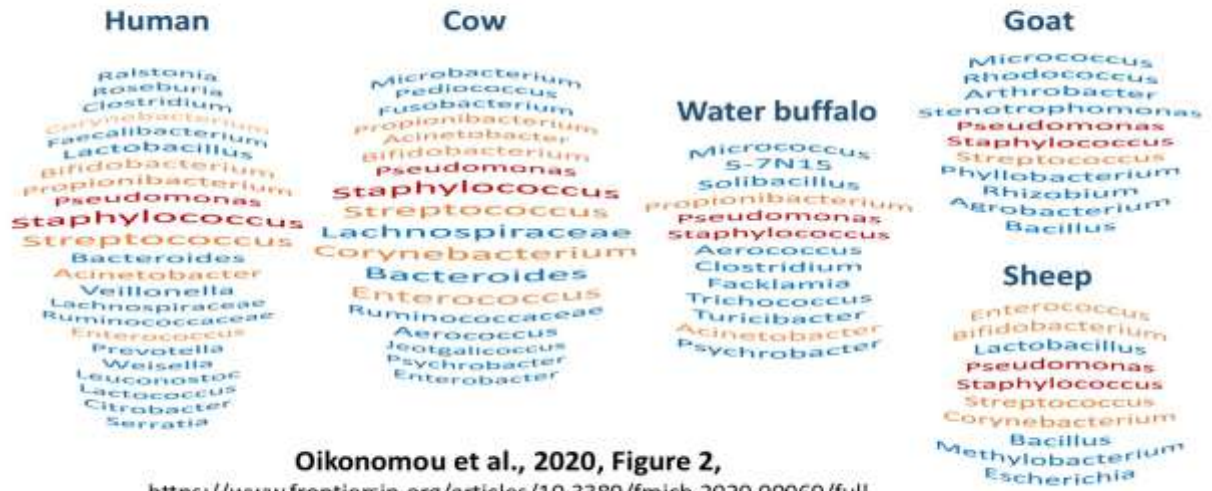
Yes. Evidence map methodologies are practical tools for transparently structuring disparate bodies of evidence and providing opportunities for public discourse and deliberations to inform decision-making. In our judgement, the case study as presented is practical and feasible to support deliberations about policies for pasteurization and access to raw milks by the panel and others.

Evidence Maps Study References

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Natural Milk Microbiota in Competition with Pathogens



Appendix Figure A-1. Major genera in natural milk microbiota across mammals including humans (Figure from Oikonomou et al., 2020).

Appendix Table A-1. Some Antimicrobial Components of Raw Milk and their Multifaceted Health-Promoting Effects (Coleman, 2025, Supplemental Table S-7), Highlighting **Heat Sensitive Components** Vulnerable to Destruction or Inactivation at Temperatures <60 to 80°C (<140°F to 176°F)

Component	Class	Health-Promoting Effects	Reference
Angiogenin	Protein, enzyme (ribonuclease 5)	Inhibits viral replication, binds actin, endothelial cells, activates proteolytic cascades that degrade basement membranes	(Ng et al. 2015) ¹²
Bovine serum albumin	Globular protein	Immunomodulator; opioid agonist; competitive binding to host cell receptors, inhibiting viral infection, complement agonist	(Buey et al. 2023) ¹³
Casein	Phosphoprotein family	Immunomodulator, anticarcinogenic, antioxidant, antimicrobial, antithrombotic, opioid agonist, toxin binding; Antiviral, immunomodulator, immunosuppressant	(Buey et al. 2023) (Santos et al. 2024) ¹⁴
Glycomacro-peptide	Derivative of casein	Immunomodulator, antimicrobial, binds viral sialic acid receptors, prevents viral infection and hemagglutination, antiinflammatory, gut microbiome modulator pre-term infants, antiallergic, regulates glucose homeostasis, improves satiety in obese patients; Immunomodulator, antimicrobial, antithrombotic, cytomodulatory, antioxidant, toxin binding	(Santos et al. 2024; Gallo et al. 2024) ¹⁵ (Buey et al. 2023)
Lactadherin	Multifunctional phosphorylated glycoprotein	Competitive binding of sialylated and galactosylated glycans with glycoconjugates on host cell, preventing binding of viruses to host cells	(Santos et al. 2024)
Lactoferricin	Derivative of	Immunomodulator, antimicrobial, anticarcinogenic,	

