The Raw Milk Movement: How M. bovis is Making a Comeback in the United States

Role of the Veterinary Profession and the USDA in Providing a Wholesome Milk Product

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Milk and other dairy products are important components of the American diet.
Milk can be a vehicle for the transmission of numerous bacteria that affect human health if not properly processed.

- Milk can be contaminated at any stage in the production-to-consumption continuum.

To Provide the Highest Quality Product

- Pasteurized Milk Ordinance (PMO, 2005, USDPH, FDA) provides standardized guidelines relating to:
  - Milk parlor and processing plant design
  - Milking practices
  - Milk handling
  - Sanitation
  - Standards for the pasteurization of Grade A milk products
Objectives

- Origin of milk contamination and potential zoonotic disease transmission
- Dairy cattle milking procedures and processing
- What is pasteurization and its role to control zoonotic diseases from milk

The Origin of Milk Contamination with Bacteria

1. Inclusion of bacteria during milking
   - Commensal bacteria:
     - Streptococcus, Bacillus, Micrococcus, Corynebacterium and coliforms
     - Mastitis
     - Staphylococcus and Streptococcus species, some coliforms
   - Systemic disease:
     - Mycobacterium bovis, Brucella abortus, Coxiella burnetti, Listeria species, Mycobacterium avium, paratuberculosis

Approaches used to minimize the possibility that milk contaminated with pathogenic organisms will reach the consumer:

- Enhanced animal health
- Improved milking hygiene
- Pasteurization
Enhanced Animal Health

- Because of veterinary care and diagnostic tests, many zoonotic diseases have been eliminated from the population of food-producing animals.
- However, some infections remain asymptomatic and could have serious public health implications.

Improving Milk Hygiene

- Implement hygienic standards for housing and milking centers.
- Cow cleanliness prior to milking.
- Milking practices that reduce contamination of milk and mastitis.

Pasteurization of Milk

- It is a process developed by Louis Pasteur in 1864 that kills harmful bacteria by heating milk to a specific temperature for a set period of time.
Why is Milk Pasteurized?

- Raw milk that has not been pasteurized can carry bacteria harmful to humans:
  - M. Bovis
  - Salmonella
  - E. Coli
  - Listeria
  - Others
- Responsible for causing numerous foodborne illnesses!

Pasteurization Process

- Refrigerated Products
  - Heat milk to at least 145 F for 30 minutes
  - High – Temperature Short – Time (flash): 161 F for 15 seconds
- Room Temperature Storage
  - Ultra-Heat Treatment (UHT): 280 F for 2 seconds

Homogenization

- Occurs after pasteurization and breaks down fat molecules in milk so that they resist separation. Without it, fat molecules will rise and form a layer of cream.
Dairy Cattle Milking Procedures and Processing
From the Farm to the Processing Plant to the Store

Veterinarians Play a Major Role in Promoting Animal Health and Well-Being

1. Disease prevention practices (preventative medicine, herd health)
2. Disease surveillance
3. Treatment of sick animals following FDA guidelines

Milking Procedures
Milking Procedures

Refrigerated Bulk Tank
- Cooled to 45°F (7°C) within 2 hours of milking
- A sample is taken prior to pumping the milk to the truck during pick up at the farm

Bulk Tank Milk Analysis (BTMA)
- Useful tool for evaluating milk quality and monitoring udder-health status in a herd
Each load is tested for antibiotic residues.

Regulatory action is taken against the farm with the positive antibiotic test.

Positive antibiotic tests are rare, and account for far less than 1% of the tank loads of milk delivered to processing plants. (CDC., 2013)
Milk at the Plant is Stored at less than 45°F (7°C) and processed within 24 hours

Alternatives to Pasteurization?

- Boiling (212.3 F): bacteria that may be in milk similar to pasteurization
- Testing schemes:
  - Are limited by assay sensitivity – both of the sampling-collection strategy and the microbiological analysis
  - Complicated by several factors:
    - Milk contamination occurs sporadically
    - Contamination may not be evenly distributed
    - Extremely small amounts are infectious (below the detectable limit) may proliferate to levels that reach unacceptable risks after testing.
When are Animals Tested for bovine TB?

