Bovine TB Public Health Implications

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Bovine TB Conference

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Background
M. bovis

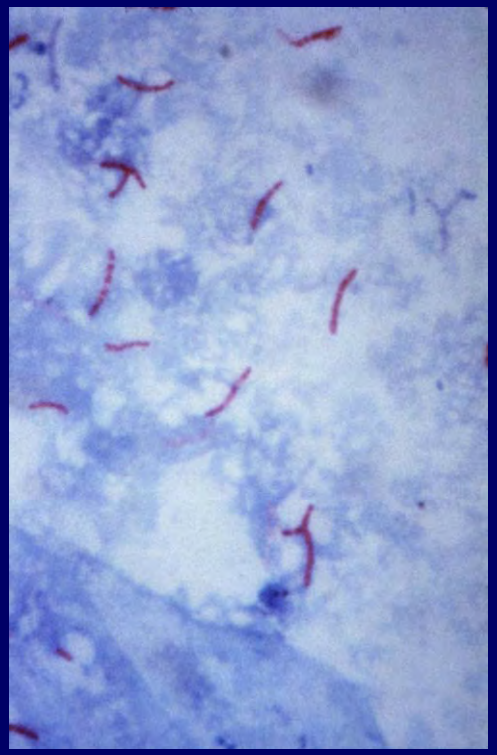


Image: CDC PHIL

- Mycobacteriacea
  - Gram positive, aerobic, non-spore forming, non-motile, slightly curved or straight rods
  - Thick cell walls containing mycolic acids with free lipids, acid fast stainer
  - Able to survive for weeks to months on inanimate objects if protected from sunlight
  - More resistant to acids, alkalis, and some chemical disinfectants than other non-spore forming bacteria
- *M. bovis* part of the *Mycobacterium tuberculosis* complex
  - *M. tuberculosis, M. africanum, M. microti*
  - Related by a >99.9% DNA homology
  - All human pathogens
  - All obligate pathogens
  - Major ecological niche – tissues of warm-blooded animals

Background

- *Mycobacterium bovis* (Bovine TB) is well established zoonotic disease
- All warm blooded animals considered susceptible
- Transmission from animals to humans documented
  - Cattle, goats, deer, elk, buffalo, sheep, camels
- Exposure under variety of circumstances
  - Farm, laboratory, slaughter house (aerosol), dairy products (consumption), butcher shop (cutaneous)

Background

- Historically - US
  - Humans exposed via consumption of unpasteurized dairy products from infected animals
  - Route of transmission virtually eliminated with adoption of Pasteurized Milk Ordinance – 1920's

Background- Outbreak

- 1979 - Michigan's livestock population certified free of Bovine TB
- 1994 - white-tailed deer positive
- 1995 - additional infected white-tailed deer found
- 1998 - three beef herds found infected
- 2002 - first suspected human case found

Background

- Outbreak of *M. bovis* in MI includes several new species of animals
  - Deer, wild carnivores, other scavenger species, rodents, one domestic cat
- Diversity of infected species creates several <u>potential</u> new routes of transmission to humans

Domestic Pet Project

- **Contrary to Federal recommendations, in Michigan, pets are allowed to remain on farm after infected livestock are depopulated**

Domestic Pet Project

- **Study Design**
  - Retrospective descriptive field study
- **Objective**
  - Collect data and clinical specimens from eligible dogs and cats to determine if they are infected with *M. bovis*
  - Assess the risk posed to humans and clean livestock from dogs and cats living on farms with infected cattle in MI.

Domestic Pet Project
Methods

- **Study Population**
  - Attempted to contact owners of the 23 MI farms that had been recently infected or were currently infected with bovine TB (as of Sept 2002)
    - 21 of 23 farms contacted
      - 9 no eligible pets (pet must have been exposed to infected herd)
      - 3 declined participation
    - 9 farms with eligible pets participated (2 dairy, 7 beef)
- Dogs and cats were eligible (potentially exposed to bovine TB infected cattle on Michigan farms)
    - n = 18 cats
    - n = 5 dogs

Domestic Pet Project

Methods

- Study Protocol - Cats
  - History – exposure, health, diet, range
  - Physical exam
  - FeLV and FIV test
  - Chest and abdominal radiographs
  - Rectal and oral swabs
  - Aspirate of enlarged superficial lymph nodes
  - Serum for *M. bovis* and *M. avium* ELISA
  - Necropsy if allowed by owner

