National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

Mycobacterium bovis Disease in Humans

Philip LoBue, MD

July 8, 2021

What is *Mycobacterium bovis*?

Etymolgy

- Bovis derives from late Latin bovinus: related to a cow
- Bos: Latin word for cow

History

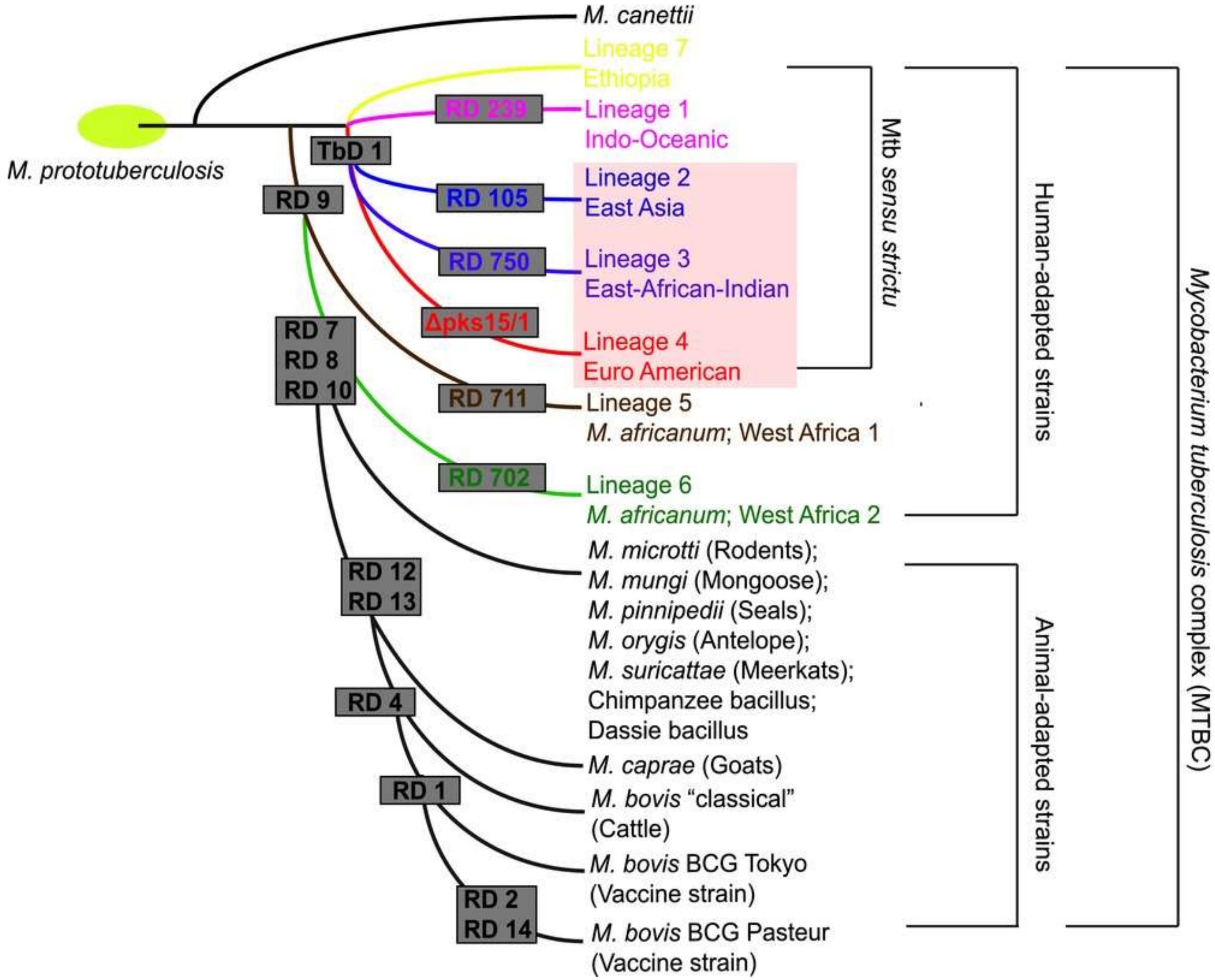
- 1882: Koch’s discovery of tubercle bacillus
- 1898: Theobald Smith identifies morphologic and biochemical differences between tuberculosis species infecting cattle (*M. bovis)* and humans (*M. tuberculosis)*
- 1901: Koch declares bovine strains of TB are not dangerous to humans and eradication in cattle is not necessary

History

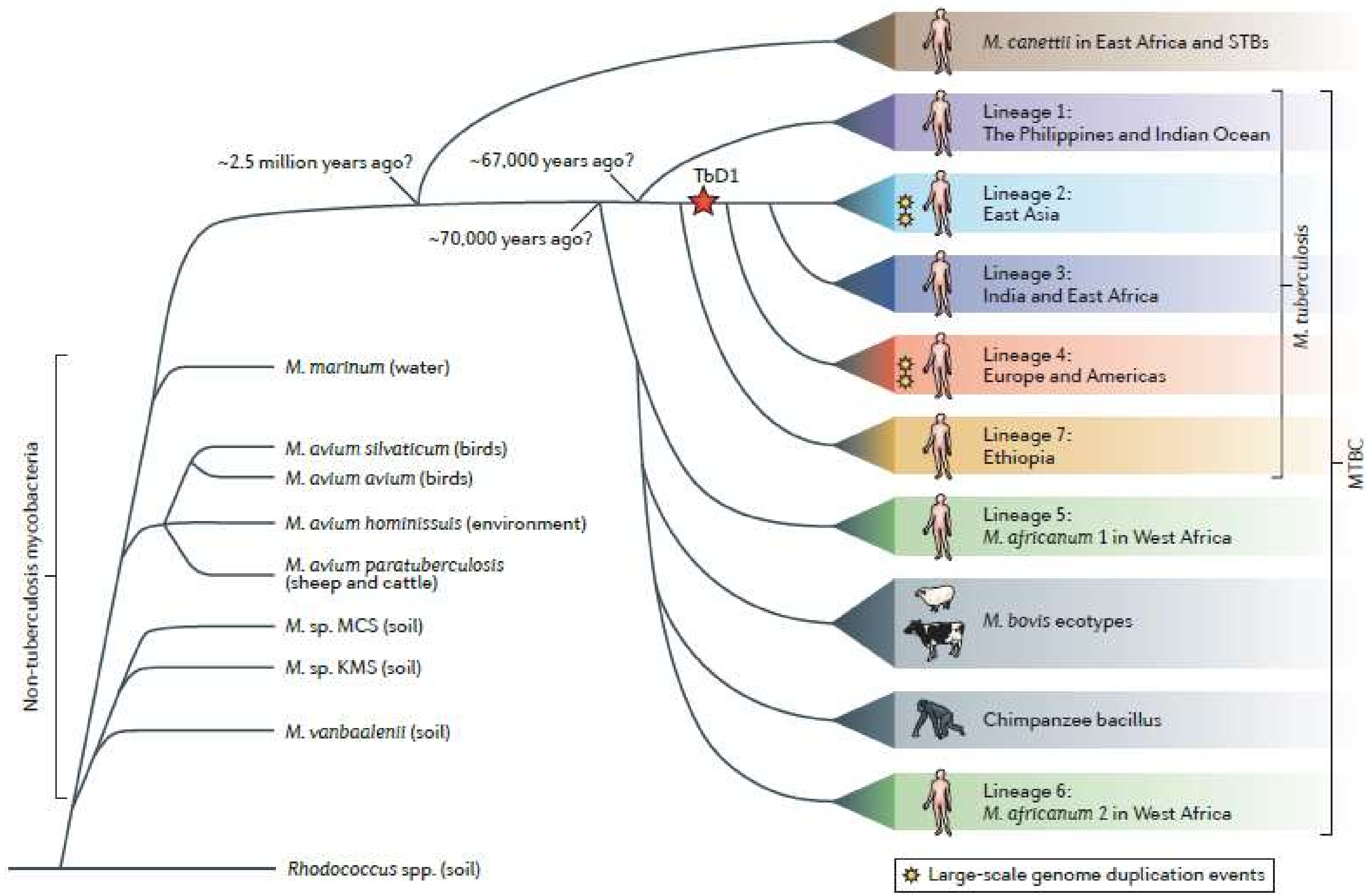
- 1902: McFaydean, Scottish veterinarian, argues that *M. bovis* is the cause of abdominal TB in children and isolates organism from child with meningitis
- 1901-1911: A British Royal Commission conducts extensive research
  - Demonstrates cow's milk contaminated with *M. bovis* caused extrapulmonary TB in people
  - Increased risk of cervical lymphadenitis in children who drank cow's milk

