Infection Source and Epidemiology of NTM lung disease

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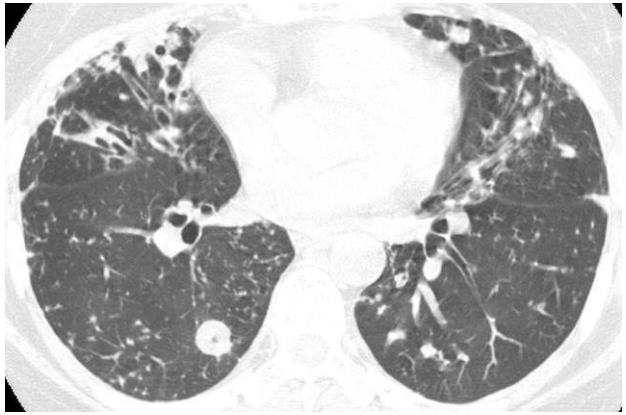
Taxonomy of Mycobacteria

Kingdom	계	Bacteria
Phylum	문	Actinobacteria
Order	강	Actinomycetales
Suborder	목	Corynebacterineae
Family	과	Mycobacteriaceae
Genus	속	Mycobacterium
Species	종	> 150 species

M. tuberculosis complex

M. leprae

Nontuberculous mycobacteria



Relapse vs Reinfection

0	1	2	3	4	5	6	7	8	9	10	11	12
AFB 1+ *M. avium*		-/-		-/-		-/-		-/-		-/-		AFB 1+ *M. avium*

- Microbiological recurrence by genotyping

	Still on Treatment	After completion
	25 / 180 (14%)	74 / 155 (48%)
Reinfection	48%	75%
True relapse	52%	25%

Wallace RJ Jr et al. Chest 2014;146:276

Infection source: Clinical implication

1. To prevent new infection in susceptible individuals
2. To prevent worsening of infection in patients who had minimal NTM lung disease
3. To achieve better control of established patients
4. To prevent recurrence after completion of treatment

I. Infection source : Key questions

- Where is NTM?
- How did people get NTM?
- Who is at risk?
- What is the preventive measures?

NTM: Environmental source

- Ubiquitous organism
- Water
  - Natural water: lakes, rivers, streams, swamps
  - Water distribution systems : water pipeline, tanks,
  - Individual homes
    - drinking water, shower head,
    - water filters, room humidifier
  - Hospital: catheters, scopes, heaters/coolers
- Soils, Dusts

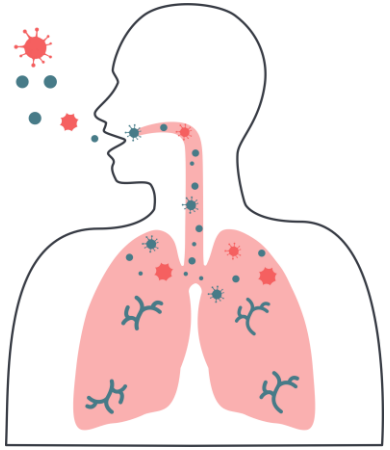
NTM: Characteristics

- Lipid-rich outer membrane

characteristic	Clinical relevance
Slow-growing	Slow-dying, adaptation
Hydrophobic	Readily aerosolized
	Biofilm formation
	Antibiotic-resistant
	Disinfectant-resistant
Oligotrophic	Grow in drinking water
Microaerobic	Stagnation-growth
Heat-resistant	Survive in hot water heater
Amoebae-resisting	Growth in amoebae

NTM: Transmission

Aerosolization & inhalation

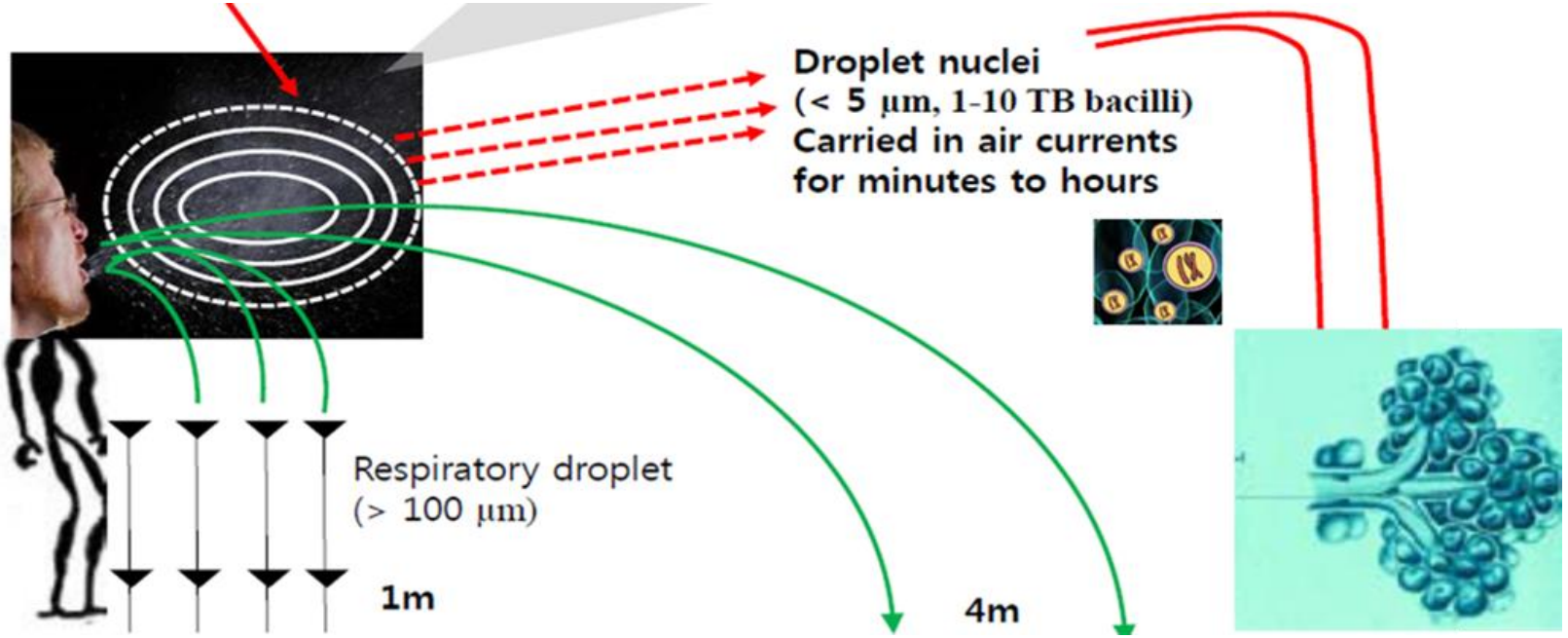


Swallowing & aspiration

Introduction into wounds

Falkinham JO 3rd. Clin Chest Med 2015;36:35.