¹² Ng et al., 2015. Antiviral Activities of Whey Proteins

¹³ Buey et al., 2015. Potential Role of Milk Bioactive Peptides on the Serotonergic System and the Gut-Brain Axis

¹⁴ Santos et al., 2024. Milk Antiviral Proteins and Derived Peptides against Zoonoses

¹⁵ Gallo et al., 2024. Milk Bioactive Compounds and Gut Microbiota Modulation: The Role of Whey Proteins and Milk Oligosaccharides

Component	Class	Health-Promoting Effects	Reference
Lactoferrin	lactoferrin	antioxidant, antithrombotic; Immunomodulator, promotes health of gut microbiota, gut barrier function	(Buey et al. 2023) (Santos et al. 2024)
	Iron-binding globular glycoprotein in transferrin superfamily	Immunomodulator, antiinflammatory; gut microbiome modulator;	(Huang et al. 2023) ¹⁶
		Immunomodulator (caspase 3), binds host cells, prevents hemagglutination, infection;	(Santos et al. 2024)
		Immunomodulator, inhibitor viral infection/replication, prevents cytokine storm;	(Zimecki, Actor, and Kruzel 2021) ¹⁷
		Antiinflammatory, antioxidant, gut microbiota modulator, enhances intestinal barrier function, reduces late-onset sepsis, respiratory/urinary tract infections, antitumor, reduces dysbiosis with chemotherapy, stabilizes gut microbiota, prevents viral infection	(Gallo et al. 2024)
α-Lactalbumin	Enzyme, globular protein (lactose synthesis)	Antiinflammatory, gut microbiome modulator, benefits growth and development, stabilizes insulin, glucose, lipid metabolism in obese patients, improved intestinal barrier integrity and infant stool consistency Immunomodulator, selective antimicrobial, sleep regulation, mood enhancement, mineral absorption,	(Santos et al. 2024)
α-, β-Lactoglobulin	Most abundant protein in cow milk	Hypocholesterolaemic; competitive binding to host cell receptors, inhibiting viral infection; opioid-neurotensin agonist, ileum-contracting, immune tolerance	(Buey et al. 2023)
Lactoperoxidase	Heme-containing glycoprotein, heat-stable	Antimicrobial (oxidizes thiocyanate or iodine anion generating reactive intermediates), inhibits viral	(Santos et al. 2024)

¹⁶ Huang et al., 2023. Lactoferrin Alleviates Inflammation and Regulates Gut Microbiota Composition in H5N1-Infected Mice

¹⁷ Zimecki et al., 2021. The Potential for Lactoferrin to Reduce SARS-CoV-2 Induced Cytokine Storm

Component	Class	Health-Promoting Effects	Reference
	enzyme	shedding	
Lysozyme	Enzyme, lyses bacterial cell walls	Antimicrobial (Gram+/- bacteria, fungi, viruses); increased colonization resistance to pathogens; Antiinflammatory, reduces coliforms; modulates, stabilizes gut microbiota; improved recovery diarrhea	(Santos et al. 2024) (Gallo et al. 2024)
Microbiota (<i>Lactobacillus</i> <i>Bifidobacteria</i> <i>Pseudomonas</i>)	Bacteria	Immunomodulator; antagonist; intestinal homeostasis; gut-lung axis; gut-brain axis	(Wang et al. 2023 ¹⁸ ; Santos et al. 2024)
Milk mucin	High molecular weight multifunctional highly glycosylated proteins present in fat globule membranes	Inhibits infection by aggregating virus via high sialic acid and sulphate content; prevents viral replication	(Ng et al. 2015)
Oligosaccharides	Fucosylated, non-fucosylated neutral, or sialylated compounds with five sugars	Immunomodulator; competes with pathogens for host cell binding sites; reduces allergy, asthma, enteric, inflammatory disease; intestinal homeostasis; promotes gut-brain axis, maintains gut mucosal barrier	(Gallo et al. 2024; Nolan, Rimer, and Good 2020 ¹⁹)
Secretory IgA, IgG, IgM	Glycoproteins	Inhibits infectivity by binding viral surface components and preventing replication	(Ng et al. 2015)
Tenacin-C	Large multimeric extracellular matrix glycoprotein	Neutralizes virus by binding viral surface protein, preventing access to host cell, interacts with viral envelope, prevents infection and transmission	(Ng et al. 2015; Santos et al. 2024)