Domestic Pet Project

Methods

- Study Protocol – Dogs
  - History - exposure, health, diet, range
  - Physical exam
  - Tb skin test – pinna (ear)
  - Chest and abdominal radiographs
  - Rectal and oral swabs
  - Aspirate of enlarged superficial lymph nodes
  - Serum - for *M. bovis* and *M. avium* ELISA
  - Necropsy if allowed by owner

Domestic Pet Project
Methods

- History – on-farm interview with owner
- PE & Sample collection - utilized one local private practitioner (Dr. Schwartz)
- Radiographs – interpreted by MSU (Dr. Perry)
- Necropsies – MSU, DCPAH (Dr. Simmons)
- Laboratory work – MDCH Laboratory (Mr. Berry)
- ELISA (unvalidated) – Iowa State University (Dr. Thoen)

Domestic Pet Project

Methods

Summarized characteristics of study participants by species

Characteristic	Cats (N=18)	Dogs (N=5)
Gender	11 Male (61%)	2 Male (40%)
Average age (yrs)	4.1 (range 1.0-12.5)	6.1 (range 2.0-11.5)
Routinely fed	Yes n=15 (83%)	Yes n=5 (100%)
Fed raw milk	Yes n=5 (28%)	Yes n=0 (0%)
Outdoor only	Yes n=12 (67%)	Yes n=4 (80%)
Known or likely to have shared barn with infected cattle	Yes n=18 (100%)	Yes n=0 (0%)
Average exposure period* (mos)	2.3 (range 1.0 -7.0)	4.0 (range 2.0-8.0)

*Calculated as the minimum possible exposure period

Domestic Pet Project
Results

- No physical, clinical, radiographic, or laboratory evidence of *M. bovis* infection in any pet examined
  - Three fecal samples were culture positive for saprophytic strains of *Mycobacterium*
  - Elisa results – 3 cats positive to *M. avium* at 1:160, two of whom also tested positive for *M. bovis* but at less than 1:160 (interpreted as cross-reacting with *M. avium*)

Domestic Pet Project

Conclusion

- No evidence was found to indicate transmission of *M. bovis* from infected cattle to pets
  - Mild infection in cattle
  - Short duration of exposure to infected cattle
- Even if infected, the risk of transmission from pets to humans is low
  - Respiratory presentation - Majority of pets were outdoor only – little face to face contact
  - Gastrointestinal presentation infection would not be transmissible
    - Cats consuming raw milk
    - Dogs consuming gut piles from deer
- Public health prevention recommendations were made to farm families
- Clear need for an ante-mortem test for pets

Project Publication

- **Wilkins MJ**, Bartlett PC, Berry DE, Perry RL, Fitzgerald SD, Bernardo TM, Kaneene JB, Thoen CO. Absence of *Mycobacterium bovis* Infection in Dogs and Cats Residing on Infected Cattle Farms -- Michigan, 2002. Epidemiology and Infection 2008. Available advance of publication electronically: dio:10.1017/S0950268808000447.

Epidemiology of *M. bovis* in Michigan Residents

- Study Population
  - Michigan residents diagnosed with *M. bovis* infection, 1995-2007
- Case review and laboratory investigation
  - Summarize all cases
  - Focus on human infection with *M. bovis* genetically and epidemiologically associated with current outbreak in deer and cattle
  - Review all cases using most current molecular (genotyping) laboratory techniques

Epidemiology of *M. bovis* in MI Humans
Methods

- Laboratory Methods - genotyping
  - Restriction Fragment Length Polymorphism (RFLP)
  - Spoligotyping
  - Mycobacterial interspersed repetitive units (MIRU)
- Epidemiologic record review
- Medical record review
- Interviews

Image: CDC PHIL

Epidemiology of *M. bovis* in MI Humans
Results

- 1995-2007
  - No increase in number of human cases in MI
  - 13 human cases
    - 11 not genotypically or epidemiologically related to current *M. bovis* outbreak in deer/cattle
      - 8 recent immigrants to US
      - 3 US-born were elderly patients with history of raw milk consumption in their youth
    - 9 specimens available for advanced molecular typing

Non-epidemiologically linked human *M. Bovis* spoligotyping and MIRU typing results, Michigan, USA.