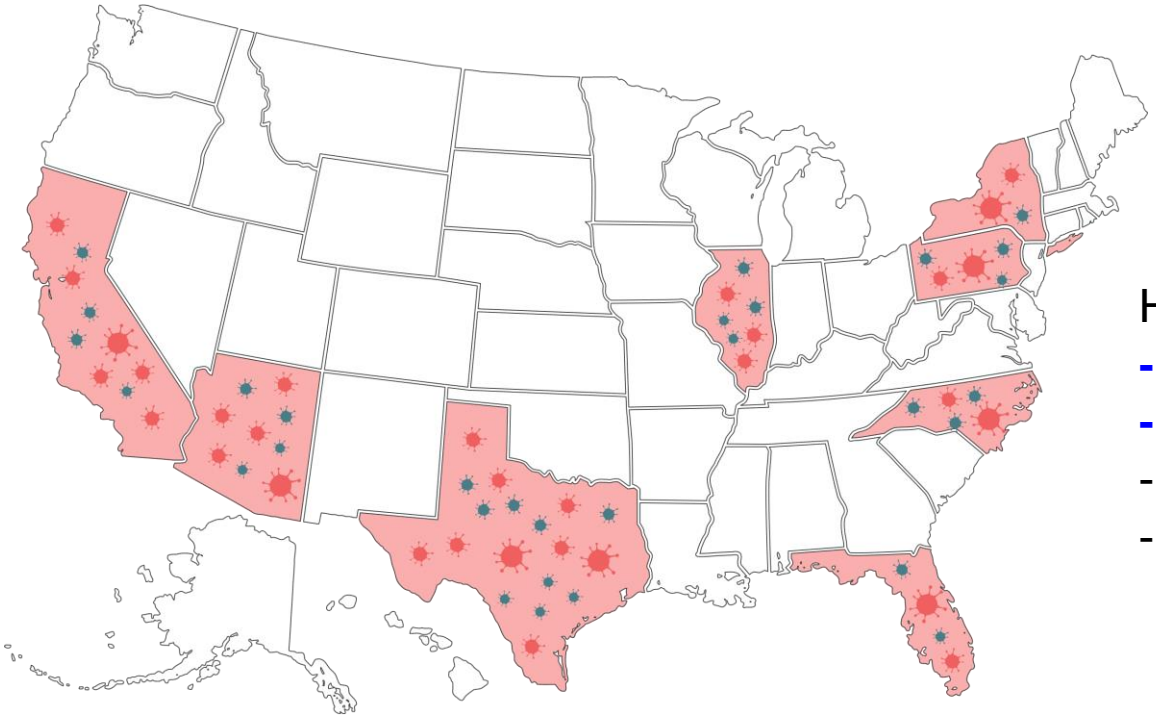
TB : airborne transmission



NTM : aerosolization from natural source

Spatial Clusters of Nontuberculous Mycobacterial Lung Disease in the United States

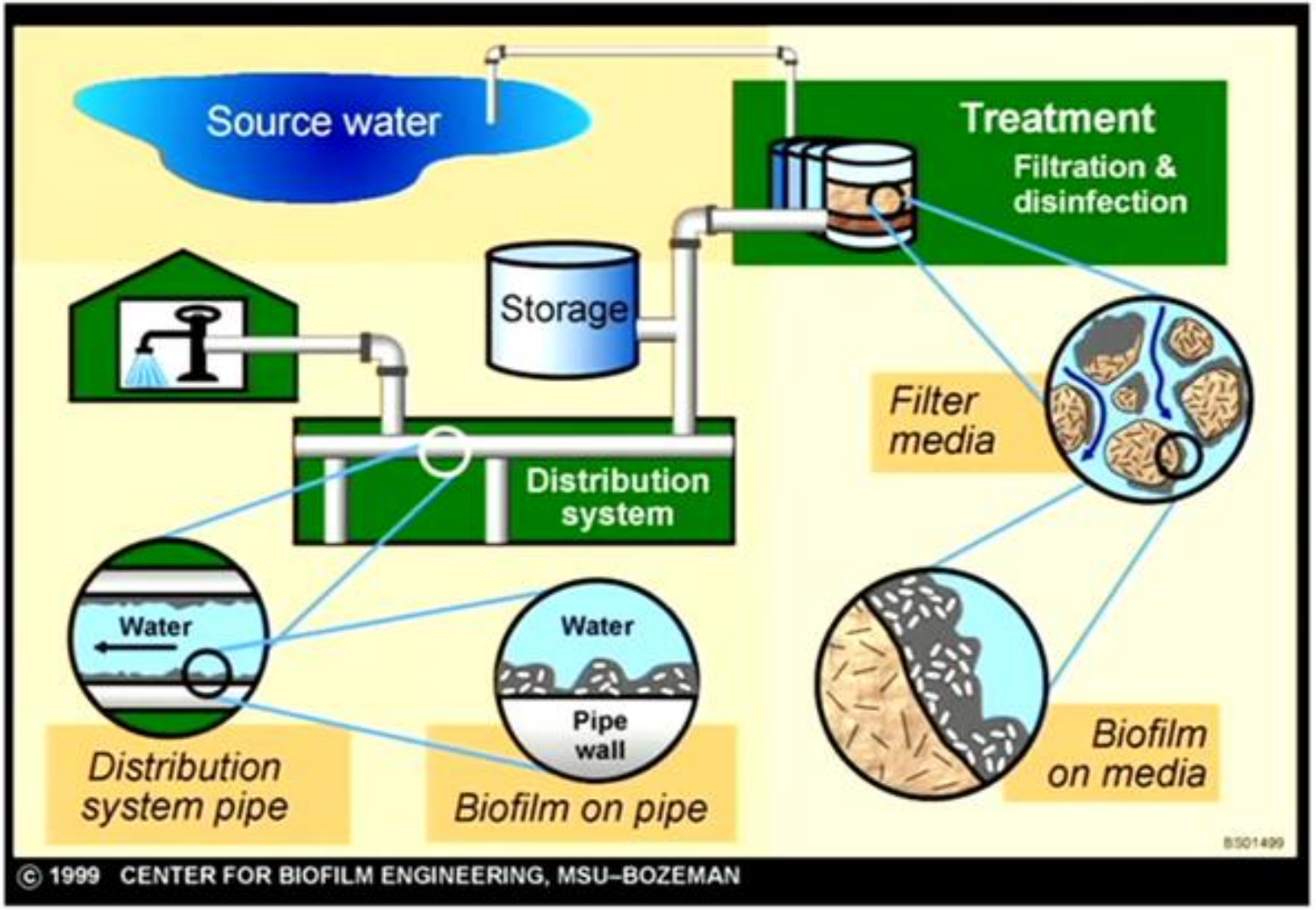
Adjemian J et al. Am J Respir Crit Care Med 2012;186:553



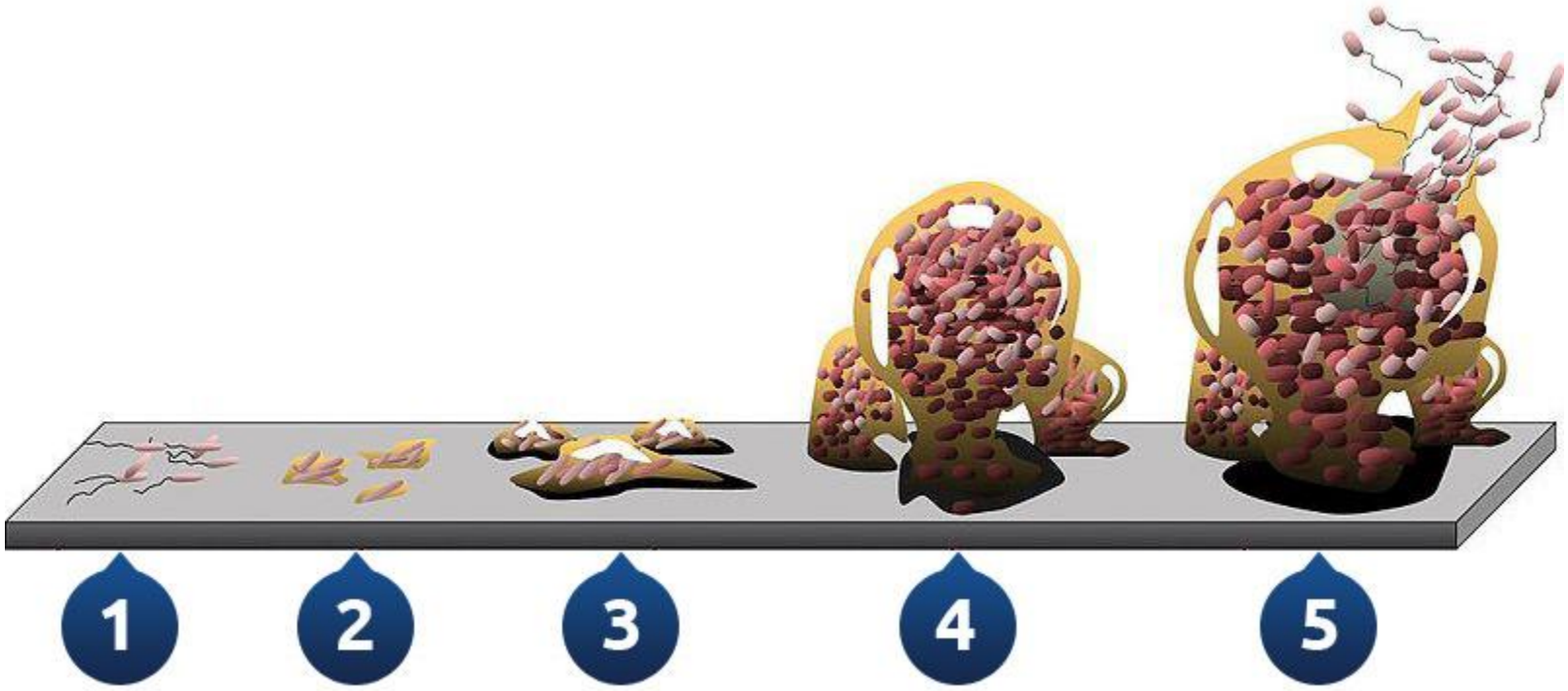
High risk states
- **Surface water (OR 4.6)**
- **Evaporation (4.0)**
- Copper (1.2) & NA+ (1.9)
- < manganese (0.7)

Eight states have the highest rates of NTM infection.
7 out of 10 of all NTM infections in the US occur along a coastal area.