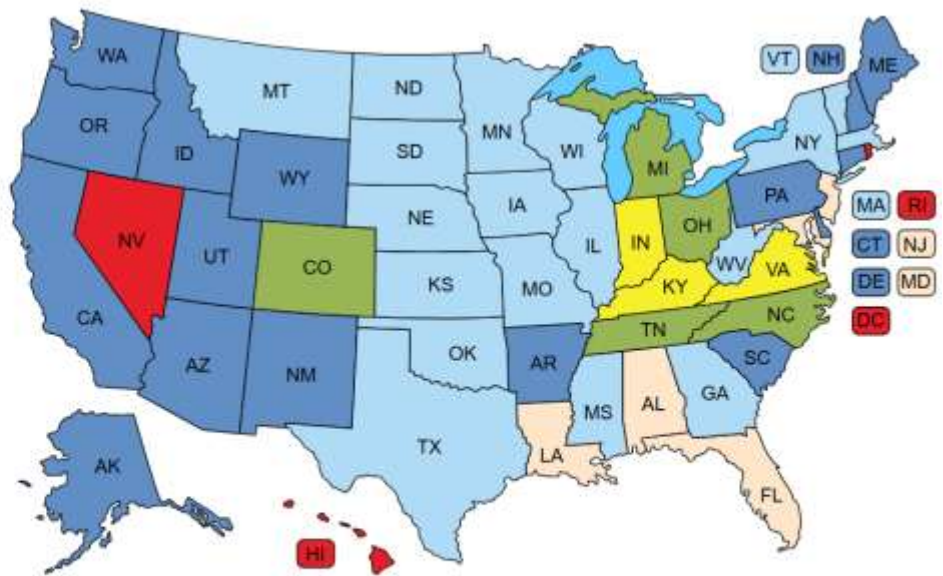
¹⁸ Wang et al., 2023. Potential Probiotics for Regulation of the Gut-Lung Axis to Prevent or Alleviate Influenza in Vulnerable Populations

¹⁹ Nolan et al., 2020. The Role of Human Milk Oligosaccharides and Probiotics on the Neonatal Microbiome and Risk of Necrotizing Enterocolitis

Appendix Table A-2. Time-Temperature Profiles for Commercial Pasteurization Based on Experimental Eradication of Highly Heat Resistant Pathogen *Coxiella burnetii* (Enright et al., 1957)²⁰, All Targeting a 5-log Kill.

Pasteurization Process	Temperature	Time
Holder	63°C (145°F)	30 minutes
Thermization	57°C to 68°C (135°F to 154°F)	15 minutes
Batch pasteurization (low-temperature long time, LTLT)	63°C (145°F)	30 minutes
High-temperature short time (HTST)	72°C (161°F)	15 seconds
Ultra-high temperature (UHT)	135°C to 140°C (275°F to 284°F)	2 to 4 seconds
Canned sterilization	115°C to 121°C (239°F to 250°F)	10 to 20 minutes

²⁰ Note that the 1957 study involved inoculating more than 100,000 bacterial cells of *Coxiella burnetii* per mL, a pathogen no longer considered a public health hazard in the US milk supply. A re-evaluation of the 1957 protocol documented up to 8-log kill, three orders of magnitude higher kill than intended 5-log kill (Cerf and Condron, 2006. *Coxiella burnetii* and milk pasteurization: an early application of the precautionary principle? *Epidemiology & Infection*). Scientists have recently noted feasibility of reducing the temperature-time profiles for pasteurization processes to select evidence-based standards aligning with current processes (Wittwer et al., 2022. Inactivation kinetics of *Coxiella burnetii* during high-temperature short-time pasteurization of milk. *Frontiers in Microbiology*).