Evolution of *M. tuberculosis* Complex Species

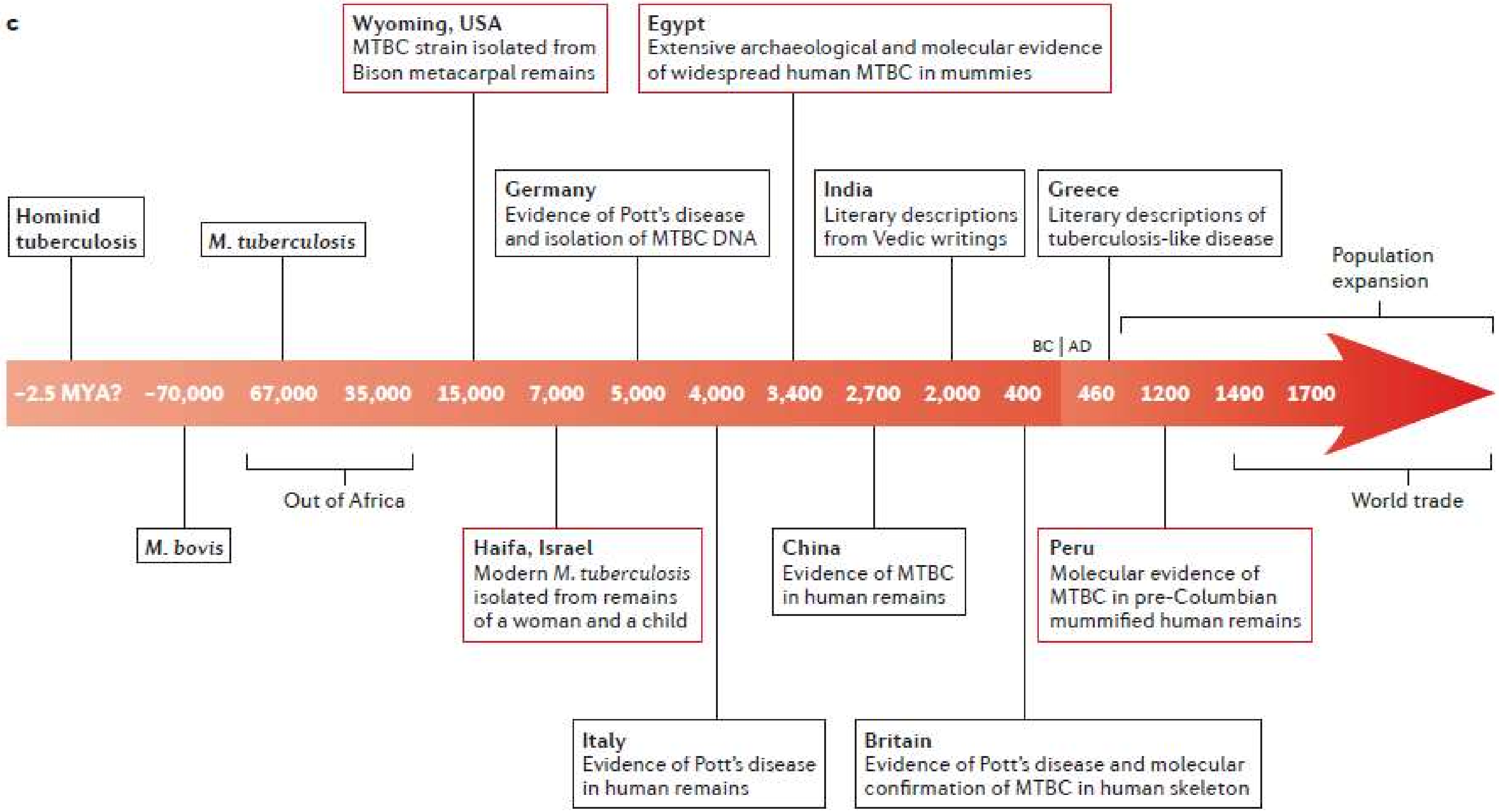
- Had been speculated that *M. tuberculosis* evolved from *M. bovis* by specific adaptation of an animal pathogen to the human host
- Genetic analysis says otherwise
  - Gene deletion analysis strongly suggests that *M. bovis* is the final member of a separate lineage represented by *M. africanum*, *M. microti* and *M. bovis* that branched from the progenitor of *M. tuberculosis* isolates (Brosch et al. PNAS, 2002 Mar 19; 99(6): 3684–3689)



European Journal of Immunology, Volume: 47, Issue: 3, Pages: 432-445



Galagan, Nature Reviews, May 2014, Volume 15, pg 310

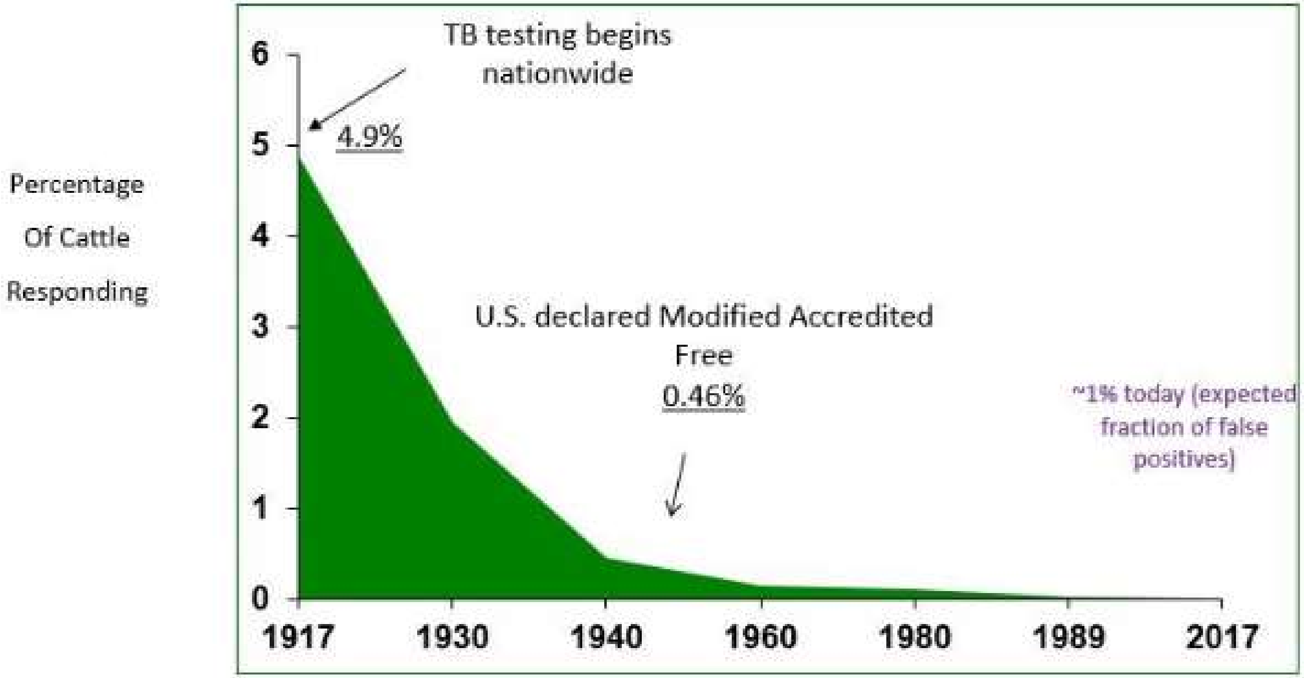


Galagan, Nature Reviews, May 2014, Volume 15, pg 312

Some More History

- 1908 first compulsory pasteurization law
- 1917 US State-Federal bovine TB eradication program
- Whole herd testing & culling of reactors
- Prior to pasteurization – estimated 10-30% of human TB cases due to *M. bovis*