NTM in water distribution system



Biofilm maturation cycle



Initial attachment

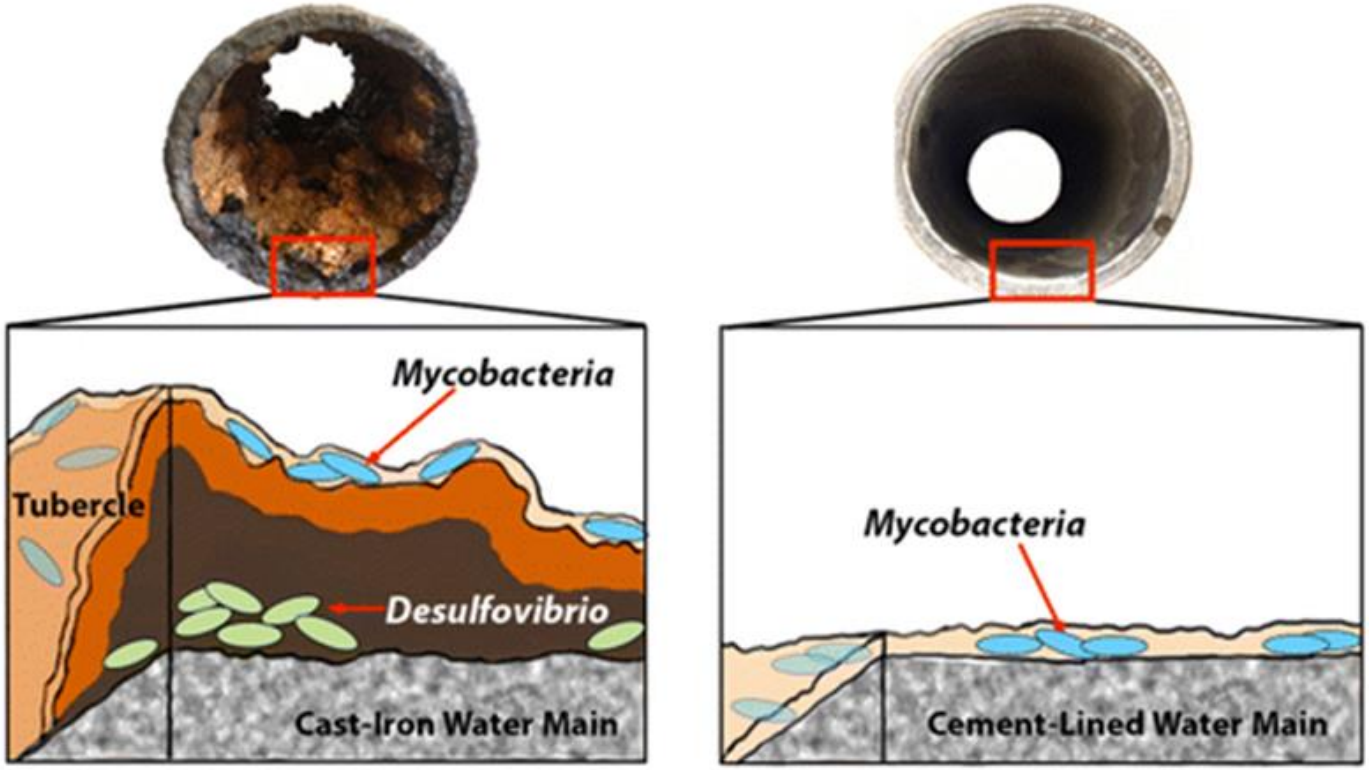
Irreversible attachment

Maturation

Dispersion

Sulfate Reducing Bacteria and Mycobacteria Dominate the Biofilm Communities in a Chloraminated Drinking Water Distribution System

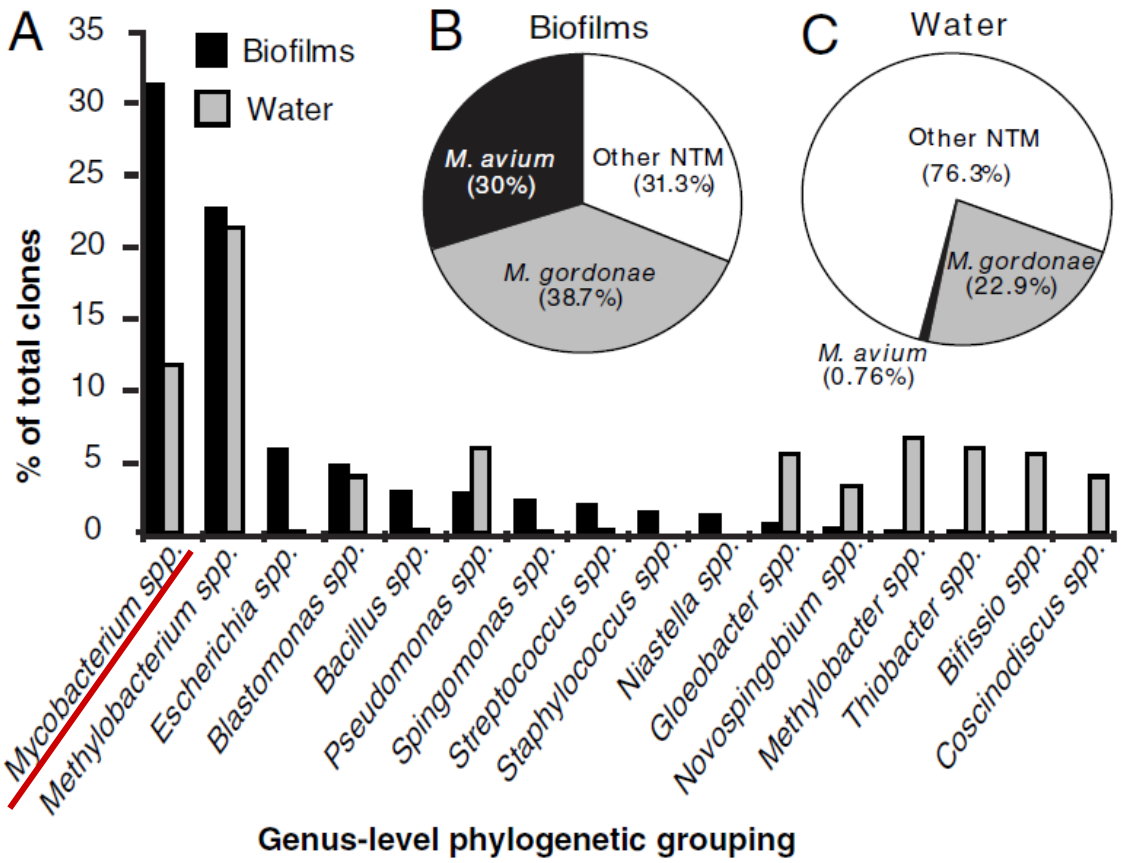
C. Kimloi Gomez-Smith,[†,‡] Timothy M. LaPara,[†,§] and Raymond M. Hozalski*[,†,§]