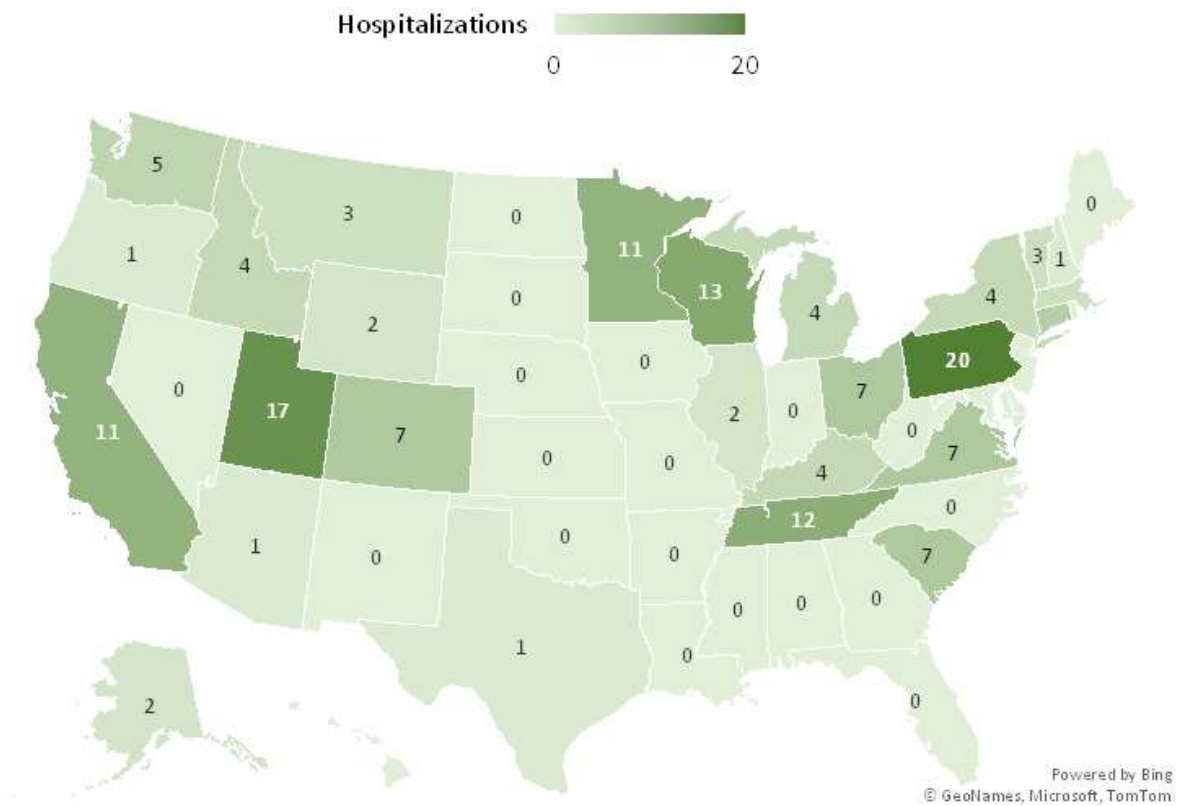
Last updated February 24, 2026.

- BLUE** Retail sales legal
- CYAN** On-farm sales legal — This category includes sales through delivery, at farmers markets, and at any other venues where direct raw milk producer-to-consumer transactions are allowed.
- GREEN** Herdshares legal — by statute, regulation, court decision, or written policy.
- YELLOW** No law on herdshares — The state is aware herdshare operations exist but has taken no action to stop them.
- PEACH/MELON** Sales of raw pet milk legal—farmers in the state are selling raw pet dairy products.
- RED** Sale or distribution of raw milk for human consumption is illegal. If sales of raw pet milk are legal, but there are no farmers in the state selling raw pet milk.