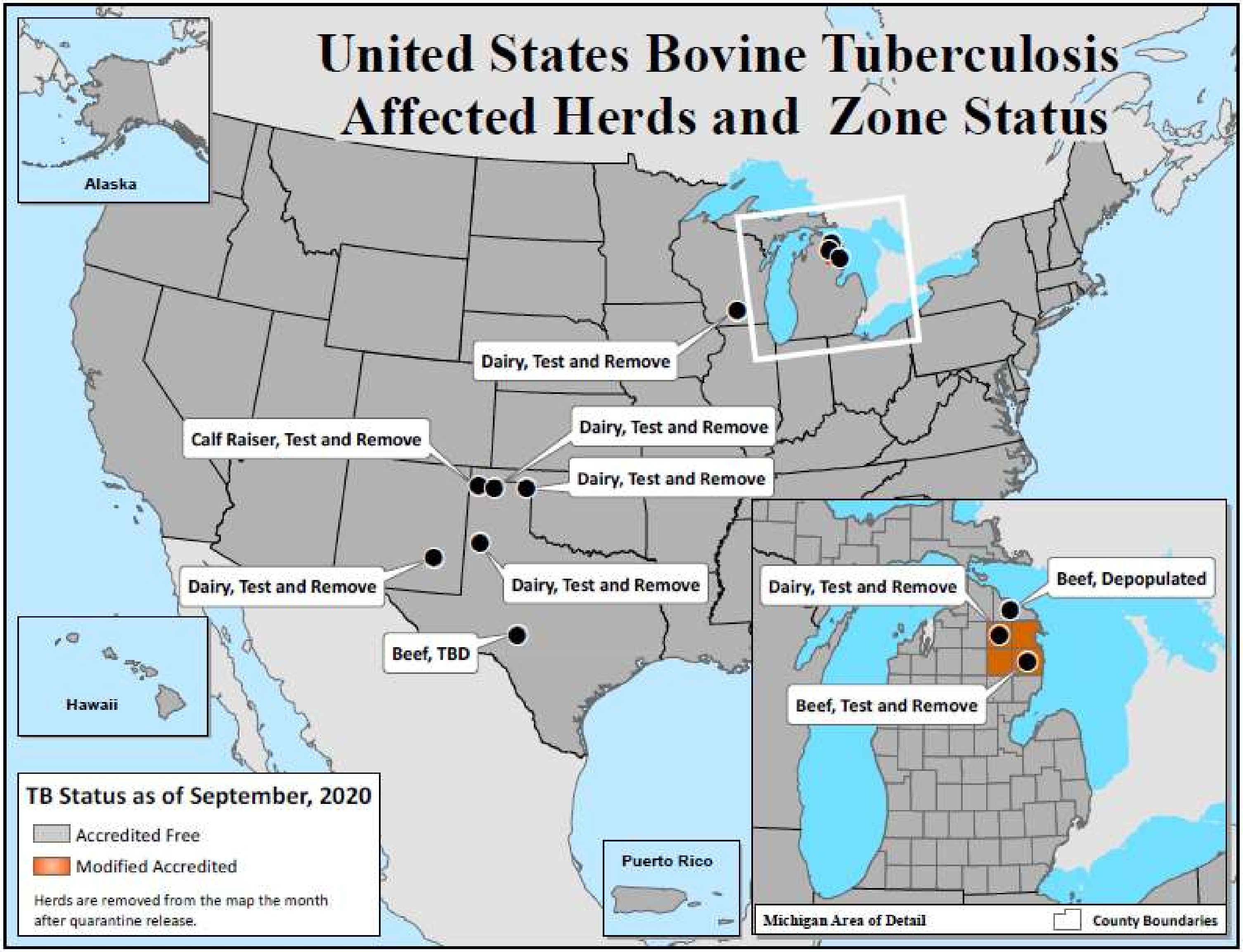
Percentage of U.S. Cattle Responding to the Skin Test, 1917 - 2017



Source: Palmer & Waters, Establishment of Bovine TB Eradication Program, Veterinary Medicine International, 2011

Has *M. bovis* been eradicated from cattle in the US?

- USDA accreditation status for US states
- Accredited-free States or zones have a herd prevalence of zero for bovine tuberculosis in cattle and bison
- Modified Accredited States or zones must have had a tuberculosis prevalence of less than 0.1 percent of the total number of cattle and bison herds in the State or zone for the most recent year


United States Bovine Tuberculosis Affected Herds and Zone Status
Alaska
Hawaii
Puerto Rico
Dairy, Test and Remove
Calf Raiser, Test and Remove
Dairy, Test and Remove
Dairy, Test and Remove
Dairy, Test and Remove
Dairy, Test and Remove
Beef, TBD
Dairy, Test and Remove
Beef, Depopulated
Beef, Test and Remove
Michigan Area of Detail
County Boundaries
TB Status as of September, 2020
Accredited Free
Modified Accredited
Herds are removed from the map the month after quarantine release.

M. bovis Susceptible Species

- Cattle
- Humans and non-human primates
- Goats, sheep, cats, dogs, pigs, buffalo, badgers, possums, deer, elk, bison, horses, foxes, hares, ferrets, antelope, camels, llamas, alpacas

Current Disease Burden and Epidemiology

Which Organisms Are the Most Important Causes of Human TB?

- Developed countries (e.g., USA), estimates
  - *M. tuberculosis*: 98-99% of cases
  - *M. bovis*: 1-2% of cases
  - Others: very rare
  - Some geographic variation, e.g., San Diego
- Developing countries
  - Unknown, but *M. bovis* likely to account for higher percentage of disease where organism is enzootic in cattle and pasteurization is not widely used (e.g., parts of Africa)

Global Estimates of *M. bovis*

- Individual country studies
  - Often not systematic
  - May only be from one location

Regional Estimates of Proportion of Zoonotic TB Cases From Systematic Review (Muller et al. Emerg Infect Dis. 2013 Jun; 19: 899–908)

- Americas: median proportion of 0.3%
- Europe: median proportion of 0.4%
- Western Pacific: median proportion of 0.2%
- Eastern Mediterranean: two studies, 2.2% and 0.6%
- Africa: median proportion of 2.8%
- WHO has provided a global estimated proportion of 1.4% based on these data and data from foodborne disease surveillance
  - 147,000 cases in 2016

Risk of Human Disease in North America

- In US and Canada, disease is rare due to pasteurization and eradication programs in cattle
  - *M. bovis* accounts for less than 2% of human TB cases
  - Higher in some areas: San Diego
- Mexico
  - From Muller et al systematic review, the median percentage of *M. bovis* cases was 7.6% (range 0%–31.6%); proportions >10% were detected in 3 independent studies
  - one report found 17% of cattle in meat processing plants were infected with *M. bovis*
  - up to 30% of milk is not pasteurized

(Muller et al. Emerg Infect Dis. 2013 Jun; 19: 899–908)

M. Bovis in the United States

Human Tuberculosis due to *Mycobacterium bovis* in the United States, 1995–2005

Michele C. Hlavsa,[1,2] Patrick K. Moonan,[2] Lauren S. Cowan,[2] Thomas R. Navin,[2] J. Steve Kammerer,[2,3] Glenn P. Morlock,[2] Jack T. Crawford,[2] and Philip A. LoBue[2]