Environ Sci Technol 2015;49:8432

Opportunistic pathogens enriched in showerhead biofilms

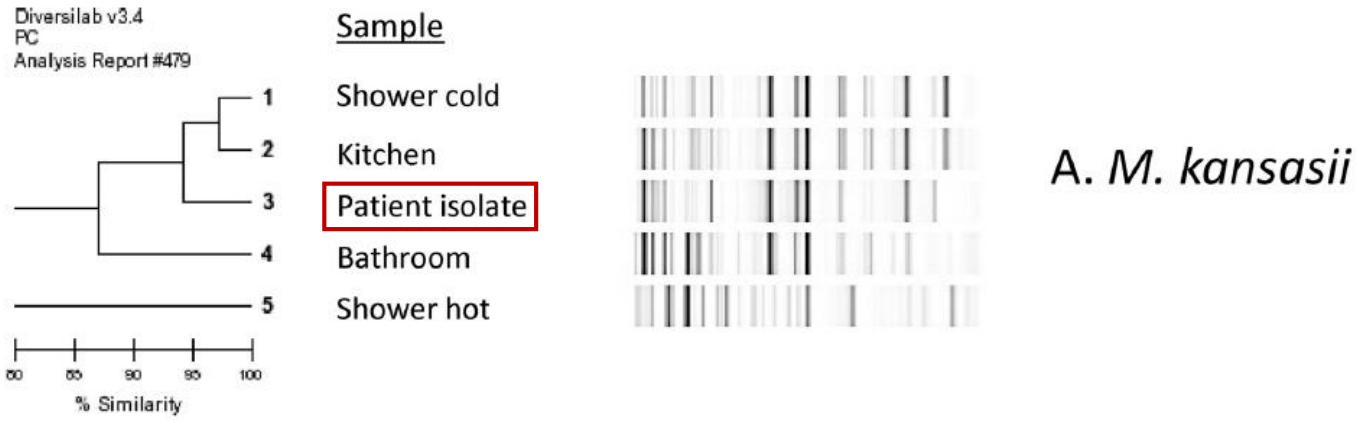
Leah M. Feazel[a], Laura K. Baumgartner[a], Kristen L. Peterson[a], Daniel N. Frank[a], J. Kirk Harris[b], and Norman R. Pace[a,1]



Proc Natl Acad Sci USA 2009;06:16393

Isolation of Nontuberculous Mycobacteria (NTM) from Household Water and Shower Aerosols in Patients with Pulmonary Disease Caused by NTM

Rachel Thomson,[a] Carla Tolson,[b] Robyn Carter,[b] Chris Coulter,[b] Flavia Huygens,[c] Megan Hargreaves[d]



J Clin Microbiol 2013;51:3006

NTM disease linked by DNA fingerprints to:

Showerheads, drinking water

Bronchoscopes, arthroscopes

Disinfectant solutions

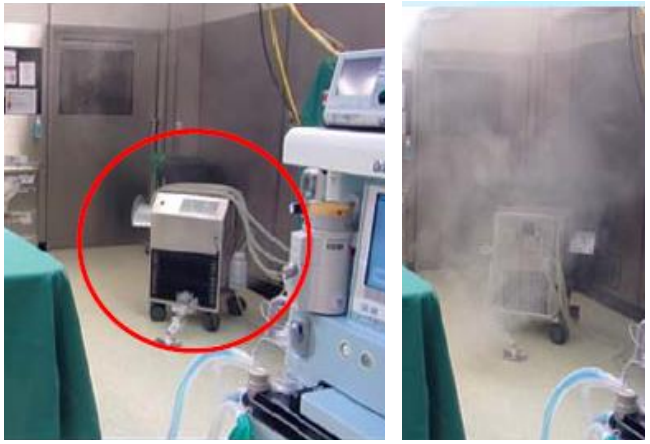
Hospital-Acquired NTM Infections

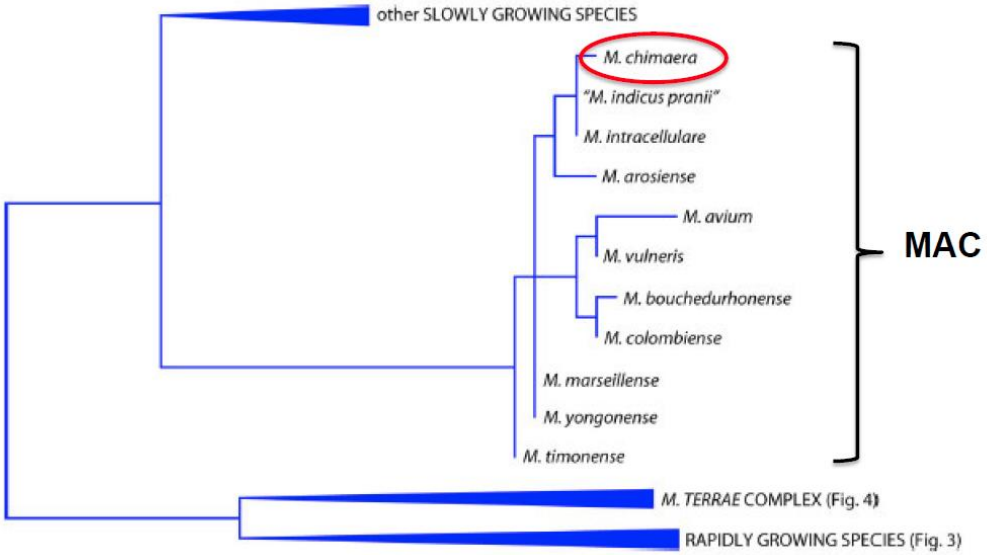
- Showerhead-associated
- Renal dialysis
- Kidney, bone marrow transplantation
- Bacteremia following cardiovascular surgery
- Patients in ICU
- Breast infection following augmentation mammoplasty
- Pulmonary infections d/t contaminated bronchoscopes
- Joint infections d/t contaminated arthroscopes
- Joint infection following steroid injections




Mycobacterium chimaera Spread from Heating and Cooling Units in Heart Surgery

- Outbreaks in USA, United Kingdom, Australia
- FDA and ECDC Alerts





Williamson D et al. N Engl J Med 2017;376:6

Exposure to NTM: everywhere & everyday

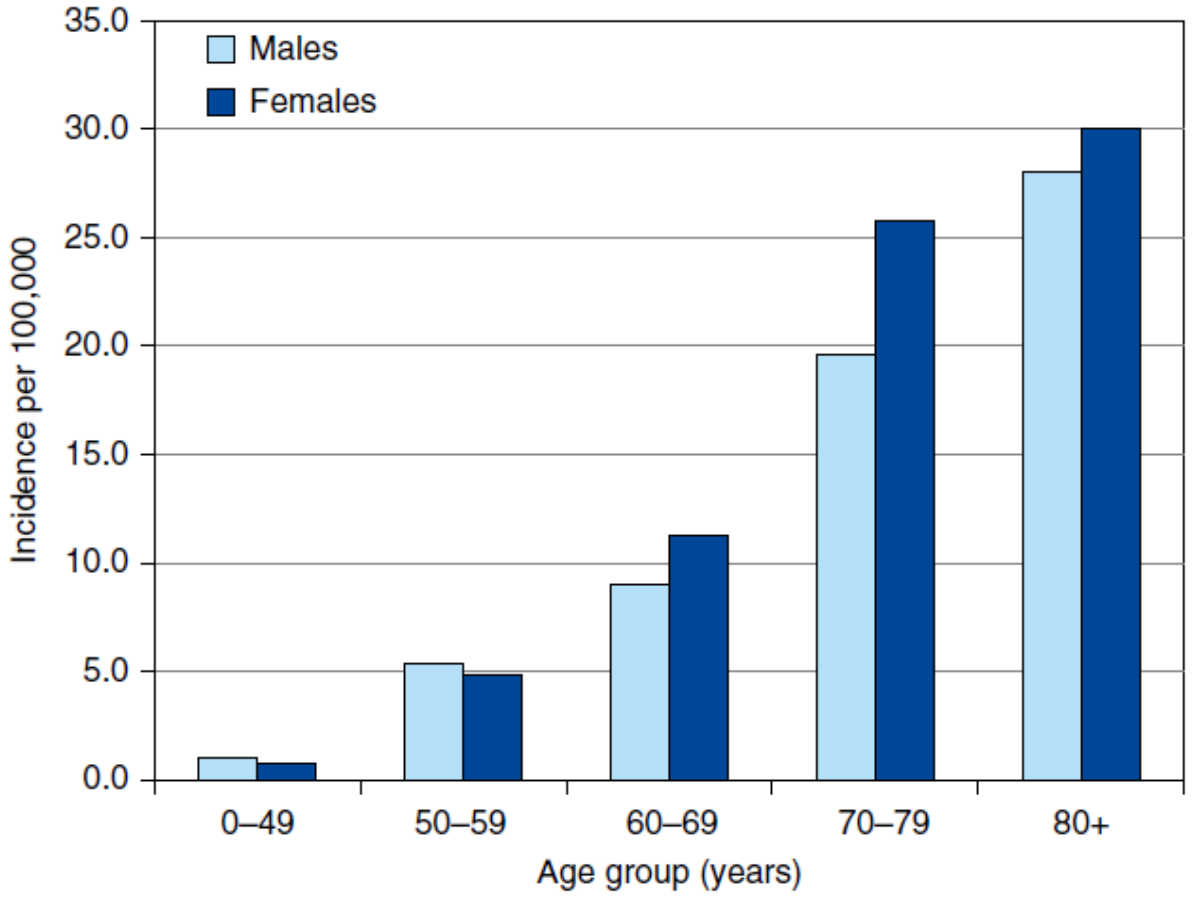







NTM exposure is universal but NTM disease is relatively rare.. Why?