Country of Birth	Site	Year Collected	International Spoligotype*	MIRU type†	Spoligotypes
USA	Cervical LN	1997	SB1210	Not available	▫▪▫▪▫▫▪▪▫▫▫▫▫▪▪▪▫▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▫▫▫▫▫
USA	Spine	1997	SB0131	Not available	▪▪▫▪▫▪▪▪▪▫▪▫▪▪▪▪▫▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▫▫▫▫▫
Mexico	Abd Abscess	1998	SB0140	232224152322	▪▪▫▪▪▪▫▪▫▫▫▫▫▪▪▪▫▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▫▫▫▫▫
Mexico	Sputum	1998	SB1210	Not available	▫▪▫▪▫▫▪▪▫▫▫▫▫▪▪▪▫▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▫▫▫▫▫
Bosnia	Cervical LN	2000	SB1215	232314353312	▪▪▫▪▪▪▪▫▫▫▫▫▫▪▫▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▫▫▫▫▫
Mexico	Sputum	2003	SB0121	232314223322	▪▪▫▪▪▪▪▪▫▪▪▪▪▪▫▪▪▪▪▫▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▫▫▫▫▫
USA	Cervical LN	2003	SB0121	232324252322	▪▪▫▪▪▪▪▪▫▪▪▪▪▪▫▪▪▪▪▫▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▫▫▫▫▫
Mexico	Cervical LN	2005	SB1216	232124233222	▫▫▫▪▪▪▪▪▫▪▫▪▪▪▪▫▪▪▪▪▪▪▪▪▪▫▫▪▪▪▪▪▪▪▪▪▪▫▫▫▫▫
Mexico	Cervical LN	2007	SB0140	231224243322	▪▪▫▪▪▪▫▪▫▫▫▫▫▪▪▪▫▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▫▫▫▫▫

•International Spoligotype Database; available from http://www.mbovis.org
•† Mycobacterial interspersed repeat units (MIRU) type described by Cowen, 2002.

Epidemiology of *M. bovis* in MI Humans
Results

- Of the 13 human cases 2 were linked both epidemiologically and molecularly to the current *M. bovis* outbreak in deer and cattle
  - Case 1
    - 2002
    - Pulmonary
  - Case 2
    - 2004
    - Cutaneous

Epidemiology of *M. bovis* in MI Humans
Results

- Case 1 clinical history
  - 74 year old male
  - Significant co-morbidities: ischemic bowel disease, cerebral and peripheral vascular disease, partial gastrectomy for peptic ulcer disease, and lobectomy for squamous cell carcinoma
  - Hospitalized for malaise, weakness, anorexia and fever
  - Initially TB skin test (TST) negative and sputum negative for acid fast bacteria (AFB)
  - Clinically deteriorated, increasing left side pulmonary infiltrate, diagnostic bronchoscopy yielded AFB
  - Initiated Tx for TB, underwent bowel resection, but expired
  - *M. bovis* isolated, genotypic match to deer/cattle outbreak strain

Epidemiology of *M. bovis* in MI Humans
Results

- Case 1 exposure history
  - Drank unpasteurized milk as a youth (50 yrs prior)
  - 1st wife reported to have had TB (40 yrs prior)
  - Moved to edge of DMU 452 in 1994
  - Ran business with buck pole on property
  - Previously avid hunter (10 yrs prior)
  - Helped friend hang and transport deer shot on his property in 2000 (friend was subsequently TST positive)
  - Several potential, but no definitive, route of exposure

Epidemiology of *M. bovis* in MI Humans
Results

- Case 2
  - 29 year old previously health male
  - Cut hand while field dressing deer, noted nodules in chest cavity, buried deer (October 1)
  - 18 days later – index finger became inflamed and painful
  - Sought treatment, placed on antibiotics for skin infection, was TST negative
  - Wound worsened, hospitalized, infectious tenosynovitis finger was incised and drained, discharged (no AFB on microscopic exam)
  - Readmitted, incised and drained, discharged
  - AFB detected on culture, November 23
  - Treatment for TB initiated November 24 (9 mo regimen)
  - TST positive at 14 wks post exposure

Epidemiology of *M. bovis* in MI Humans
Results

- Case 2
  - 9 weeks after burying deer, case 2 led DNR staff to site
  - Deer carcass was retrieved
  - *M. bovis* isolated from deer
  - Genotyping revealed exact match between the isolate from case 2, his deer, and currently circulating deer/cattle strain

Chest cavity of deer shot by Case 2

Photo: J.S. Fierke, DJ O'Brien, SM Schmitt, Wildlife Disease Laboratory, Michigan Department of Natural Resources

Epidemiologically linked *M. Bovis* spoligotyping and MIRU typing results, Michigan, USA.