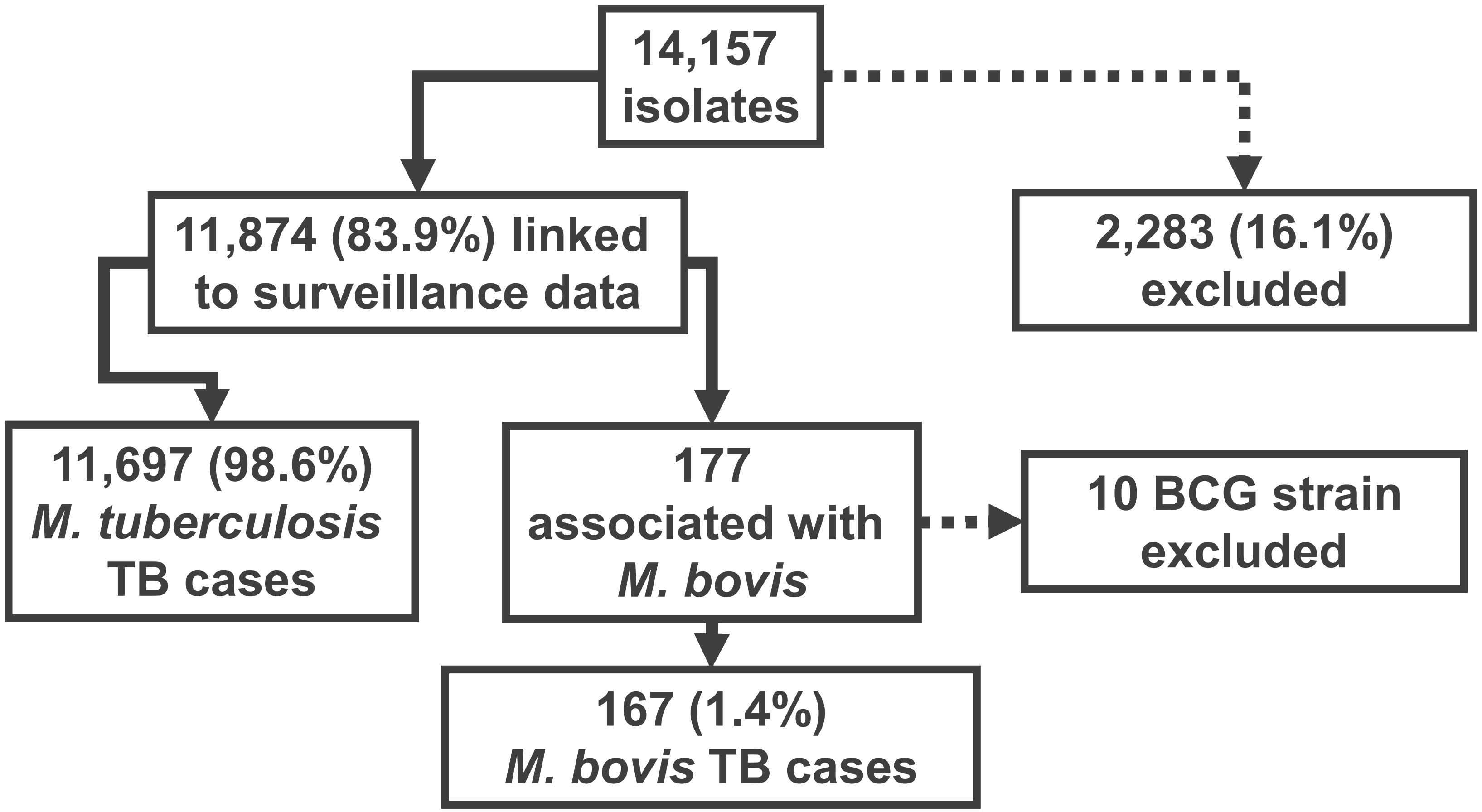
[1]Epidemic Intelligence Service, Office of Workforce and Career Development, and [2]Division of Tuberculosis Elimination, National Center for HIV/AIDS, Viral Hepatitis, Sexually Transmitted Diseases, and Tuberculosis Prevention, Centers for Disease Control and Prevention, and [3]Northrup Grumman, Atlanta, Georgia

Hlavsa et al. Clin Infect Dis. 2008 Jul 15;47(2):168-75.

Methods

- Linked laboratory and surveillance data
- *M. bovis* identified by genotyping
- Reviewed associated demographic and clinical factors

Derivation of Study Population



M. bovis Patient Characteristics

- 89% Hispanic
- 62% born in Mexico
- 19% age < 15 y.o. (compared with 2% for *M. tuberculosis)*
- 65% extrapulmonary disease site
- 26% HIV infected

Table 18. Genotyped Tuberculosis Cases with *Mycobacterium bovis*[1] by Origin of Birth: United States, 2004–2019

	Total Genotyped Cases	*Mycobacterium bovis* Cases					
		Total		U.S.-Born		Non-U.S.-Born	
Year	No.	No.[2]	(%)	No.	(%)[3]	No.	(%)[3]
2004	5,954	73	(1.2)	23	(31.5)	50	(68.5)
2005	7,497	80	(1.1)	22	(27.5)	58	(72.5)
2006	7,529	116	(1.5)	25	(21.6)	90	(77.6)
2007	8,425	113	(1.3)	17	(15.0)	95	(84.1)
2008	8,176	129	(1.6)	29	(22.5)	100	(77.5)
2009	7,700	113	(1.5)	27	(23.9)	86	(76.1)
2010	7,685	108	(1.4)	20	(18.5)	88	(81.5)
2011	7,600	117	(1.5)	30	(25.6)	87	(74.4)
2012	7,225	109	(1.5)	18	(16.5)	91	(83.5)
2013	7,052	96	(1.4)	22	(22.9)	74	(77.1)
2014	6,973	108	(1.5)	24	(22.2)	84	(77.8)
2015	7,200	125	(1.7)	31	(24.8)	94	(75.2)
2016	6,989	107	(1.5)	18	(16.8)	89	(83.2)
2017	6,954	99	(1.4)	18	(18.2)	80	(80.8)
2018	6,964	115	(1.7)	22	(19.1)	93	(80.9)
2019	6,875	133	(1.9)	23	(17.3)	110	(82.7)

M. bovis in San Diego

Table 1. Proportional contribution of *Mycobacterium bovis* and *M. tuberculosis* to total culture-positive TB cases, San Diego County, California, 1994–2005*

Year	Total TB cases	Total no. (%) culture-positive TB cases†	No. (%)‡ *M. bovis* cases	No. (%)‡ *M. tuberculosis* cases
1994	420	334 (80)	17 (5)	317 (95)
1995	438	308 (70)	18 (6)	290 (94)
1996	384	302 (79)	11 (4)	291 (96)
1997	332	266 (80)	17 (6)	249 (94)
1998	342	270 (79)	31 (11)	239 (89)
1999	299	225 (75)	19 (8)	206 (92)
2000	295	262 (89)	20 (8)	242 (92)
2001	330	274 (83)	23 (8)	251 (92)
2002	317	272 (86)	25 (9)	247 (91)
2003	315	258 (82)	29 (11)	229 (89)
2004	320	271 (85)	27 (10)	244 (90)
2005	305	249 (82)	28 (11)	221 (89)

*TB, tuberculosis.
†Excludes 11 case-patients who had an isolate of *M. tuberculosis complex* resistant to pyrazinamide, but did not have species-level identification. Percent given is of all TB cases.
‡Percent given is of total culture-positive TB case-patients.

Rodwell TC, Moore M, Moser KS, Brodine SK, Strathdee SA. Mycobacterium bovis tuberculosis in binational communities. Emerg Infect Dis June 2008

Characteristics of cases

Table 3. Odds ratios from final logistic regression model of variables correlated with TB from *Mycobacterium bovis* versus *M. tuberculosis*, San Diego County, California, 2001–2005*

Risk factors	*M. bovis* vs. *M. tuberculosis* (n = 130 vs. n = 1,186)	
	OR (95% CI)	p value
Age group, y (ref ≥65 y)		0.002
0–4	2.43 (0.81–7.28)	0.11
5–14	4.38 (1.38–13.9)	0.01
15–24	1.06 (0.45–2.49)	0.90
25–44	0.68 (0.31–1.45)	0.32
45–64	0.50 (0.21–1.15)	0.10
Race/ethnicity (ref = white)		<0.001
Hispanic	7.97 (2.36–26.93)	<0.001
Asian	0.08 (0.01–0.76)	0.03
Black	0	0.99
Other	0	0.99
Extrapulmonary disease	4.51 (2.36–8.62)	<0.001
Normal chest radiograph results	3.16 (1.63–6.11)	<0.001
Multisite disease	4.31 (2.54–7.3)	<0.001
HIV status† (ref = negative)		0.13
Positive	1.75 (0.93–3.29)	0.08
Unknown	0.87 (0.48–1.58)	0.65

*n = 1,316. TB, tuberculosis; OR, odds ratio; CI, confidence interval; ref, referent.
†Variable not significant in multivariate analysis.