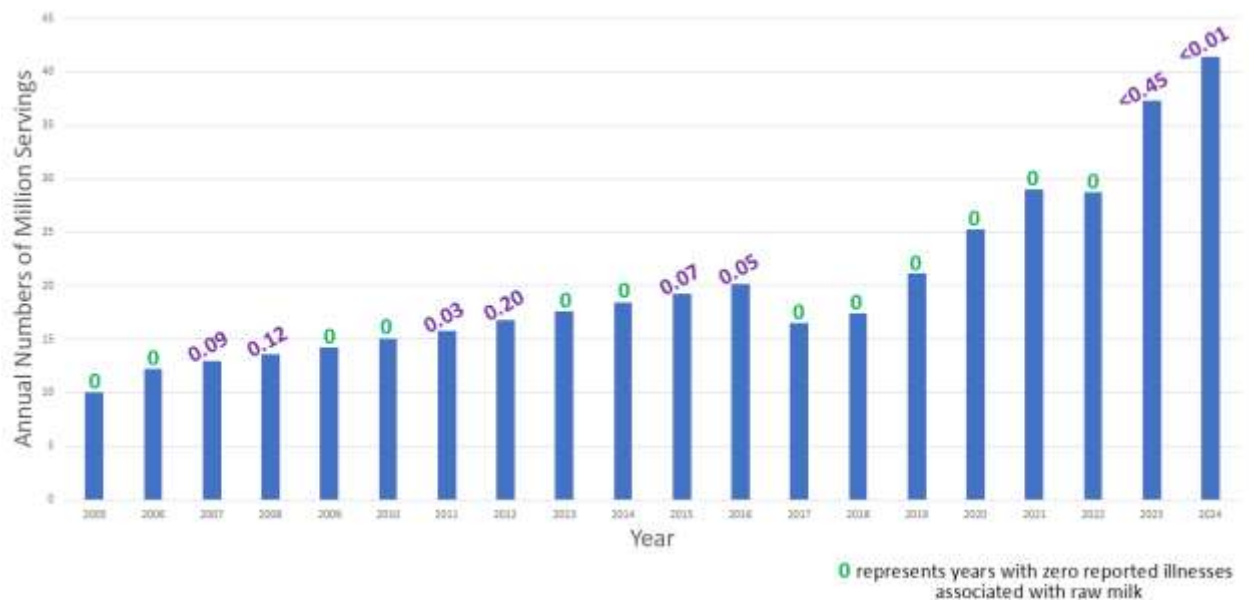
Appendix Figure A-2. Legal access to raw cow milk by state as of February 2026
(<https://www.realmilk.com/real-milk-legal-map/>)

Appendix Table A-3. Definition and strength of causal evidence that can be demonstrated by different study types identified in a systematic review (Jaros et al., 2008, Table 4).

Study type	Definition/example	Strength to show causal association
<i>Type 1</i>		
Experiment	Human volunteers drink milk sample with known dose of pathogen; investigator observes and takes samples during disease development	Very high
Cohort	Measuring the occurrence of particular disease in specified groups which either consume or do not consume contaminated dairy products over a set period of time	High
Case-control	Contrasting dietary history of patients (cases) with non-affected controls to identify dietary risk factor(s) such as contaminated dairy product(s)	Moderate
Cross-sectional	Selected groups are examined for their health status of a particular disease and interviewed about their consumption of dairy products at the same time	Low
Outbreak investigation with denominator	Investigating an outbreak of food poisoning in order to identify contaminated dairy product(s) as the source of infection; total number of exposed and non-exposed subjects (both ill or healthy) is known	Low
<i>Type 2</i>		
Outbreak investigation without denominator	Investigating an outbreak of food poisoning to identify contaminated dairy product(s); only number of exposed subjects (ill or healthy) is given	Non-Applicable
Survey	Providing data about frequency/distribution of cases with disease of interest in a defined population	Non-Applicable
Case series	Describing a series of cases with disease of interest (might provide hypothesis of causal dairy product)	Non-Applicable
Case reports	Reporting an unusual case of particular disease (hypothesis about indigestion of contaminated dairy product)	Non-Applicable



Appendix Figure A-3. State-level hospitalization data from CDC dataset for the 16-year period from 2005 to 2020 (Stephenson et al., 2024, 2026)



Appendix Figure A-4. Millions of annual retail raw milk servings for one California dairy (blue histograms) with annotations for estimated statewide rates of annual illnesses per 100,000 servings. Note that estimated rates would decrease when accounting for other California producers.