Species	Year Collected	International Spoligotype*	MIRU type†	Spoligotypes
Deer 1	1997	SB0145	Not available	▪▪▫▪▫▫▫▫▫▫▫▫▫▫▪▫▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▫▫▫▫▫
Bovine 1	1998	SB0145	Not available	▪▪▫▪▫▫▫▫▫▫▫▫▫▫▪▫▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▫▫▫▫▫
Bovine 2	1999	SB0145	232224253322	▪▪▫▪▫▫▫▫▫▫▫▫▫▫▪▫▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▫▫▫▫▫
Bovine 3	1999	SB0145	232224253322	▪▪▫▪▫▫▫▫▫▫▫▫▫▫▪▫▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▫▫▫▫▫
Bovine 4	2002	SB0145	232224253322	▪▪▫▪▫▫▫▫▫▫▫▫▫▫▪▫▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▫▫▫▫▫
Human Case 1	2002	SB0145	232224253322	▪▪▫▪▫▫▫▫▫▫▫▫▫▫▪▫▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▫▫▫▫▫
Deer 2	2003	SB0145	232224253322	▪▪▫▪▫▫▫▫▫▫▫▫▫▫▪▫▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▫▫▫▫▫
Human Case 2	2004	SB0145	232224253322	▪▪▫▪▫▫▫▫▫▫▫▫▫▫▪▫▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▫▫▫▫▫
Deer 3‡	2004	SB0145	232224253322	▪▪▫▪▫▫▫▫▫▫▫▫▫▫▪▫▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▪▫▫▫▫▫

* International Spoligotype Database; available from http://www.mbovis.org
† Mycobacterial interspersed repeat units (MIRU) type described by Cowen, 2002.
‡Deer shot by Case 2.

Epidemiology of *M. bovis* in MI Humans Summary

- Based on CDC definitions, Case 1 and Case 2 are part of an epidemiologically confirmed genotyping cluster
- Confirmed deer as a source of infection for humans
- As predicted, hunters can be exposed and infected via the cutaneous route of exposure
- Recreational exposure to infected deer in MI is a potential, albeit low, risk for acquisition of *M. bovis* in humans

Side note

- How unique is the MI deer/cattle strain (SB0145) circulating in Michigan?
- CDC human TB genotyping database 2004-2007
  - 20,000 isolates with spoligotyping results
  - Of these, 354 are *M. bovis* or BCG (vaccine strain of *M. bovis*)
  - Of these 166 considered *M. bovis (*not BCG)
  - 49 isolates in the database match our pattern (SB0145)
  - CA (25), NY (7), MI (2), MN (2), OR (2), AL (2), AR, AZ, CO, IA, IL, NC, NV, TX, WI – 1 each
- So not very unique among humans!

Project Publication

- **Wilkins MJ**, Meyerson J, Bartlett PC, Spieldenner SL, Berry DE, Mosher LB, Kaneene JB, Robinson-Dunn B, Stobierski MG, Boulton ML. Human *Mycobacterium bovis* infection associated with the bovine TB outbreak in Michigan, 1994-2007. Emerging Infectious Diseases 2008;14(4):657-660.

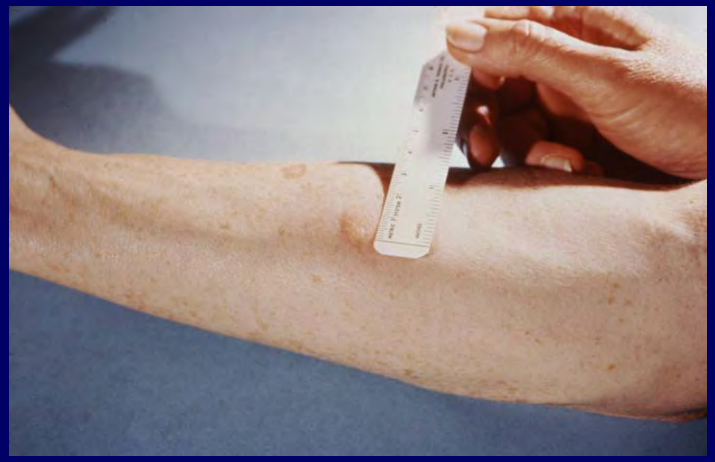
Comparison of Risk Factors for Exposure to *M. tuberculosis* and *M. bovis*

- **Objective**
  - **Determine if human subpopulations may be at increased risk of exposure to *M. bovis* based on their occupational or recreational exposure to infected animals**
- **Study Design**
  - **Prospective cohort**
  - **Collected exposure risk factor data for both *M. bovis* and *M. tuberculosis* from residents of 12 counties in northern MI seeking TB skin tests (TST) from local health departments**