M. bovis in New York City

- March 2004: 15 m.o. child died from peritoneal *M. bovis* infection
- Initiating event for investigation
- Review of genotyping data from TB cases, 2001-2004 revealed 35 cases of *M. bovis*
  - 1% of all TB cases in NYC

CDC. *MMWR*. 2005; 54: 605-608

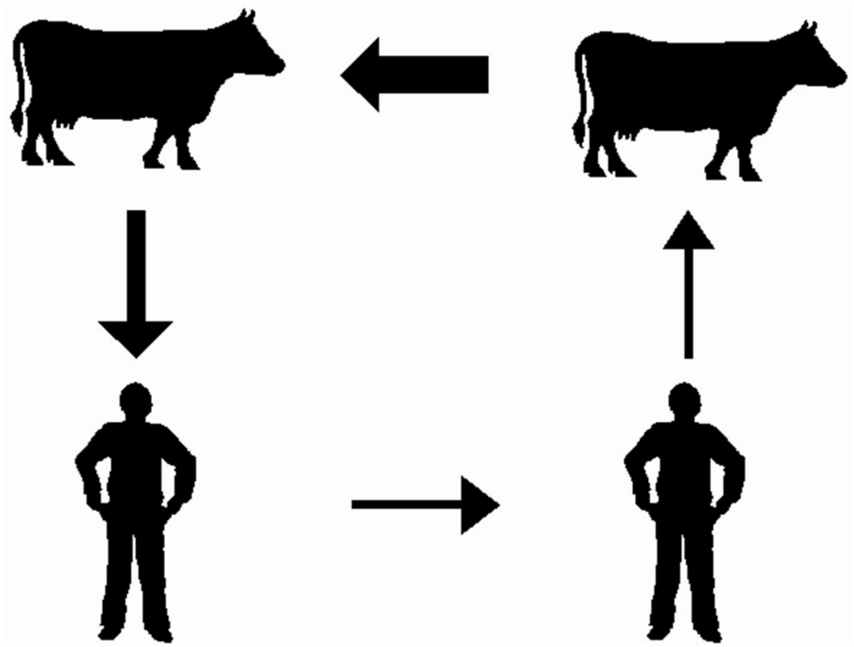
Characteristics of cases

- Of 23 adults, 22 were non-US-born
  - Mexico, Dominican Republic, Guatemala, Guyana
- Of 12 children (<15 years old), 10 were US born of Mexican parents
- Disease site: extrapulmonary 60%, pulmonary 26%, both 14%

CDC. *MMWR*. 2005; 54: 605-608

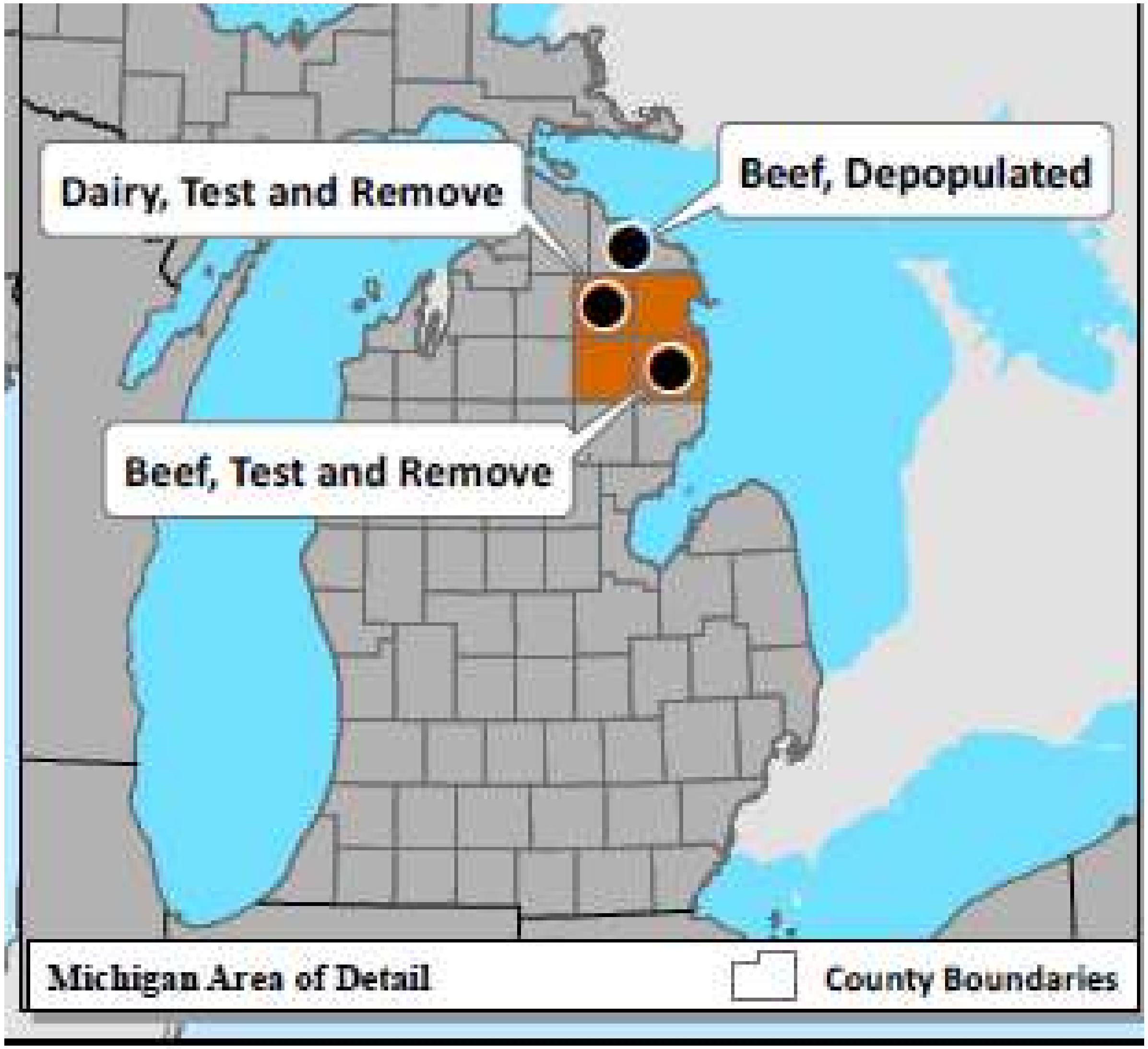
Transmission

- **Foodborne: ingestion of contaminated unpasteurized dairy products**
- Airborne: same as for *M. tuberculosis*
- Direct inoculation (cutaneous)
  - Butcher's wart
  - Hunters



Cycle of *Mycobacterium bovis* transmission between cattle and humans. The thickness of the arrows suggests probability. Adapted from *Collins and Grange* (1987).

But it can be more complicated…


Dairy, Test and Remove
Beef, Depopulated
Beef, Test and Remove
Michigan Area of Detail
County Boundaries