Appendix Table A-4. Subsequent Studies Linking Diets Enriched in Microbes with Protection from Acute and Chronic Diseases

Subsequent Study	Title
Anukam et al., 2007. <i>Communicating Current Research and Educational Topics and Trends in Applied Microbiology</i>	Probiotics: 100 years (1907-2007) after Elie Metchnikoff 's Observation
Baars et al., 2023. <i>Food & Function</i>	Raw milk kefir: Microbiota, bioactive peptides, and immune modulation
Baars et al., 2025. <i>International Dairy Journal</i>	Bacterial diversity, bioactive peptides, and enhanced immunomodulatory effects in raw milk kefir made with defined starter cultures versus backslipping
Bui & Marco 2025. <i>Nutrition Reviews</i>	Impact of fermented dairy on gastrointestinal health and associated biomarkers
Chen et al., 2025. <i>Journal of Affective Disorders</i>	Effect of dietary live microbe intake on the prevalence and mortality risks of depression and suicidal ideation in adults: Evidence from a nationwide population-based study
Han & Wang, 2022. <i>Nutrients</i>	Association of dietary live microbe intake with cardiovascular disease in us adults: a cross-sectional study of NHANES 2007–2018
Hill, 2018. <i>The Biochemist</i>	RDA for microbes—Are you getting your daily dose?
Hill et al., 2023. <i>The Journal of Nutrition</i>	Positive health outcomes associated with live microbe intake from foods, including fermented foods, Assessed using the NHANES Database
Huo et al., 2024. <i>The Journal of Nutrition, Health and Aging</i>	Association of dietary live microbe intake with frailty in US adults: Evidence from NHANES
Li et al., 2025. <i>Diabetes Research and Clinical Practice</i>	Impact of live microbe intake on cardiovascular disease and mortality in adults with diabetes: A nationwide cohort study
Marco et al., 2020. <i>The Journal of Nutrition</i>	Should there be a Recommended Daily Intake of Microbes?
Marco et al., 2022. <i>The Journal of Nutrition</i>	A classification system for defining and estimating dietary intake of live microbes in us adults and children
Parente et al., 2020. <i>International Dairy Journal</i>	The microbiota of dairy milk: A review
Quigley et al., 2013. <i>FEMS Microbiology Reviews</i>	The complex microbiota of raw milk
Shi et al., 2024. <i>Environmental Health and Preventive Medicine</i>	Association of dietary intake of live microbes with bowel health and depression in US adults: A cross-sectional study of NHANES 2005–2010
Sionek et al., 2023. <i>Microorganisms</i>	Beneficial Bacteria Isolated from Food in Relation to the Next

Subsequent Study	Title
	Generation of Probiotics
Tang et al., 2024. <i>The Journals of Gerontology</i>	Association of dietary live microbes and nondietary prebiotic/probiotic intake with cognitive function in older adults: Evidence from NHANES
Valentino et al., 2024. <i>Microbial Biotechnology</i>	Fermented foods, their microbiome and its potential in boosting human health
Wang et al., 2024. <i>Journal of Affective Disorders</i>	High dietary live microbe intake is correlated with reduced risk of depressive symptoms: A cross-sectional study of NHANES 2007–2016
Yan et al., 2024. <i>Clinical Nutrition</i>	Higher dietary live microbe intake is associated with a lower risk of sarcopenia
Yang et al., 2024. <i>The Journal of Nutrition</i>	Association between dietary intake of live microbes and chronic constipation in adults
You et al., 2024. <i>Nutrients</i>	Mediation role of recreational physical activity in the relationship between the dietary intake of live microbes and the systemic immune-inflammation index: A real-world cross-sectional study
Yuan, 2024. <i>Archives of Osteoporosis</i>	Association of dietary live microbe intake with prevalence of osteoporosis in US postmenopausal women: A cross-sectional study

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