Comparison of Risk Factors for Exposure Methods

- *M. tuberculosis* (*M. tb*) exposure risk factors are well known:
  - Foreign born
  - Healthcare worker
  - Congregate setting
  - Contact of case

- Created a list of *M. bovis* exposure risk factors, specific to MI
  - Hunter
  - Trapper
  - Taxidermist
  - Venison processor
  - Beef or dairy producer
  - Farm or livestock worker

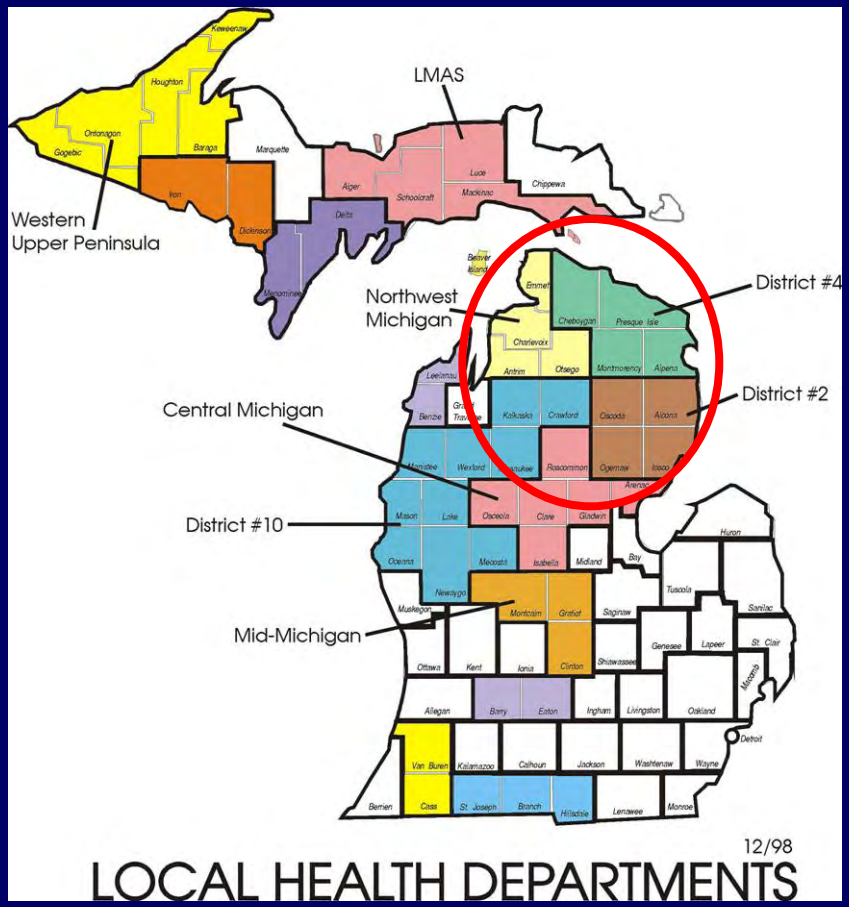


- ***Human TST does not distinguish between M. bovis and M. tb***

Images: CDC PHIL

Comparison of Risk Factors for Exposure Methods

- Mini survey developed including *M. bovis* and *M. tb* risk factor list
- 12 county health departments in northern lower peninsula were asked to complete the survey for individuals seeking TB skin testing (TST) and mail the survey with TST results, to MDCH for a 12 month period
  - Study population was very homogeneous, lacking several key risk factors for *M. tb*
- Relative risk or Fisher's exact test used to measure association between TST positive test rate and each risk factor



Comparison of Risk Factors for Exposure Results

- 1268 surveys submitted
- 29 positive TB skin tests
- Positivity rate of 2.3% (29/1268)
  - MI rate lower than national estimate of 3.3% - 5.2%
- Being foreign-born (a known risk factor for *M. tb*) was associated with TST positivity (RR = 9.36, p=0.019) as expected
- Being a venison processor was found to be associated with TST positivity (RR= 2.49, p=0.047)
- Increased risk associated with being a beef or dairy producer and a farm/livestock worker – not statistically significant

Comparison of Risk Factors for Exposure
Conclusion

- Results suggest that these populations may benefit from increased surveillance efforts and targeted prevention messages to reduce the likelihood of exposure to *M. bovis*
- *Would like to repeat/expand this study*

Thank you!

- Questions?