M. bovis in Michigan

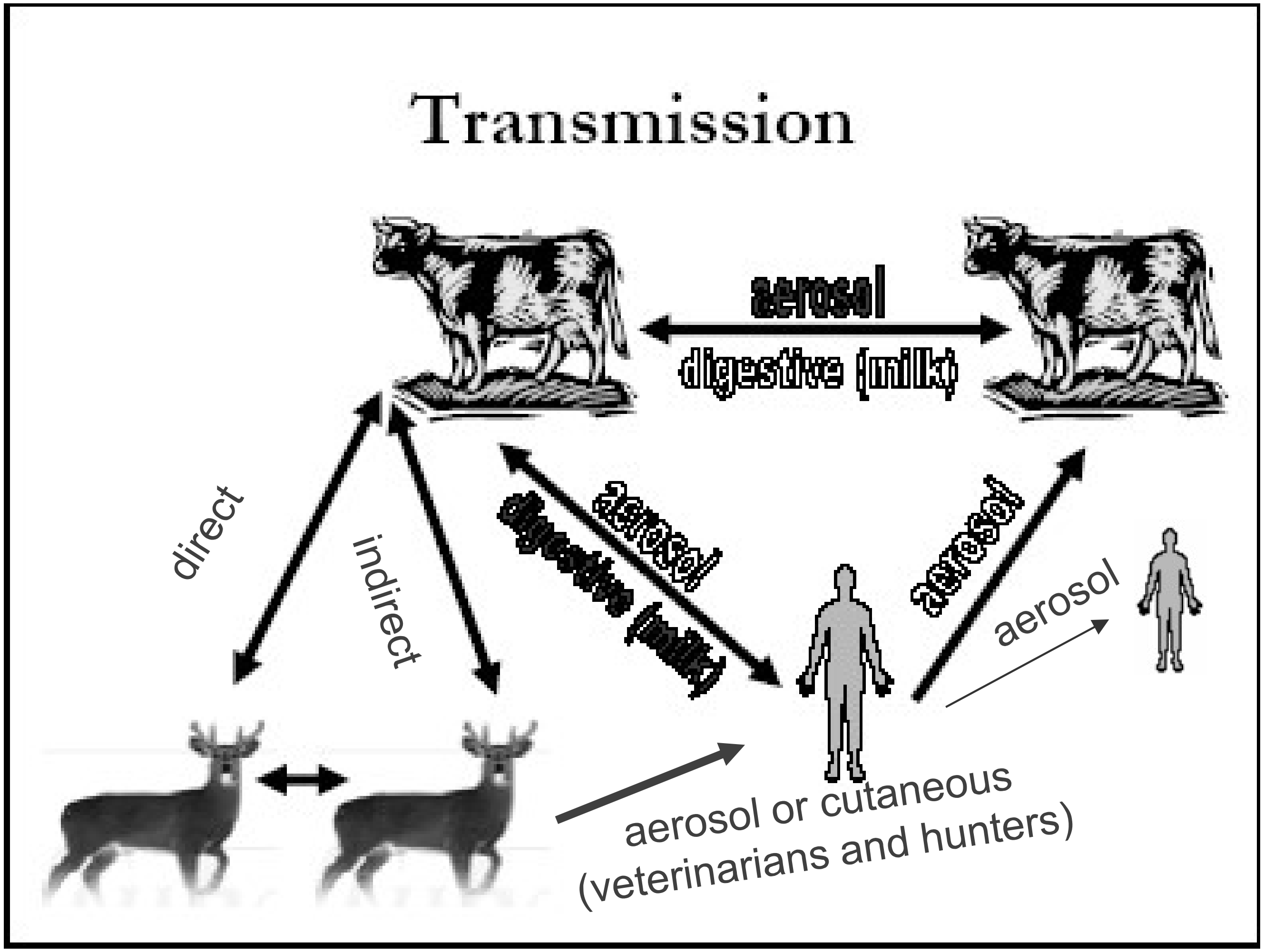
- 1979: Michigan declared TB free for cattle
- 1995-2013: 57 cattle herds in Michigan identified as *M. bovis* infected
- How did this happen?

Palmer, Transboundary and Emerging Diseases. 60 (Suppl. 1) (2013) 1–13

TB in Wildlife

Indirect Bidirectional Transmission

- Likely cattle originally infected deer
- Deer density increased because of hunting restrictions and supplemental feeding
- As *M. bovis* prevalence increased in deer, it was transmitted back to cattle
- Mechanism is likely indirect
  - Contamination of shared food source by shedding of organisms in secretions from infected animals
  - Experimentally demonstrated by USDA (Palmer et al., AJVR, Vol 65, No. 11, November 2004)


Transmission
aerosol
digestive (milk)
direct
indirect
aerosol
digestive (milk)
aerosol
aerosol
aerosol or cutaneous
(veterinarians and hunters)

Three Patients with *M. bovis* related to deer in Michigan (2002-2017)

- 74 y.o. with pulmonary *M. bovis*
  - Multiple deer exposures including running a business with a buck pole where hunters display killed deer
  - Isolate matched the circulating deer/cattle strain in Michigan
- 29 y.o. punctured finger while field dressing a deer
  - Developed wound infection with *M. bovis*
  - Isolate from wound and deer carcass matched the circulating deer/cattle strain in Michigan

Deer-related human *M. bovis* in Michigan

- 77 y.o. with rheumatoid arthritis (taking low dose prednisone) and pulmonary *M. bovis* disease
  - Lived in areas of Michigan where *M. bovis* present in deer
  - Regularly hunted and field dressed deer

Wilkins et al. Emerging Infectious Diseases. Vol. 14, No. 4, April 2008
Sunstrum et al. MMWR Weekly, September 20, 2019 / Vol. 68 / No. 37

Badger (*Meles meles*)

United Kingdom

An example from UK

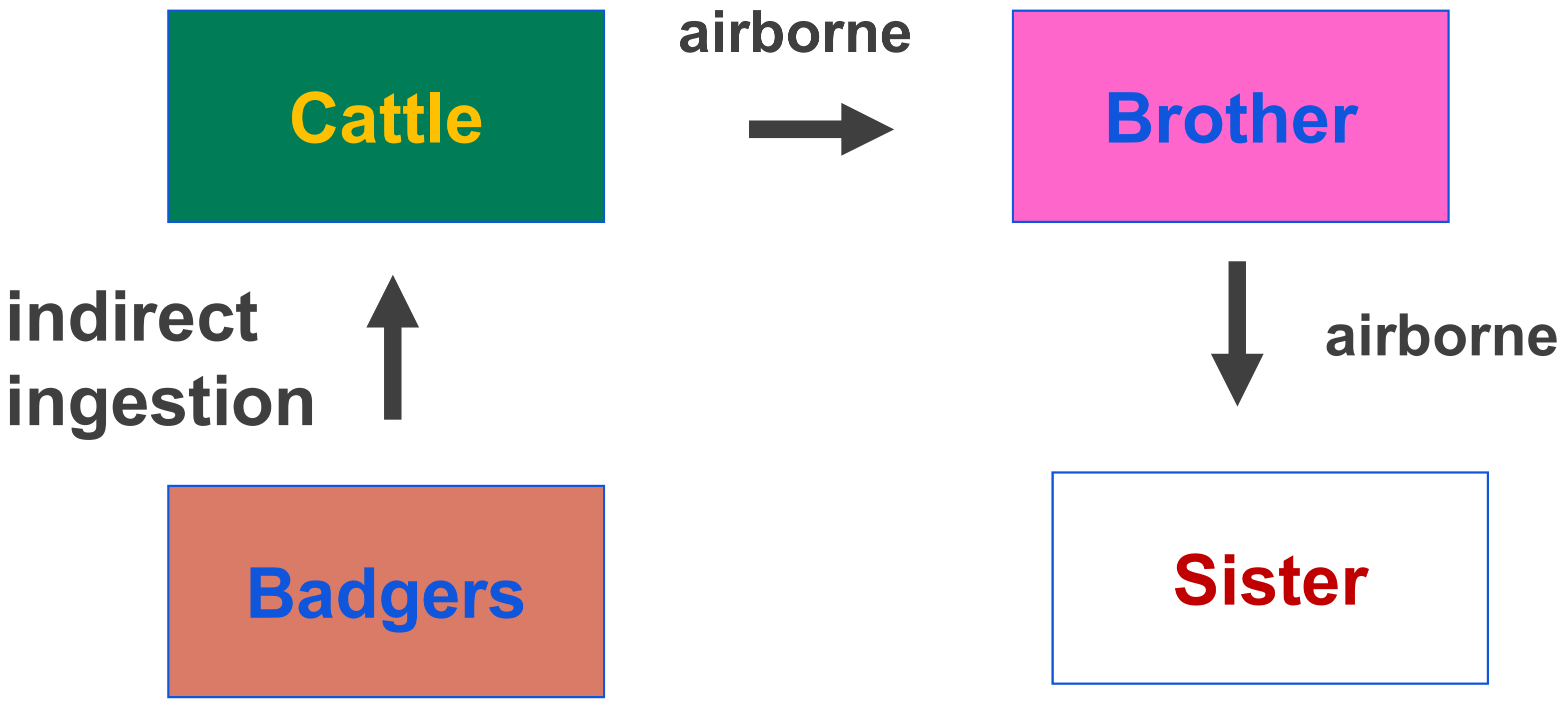
- Brother and sister living on farm diagnosed with *M. bovis*
  - Brother AFB smear negative, cavitary disease
  - Sister AFB smear negative pulmonary disease
- Neither drank unpastuerized milk
- Brother assisted at veterinary examinations of cattle
  - Became covered in cow mucus and saliva
- Sister had no contact with cattle

Smith et al. Emerg Infect Dis 2004; 10: 539-541

Example from UK

- 6 years prior, 5 of 15 cattle had *M. bovis* and herd was slaughtered
  - 5 badgers were trapped: 4 had *M. bovis*
- 3 years later, 3 of 8 cattle had *M. bovis* and herd was slaughtered
  - 1 badger trapped: it had *M. bovis*

Smith et al. Emerg Infect Dis 2004; 10: 539-541


Cattle
airborne
Brother
indirect ingestion
airborne
Badgers
Sister

Human-to-Human Transmission

"Possibly as a consequence of the assumption that *M. bovis* is less virulent than *M. tuberculosis* for humans, there has been a widespread assumption that human-to-human transmission of *M. bovis* leading to disease occurs very rarely or not at all."