- Suspected of having bovine TB
- Participation in a show or exhibition
- Change of ownership
- Interstate movement
- Part of surveillance activities at slaughter

Bovine TB (M. bovis) Testing

- Slaughter check for TB pathology (lesions): trace back and individual animal testing of cattle on the farm of origin

Bovine TB (M. bovis) Testing

- Caudal fold tuberculin test: hypersensitivity immune response, similar to the skin test used in humans
How M. bovis is making a comeback in the US

Bovine TB (M. bovis) Testing

- Comparative cervical test (regulatory veterinarians): Differentiates infection with mammalian TB versus avian TB organisms

The Problem of Cervids

- M. bovis is being increasingly detected in deers
- Source of bovine TB cases in WI and MI since 1995
- A 1996 survey of deer in MI found 1.2-2.4% infection rates, with spillover into 10 cattle herds
- Since 1997 all farm-raised cervids must be TB tested

For More Information visit USDA’s Animal and Plant Health Inspection Service web site:

www.aphis.usda.gov
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The Human Health Perspective
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Objectives
• Explain the epidemiology and zoonotic potential of M. bovis
• Recognize clinical settings where M. bovis may be the etiologic agent causing tuberculosis
• Understand why it is important to differentiate tuberculosis caused by M. bovis from M. tuberculosis

Consumer Misperceptions About Raw Milk Consumption
Consumer misperceptions:
• Raw milk has superior microbiological, nutritional and health benefits, ...and that these are destroyed by commercial heating measures
• Pasteurization increases risk of conditions such as milk allergy, lactose intolerance, diabetes, osteoporosis, arthritis
• Heating reduces the nutritional value of milk
Health Facts About Heating Raw Milk

- Mainly modifies functional properties of milk proteins (e.g., emulsifying and water binding properties, solubility), but has little effect on their digestibility and nutritional properties
- May alter the organoleptic profile (what individuals experience via the senses: taste, sight, smell and touch)
- Heating does not substantially change nutritional value or other benefits of milk
- No evidence supporting increased risk of various medical conditions from pasteurization

Claeys et al., 2013

Figure. Vitamin content of raw and heated milk in terms of percentage of the recommended daily intake (RDI) based on the consumption of 1 large glass of milk (250 ml). No data for vitamins B2, B5, A, D, E, K, niacin and biotin in pasteurized and boiled milk, and for vitamin K in UHT- and sterilized milk.

Claeys et al., 2013

Figure. Contribution of minerals and trace elements to the recommended daily intake (RDI) based on the consumption of one large glass of raw or heat-treated milk (250 ml); no data for Se in UHT milk and for Fe, Cu and Zn in UHT- and sterilized milk.

Claeys et al., 2013
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Human Pathogens Potentially Encountered in Raw Cow Milk

<table>
<thead>
<tr>
<th>Pathogenic bacteria</th>
<th>Pathogenic viruses</th>
<th>Pathogenic parasites</th>
<th>Microbial toxins</th>
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<tbody>
<tr>
<td>Salmonella spp. **</td>
<td>Rift valley fever virus</td>
<td>Cryptosporidium parvum</td>
<td>Type B toxins of</td>
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<td>Brucella abortus</td>
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<td>Clostridium botulinum</td>
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<td>Mycobacterium bovis</td>
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<td>Coxiella burnetii</td>
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<td>Mycobacterium avium subsp.</td>
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<td>Paratuberculosis</td>
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<td>Paratuberculosis</td>
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<td>Campylobacter coli and jejuni</td>
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<td>Mycoplasma pneumonia</td>
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<td>Corynebacterium pseudotuberculosis</td>
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<td>Listeria monocytogenes</td>
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<td>Human pathogenic verocytotoxigenic E. coli</td>
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<td>Campylobacter jejuni</td>
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<td>Enterotoxin producing Staph aureus</td>
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<tr>
<td>Arcanobacter pyogenes</td>
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<td>Streptococcus zooepidemicus</td>
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<td>Leptospira</td>
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* Denotes the most common pathogens causing disease in humans

Table adapted from Claeys et al., Food Control. 2013; 31: 251-262.

Zoonotic Infections From Consuming Raw Dairy Products

- Before pasteurization (1938), ~25% U.S. food- and water-borne disease outbreaks associated with milk compared with <1% today
  - Brucellosis and Tuberculosis most common pathogens
- Eradicated in developed countries through:
  - Herd certification programs (culling of infected animals)
  - Refrigerated bulk tanks for milk collection on farms
  - Pasteurization
- Today, vast majority of milk-borne outbreaks in U.S. are in states that permit the sale of raw milk

Global Burden of TB

- TB remains significant public health threat
- Substantial morbidity, mortality, economic impact
  - 2013, 9 million people fell ill with TB and 1.5 million died
  - Due to global health efforts, an estimated 37 million lives were saved through TB diagnosis and treatment between 2000 and 2013
  - Areas of persistent challenge include limited resources, need for improved and more available diagnostics and treatment, TB and HIV, and drug-resistant TB

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M. Tuberculosis Complex
- M. tuberculosis complex (MTBC)
  - M. tuberculosis
  - M. bovis
    - BCG strains (attenuated M. bovis developed for vaccine)
  - M. africanum
  - M. microti
  - M. canetti
  - M. caprae
  - M. pinnipedii
  - M. mungi

Contribution of M. bovis to Global TB Burden
- Worldwide incidence of M. bovis unknown
  - Developing countries rely on AFB smear for TB diagnosis
- Higher burden where enzootic in cattle and pasteurization not widely used
  - In Africa, 80% of population co-exists with cattle in areas with no organized control of bovine TB
- Transmissible between animals and humans
- Increased concern where HIV is prevalent
- Multi-drug resistant M. bovis strains reported
  - Sporadic cases and outbreaks

Global Animal-human Interface

9/18/2015
Contribution of *M. bovis* to U.S. TB burden (1)

- TB incidence becoming concentrated in foreign-born persons (65% of reported cases, 2013)
- Immigrants infected in regions where bovine TB is still prevalent can reactivate to active TB in U.S.
- Most labs don’t identify organism beyond ‘MTBC’
- In 2013, among all genotyped cases, 1.6% had genotype consistent with *M. bovis*; 67.3% were foreign-born


Contribution of *M. bovis* to U.S. TB burden (2)

- *M. bovis* contributes to TB incidence in bi-national communities with close ties to Mexico
  - 2001–2005, *M. bovis* ~10% culture (+) TB isolates in San Diego; 54% of those from children <15y, 8% of adults
- Impact beyond border states
  - 2003-2004 outbreak of 35 cases of human *M. bovis* infection in NYC associated with consumption of queso fresco brought from Mexico

1Rodwell et al. Emerg Infect Dis. 2008; 2CDC. MMWR 2005
Transmission of *M. bovis*

- Foodborne (most common): ingestion of contaminated unpasteurized dairy products
- Airborne
- Direct inoculation (cutaneous, i.e., butcher's wart)
  - Cattle, bison, or cervids (e.g. deer, elk) and their hides, milk, or meat
  - Ranching, dairy farming, working in a slaughterhouse or as a butcher, hunting
- Immunotherapy with BCG derived from attenuated strain of *M. bovis* (Bladder cancer, melanoma)

Foodborne Transmission

- *M. bovis* can survive in raw milk and cheese
- Mexican dairy products brought into the U.S. for personal use; sometimes distributed illegally
  - Bypasses FDA/USDA regulation and inspection
  - *M. bovis* persists in both dairy herds and beef cattle destined for the U.S.
  - 17% of 1201 carcasses inspected in Queretaro, 2000, condemned due to TB lesions, *M. bovis* grew in 79%
  - 30% of 7 M L of milk produced in Mexico unpasteurized

Airborne Transmission

- Transmission between animals thought to occur mainly by inhalation of contaminated aerosol
- Human-to-human considered infrequent, except in immunosuppressed persons (e.g., HIV)
- Magnitude of respiratory transmission not clear
Cluster of human TB caused by *M. bovis*: evidence for person-to-person transmission in the UK

- Cluster of 6 patients with TB caused by *M. bovis*
  - All were young, born and living in UK, documented social links to at least one other person in the cluster
  - 4 had predisposing factors for TB, high-dose use of steroids, alcohol misuse, IDDM, and HIV infection
  - Only one had history of zoonotic exposure and consumption of unpasteurized dairy products.
  - 5 had pulmonary disease; 5 received BCG vaccine as children, 1 developed meningitis and died
- All *M. bovis* isolates identical by genotyping


Clinical Manifestations of *M. bovis*

- Not all *M. bovis* infections progress to TB disease, may have no symptoms (TB infection)
  - TST and IGRAs don’t distinguish *M. bovis* from *M. tuberculosis*
  - Pathogenic *M. bovis* strains secrete ESAT-6, CFP-10, TB7.7 (BCG strains don’t)
- *M. bovis* is clinically, radiographically, and pathologically indistinguishable from *M. tuberculosis* in humans
- Higher proportion of extrapulmonary disease

Extrapulmonary TB due to *M. bovis*

- TB of the tongue due to *M. bovis*, Majoor et al. EID 2011
- Cutaneous TB caused by *M. bovis* in veterinarian exposed to infected alpaca, Veterinary Record 2010
I need to know if my patient has *M. bovis* or *M. tuberculosis* because....

1. It doesn’t matter—*M. Bovis* and *M. tuberculosis* disease are both treated with standard TB therapy (INH/RIF/PZA/EMB)
2. *M. bovis* disease is not as serious as *M. tuberculosis* so I don’t have to monitor those patients as closely
3. My public health investigation may be different
4. I will have to treat infected contacts with different LTBI regimen

Distinguishing *M. Bovis* from *M. tuberculosis*

- Culture on egg media-containing pyruvate or other rich semi-synthetic liquid media systems
- Genetic probes on liquid culture growth
- Most *M. bovis* isolates have intrinsic resistance to pyrazinamide (PZA) (pncA mutation)
  - Not all PZA resistance is due to *M. bovis*
- DNA fingerprinting
  - Spoligotyping results
  - MIRU-VNTR may be even more discriminatory
  - Whole genome sequencing

TB from *M. bovis* in Bi-national Communities, U.S. (1)

- Retrospective analysis of TB case surveillance data from San Diego, CA region from 1994 - 2005
- *M. bovis* accounted for:
  - 45% (62/138) of culture (+) TB in children <15 y
  - 6% (203/3,153) of adult cases
- *M. bovis* incidence increased significantly (p = 0.002) while *M. tuberculosis* incidence declined (p<0.001).
- Predominately Hispanic ethnicity, ~40% US born
- Risk of death during treatment 2.55x higher among persons with *M. bovis* than *M. tuberculosis* (p = 0.01) (all adults)
Tuberculosis from *M. bovis* in Binational Communities, U.S. (2)

- Given intrinsic resistant to PZA, treatment extended to 9 mo. for many young children with culture (-) TB
  - Consider for populations where *M. bovis* is more common, such as southern CA and other Hispanic communities with close ties to Mexico, particularly if history of consuming unpasteurized dairy products

Epidemiology of Human *M. bovis* Disease, California, 2003–2011

- Retrospective review: TB registry, genotyping data
- Increase in annual TB cases attributable to *M. bovis*, 3.4% in 2003 to 5.4% 2011 (p = 0.002)
- *M. bovis* disease accounted for nearly 25% of culture (+) TB cases in children.
- Patients with *M. bovis* disease more likely to die during treatment than those with *M. tuberculosis* disease (15.8% vs. 8.6%, p<0.006)
- Most deaths were among adults with concurrent immunosuppressive conditions.

Conclusions

- Zoonotic TB is a public health concern
- Heat-treatment of raw dairy products prevents transmission of human pathogens, including *M. bovis*
- Consider *M. bovis* TB: foreign-born, US born in bi-national communities, raw dairy product consumption
- PZA resistance necessitates a 9-mo. treatment duration
- Higher mortality rates during treatment
- MDR *M. bovis* has been reported
- Discriminating *M. tuberculosis* and *M. bovis* important for epidemiological investigations and implementation of measures to prevent and control the spread of disease
Future Directions

- Define actual incidence and impact of M. bovis
- Especially in areas where M. bovis is enzoonotic, there is significant animal-human interaction, HIV is widespread, and pasteurization is less common
- Global prevention strategies
  - Education, regulation of the production of unpasteurized dairy products, elimination of M. bovis from dairy cattle
- Rapid identification of specific species in MTBC among all TB isolates in the U.S.
- Collaboration between veterinary and medical professionals for eradication

Thank you!

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The Raw Milk Movement

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Contribution of M. bovis in Animals

• Reservoirs of M. bovis in wildlife challenge TB control and eradication
• M. bovis in MI deer population infected cattle herds
  • Quarantine and depopulation of infected herds
  • Loss of valuable bloodlines
  • Limitations of international export of valuable breeding animals and semen
  • Overall cost > US$100 million over 10 years
• European badger is M. bovis reservoir in British Isles
• M. bovis infection in animal keepers and meat industry workers
The Raw Milk Movement

Background

• Raw milk consumption is becoming more popular
• Perception that heating destroys nutritional and health benefits of milk, is detrimental to health
• Prevalence of foodborne pathogens in raw cow milk is well-established
• Commercial milk is heat treated to guarantee its microbial safety and to prolong its shelf-life

Claeys et al., 2013

Health Facts About Heating Raw Milk

• Heat treatment (and homogenization) has no significant effect on the bioavailability of calcium
• Very low effect on nutritionally relevant vitamins B2 (riboflavin) & B12 (cyanocobalamin)
• Small or no losses reported for B6 (pyridoxine), niacin, panthothenic acid (B5), biotin (B7) and vitamins A, D and E
• No difference in minerals and trace elements between raw and commercially heated milk.

Claeys et al., 2013

Human M. bovis Tuberculosis United States, 1995–2005

• US-wide epidemiologic study of human M. bovis TB linking the National TB Genotyping Service results to corresponding surveillance data
• 1.4% of 11,860 TB cases with genotyping results
  • 89% Hispanic, 62% born in Mexico
  • 19% age <15 y.o. (only 2% for M. tuberculosis)
  • 65% extra-pulmonary disease site
  • 26% HIV infected

Why Does it Matter?

• Most M. bovis isolates have intrinsic resistance to pyrazinamide (PZA) (pncA mutation)
  - Not all PZA resistance is due to M. bovis

• National study found 0.7% (196/27,428) of MTBC isolates PZA monoresistant

• Florida DOH: 2013-2014 pncA sequencing data
  - 61 of 1,238 (4.9%) MTBC isolates had pncA mutation
    (Personal communication, Marie-Claire Rowlinson)

1Thomas et al, Int J Tuberc Lung Dis. 2014; 2
2Kurbatova Clin Infect Dis. 2013