Host factor : Age



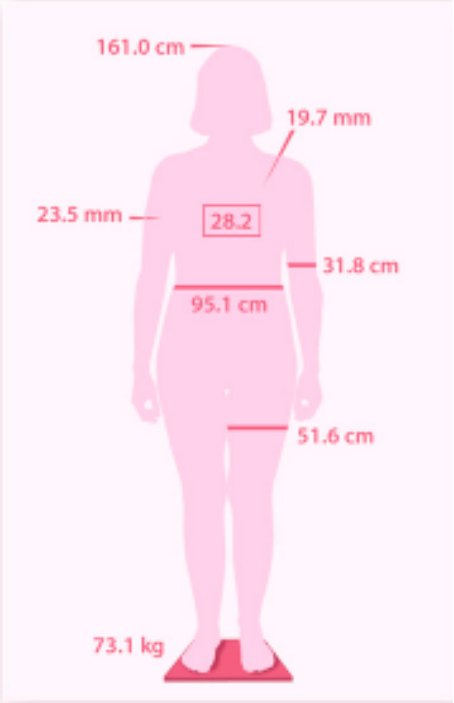
Henkle E et al. Ann Am Thorac Soc 2015;12:642

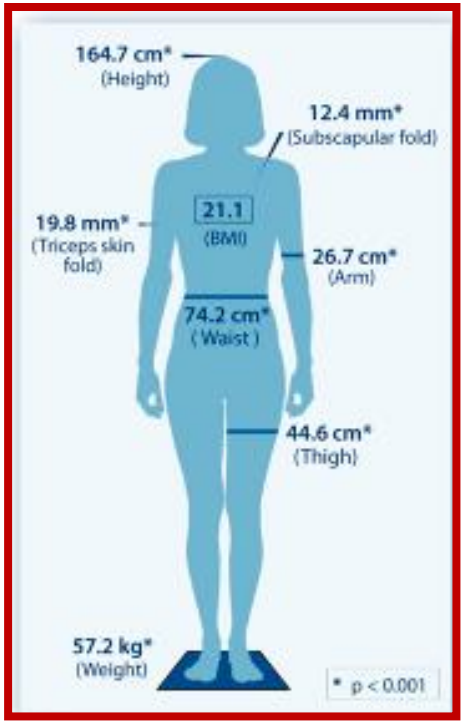
Host factors

Risk Factor	RR or OR
Lung disease	
Bronchiectasis	44-187.5
COPD	2 – 10
Lung cancer	3.4
Immunosuppression	
Rheumatoid arthritis	1.5, 1.9
Ant-TNF agents	2.2
Other	
Thoracic skeletal abnormalities	5.4
Low body weight	9.1
GERD	1.5, 5.3

Prevots DR, Marras TK. Clin Chest Med 2015;36:13

NTM Morphotype





Middle aged white females

Slender, tall,

Scoliosis, Pectus excavatum

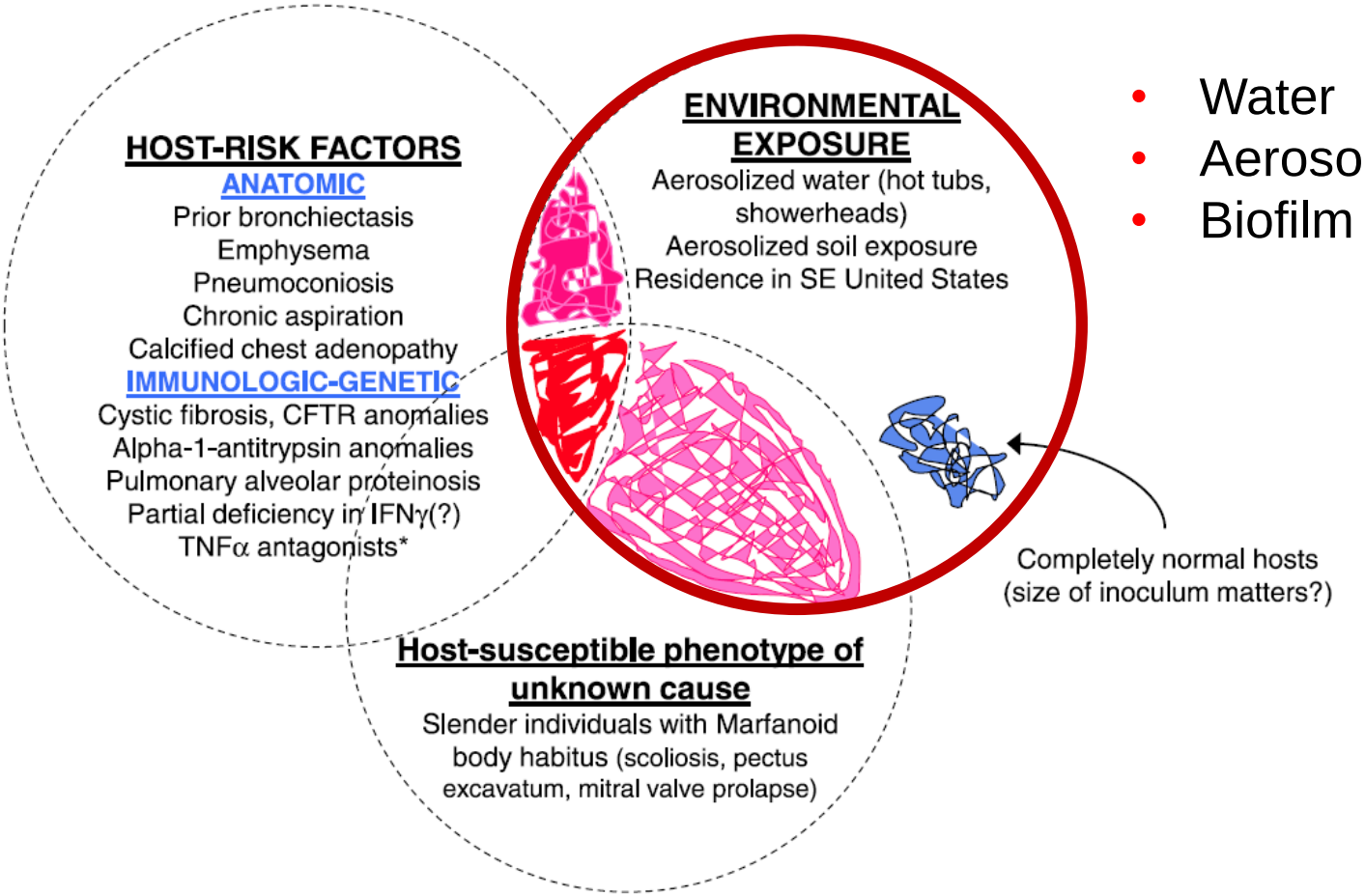
Mitral Valve prolapse

Higher % of CFTR genes

No cellular immune defects

Kim et al. Am J Resp Crit Care Med 2008;178:1066

Pathogenesis: Two Hit Hypothesis



- Water
- Aerosol
- Biofilm

Honda JR et al. Clin Chest Med 2015;36:1

Measures to reduce NTM number

- Raise hot water heater temperature to 55^{o}C
- For drinking, boiling (ie, 100^{o}C) for 10 minutes
- Use well water, rather than piped utility supply
- Use bacteriologic filters (pore size ≤ 0.45 um) on taps and showerheads
- Use showerhead with large holes to reduce mist formation
- Disinfect showerhead by submerging in household bleach for 30 minutes
- Increase bathroom exhaust rate
- Avoid dust inhalation when gardening; moisten garden and potting soils

#. These recommendation is not based on direct trials.

Falkinham JO 3rd. Clin Chest Med 2015;36:35.

II. Epidemiology : Key questions

- Global trend in NTM burden
- Geographic diversity of NTM species
- Impact on public health
- Evidence on human-to-human transmission

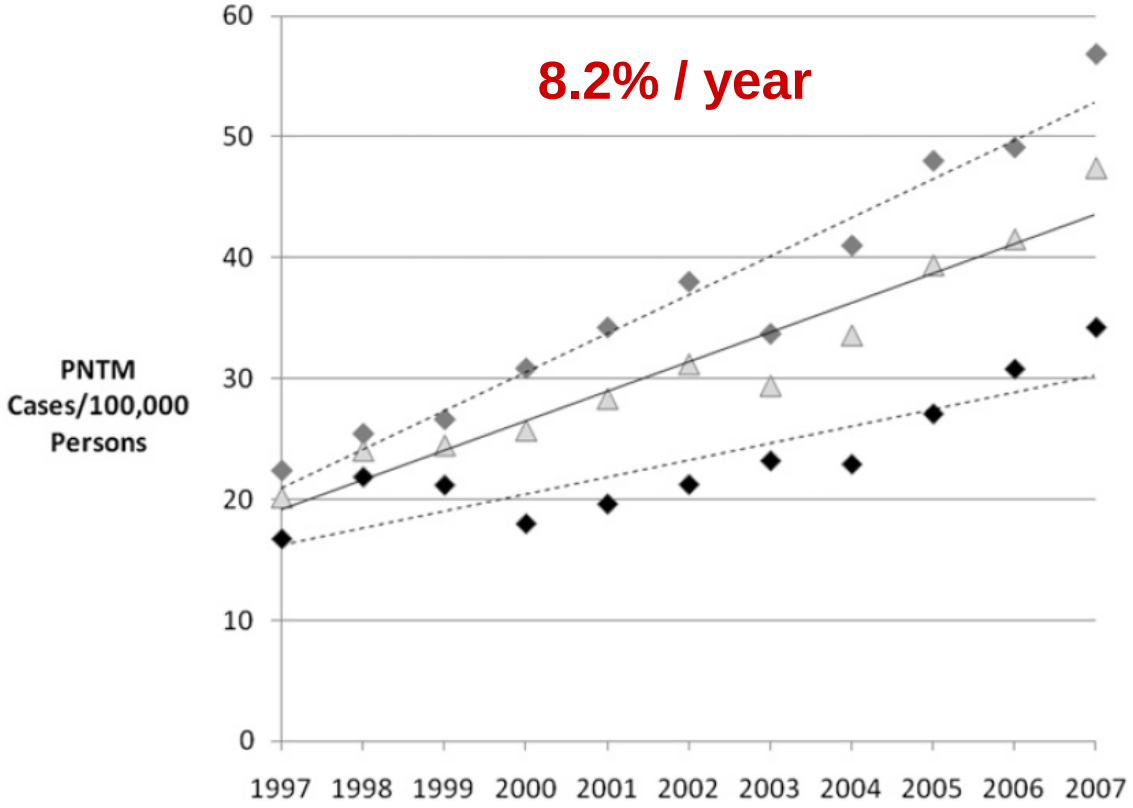
Methodologies to understand epidemiology of NTM-LD

- Notification data
- Population based study
- Analysis of large linked datasets
  - Diagnosis code (ICD 10 or ICD 10)
  - Healthcare claim data
- Laboratory-based convenience samples

Not reportable disease
Difficulty in diagnosis

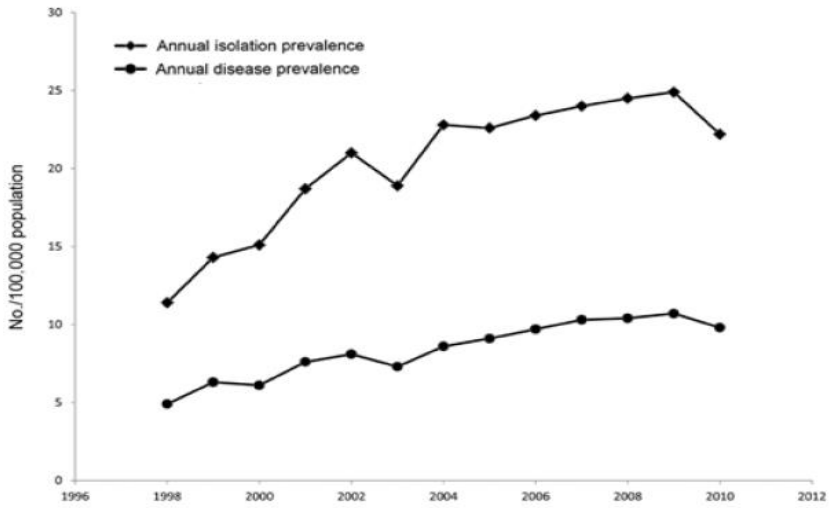
Prevalence of Nontuberculous Mycobacterial Lung Disease in U.S. Medicare Beneficiaries

Jennifer Adjemian[1], Kenneth N. Olivier[1], Amy E. Seitz[1], Steven M. Holland[1], and D. Rebecca Prevots[1]

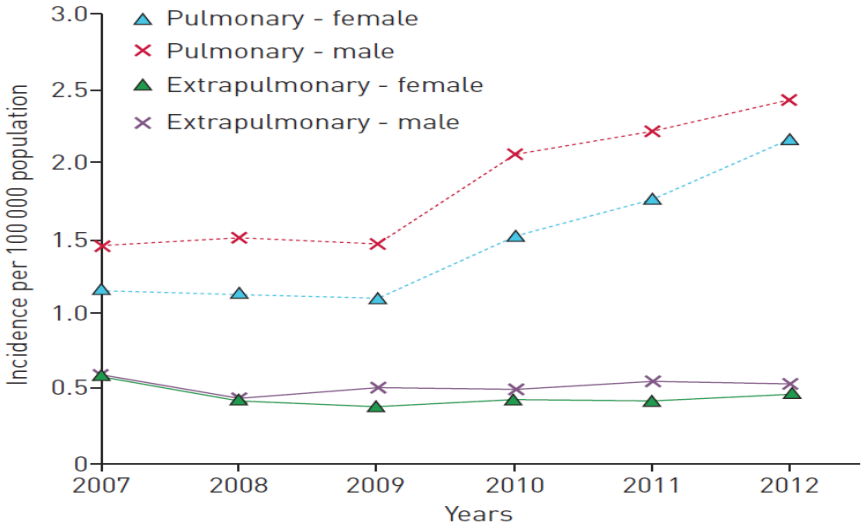


Am J Respir Crit Care Med 2012;185:881

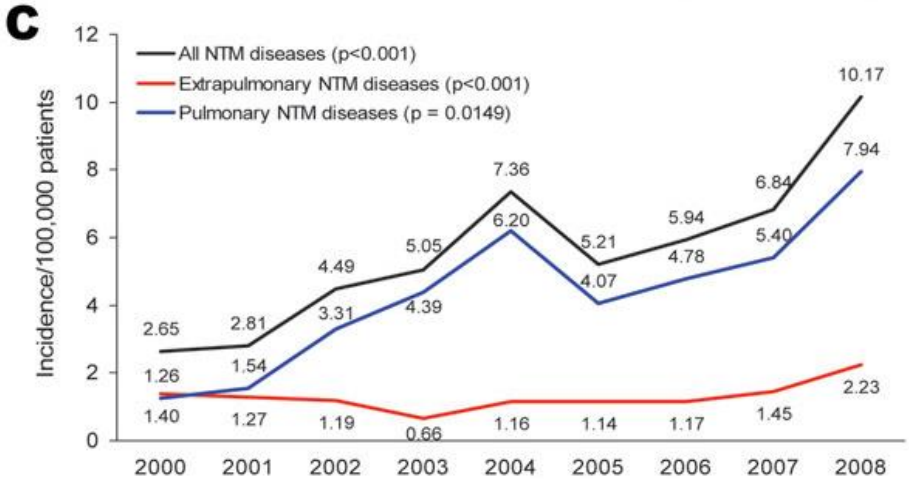
Ontario, Canada, Emerg Infect Dis 2015



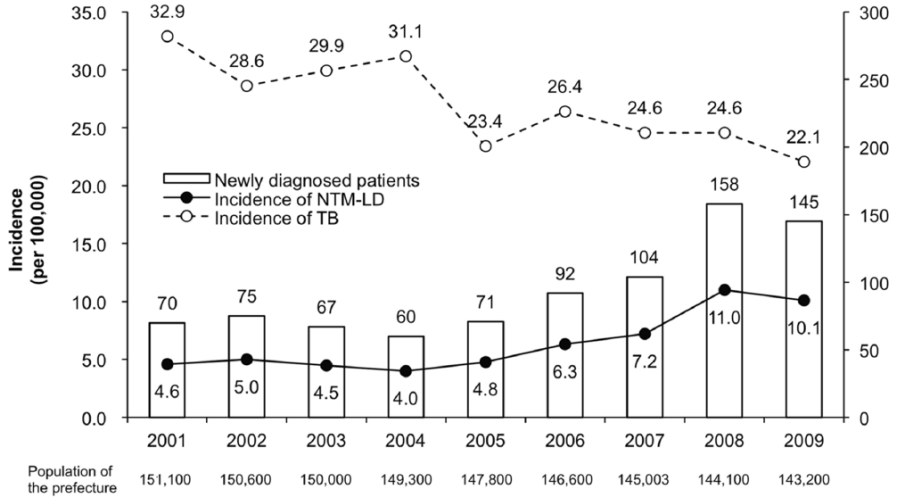
UK, BMC Infect Dis 2016



Taiwan, Emerg Infect Dis 2010



Nagasaki, Japan, PLoS One 2015



Korea: Trend in proportion of NTM isolates

Author, yr	Hospital	Study period	Proportion of NTM isolates	
			Initial	End
Park, 2010	SNUH	2002 - 8	427 /1921 (22%)	781 /170 (46%)
Lee, 2012	Severance	2006 - 10	268 /1041 (26%)	970 /2064 (47%)
Yoo, 2012	Asan	2002 - 10	403 /1921 (21%)	1530 /2648 (59%)
Koh, 2013	Samsung	2001 - 11	548 /1283 (43%)	3341 /4800 (70%)
Kim, 2013	Dankook	2005 - 11	26%	44%
Lee, 2014	Ulsan	2010-13	25%	38%
Kim, 2017	PNUH	2009 - 15	24.8%	44.8%

Kwon YS et al. J Korean Med Sci 2016; 31: 649

Korea: Trend in NTM prevalence

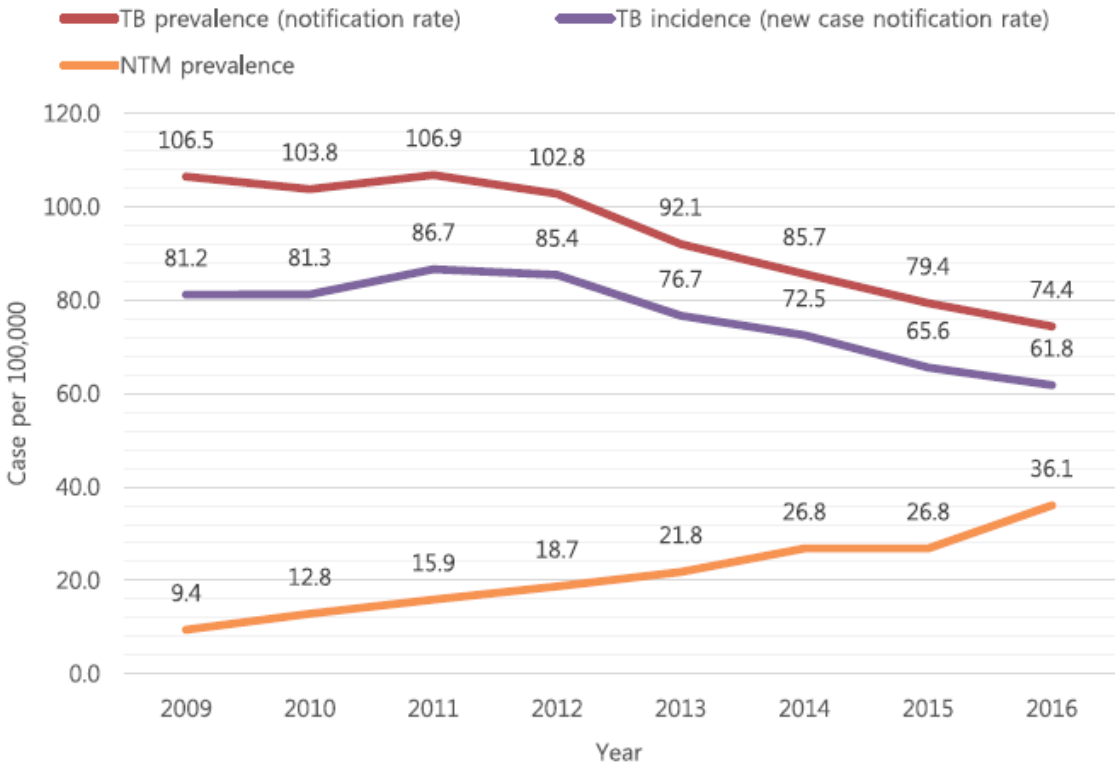


Fig. 1 Prevalence and incidence of tuberculosis, and prevalence of nontuberuclous mycobacterial diseases per 100,000 population, 2009–2016, South Korea

Yoon HJ et al. BNC infect Dis 2017;17:432

Why are NTM increasing?

- Exposure
  - Exposure to aerosols ↑
  - Change in water distribution system
- Diagnostics
  - More sensitive culture methods
  - More CT scans
- Organism
  - Increased virulence?
- Host factors
  - Aging population, more lung disease
  - More immunosuppressed patients
  - Decreasing cross-immunity to *M. tuberculosis*

Geographic diversity of NTM

An NTM-NET collaborative study. Eur Respir J 2013;42:1964

Korea: Species causing NTM-LD

	Koh, 2006	Park, 2010	Lee, 2012	Jang, 2014	Lee, 2014
Study period	2002-3	2002-8	2006-10	2012	2010-13
No. of patients	195	651	345	111	245
M. avium complex	94 (48%)	63%	263 (76%)	73 (66%)	132 (54%)
M. avium	38	NA	141	32	39
M. intracellulare	56	NA	122	41	93
M. abscessus complex	64 (33%)	27%	63 (18%)	32 (29%)	22 (9%)
M. abscessus	NA	NA	NA	21	NA
M. massiliense	NA	NA	NA	11	NA
M. Kansasii	7 (4%)	NA	7 (2%)	1 (1%)	80 (33%)
Others	30 (15%)	10%	12 (3%)	5 (5%)	11 (4%)

Kwon YS et al. J Korean Med Sci 2016; 31: 649

Impact of non-tuberculous mycobacteria on pulmonary function decline in chronic obstructive pulmonary disease

Huang CT et al. Int J Tuberc Lung Dis 2012;16:539-45.

	Multiple NTM (n = 47)	Single NTM (n=63)	No NTM (n=141)	p
Exacerbation				
per patient-year	0.82 ± 1.08	0.88 ± 1.20	0.47 ± 1.24	0.046
≥ 1.0 per year, n (%)	18 (38.3)	20 (31.7)	24 (17.0)	0.004
FEV1 decline, ml/year	-79.4±32.8	-61.6±31.9	-56.2±31.5	

Conclusion: NTM may play a role in disease progression and deterioration of pulmonary function in COPD patients

Mortality in NTM

- **5-year mortality**

- Hayashi, AJRCCM 2012 – Japan: 25%
- Ito, IJTKD 2012 – Japan: 28%
- Andrejak AJRCCM – Denmark: 40%
- Kotilainen SJID – Finland: 28% (4 year)
- Novosad ATS 2017 – Canada: 35.1%

Increasing burden /c substantial costs

- Burden of NTM-LD in Germany

	NTM-PD patients (n=125)	Matched controls (n=1250)
All-cause mortality (%)	22.4	6
Mean direct cost (Euros) per patient	39,559.60	10,006.71
Annual direct and indirect cost associated with loss of work (Euros) per patient	9093.20	1221.05

Diel R, *et al*. *Eur Respir J* 2017;49:1602109.

Whole-genome sequencing to identify transmission of *Mycobacterium abscessus* between patients with cystic fibrosis: a retrospective cohort study

Josephine M Bryant, Dorothy M Grogono*, Daniel Greaves, Juliet Foweraker, Iain Roddick, Thomas Inns, Mark Reacher, Charles S Haworth, Martin D Curran, Simon R Harris, Sharon J Peacock, Julian Parkhill, R Andres Floto*

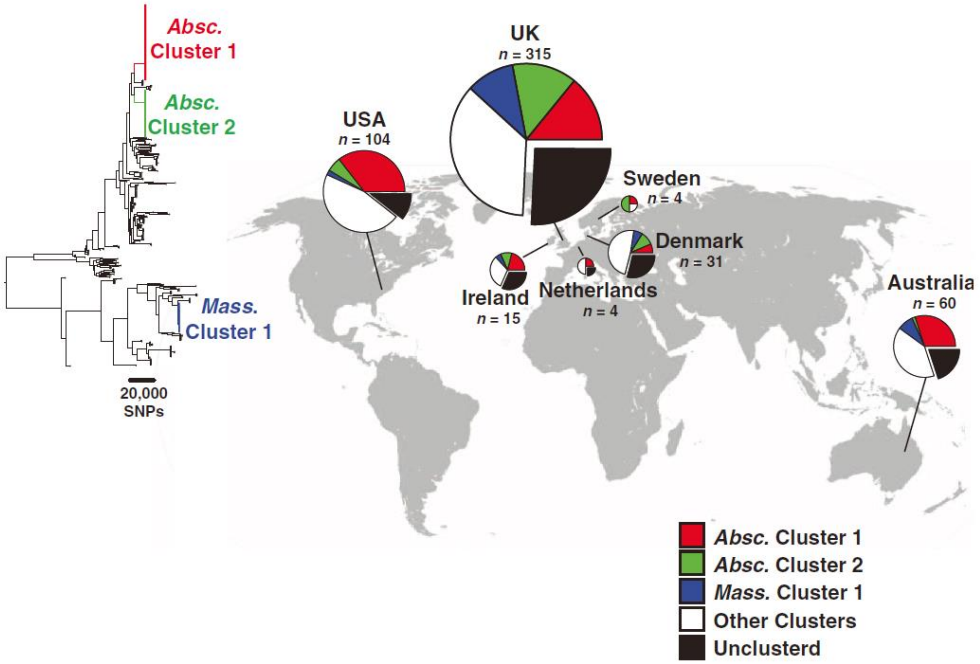
- Whole genome sequencing and DST were done on 168 consecutive isolates of *M. abscessus* from 31 patients attending an adult cystic fibrosis centre in the UK between 2007 and 2011.
- Two clustered outbreaks of near-identical isolates of the M *abscessus subspecies massiliense* (from 11 patients)
- All patients within these clusters had numerous opportunities for within-hospital transmission from other individuals

Lancet 2013;381:1551

EMERGING INFECTIONS

Emergence and spread of a human-transmissible multidrug-resistant nontuberculous mycobacterium

- WGS for 1,080 isolates of *M. abscessus* from 517 CF patients



Majority of *M. abscessus infections* are acquired through transmission, potentially via fomites and aerosols

Bryant JM et al, Science 2016;354:751

Summary: Epidemiology

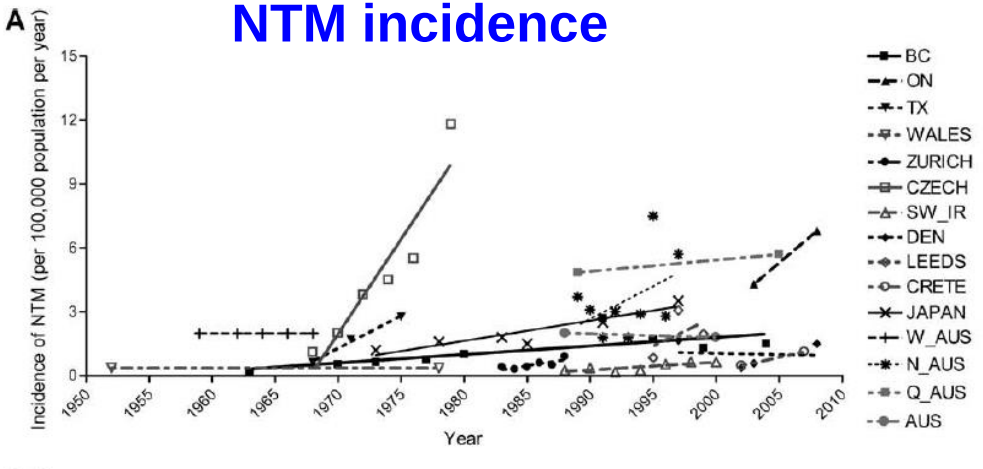
- Prevalence of NTM-LD is increasing globally;
  - more common than TB in some countries.
- The prevalence increases with age, especially in women.
- *M. avium* complex is the predominant isolates worldwide.
- NTM-LD adversely effects lung function and associated with increased mortality and medical costs.
- There is growing concern that person-to-person transmission might occur in CF patients.

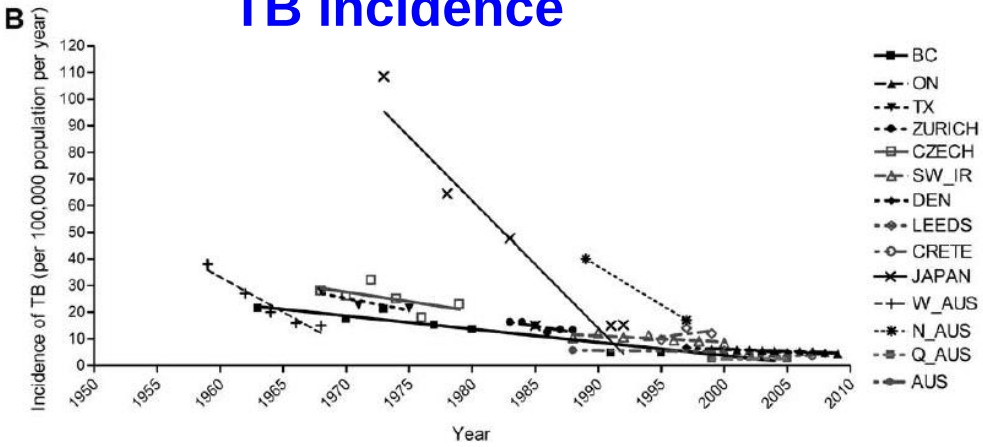
TB vs NTM:

A Changing of the Guard in the 21st Century?

	TB	NTM
Disease burden	↓↓	↑↑
Cure rate	>>	
Infection source	Human	Environment
Impact on disease control		
Active case finding & Tx	Yes	No
Preventive treatment	Yes	No

The epidemiologic relationship between tuberculosis and non-tuberculous mycobacterial disease: a systematic review





N=22 studies

Trends in NTM
- 75%: increasing rates
- 12.5%: stable rates
- 12.5%: declining rates

Proportion of NTM among mycobacterial ds
- Rising in 94% of geographic area

Brode SK et al. Int J Tuberc Lung Dis 2014;18:1370

National Jewish Health®

PREVENTION

- Clean your shower head by soaking in vinegar or water.
- Replace shower heads periodically as needed.
- Set water heater to 140° (use caution to avoid scalding).
- Remove the shower head completely.
- Take baths instead of showers.
- Avoid steam rooms, hot tubs, etc., where steam or droplets with bacteria particles could be inhaled.
- Wear a mask and gloves while gardening.