From Grange JM. *Mycobacterium bovis infection in human beings.* Tuberculosis 2001; 81: 71-77

Evidence for Human-to-Human Transmission

- MDR *M. bovis* outbreaks in HIV-infected patients
  - Matching genotypes
- Sporadic case reports of contacts of pulmonary *M. bovis* patients who became infected with no other source

Additional Evidence from San Diego

- *M. bovis* patients with pulmonary disease have similar frequency of infectious characteristics (e.g., cavities on CXR, positive AFB smear)
- TST conversion rates (indicator of recent transmission) among contacts of pulmonary *M. bovis* and contacts of pulmonary *M. tuberculosis* patients are similar
- Cluster of 3 pulmonary *M. bovis* patients in one family with matching genotypes

LoBue et al. *Int J Tuberculosis Lung Dis*. 2004; 8: 868-872

LoBue et al. Int J Tuberculosis Lung Dis. 2004; 8: 1142-1146

Cluster of human tuberculosis caused by *Mycobacterium bovis*: evidence for person-to-person transmission in the UK

Jason T Evans, E Grace Smith, Ashis Banerjee, Robert M M Smith, James Dale, John A Innes, David Hunt, Alan Tweddell, Annette Wood, Charlotte Anderson, R Glyn Hewinson, Noel H Smith, Peter M Hawkey, Pam Sonnenberg

	Sex	Age at onset (years)	Site of disease	Smear status	Cattle contact or consumption of unpasteurised milk	Disease onset	Diagnosis	Follow-up
1	M	36	Lung, LN	Positive	Unpasteurised milk consumption, history of occupational cattle contact	April, 2003	July, 2004	Completed treatment June, 2005
2	M	29	Lung	Positive	Recreational fishing—limited cattle contact	Nov, 2004	Sept, 2005	Completed treatment June, 2006
3	F	29	Lung	Positive	Not known	April, 2005	Sept, 2005	Completed treatment June, 2006
4	M	42	CNS	Negative	Not known	Feb, 2005	Nov, 2005	Died February, 2006
5	M	31	Lung, LN	Initially negative, then positive	Milked cattle as a child	May, 2005	June, 2005	Poor initial compliance; completed treatment December, 2006
6	M	23	Lung	Positive	Childhood farm visits	Aug, 2005	Feb, 2006	Still on treatment, but well

M=male. F=female. LN=lymph node.

Table 1: Characteristics of the six patients in the cluster

Lancet 2007; 369: 1270–76

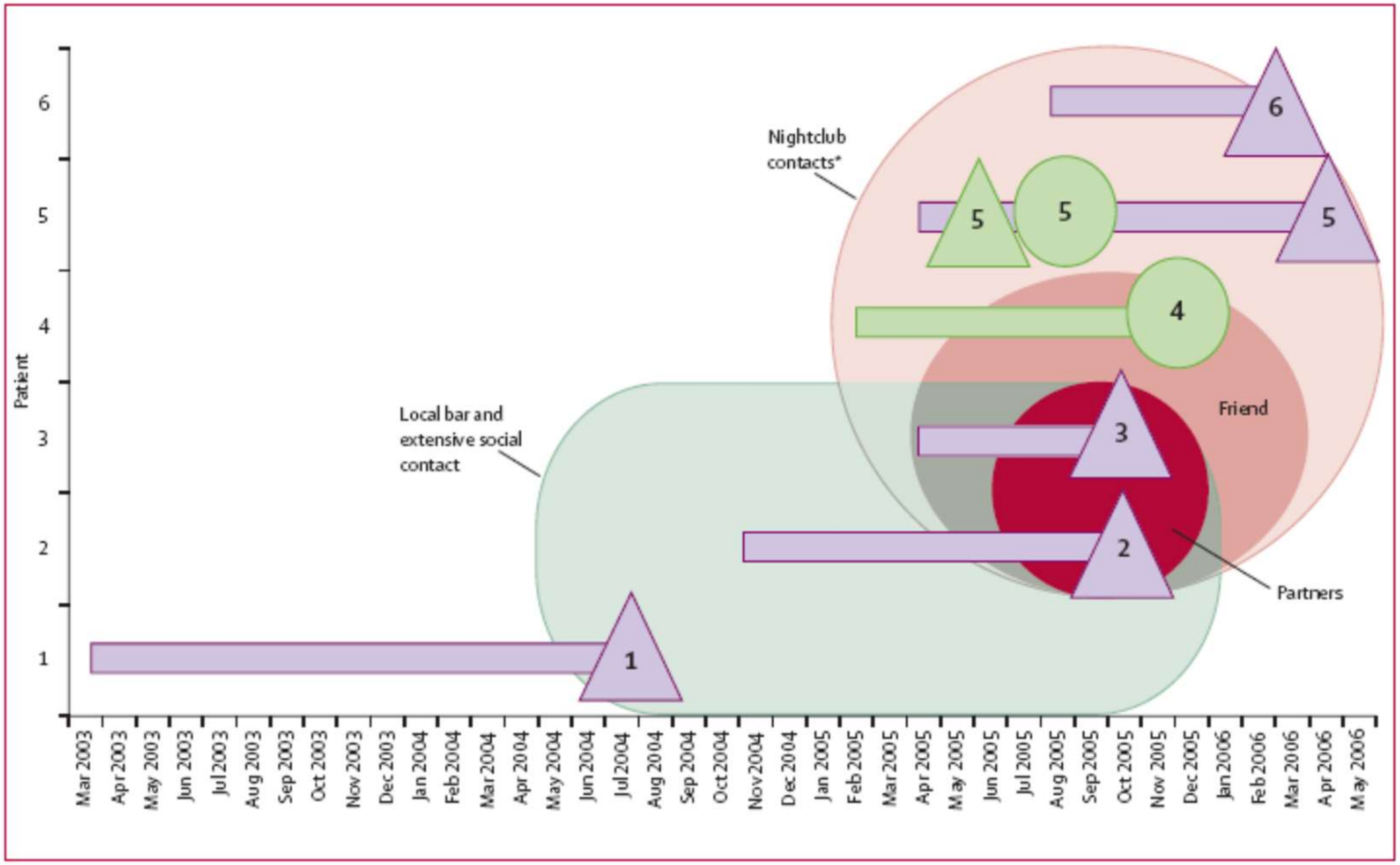


Figure 2: **Timeline of six cases of human *M bovis* tuberculosis in the West Midlands cluster**
Horizontal bars indicate time from symptom onset to treatment initiation (duration of infectiousness). Purple triangles represent culture positive smear-positive pulmonary specimens. Green triangles represent culture-positive smear-negative pulmonary specimens. Green circles represent culture-positive smear-negative non-pulmonary specimens. Venn circles represent social links between cases. X-axis represents probable duration of infectiousness and not duration of exposure in different settings. Y-axis represents each of the six patients. *Patients 4 and 5 were nightclub workers.

Foodborne Transmission in the United States

Real (Baja) California Cheese

- Fresh cheese (e.g., queso fresco) made in Mexico often from unpasteurized milk
- Not the type commercially available in United States; imported by individuals for their own consumption
- Bypasses FDA/USDA regulation and inspection

Queso Fresco

Discount Price: $7.56
every day
Volume price: $6.81
w/ $100.00 purchase
Wholesale price: $6.05
w/ $300.00 purchase

One of the most favorite Mexican cheeses, Queso Fresco is a fresh cheese of various sizes and shapes made from 100% cow's milk. The cheese has a grainy feel and very mild, fresh acidity. Queso Fresco is used for grilling and baking and it can also be used in salads. It softens but does not melt when heated.

Evidence Implicating Mexican Cheese in Foodborne Transmission

- San Diego
  - Most studied because of high incidence
  - Comparison of human (San Diego) and cattle (Mexico) genotypes
- FDA/USDA sampling program
- New York City
- Maryland

San Diego

- Epidemiology suggestive
  - Disproportionately extrapulmonary (GI TB 9 times more likely), Mexican or US-born Hispanic
  - Children age < 12 months, *M. bovis* 6% of culture-positive TB (Dankner, Davis Pediatrics 2000;105:e79; all children (age < 15 years) *M. bovis* > 35% of culture-positive TB
- Studies showing
  - Continuing problem with disease in Mexican cattle herds
  - Up to 30% of milk is not pasteurized in some parts of Mexico
- Pediatric LTBI study by Besser et al. (Pediatrics 2001;108:305-10)
  - Children who consumed raw milk or cheese were 3 times more likely to have a positive TST

FDA/USDA Sampling

- FDA program at US-Mexico border in San Diego
- Collected samples of cheese from persons bringing it in from Mexico
- Samples sent to USDA lab for culture
- Isolated *M. bovis* from one of the samples

Harris et al. Appl Environ Microbiol. 2007;73:1025-8

How Widespread is Queso Fresco Consumption in San Diego?

- Study of over 1000 Latino adolescents in San Diego (EJ Blumberg et al. Proc Am Thoracic Soc. 2006;3:A505)
- 1/3 indicated they ate queso fresco

Genotypic Matching of Human and Cattle *M. bovis* Isolates

- 106 human isolates from San Diego
- 496 Mexican cattle isolates
  - Convenience sample from surveillance program
- 91% of human isolates had an identical spoligotype to one found in Mexican cattle

Rodwell et al. Int J Infect Dis. 2010 September ; 14S3: e129–e135

New York City Investigation

- Interviewed 23/35 patients with *M. bovis* disease
- 19/23 (83%) reported eating cheese imported from Mexico
- Sources of cheese:
  - courier agency bringing products from Mexico
  - visitor carrying food in luggage
  - Mexican specialty grocery
  - door-to-door vendor

CDC. *MMWR*. 2005; 54: 605-608

Maryland, 2005

- Five pediatric cases of *M. bovis* in Montgomery and Prince Georges counties during 2005
- One death occurred
- All five cases involved Mexican-American children born in the US
- In all five cases, the children consumed Mexican cheese or cream products that were believed to be unpasteurized

Clinical and Radiographic Manifestations of Tuberculosis Caused by *M. bovis*

- *M. tuberculosis* disease and *M. bovis* disease in humans are clinically and radiographically indistinguishable
  - Demographic, clinical and social characteristics may be suggestive
  - Younger age, extrapulmomary disease, born in or travel to Mexico
- Differentiation depends upon laboratory isolation and identification

Distinguishing Microbiological Characteristics

- In solid egg-based media, requires pyruvate supplementation
- (Essentially) universally resistant to PZA
- TCH* sensitive
- Niacin test negative
- Nitrate test negative
- Genotyping techniques (e.g., combination of spoligotyping and MIRU)
- Gene deletion analysis
- Whole genome sequencing

*thiphen-2-carboxylic acid hydrazide

Treatment – Drug Susceptible

- *M. tuberculosis:* Standard is isoniazid, rifampin, and pyrazinamide for 2 months, then isoniazid and rifampin for 4 months
- *M. bovis* (pyrazinamide resistant): standard is isoniazid and rifampin for 9 months
  - Some clinicians may add ethambutol

Systematic Review of Treatment (1)

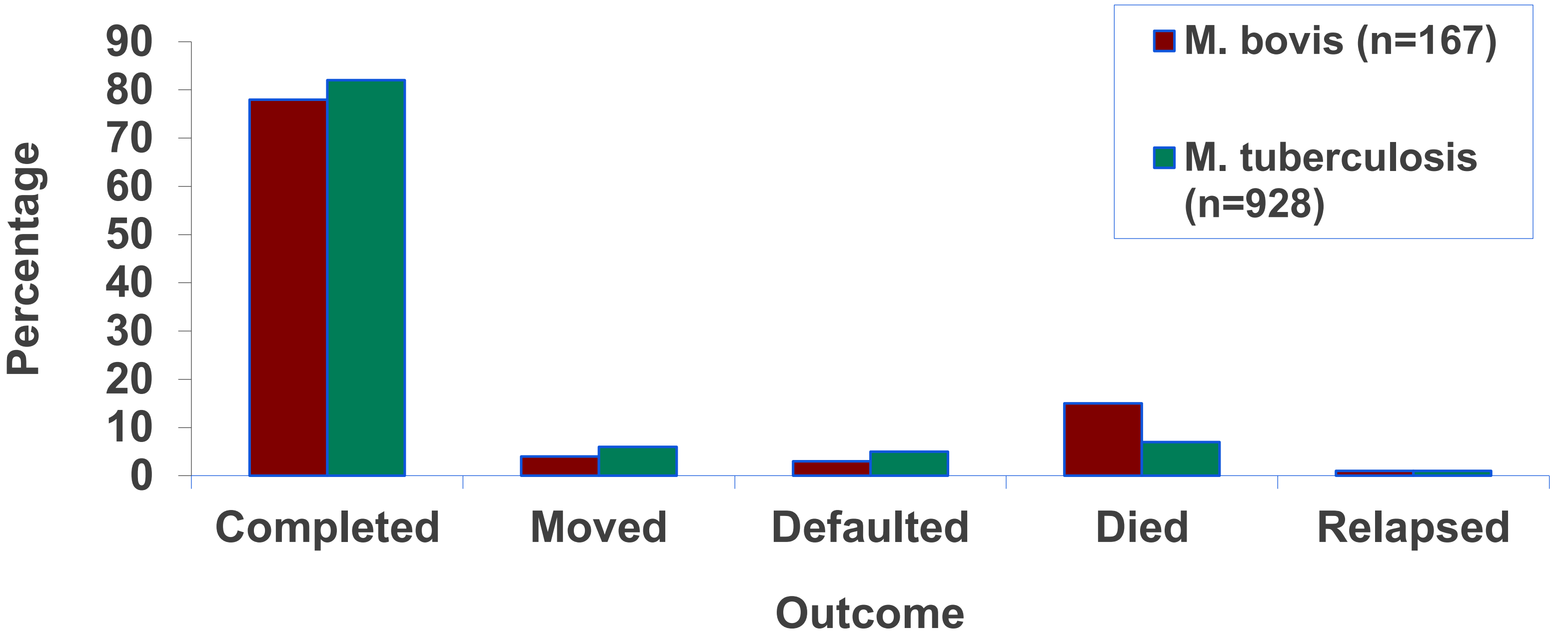
- 3 observational studies
- Grouped into 2 cohorts of 156 patients receiving isoniazid and rifampin for 6-9 months and 2 cohorts of 113 patients of isoniazid, rifampin and ethambutol for 6-12 months
- When denominator for success rate included all poor outcomes (including death) success was 74% for the isoniazid-rifampicin regimen and 79% for the isoniazid-rifampicin-ethambutol regimen, respectively
- When denominator included only success + fail + relapse, success rates were 99% and 93% for the isoniazid-rifampicin regimen and the isoniazid-rifampicin-ethambutol regimen, respectively

Lan et al. European Respiratory Journal 2016 48: 1500-1503

Systematic Review of Treatment (2)

- Impact on treatment outcomes of 6 months’ or 9 months’ duration or from the added use of ethambutol could not be estimated due to the limited number of studies and patients.
- Major reason for low success rates when all outcomes were considered was the high mortality in all three studies.
  - In two studies high mortality could have been due to the high rates of HIV co-infection in the patients.

Treatment Outcomes
San Diego, 1994-2003



LoBue et al. Int J Tuberculosis Lung Dis. 2005; 9: 333-338

Latent TB Infection

- No data
- In theory, recommended *M. tuberculosis* regimens should work if INH/rifamycin susceptible

Questions?

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov