Current Trends in Nontuberculous Mycobacterial Lung Disease

National Jewish Health NTM Lecture Series for Providers – April, 2024

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Disclosures

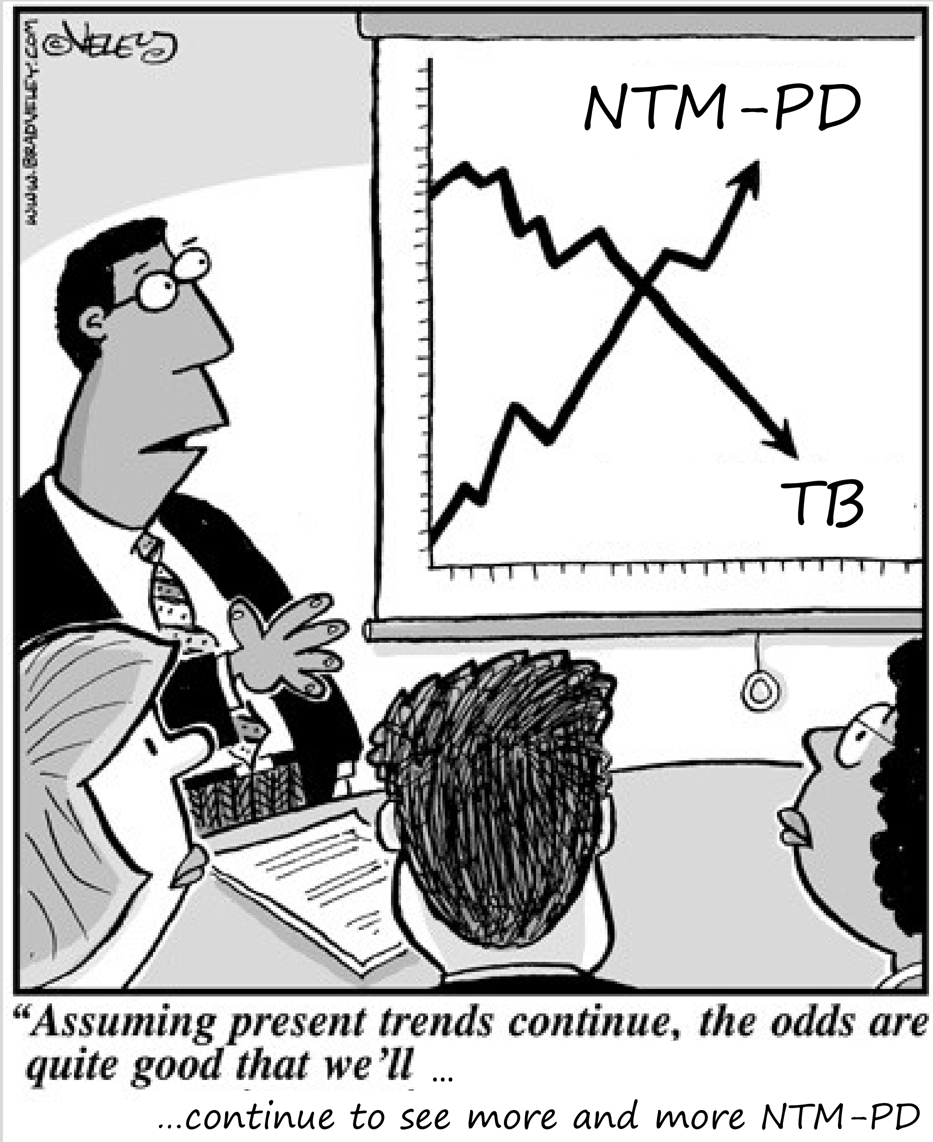
- Research
  - Insmed – site investigator
  - Ontario Thoracic Society – Lung Foundation
  - OHSU/PCORI
- Consultant
  - Mannkind, Partner Therapeutics, Pfizer
- CME
  - OHSU, NYU Langone, Lucid Group

Objectives

To discuss:

- **Epidemiology**
- **Risk factors** (population level)
- **Transmission**
- **Financial costs**
- **Outcomes and survival**

Relevant to NTM-PD



Epidemiology

- Challenges
- Recent data

Measuring the unmeasured

If a person develops NTM-PD and we don't report it…

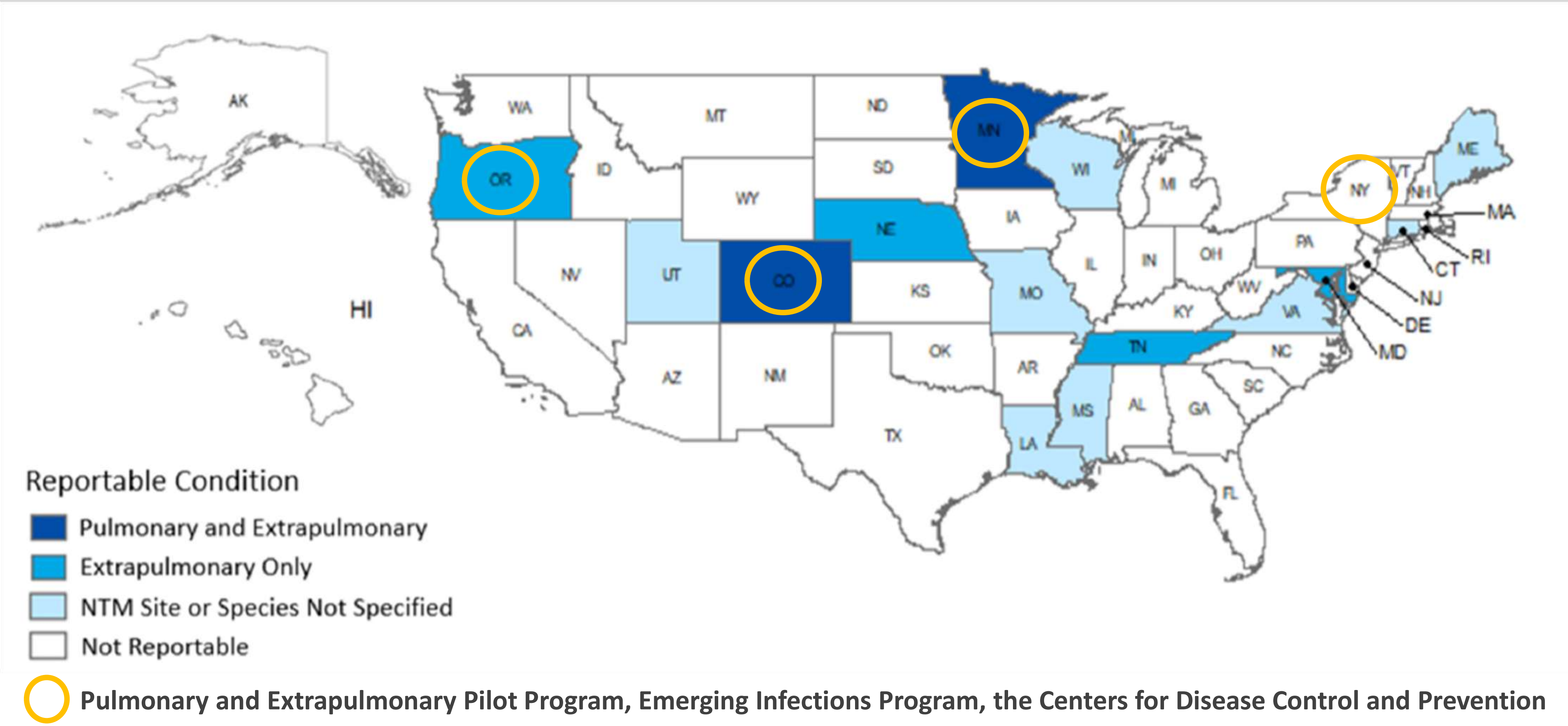
…they still have the disease!

NTM reportability

Measuring the unmeasured

	Diagnosis NTM-PD
Microbiology	With ≥ 2 sputa → 2 positive cultures, or With 1 BAL/wash → 1 positive bronchial wash, or With biopsy → + biopsy culture / 1+ culture & biopsy evidence of disease
Clinical	*Pulmonary / systemic symptoms not otherwise explained*
Radiology	*CXR – nodules / cavities* *CT – bronchiectasis with nodules / cavitation*

NTM Reportable in Only 14 States



Mercaldo et al. Tuberculosis 2023: 139

Measuring the unmeasured

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Disease Likely if:

- ~50% with MAC isolate
- ~70-90%* with ≥2 sputum +

⇨ Association between isolation and disease permits inferences on disease rates and trends

* Winthrop, Am J Respir Crit Care MeD 2010
Andrejak, Am J Respir Crit Care Med 2010
Marras, Lung 2010
Prevots, Am J Respir Care Crit Care Med 2010
Winthrop, Pharmacoepidemiol Drug Saf 2011

Measuring the unmeasured

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Oregon (Winthrop et al. Annals ATS 2017)
Queensland, Australia (Thomson et al. Annals ATS 2017)

Detailed reporting
Ongoing lab-based

Measuring the unmeasured

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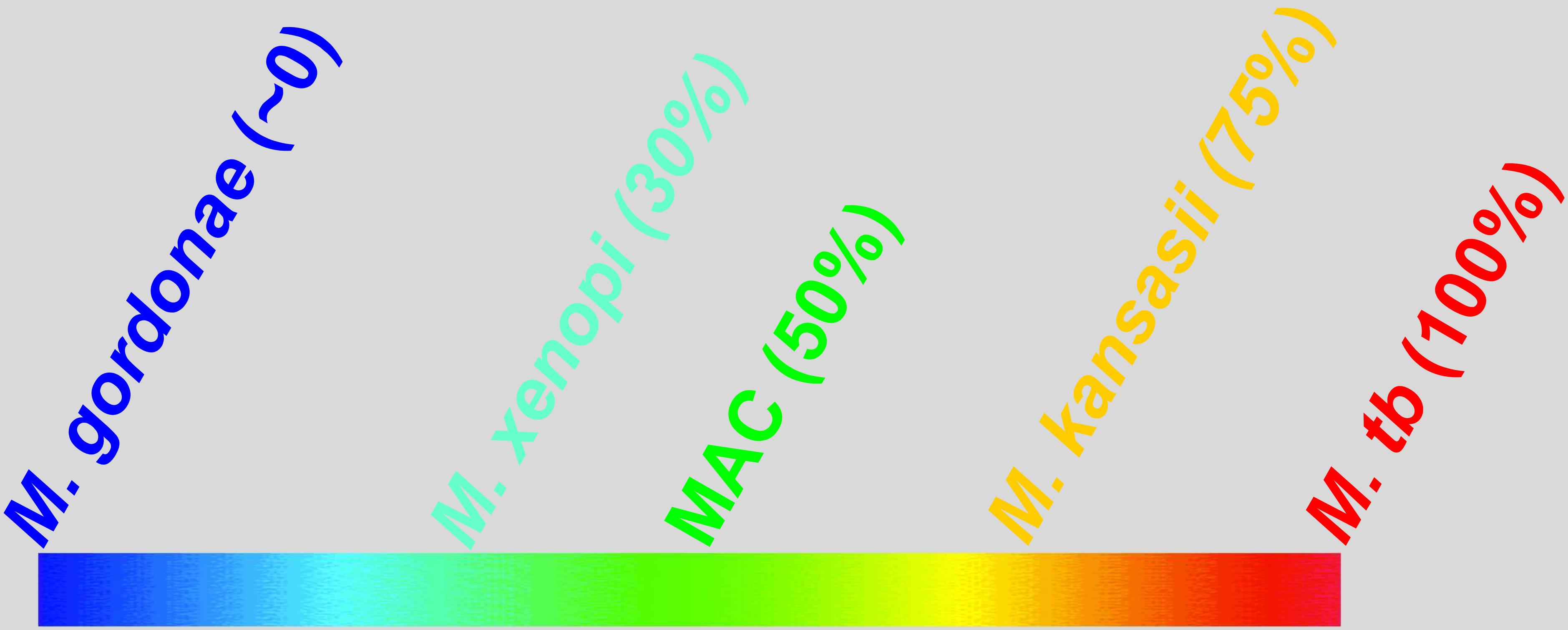
Underestimate Undetected cases

Lack of ongoing sputum sampling

Overestimate Unknown (and variable) proportion meeting micro criteria lack disease

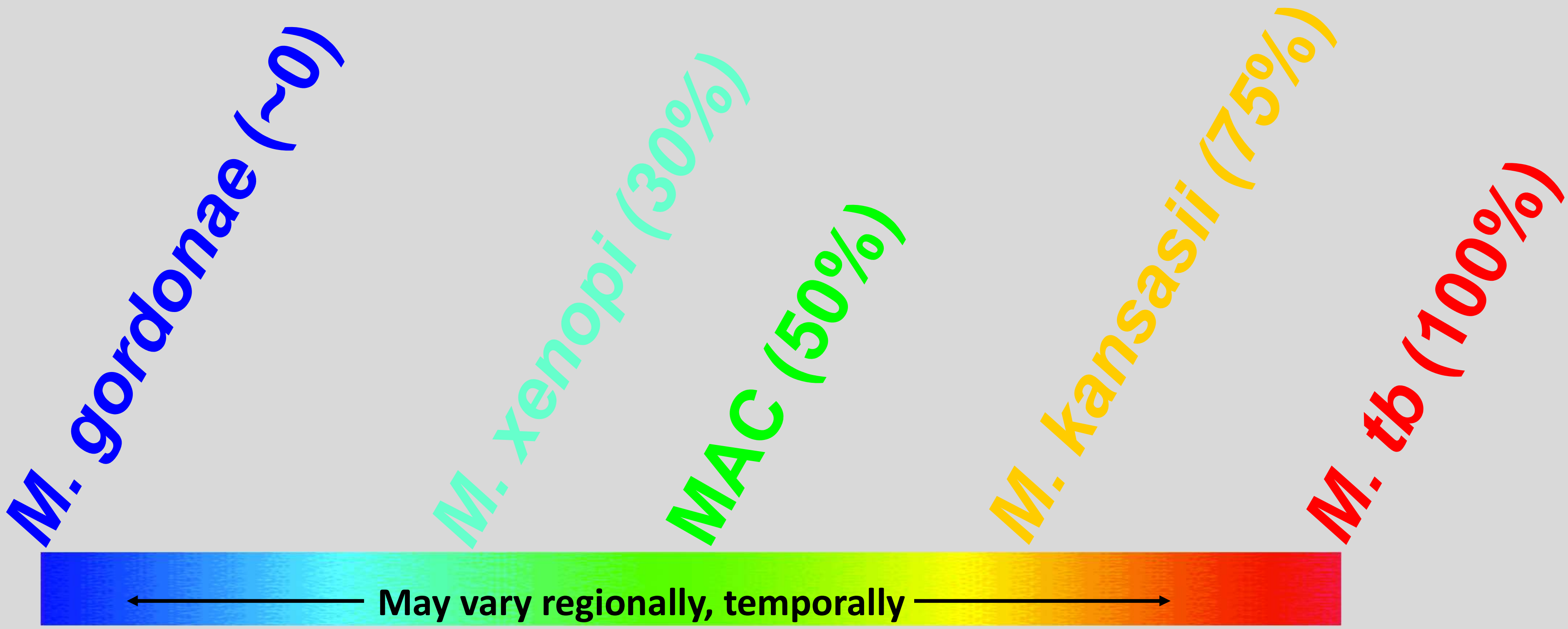
NTM species

- pathogenic potential



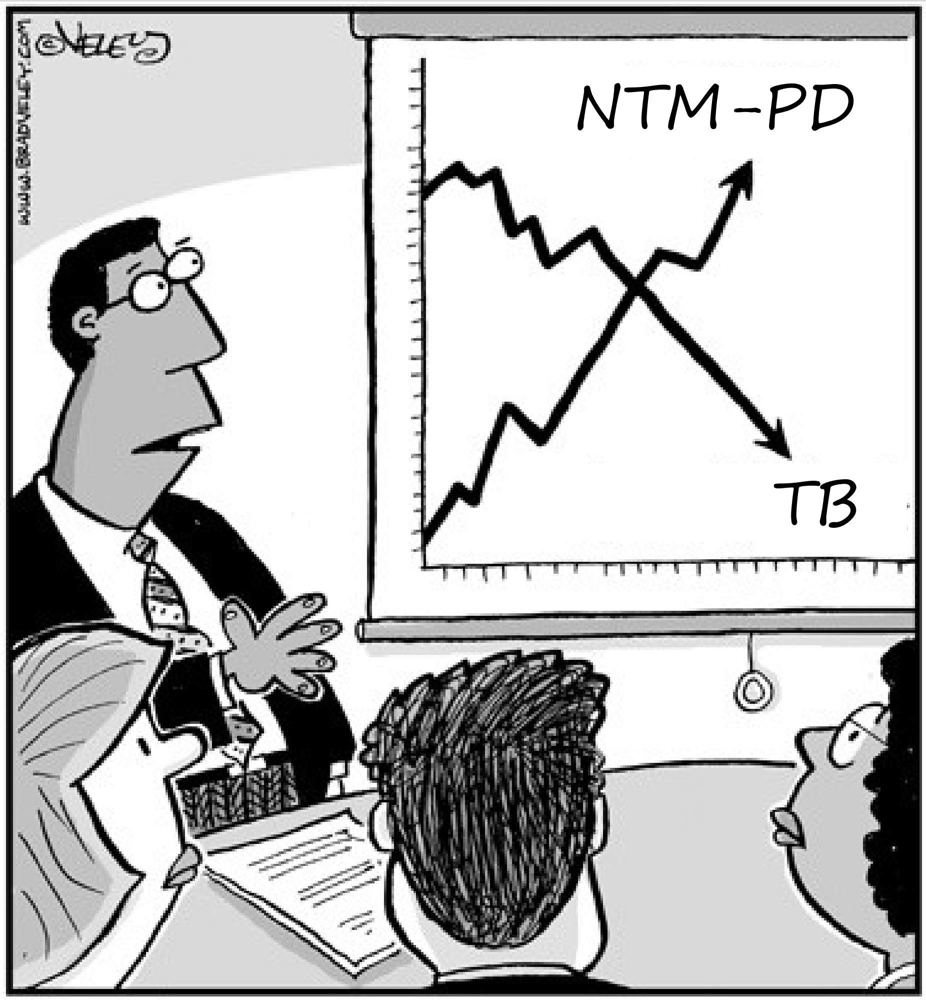
NTM species

- pathogenic potential



Applying microbiological criteria by species (and at the population level)

- Daley et al. Eur Respir J 2020, Lange et al. Lancet Infect Dis 2022



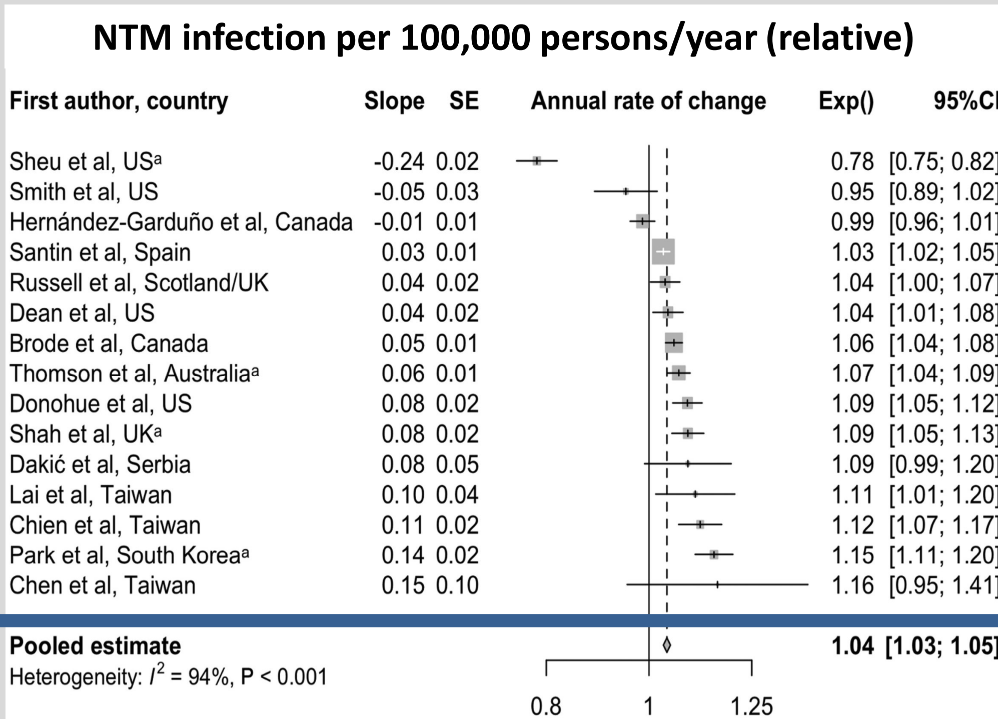
"Assuming present trends continue, the odds are quite good that we'll ...

...continue to see more and more NTM-PD

Epidemiology

- Challenges
- Recent data

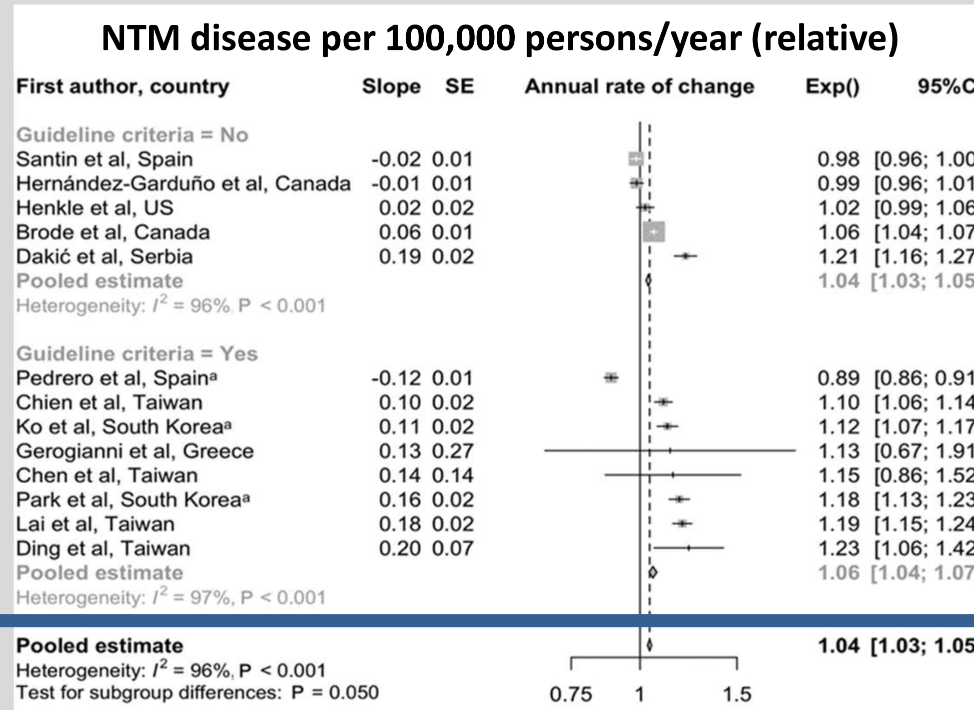
Systematic Review: 82% of studies reported increased isolation, 66.7% increased disease



NTM infection per 100,000 persons/year (relative)

First author, country	Slope	SE	Exp()	95%CI
Sheu et al, US[a]	-0.24	0.02	0.78	[0.75; 0.82]
Smith et al, US	-0.05	0.03	0.95	[0.89; 1.02]
Hernández-Garduño et al, Canada	-0.01	0.01	0.99	[0.96; 1.01]
Santin et al, Spain	0.03	0.01	1.03	[1.02; 1.05]
Russell et al, Scotland/UK	0.04	0.02	1.04	[1.00; 1.07]
Dean et al, US	0.04	0.02	1.04	[1.01; 1.08]
Brode et al, Canada	0.05	0.01	1.06	[1.04; 1.08]
Thomson et al, Australia[a]	0.06	0.01	1.07	[1.04; 1.09]
Donohue et al, US	0.08	0.02	1.09	[1.05; 1.12]
Shah et al, UK[a]	0.08	0.02	1.09	[1.05; 1.13]
Dakić et al, Serbia	0.08	0.05	1.09	[0.99; 1.20]
Lai et al, Taiwan	0.10	0.04	1.11	[1.01; 1.20]
Chien et al, Taiwan	0.11	0.02	1.12	[1.07; 1.17]
Park et al, South Korea[a]	0.14	0.02	1.15	[1.11; 1.20]
Chen et al, Taiwan	0.15	0.10	1.16	[0.95; 1.41]
Pooled estimate			**1.04**	**[1.03; 1.05]**

Heterogeneity: I^2 = 94%, P < 0.001



NTM disease per 100,000 persons/year (relative)

First author, country	Slope	SE	Exp()	95%CI
Guideline criteria = No				
Santin et al, Spain	-0.02	0.01	0.98	[0.96; 1.00]
Hernández-Garduño et al, Canada	-0.01	0.01	0.99	[0.96; 1.01]
Henkle et al, US	0.02	0.02	1.02	[0.99; 1.06]
Brode et al, Canada	0.06	0.01	1.06	[1.04; 1.07]
Dakić et al, Serbia	0.19	0.02	1.21	[1.16; 1.27]
Pooled estimate			1.04	[1.03; 1.05]
Heterogeneity: I^2 = 96%, P < 0.001				
Guideline criteria = Yes				
Pedrero et al, Spain[a]	-0.12	0.01	0.89	[0.86; 0.91]
Chien et al, Taiwan	0.10	0.02	1.10	[1.06; 1.14]
Ko et al, South Korea[a]	0.11	0.02	1.12	[1.07; 1.17]
Gerogianni et al, Greece	0.13	0.27	1.13	[0.67; 1.91]
Chen et al, Taiwan	0.14	0.14	1.15	[0.86; 1.52]
Park et al, South Korea[a]	0.16	0.02	1.18	[1.13; 1.23]
Lai et al, Taiwan	0.18	0.02	1.19	[1.15; 1.24]
Ding et al, Taiwan	0.20	0.07	1.23	[1.06; 1.42]
Pooled estimate			1.06	[1.04; 1.07]
Heterogeneity: I^2 = 97%, P < 0.001				
Pooled estimate			**1.04**	**[1.03; 1.05]**

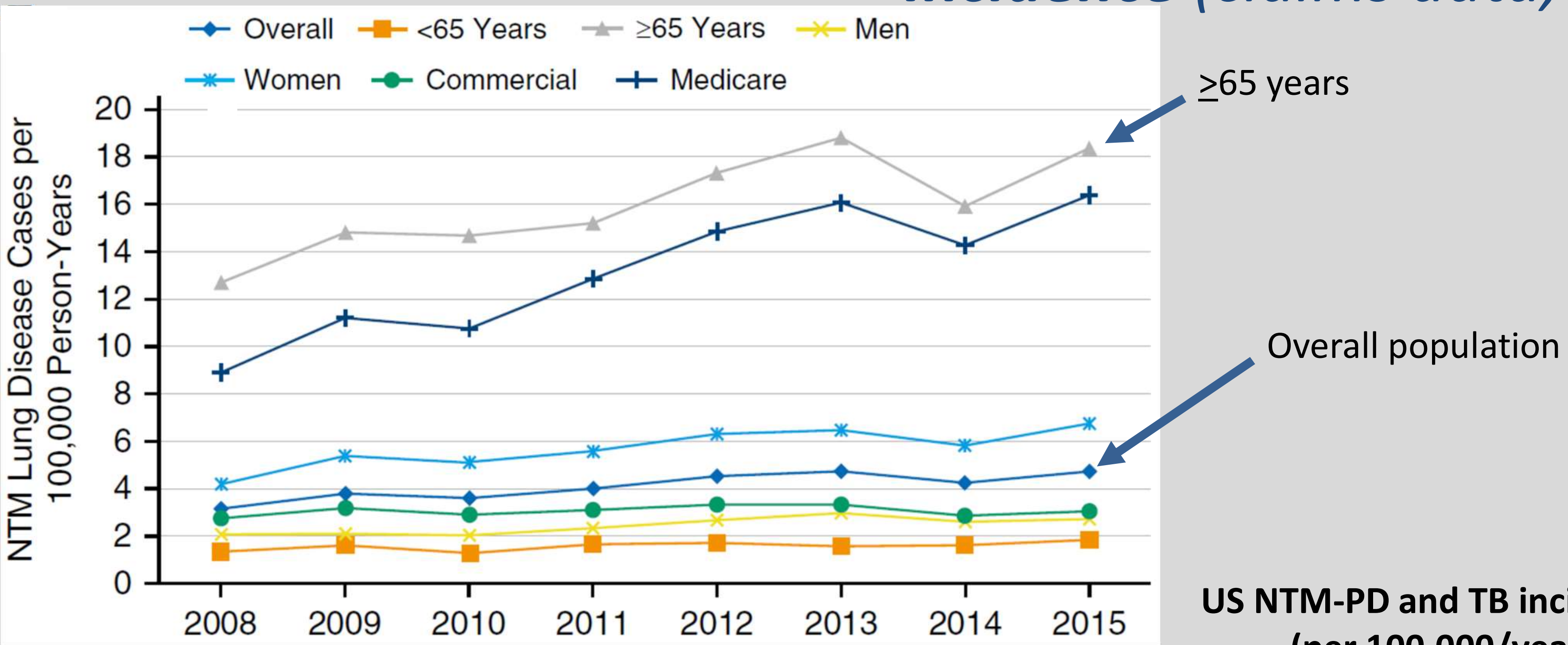
Heterogeneity: I^2 = 96%, P < 0.001
Test for subgroup differences: P = 0.050

- Restricted to studies with culture-based data for at least 3 years and at least 200 samples
- 47 publications from 18 countries
- Increase of 4% per year for isolation and 4% for disease

Dahl et al. Int J Infect Dis 2022

Increasing NTM-PD / Decreasing TB

- ***Incidence*** *(claims data, USA)*

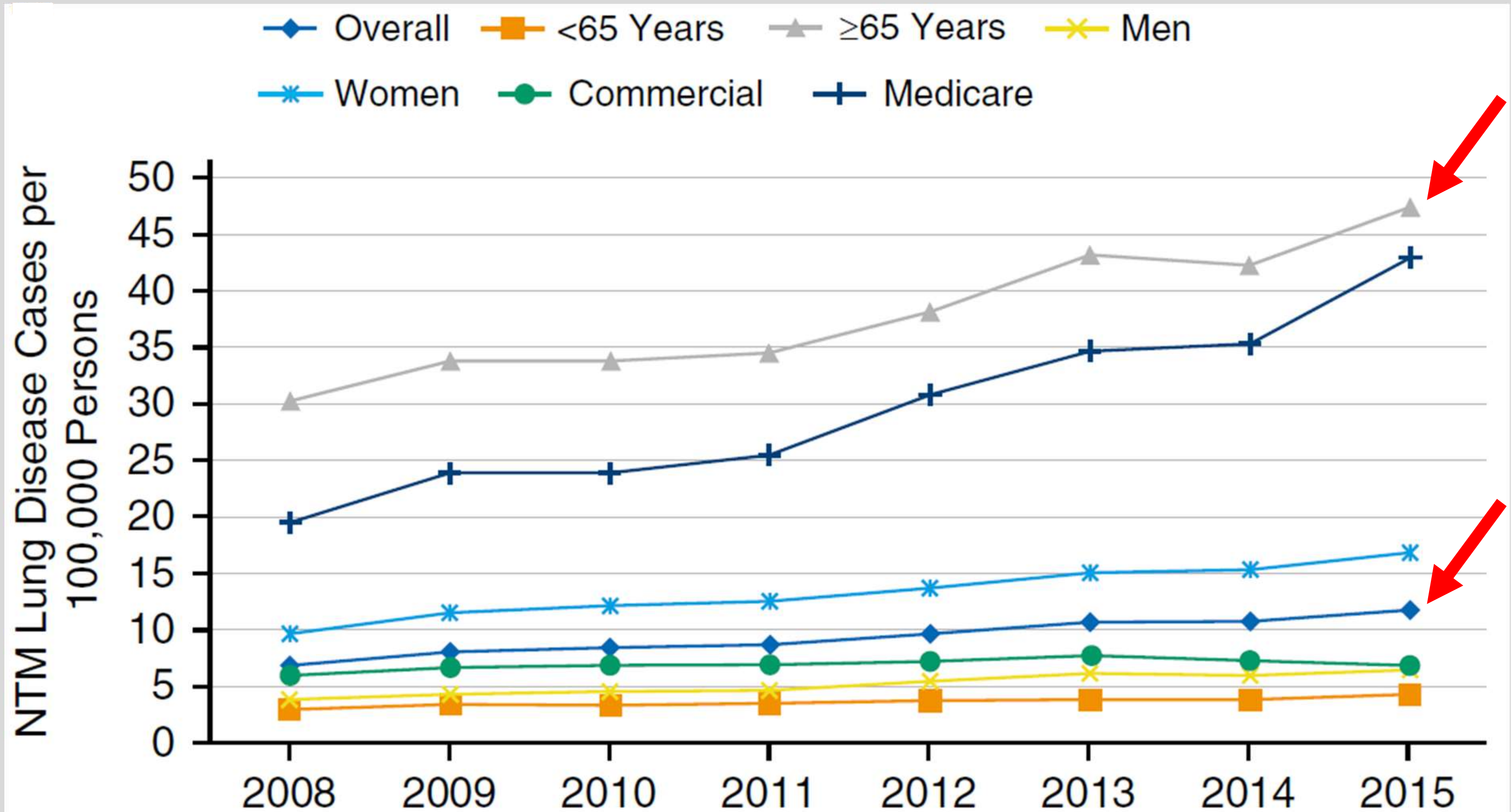


Winthrop et al. Ann Am Thor Soc. 2020

US NTM-PD and TB incidence: (per 100,000/year)

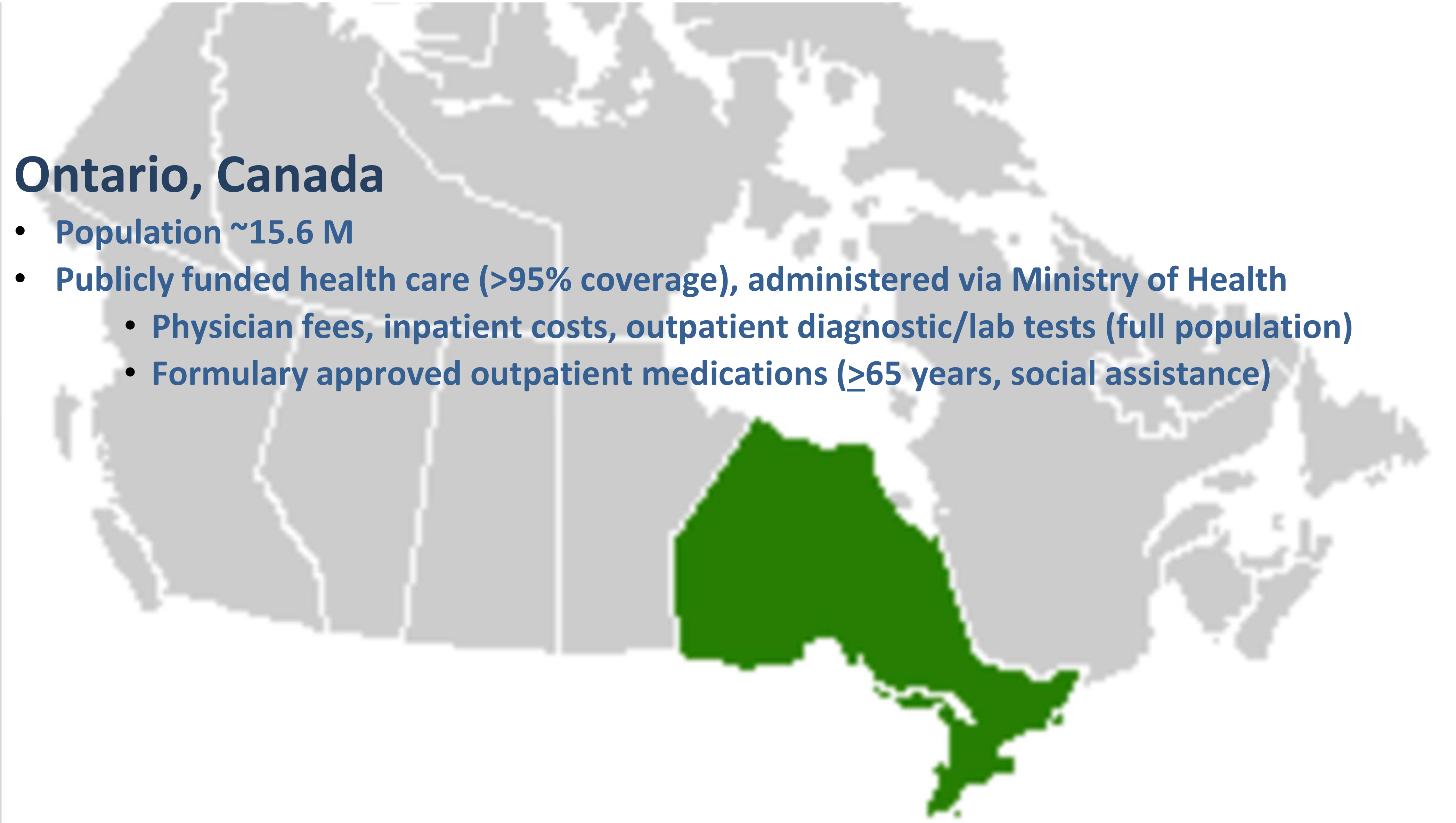
	2008	2015
NTM-PD	**3**	**5**
TB	**4**	**3**

Recent US data NTM-PD – Prevalence (population burden)



Prevalence 2008-2015 (per 100,000/yr) increased from 7→12 overall and from 30→47 in seniors

Winthrop et al. Ann Am Thor Soc. 2020



Ontario, Canada

- Population ~15.6 M
- Publicly funded health care (>95% coverage), administered via Ministry of Health
    - Physician fees, inpatient costs, outpatient diagnostic/lab tests (full population)
    - Formulary approved outpatient medications (≥65 years, social assistance)

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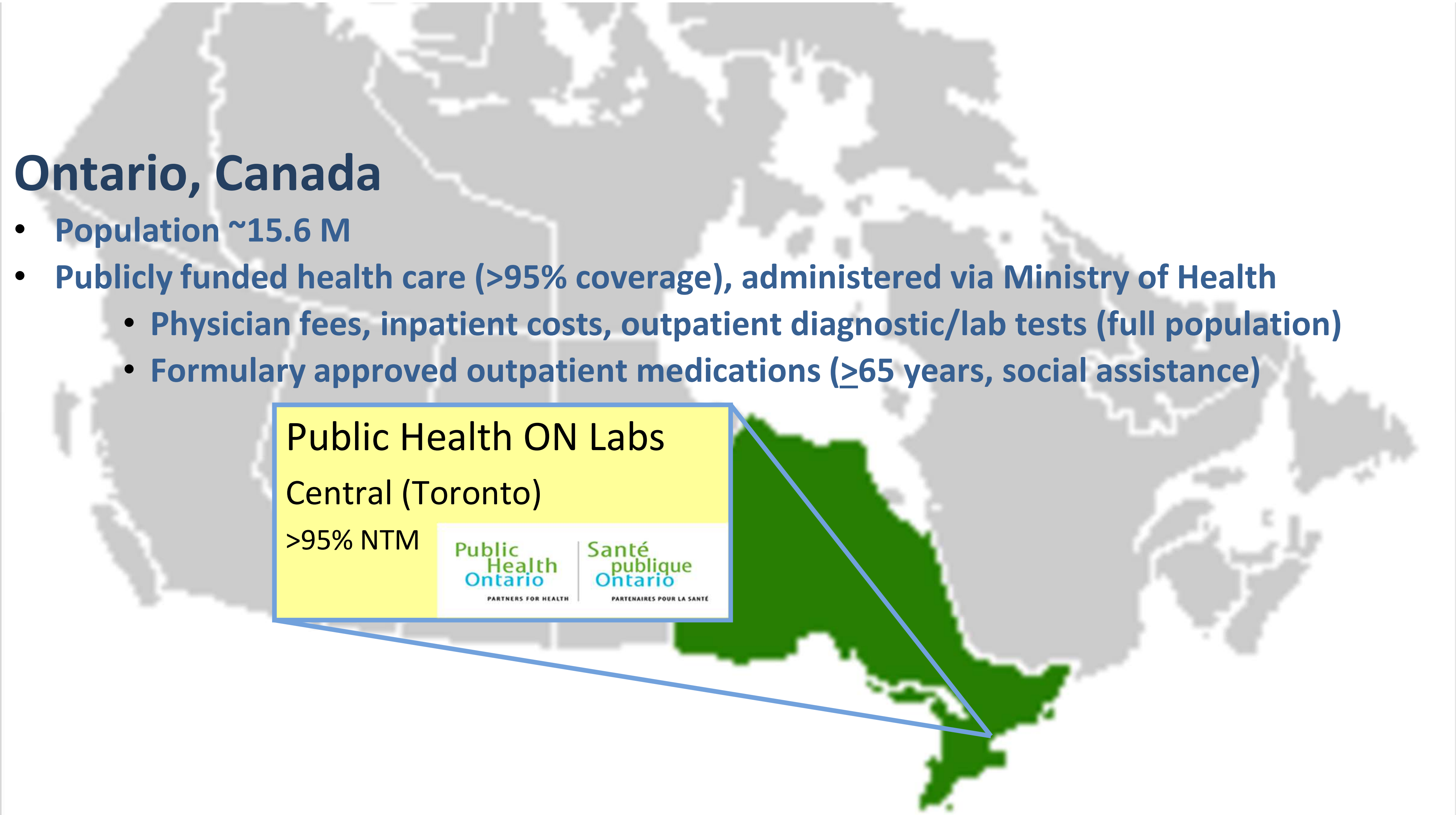
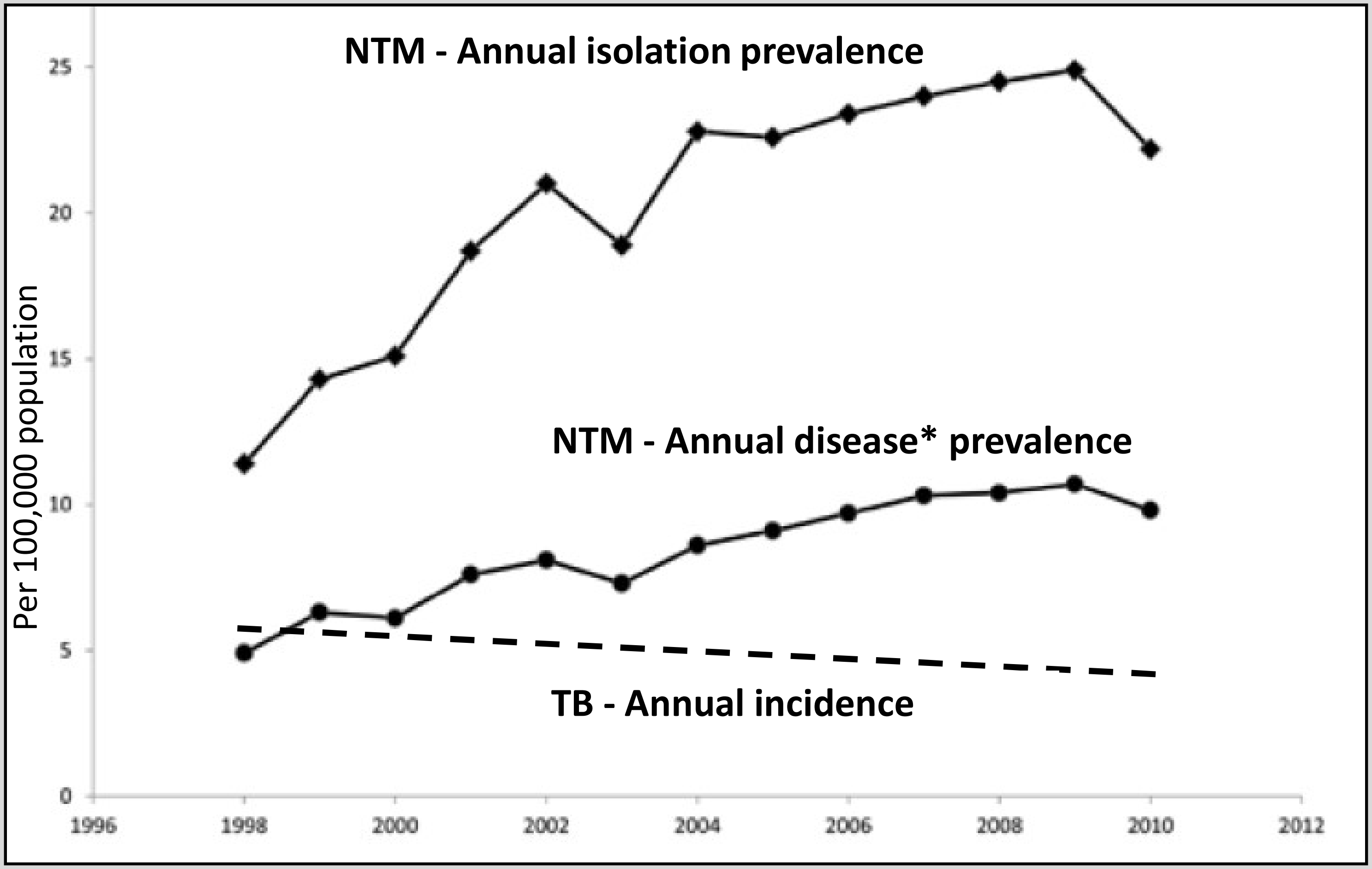


Pulmonary NTM isolation annual prevalence, Ontario, Canada 1998-2010



Marras et al. Emerg Infect Dis 2013

*Microbiologically defined

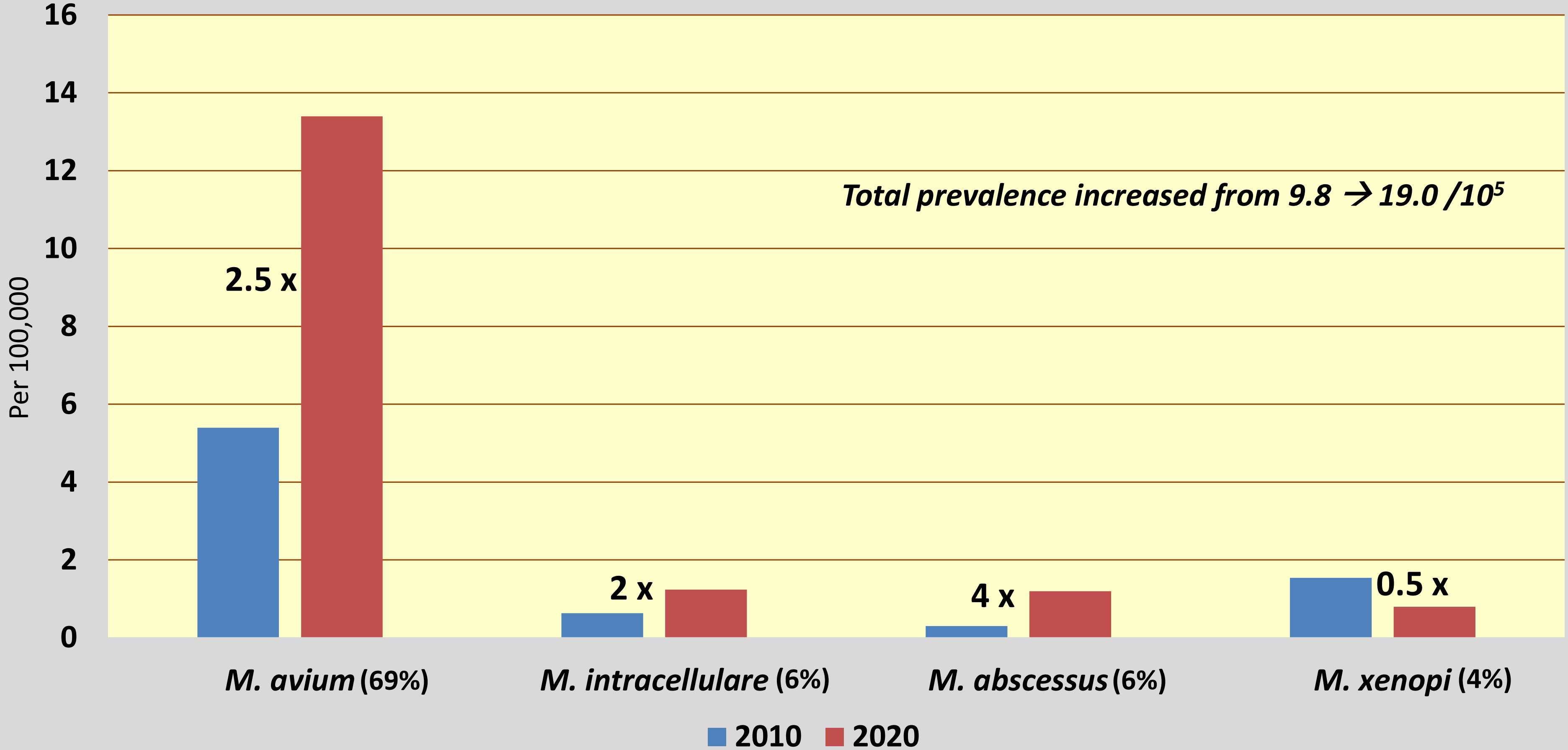
NTM-PD in Ontario, Canada

Population-based, microbiological definitions

Annual Metric (per 100,000)	1998	2010	2020
Isolation	11	22	32
Disease	5	10	19

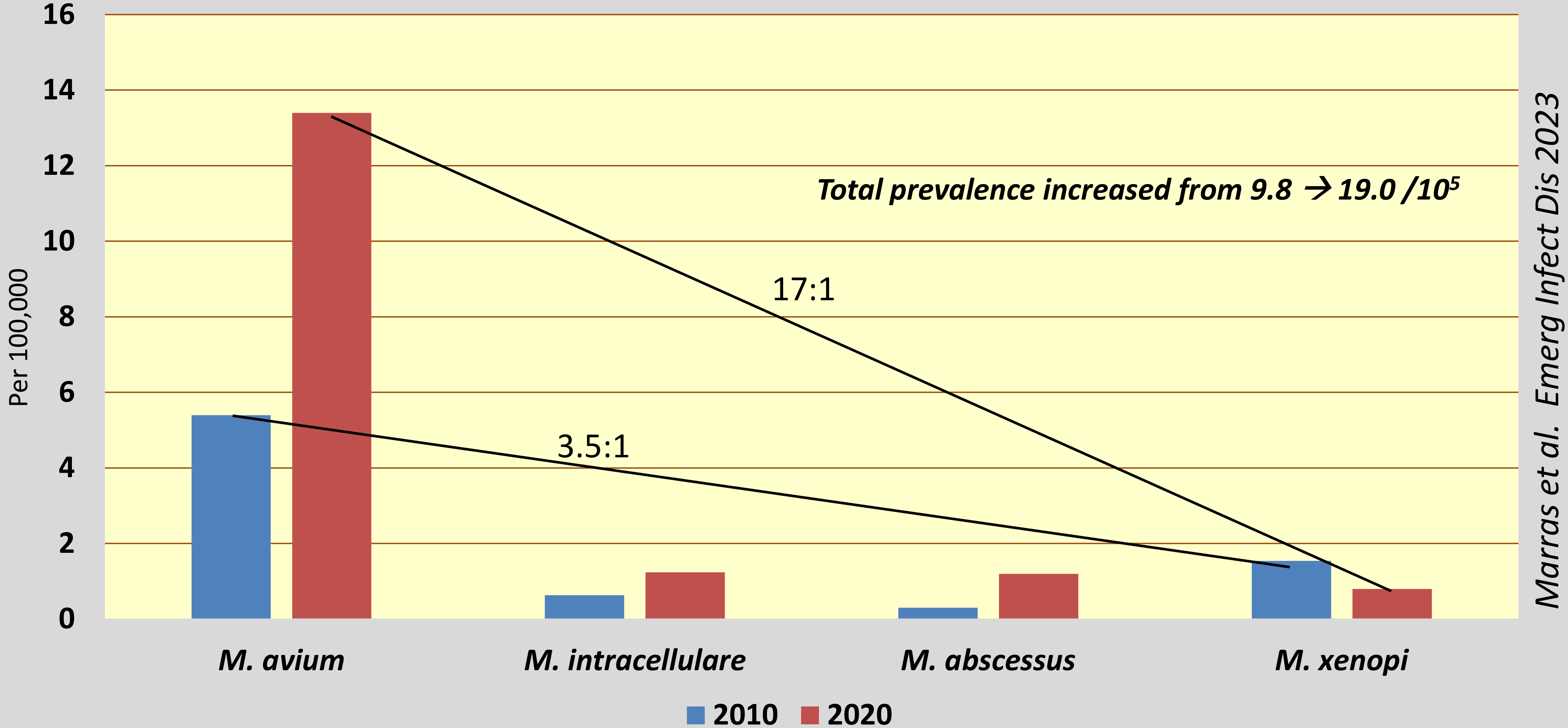
- *Marras et al. Emerg Infect Dis 2013*
- *Marras et al. Emerg Infect Dis 2023*

NTM-PD, Ontario, Canada: 2010 vs 2020



Marras et al. Emerg Infect Dis 2023

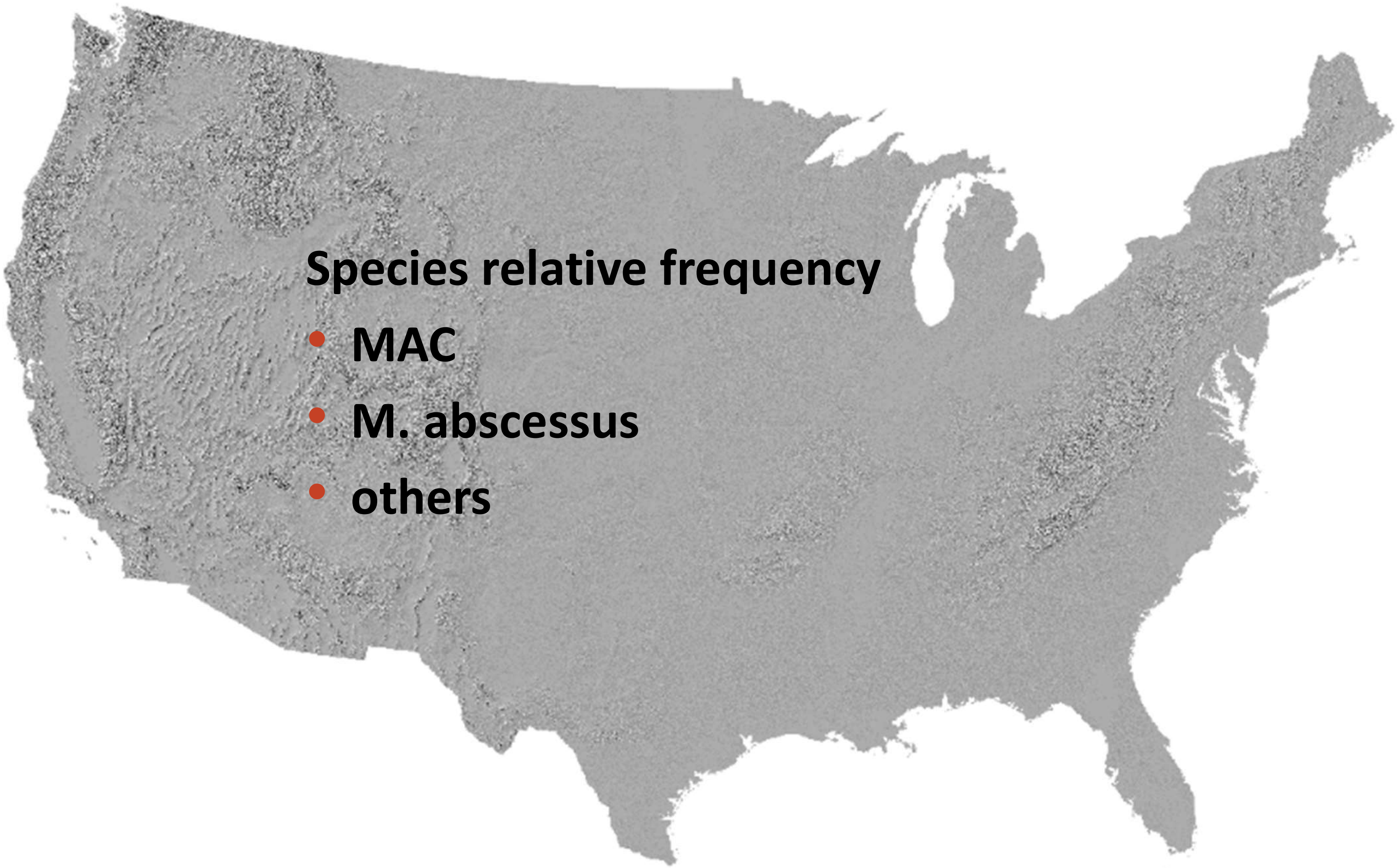
NTM-PD, Ontario, Canada: 2010 vs 2020



MAC drove recent increases in NTM-PD

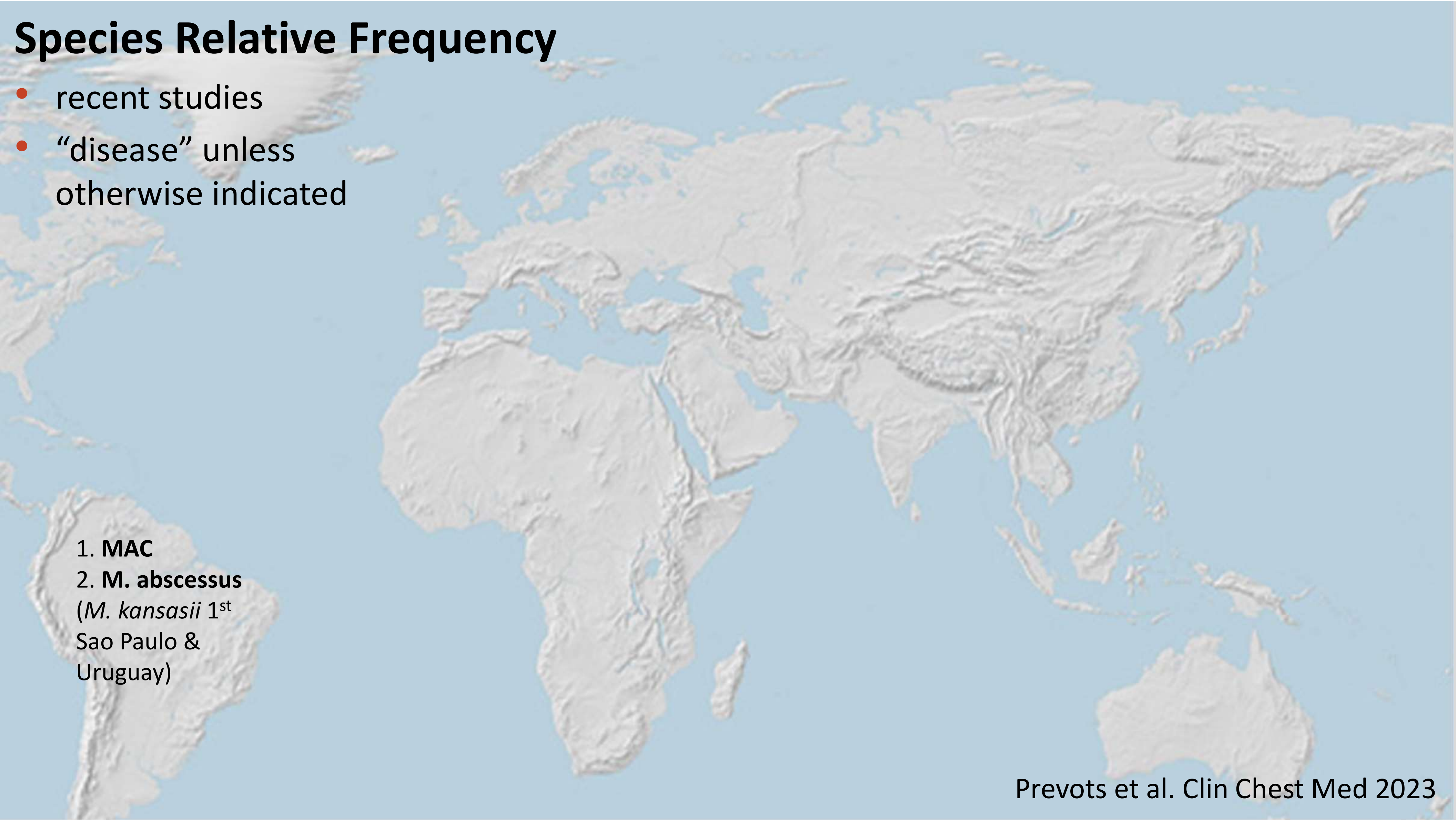
Population-based studies

Location	Time period	First author	Journal, Year
Barcelona (MAC)	1994-2014	Santin	Emerg Infect Dis, 2018
Queensland (MAC)	1999-2005	Thomson	Emerg Infect Dis, 2010
UK (MAC)	2007-2012	Shah	BMC Infect Dis, 2016
Netherlands (*M. avium*)	2000-2006	van Ingen	Int J Tuberc Lung Dis, 2010
Belgium (*M. avium*)	2007-2016	Soetaert	Euro Surveill, 2019
Hawaii (MAC, one HMO)	2005-2013	Adjemian	Emerg Infect Dis, 2017
Israel (MAC)	2010-2020	Enghelberg	ATS conference 2022


Species relative frequency
MAC
M. abscessus
others

Species Relative Frequency

- recent studies
- “disease” unless otherwise indicated



Prevots et al. Clin Chest Med 2023

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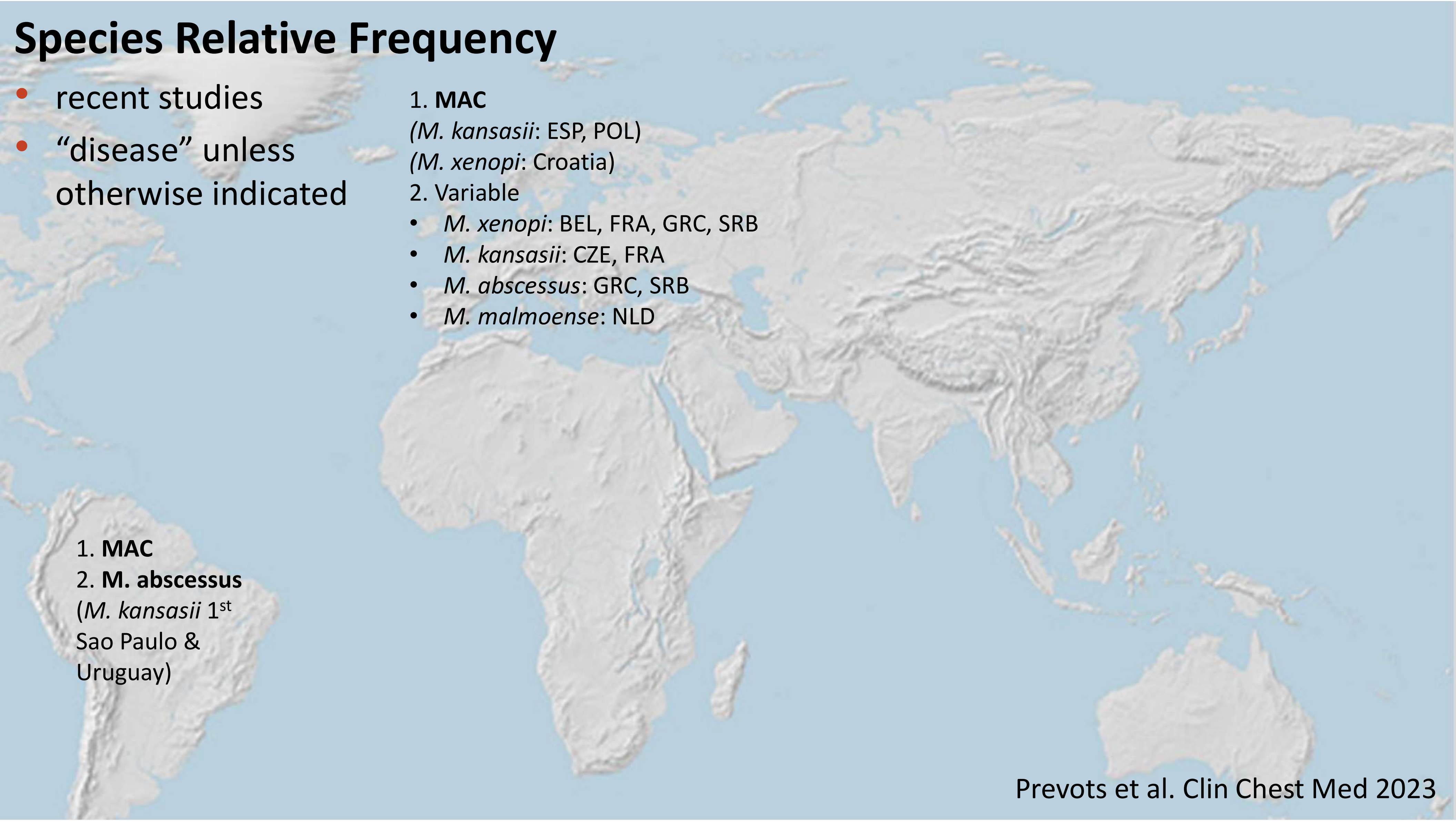

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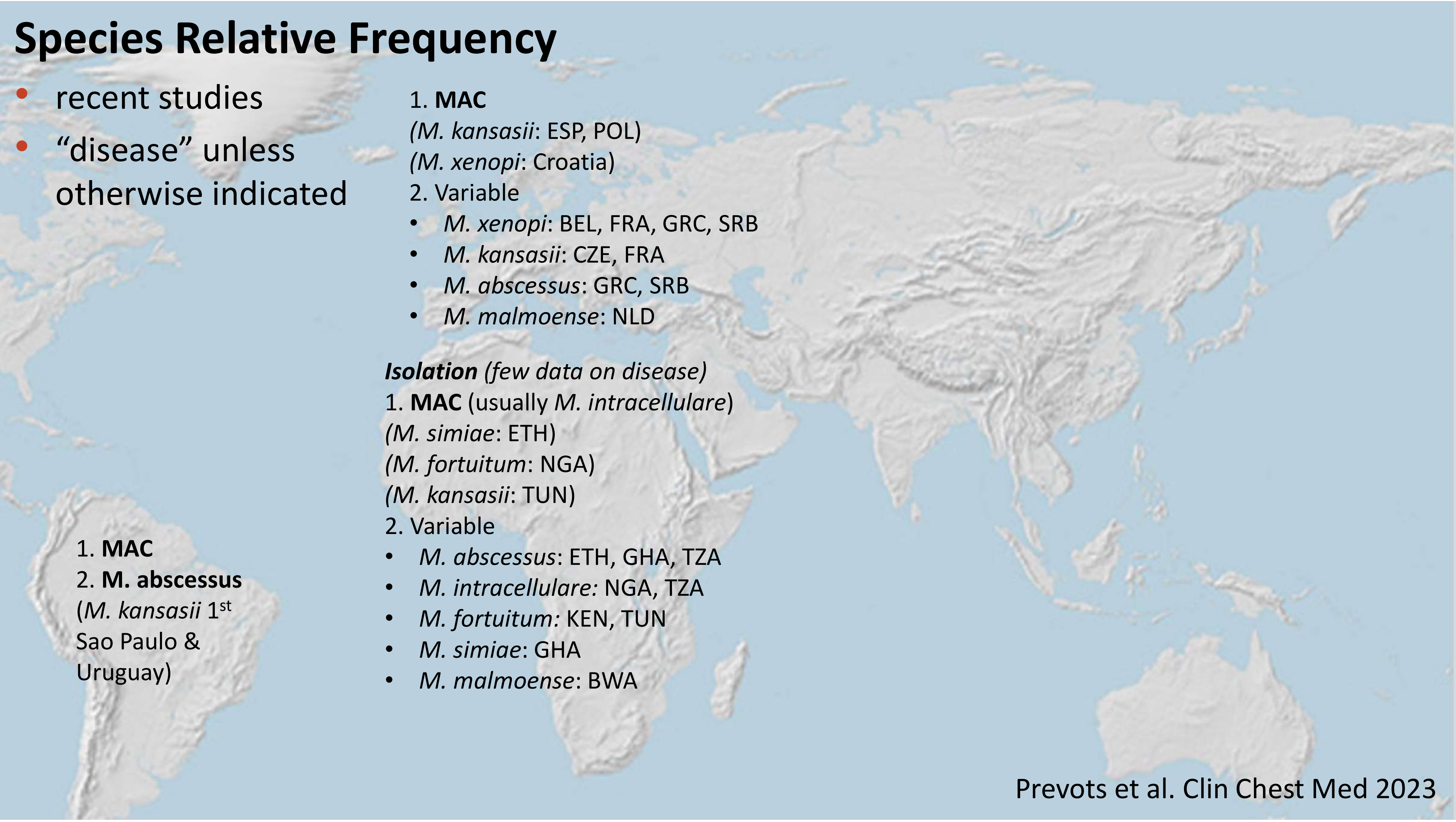

Prevots et al. Clin Chest Med 2023

Species Relative Frequency

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1. **MAC**

(*M. kansasii*: ESP, POL)
(*M. xenopi*: Croatia)

2. Variable

- *M. xenopi*: BEL, FRA, GRC, SRB
- *M. kansasii*: CZE, FRA
- *M. abscessus*: GRC, SRB
- *M. malmoense*: NLD

1. **MAC**
- *M. intracellulare*: CHN (4), JPN (1)
- *M. avium*: JPN (2)
- MAC: KOR (2), TWN (2), JPN (1)

2. ***M. abscessus***
- Multiple studies – CHN, JPN, KOR, TWN

Isolation *(few data on disease)*

1. **MAC** (usually *M. intracellulare*)

(*M. simiae*: ETH)
(*M. fortuitum*: NGA)
(*M. kansasii*: TUN)

2. Variable

- *M. abscessus*: ETH, GHA, TZA
- *M. intracellulare:* NGA, TZA
- *M. fortuitum:* KEN, TUN
- *M. simiae*: GHA
- *M. malmoense*: BWA

1. **MAC**
2. **M. abscessus**

(*M. kansasii* 1st Sao Paulo & Uruguay)

Prevots et al. Clin Chest Med 2023

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- *M. malmoense*: BWA

Isolation *(few data on disease)*
1. Variable
- *M. abscessus*: IND (2), SGP (2)
- MAC: IND (2), PAK (1)
- *M. chelonae*: IND (1)
2. Variable
- *M. fortuitum*: IND (4), SGP (2)
- *M. abscessus*: PAK (1)
- *M. chelonae*: IND (1)

1. **MAC**
2. **M. abscessus**
(*M. kansasii* 1st Sao Paulo & Uruguay)

Prevots et al. Clin Chest Med 2023

Species Relative Frequency

- recent studies
- "disease" unless otherwise indicated

Isolation (mostly)

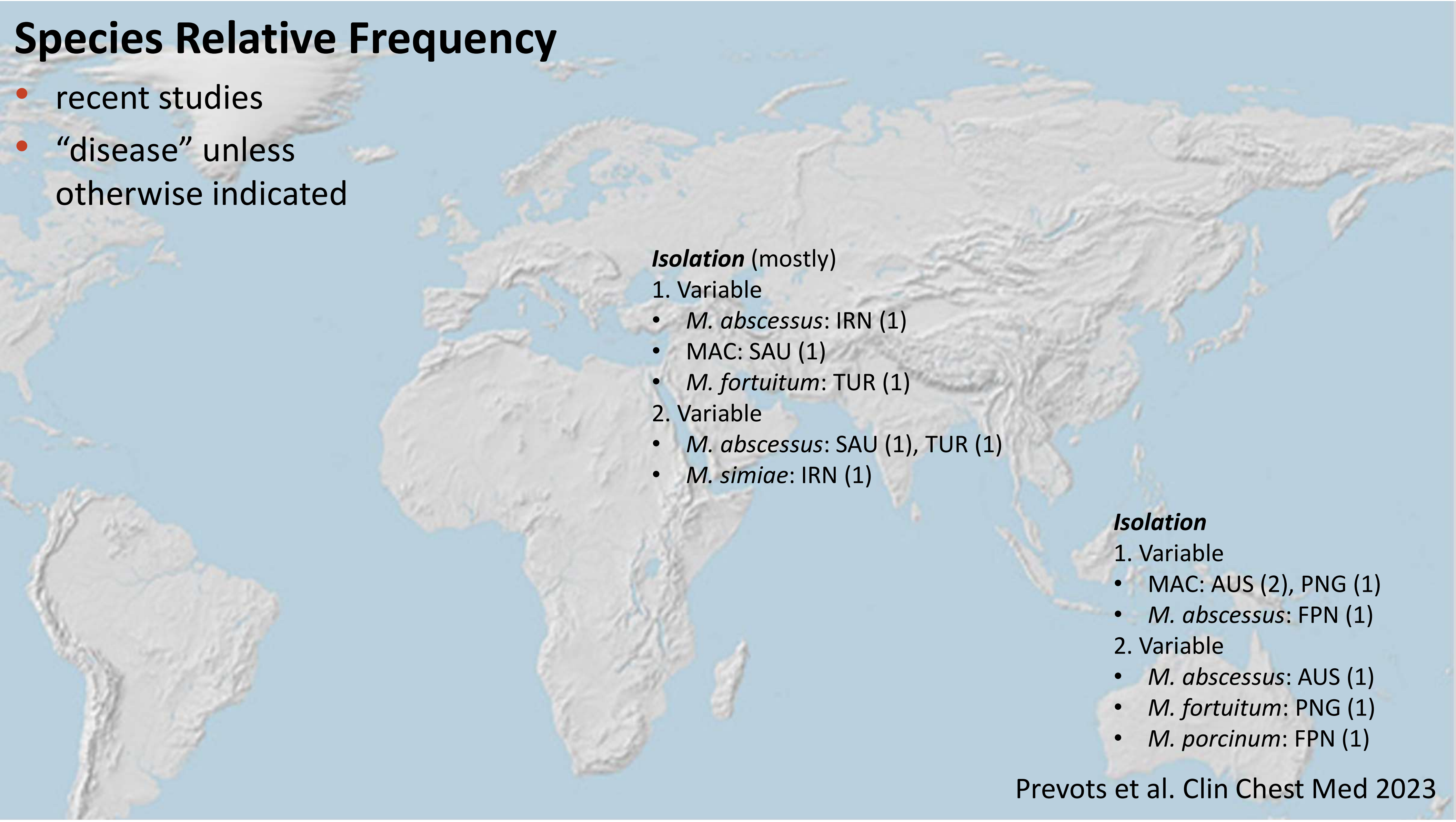
1. Variable
- *M. abscessus*: IRN (1)
- MAC: SAU (1)
- *M. fortuitum*: TUR (1)

2. Variable
- *M. abscessus*: SAU (1), TUR (1)
- *M. simiae*: IRN (1)

Prevots et al. Clin Chest Med 2023

Species Relative Frequency

- recent studies
- "disease" unless otherwise indicated



Isolation (mostly)

1. Variable
- *M. abscessus*: IRN (1)
- MAC: SAU (1)
- *M. fortuitum*: TUR (1)

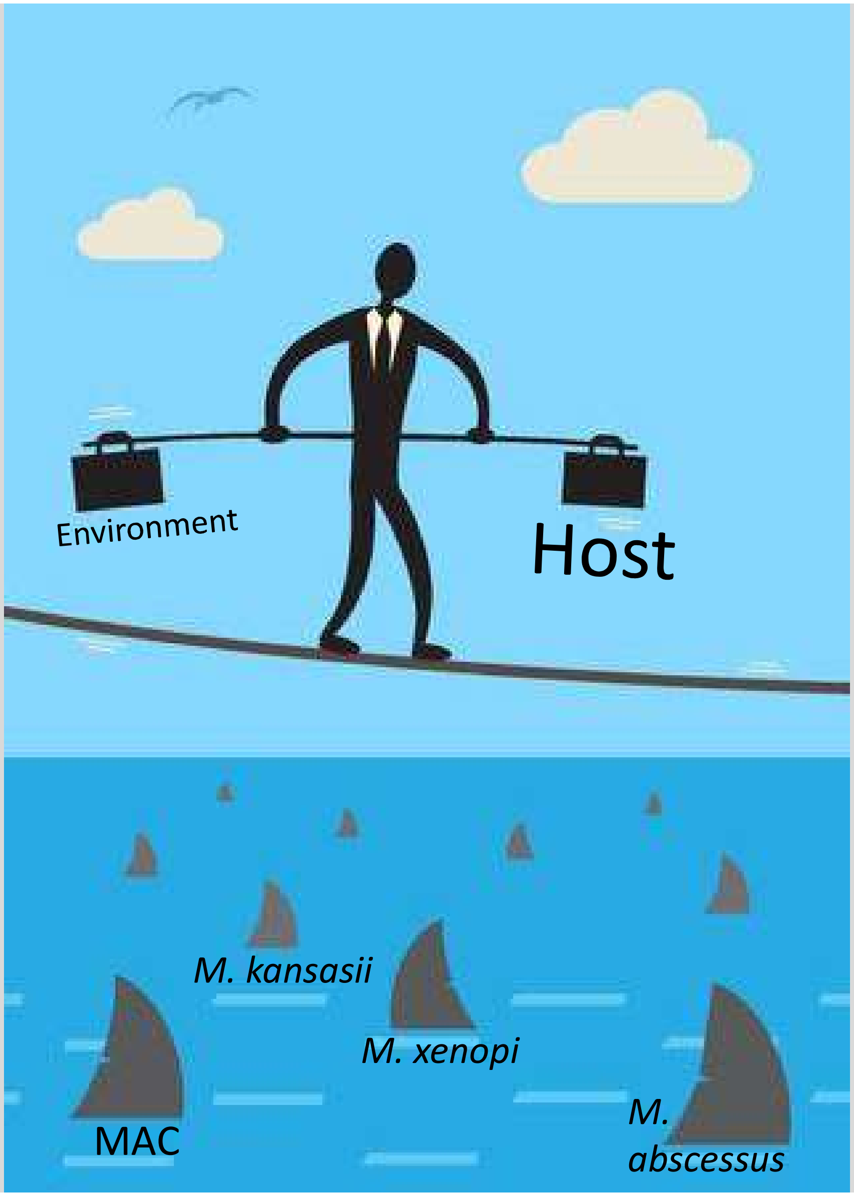
2. Variable
- *M. abscessus*: SAU (1), TUR (1)
- *M. simiae*: IRN (1)

Isolation

1. Variable
- MAC: AUS (2), PNG (1)
- *M. abscessus*: FPN (1)

2. Variable
- *M. abscessus*: AUS (1)
- *M. fortuitum*: PNG (1)
- *M. porcinum*: FPN (1)

Prevots et al. Clin Chest Med 2023



Risk Factors

- NTM very widespread → exposure extensive
- Disease uncommon (~40/100,000)

Risk Factors

Older Age

- Mean age at diagnosis
  - North America 68 years
  - Europe 60 years
  - East Asia 61 years

- Prevots et al. Clin Chest Med 2023

Risk Factors

Older Age

- Mean age at diagnosis *- Prevots et al. Clin Chest Med 2023*
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Female Sex

- All NTM-PD *- Prevots et al. Clin Chest Med 2023*
  - North America 60%
  - Europe 46%
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Risk Factors

Older Age

- Mean age at diagnosis — *- Prevots et al. Clin Chest Med 2023*
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Female Sex

- All NTM-PD — *- Prevots et al. Clin Chest Med 2023*
  - North America 60%
  - Europe 46%
  - East Asia 61%
- Nodular Bronchiectasis
  - Samsung Medical Center (1997-2013) 68% — *- Jhun et al. Eur Respir J 2020*
  - TWH Clinic (2003-2023) 77%

Risk Factors

Pre-existing structural lung disease

- **Emphysema / COPD**
  - Strong association - *Andrejak Thorax 2019, Marras ERJ 2016*
  - NTM w COPD (recent US studies) 44% *- Prevots et al. Clin Chest Med 2023*
- **Bronchiectasis**
  - Recent US studies 35% (underestimate?) *- Prevots et al. Clin Chest Med 2023*
- **Fibrosis**
  - 2% IPF patients (Seoul) *- Park J Korean Med Sci 2012*
  - Recent US studies limited 4-10% *- Prevots et al. Clin Chest Med 2023*

Risk Factors

Covert impairment of muco-ciliary / pulmonary defense

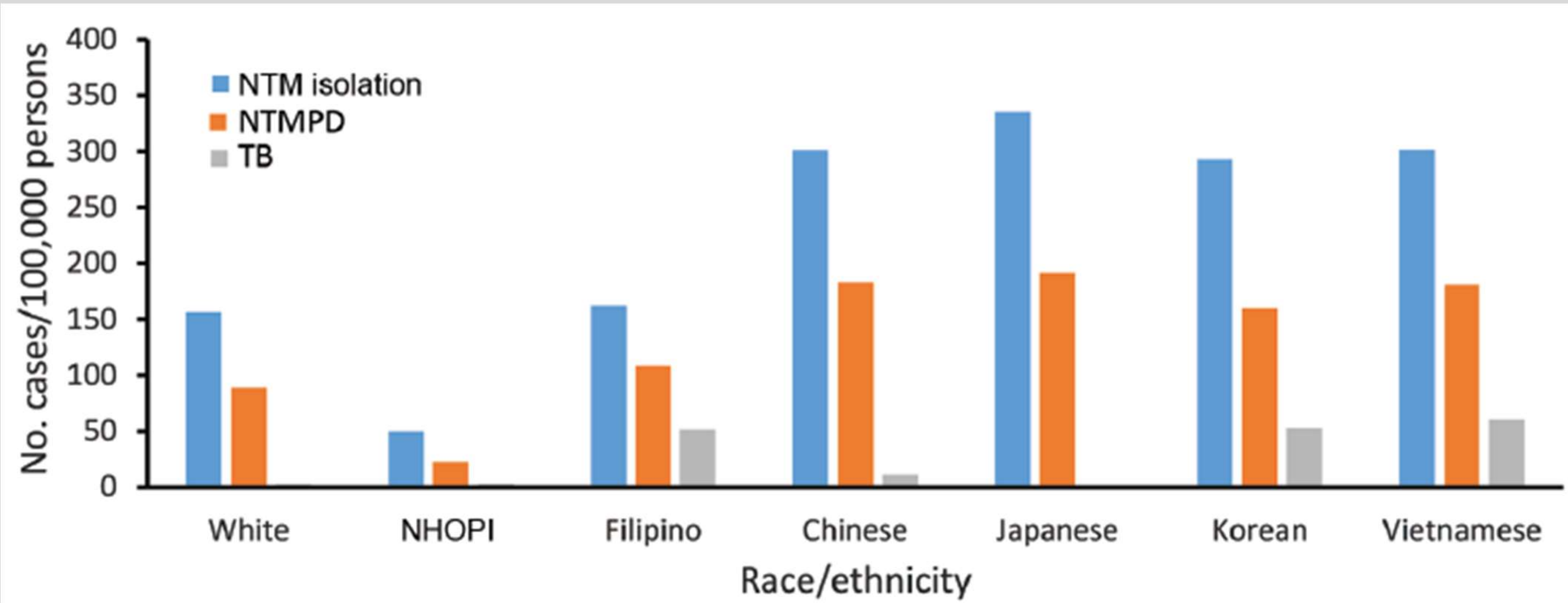
- CFTR mutations
  - NTM clinic: 20% CF, 50% mutation(s) - *Ziedalski Chest 2006*
- Ciliary impairment
- Immune dysregulation (autoimmunity, medications, etc.)

  - *Szymanski, Am J Respir Crit Care Med 2015*
- Medications / immune suppression (anti TNFs, etc.)

  - *Brode et al. Thorax 2015*

Race

- **Hawaii** – HMO, 2005-2013, self-reported race, NTM-PD defined microbiologically

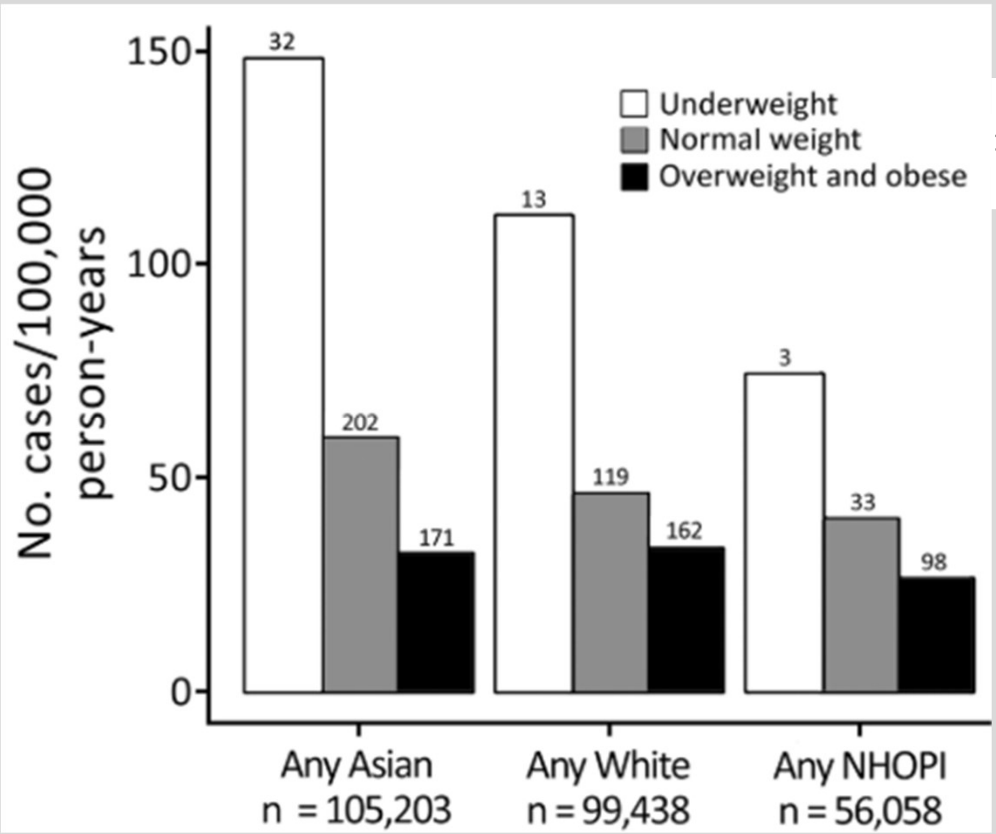


Adjemian et al. Emerg Infect Dis 2017

"Substantial differences exist in the epidemiology of NTMPD by race/ethnicity, suggesting behavioral and biologic factors that affect disease susceptibility."

Race

- **Hawaii** – HMO, 2005-2019, self-reported race, NTM-PD defined microbiologically



<18.5 kg/m²
18 - <25 kg/m²
≥25 kg/m²

Figure. Nontuberculous mycobacterial pulmonary infection incidence among Kaiser Permanente Hawaii beneficiaries, by ethnicity and body mass index category, Hawaii, USA, 2005–2019. Numbers above bars indicate case count by BMI category. Underweight, <18.5 kg/m²; normal weight, 18.5 to <25 kg/m²; overweight/obese, ≥25 kg/m². NHOPI, Native Hawaiian and Other Pacific Islander.

"Low BMI may increase susceptibility to NTM-PI, and risk may be higher for persons who self-identify as Asian, independent of BMI."

Blakney et al. Emerg Infect Dis 2022

Race

- **Wisconsin** – state-wide, 2011-2018, NTM isolation (≥1 positive)

	Total		Respiratory	
	Number (%) of Persons	Cumulative Incidence per 100,000 (95% CI)	Number (%) of Persons	Cumulative Incidence per 100,000 (95% CI)
Total	6,811 (100)	154 (150–157)	6,088 (100)	137 (134–141)
Gender				
Female	3,545 (52.1)	157 (152–163)	3,183 (52.3)	141 (136–146)
Male	3,238 (47.5)	148 (143–154)	2,879 (47.3)	132 (127–137)
Not reported	28 (0.4)	—	26 (0.4)	—
Age, yr, median (IQR)	66 (54–76)	—	67 (56–76)	—
Race				
Unascertained	2,058 (30.2)	—	1,774 (29.1)	—
Ascertained	4,753 (69.8)	—	4,314 (70.9)	—
White	3,833 (80.6)	96.5 (93.4–99.5)	3,466 (80.3)	87.2 (84.3–90.1)
Black	563 (11.8)	224 (205–242)*	507 (11.8)	202 (184–219)*
Asian	247 (5.2)	244 (214–275)*	241 (5.6)	238 (208–268)*

Vonasek et al. Ann Am Thor Soc 2023

Race

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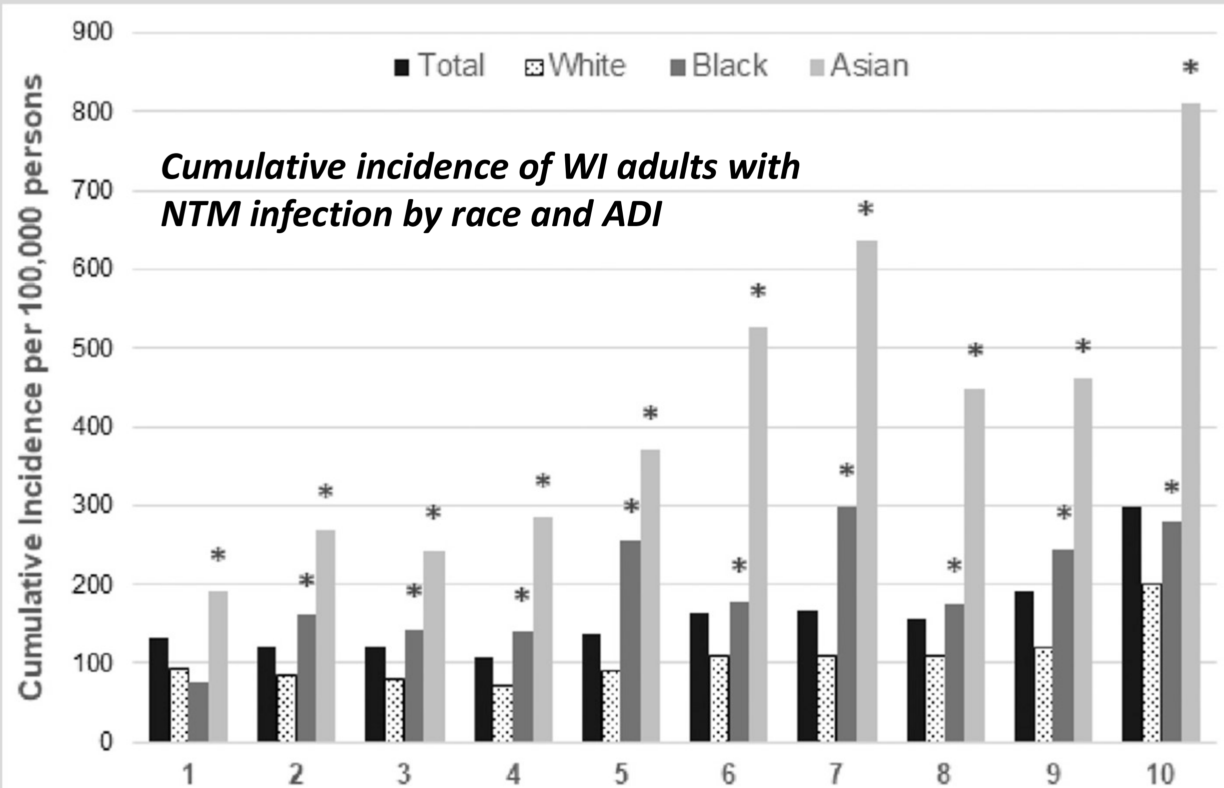


Area Deprivation Index
("inverse" of socioeconomic status)

NTM isolation more frequent in non-White racial groups and in individuals with social disadvantage…

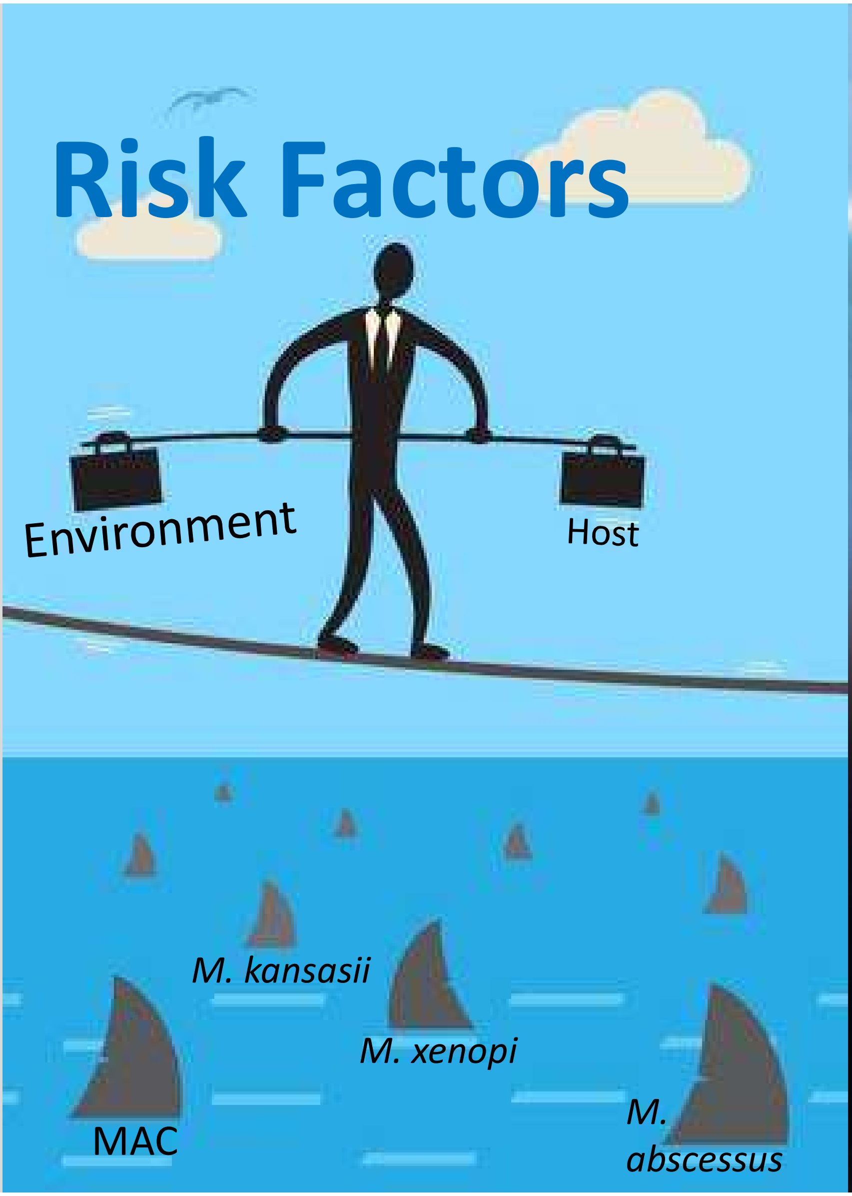
NTM disease may be more frequent in these groups

Could access to care could explain prior results?

Limitations

- Isolation only
- Sampling

Vonasek et al. Ann Am Thor Soc 2023


Risk Factors
Environment
Host
M. kansasii
M. xenopi
MAC
M. abscessus


MAC

Risk Factors

-Environment & Exposures

Association between MAC-PD and Mycobacteria in Home Water and Soil: A Case-Control Study

- Test associations between MAC-PD and NTM colonization of potential home point-of-use exposure sources
- WA/OR residents with MAC-PD (cases, n=56) and population controls (n=51) matched by age, sex, geography
- Sampled water from bathroom & kitchen faucets, shower aerosols, indoor & outdoor soil
- NTM isolation from case vs control homes compared using conditional logistic regression adjusted for potential confounders

Tzou et al. Ann Am Thor Soc 2019

Risk Factors

-Environment & Exposures

Association between MAC-PD and Mycobacteria in Home Water and Soil: A Case-Control Study

Table 1. Association of residential nontuberculous mycobacteria and *M. avium* complex pulmonary disease by point-of-use source

Household site	*N* (Positive)*		Unadjusted Analysis		Age-adjusted Analysis†		Fully Adjusted Analysis‡	
	Cases	Control Subjects	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Bathroom faucet	40 (23)	48 (20)	1.7	0.8–4.0	1.8	0.7–4.3	2.1	0.8–5.5
Kitchen faucet	40 (23)	48 (22)	1.6	0.7–4.0	1.4	0.6–3.5	1.6	0.6–4.2
Shower aerosols	39 (18)	46 (10)	3.2	1.1–8.9	3.8	1.2–11.7	4.0	1.2–13.4
Indoor soil	30 (17)	38 (13)	2.0	0.7–5.4	1.6	0.6–4.6	1.4	0.5–4.4
Outdoor soil	39 (10)	46 (9)	1.2	0.4–3.4	1.1	0.4–3.2	1.2	0.4–3.4

Definition of abbreviations: CI = confidence interval; *M. avium* = *Mycobacterium avium*.
*Some case–control pairs had more than one control. Positives were samples with at least nontuberculous mycobacteria isolate.
†Adjusted for age > 80 years.
‡Adjusted for age, race, and education level.

Having "any NTM" in shower aerosol associated with MAC-PD

Tzou et al. Ann Am Thor Soc 2019

Risk Factors

-Environment & Exposures

Association between MAC-PD and Mycobacteria in Home Water and Soil: A Case-Control Study

Table 2. Association of residential *M. avium* complex and *M. avium* complex pulmonary disease by point-of-use source

Household site	*N* (Positive)*		Unadjusted Analysis		Age-adjusted Analysis†		Fully Adjusted Analysis‡	
	Cases	Control Subjects	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Bathroom faucet	40 (15)	48 (11)	1.8	0.7–4.5	1.7	0.6–4.5	1.8	0.6–4.9
Kitchen faucet	40 (15)	48 (14)	1.2	0.5–2.6	1.1	0.5–2.5	1.2	0.5–2.8
Shower aerosols	39 (10)	46 (6)	2.6	0.7–10.4	2.9	0.7–12.5	2.9	0.7–12.4
Indoor soil	30 (7)	38 (4)	1.9	0.5–6.4	1.3	0.3–5.0	1.1	0.3–4.5
Outdoor soil	39 (8)	46 (8)	1.0	0.3–3.1	0.9	0.3–2.8	0.9	0.3–2.8

Definition of abbreviations: CI = confidence interval; *M. avium* = *Mycobacterium avium*.
*Some case–control pairs had more than one control. Positives were samples with at least nontuberculous mycobacteria isolate.
†Adjusted for age > 80 years.
‡Adjusted for age, race, and education level.

Having "MAC" in shower aerosol associated (not statistically significantly) with MAC-PD

Tzou et al. Ann Am Thor Soc 2019

Risk Factors

-Environment & Exposures

Drinking water characteristics and NTM-PD in Ontario, Canada

- **Objective**: assess for associations between drinking water characteristics and frequency of NTM isolation and disease
- **Unit of study** – drinking water distribution regions
  - Mapped water/treatment attributes to combined census areas for areas served by the 42 largest ON drinking water distribution systems (~75% of the population ~9.5M people)
- **Predictor variables** = Water variables
  - Source-type (surface-containing n=35 vs exclusively ground n=7)
  - Secondary disinfectant (chloramine n=11 vs chlorine n=31)
  - Trihalomethane and nitrogen levels
  - Heterotrophic plate count (HPC)
  - Coliform CFU's
- **Outcome variables** = Period prevalence of NTM-PD (standardized incidence ratios)
  - May 2010 - June 2015
  - Expected based on provincial average, adjusted for age, sex and population
  - *M. avium*, *M. xenopi*, *M. intracellulare*, and *M. abscessus*

Minnery et al. ATS Meeting 2017

Drinking water and NTM-PD in Ontario

Results

NTM pulmonary disease, Ontario 2010-2015

Species	Number patients (period prevalence / 100,000)
M. avium	3806 (28.2)
M. xenopi	1057 (7.8)
M. intracellulare	497 (3.7)
M. abscessus	185 (1.4)

Mid-point population 13.5 M

Drinking water and NTM-PD in Ontario

Results

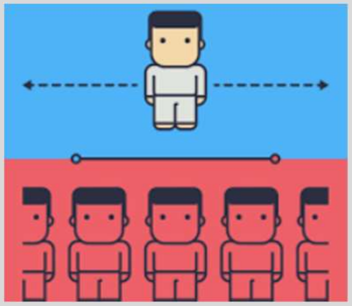
NTM-PD by Population density§

	M. avium	M. xenopi	M. intracellulare	M. abscessus
RR†	**1.51 (1.12, 2.03)**	**1.42 (1.09, 1.85)**	0.92 (0.70, 1.22)	0.92 (0.70, 1.22)
p^{unadj}	0.0005	0.002	0.12	0.65
p^{adj}	**0.004**	**0.01**	0.60	1.0

§ Median (IQR) 1,115 (587 - 1,558); range 127-4,239

† Unit for analysis - 1000 people / km2

^unadj – unadjusted, ^adj – adjusted for multiple comparisons via False Discovery Rate method



Drinking water and NTM-PD in Ontario

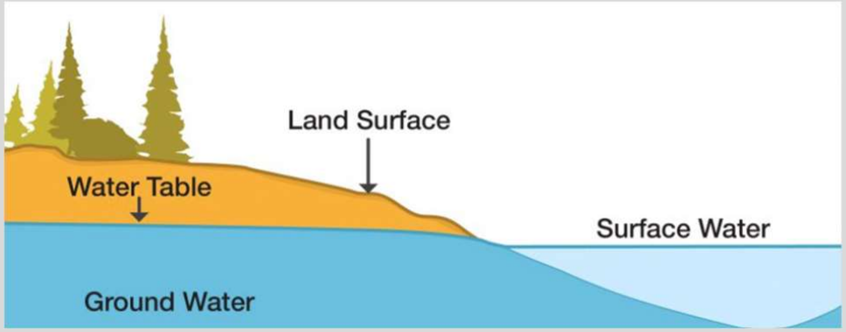
Results

Source water

Surface/Mixed (n=35) vs Ground (n=7): NTM-PD

	M. avium	M. xenopi	M. intracellulare	M. abscessus
RR	**1.82** (0.44, 7.53)	**7.85** (1.00, 61.9)	1.44 (0.68, 3.05)	0.53 (0.22, 1.25)
p^{unadj}	0.45	0.02	0.37	0.08
p^{adj}	1.0	0.18	1.0	0.56

^unadj – unadjusted, ^adj – adjusted for multiple comparisons via False Discovery Rate method



Drinking water and NTM-PD in Ontario

Results

Secondary disinfection

Chloramine (n=11) vs Chlorine (n=31): NTM-PD

	M. avium	M. xenopi	M. intracellulare	M. abscessus
RR	1.41 (0.62, 3.2)	1.06 (0.55, 2.03)	1.17 (0.73, 1.90)	1.80 (0.86, 3.76)
p^{unadj}	0.05	0.28	0.48	0.08
p^{adj}	0.40	1.0	1.0	0.60

^unadj – unadjusted, ^adj – adjusted for multiple comparisons via False Discovery Rate method

Drinking water and NTM-PD in Ontario

Results

Treated water quality (microbial content)

Heterotrophic Plate Count §

	M. avium	M. xenopi	M. intracellulare	M. abscessus
RR†	**0.60 (0.37, 0.96)**	**0.49 (0.31, 0.77)**	1.08 (0.87, 1.34)	0.59 (0.36, 0.97)
p^{unadj}	<0.0001	<0.0001	0.25	0.02
p^{adj}	**<0.0001**	**<0.0001**	0.50	0.08

§ Median (IQR) 4.1 (1.7 - 13); range 0.67-34 cfu/mL

† Unit of analysis 10 cfu/mL

^unadj – unadjusted, ^adj – adjusted for multiple comparisons via False Discovery Rate

Drinking water and NTM-PD in Ontario

Results

Treated water quality (microbial content)

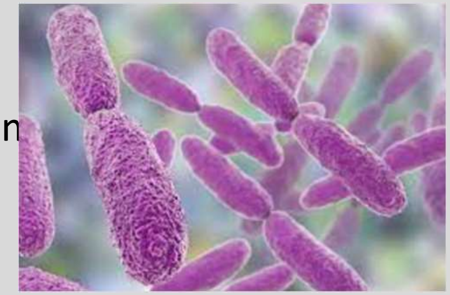
Total Coliforms§ (cfu/100 mL)

	M. avium	M. xenopi	M. intracellulare	M. abscessus
RR†	**1.94** (0.31, 12.3)	1.46 (0.29, 7.34)	0.22 (0.06, 0.73)	**4.66** (0.79, 27.6)
p^{unadj}	0.49	0.65	0.02	0.10
p^{adj}	0.69	0.71	0.10	0.22

§ Median (IQR) 0.014 (3.7×10^{-5} – 0.00033); range 0-0.0011 cfu/100 mL

† Unit of analysis cfu/100 mL

^unadj – unadjusted, ^adj – adjusted for multiple comparisons via False Discovery Rate n



Drinking water and NTM-PD in Ontario

Results

Treated water quality (nutrients)

	M. avium	M. xenopi	M. intracellulare	M. abscessus
Trihalomethanes§	0.98 (0.95, 1.00) P = 0.11 / 0.37	0.97 (0.95, 0.99) P = 0.011 / 0.05	1.00 (0.99, 1.01) P = 0.93 / 0.93	0.99 (0.97, 1.01) P = 0.24 / 0.45
Nitrogen† (from nitrate and nitrite)	0.88 (0.56, 1.4) P = 0.60 / 0.92	0.71 (0.38, 1.33) P = 0.29 / 0.80	1.05 (0.82, 1.33) P = 0.71 / 0.93	0.93 (0.69, 1.27) P = 0.66 / 0.93

§ Surrogate of dissolved organic carbon – median (IQR) 27 (16-45); range 6.5-77 ppb; analyzed per ppb

†Surrogate of nutrient levels – median (IQR) 0.31 (0.13-0.42); range 0.013-5.9 ppm; analyzed per ppm

p-values presented as unadjusted / **adjusted** for multiple comparisons via False Discovery Rate method

Drinking water and NTM-PD in Ontario

Results Summary

- **Population density -** positively associated with *M. avium* (1.5) and *M. xenopi* (1.4) - per 1000 people/km^2 - statistically significant
- **Surface/mixed water source -** positive associations with *M. xenopi* (7.9), *M. avium* (1.8) - not statistically significant
- **Chloramine (vs chlorine)** secondary disinfection - possibly some association with *M. avium* (1.4) and *M. abscessus* (1.8) - not statistically significant
- **HPCs** - inverse association with *M. avium* (0.6) and *M. xenopi* (0.5) - statistically significant; *M. abscessus* (0.6) - not statistically significant
- **Coliform counts -** positive associations with *M. avium* (1.9), *M. xenopi* (1.5), *M. abscessus* (1.7) - not statistically significant
- **THMs, nitrogen** (surrogates of water nutrients) – no observed association with NTM-PD

Drinking water and NTM-PD in Ontario

Wrap up

Limitations

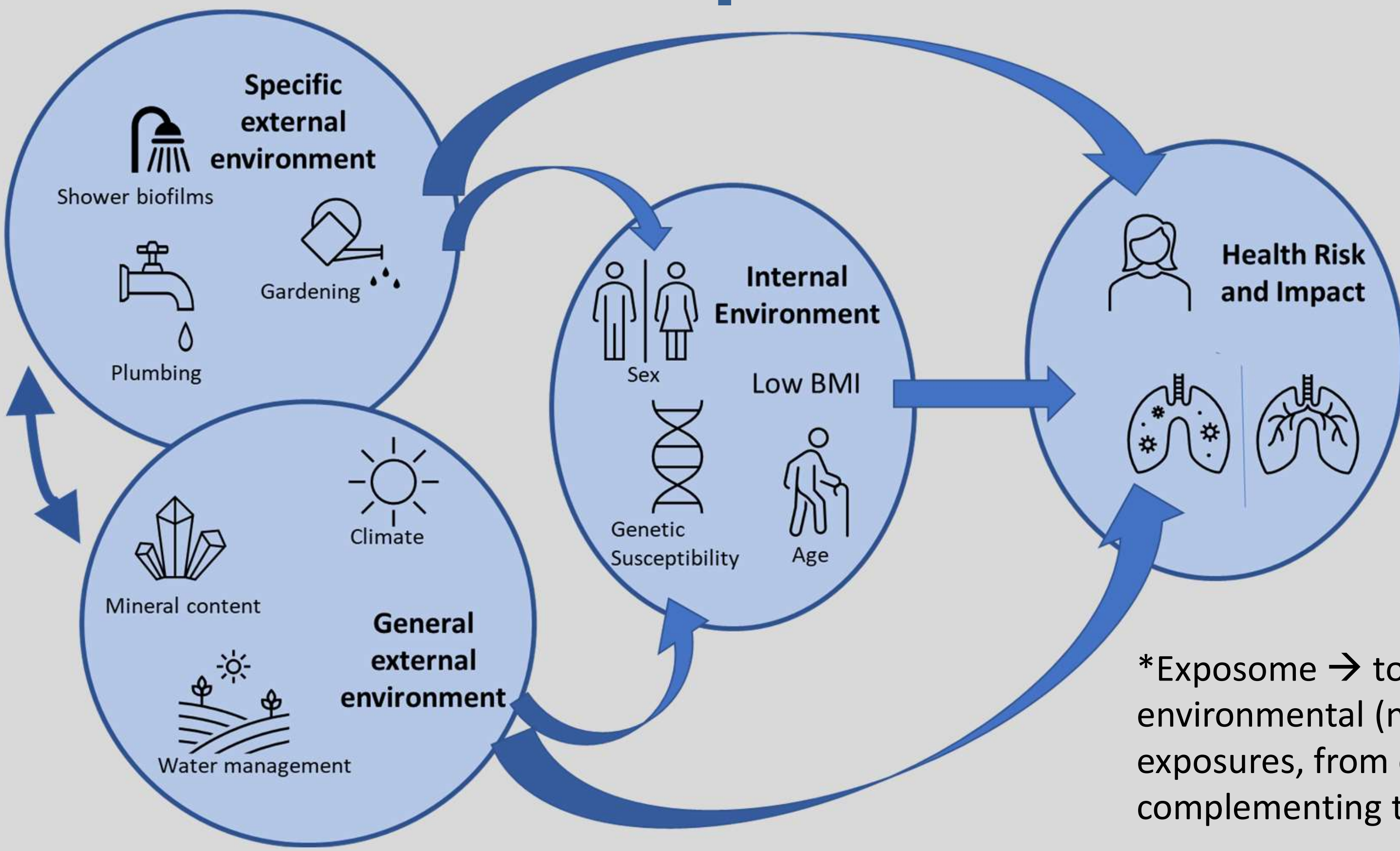
- Sample size (n=42) - analysis at the level of the water distribution system
- Multiple comparisons
- Limited data on *M. abscessus, M. intracelllulare* – few cases
- Lacked clinical data to define NTM-PD

Conclusions

- Water characteristics are associated with NTM-PD
- HPCs and possibly surface/mixed water sources and chloramine secondary disinfection associated with NTM-PD

Risk Factors

NTM Exposome*



*Exposome → totality of human environmental (non-genetic) exposures, from conception onwards, complementing the genome

Transmission?

- Historical assertion: no public health concerns
- Theoretical risk of interpersonal transmission
  - High burden patient, close contact with highly susceptible person
  - Unproven

- *M. abscessus,* subspecies *massiliense*
  - 22 year old man with CF moved into Seattle program
  - 8 months later, 4 additional CF patients newly-identified with *Mabs ssp. massiliense*
  - Isolates indistinguishable by PFGE
  - Authors hypothesized either direct patient-to-patient spread or indirectly through contamination of clinic environment

Aitken et al. Am J Respir Crit Care Med 2012

Genetically similar *M. abscessus* isolates from different patients, regions

Whole genome sequencing studies demonstrated high degrees of genetic similarity between Mabs isolates from different patients; generally limited environmental sampling and traditional contact opportunity investigation

Bryant et al. Science 2016

- "Using whole-genome analysis of a global collection of clinical isolates, we show that the majority of *M. abscessus* infections are acquired through transmission, potentially via fomites and aerosols, of recently emerged dominant circulating clones that have spread globally."

Tettelin et al. Emerg Infect Dis 2014

- "High-level relatedness among Mycobacterium abscessus subsp. massiliense strains from widely separated outbreaks"

Bryant et al. Lancet 2013

- "WGS revealed frequent transmission of…NTM between patients with CF despite conventional cross-infection measures. Although the exact transmission route is yet to be established, our epidemiological analysis suggests that it could be indirect."

Clinical & Environmental and Epidemiological Investigations Required

Gross et al. Am J Respir Crit Care Med 2023

- M. avium in Colorado adult CF program; clusters identified; some epi links present; no environmental matches, limited sampling
- Concluded more standardized epi / environmental investigations required

Van Tonder et al. Eur Respir J, 2023

- Single London Specialty hospital, 996 MAC isolates from 354 patients isolated yielding multiple putative clusters, most without epi links (indirect transmission?)
- Lacked environmental sampling

Gross et al. Ann Am Thor Soc 2023

- Vermont adult CF program
- 2 clusters (M. avium & M. intracellulare ssp. chimaera), both had epi links
- Water fountain M. intracellulare ssp. chimaera appeared to be a source for a cluster

Programmatic concerns, despite uncertain risks

- Congregate settings – clinics, wards
- High-risk cohorts – CF
- More difficult organisms (*M. abscessus*)
- CF IPAC
  - *Patients with CF with M. abscessus colonisation/infection must be segregated from each other and from all other people with CF. The methods used to segregate patients should be determined by local guidelines and must take into account communal areas such as pharmacy and radiology [C]**

*Grade C evidence - expert committee reports or opinions and/or clinical experience of respected authorities (absence of directly applicable studies of good quality)

- CF Mabs Infection Control Working Group Report (cysticfibrosis.org.uk)

Financial costs

Financial Costs

Patient-level, comprehensive

Objective - Healthcare costs attributable to NTM-PD (payer perspective), Ontario, Canada

Methods - Matched cohort

- Incident NTM-PD patients 2002–2012 (linked lab + health admin data)
- Matched to population controls (1:3) on age, sex, index date, propensity score (including measures of rurality, income, comorbidities).
- Phase-of-care specific attributable costs for acute and long-term illness (initial, subsequent, continuous, final)

Ramsay et al. Emerg Infect Dis 2020

Financial Costs

Patient-level, comprehensive

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- Phase-of-care specific attributable costs for acute and long-term illness (initial, subsequent, continuous, final)

Characteristic	NTM-PD	Controls
N	7,243	21,729
Mean age at index	66	66
Female sex	50.7%	50.7%

Ramsay et al. Emerg Infect Dis 2020

Financial Costs

Patient-level, comprehensive

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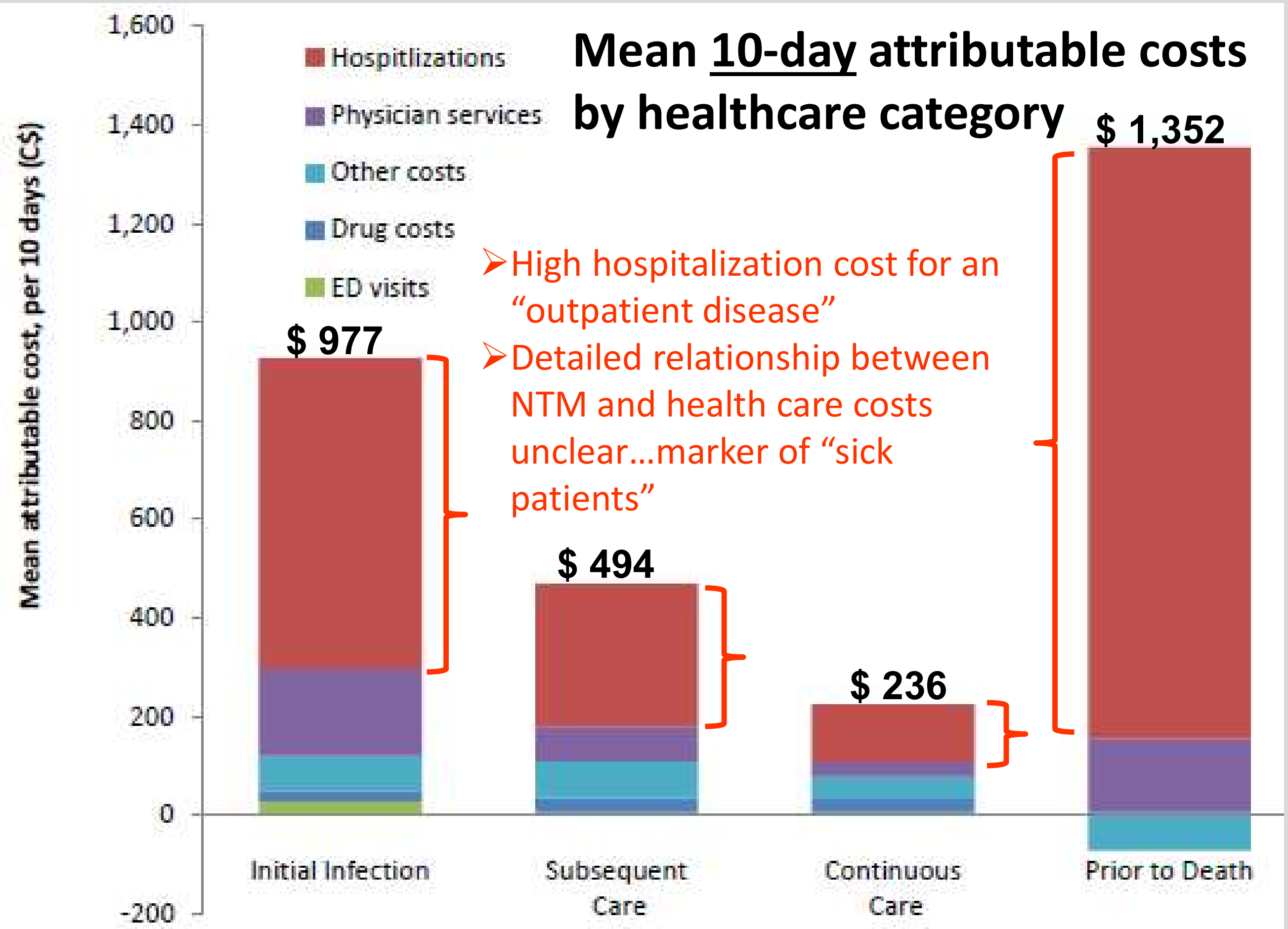
Characteristic	NTM-PD	Controls
N	7,243	21,729
Mean age at index	66	66
Female sex	50.7%	50.7%

Phase	Start Date	End Date
Initial	Index (30 days before lab date)	60 days post index / Death / End observation period
Subsequent	61 days post index	150 days post index date
Continuous	151 days post index	Start of final phase / End observation period
Final	70 days before death	Death date

Ramsay et al. Emerg Infect Dis 2020

Financial Costs

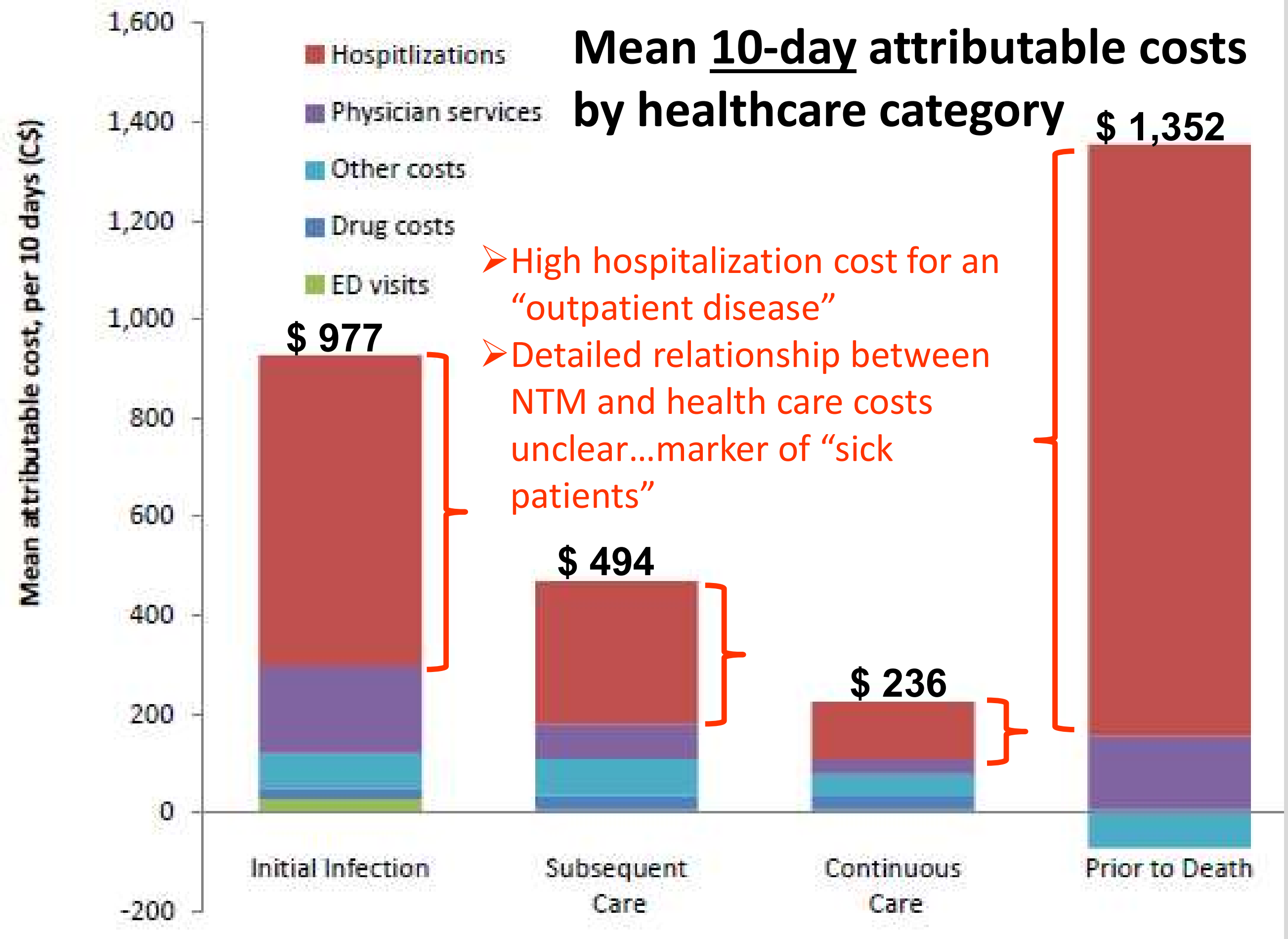
Patient-level, comprehensive



Ramsay et al. Emerg Infect Dis 2020

Financial Costs

Patient-level, comprehensive



Attributable mean 1-year cost (adjusted for survival):

CAD **$14,953**
(USD $11,541)

Ramsay et al. Emerg Infect Dis 2020

Financial Costs

Patient-level, comprehensive

Objective

- Study healthcare expenditure among patients with newly diagnosed NTM-PD, and estimate expenditure attributable to NTM-PD in the US

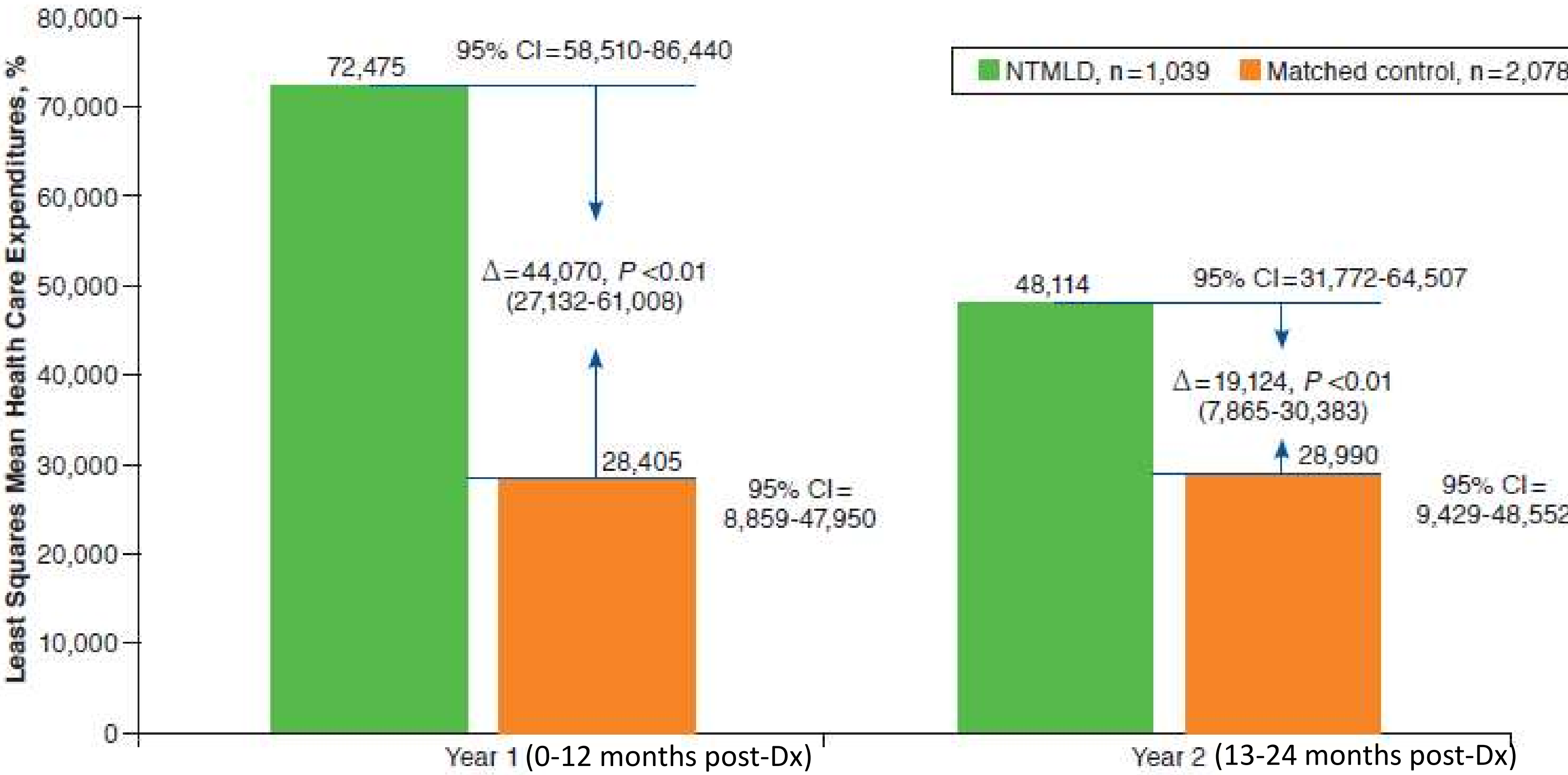
Methods

- Matched cohort
- Large managed care insurance database, incident NTM-PD by diagnostic claim codes, matched 2:1 by age, sex, coverage period
- Expenditures adjusted for all comorbid illnesses and Charlson Comorbidity Index (CCI)

	Patients with NTMLD (n = 1,039)	Controls (n = 2,078)	P Value[b]
Age, mean (SD)	68 (14.1)	68 (14.1)	
Female, % (n)	67 (699)	67 (1,392)	
CCI score, mean (SD)	2.0 (2.16)	0.5 (1.25)	<0.001

Marras et al. J Manag Care Spec Pharm 2018

FIGURE 2 Adjusted Total Direct Health Care Expenditures for NTMLD and Control Cohorts Across Years 1 and 2



CI=confidence interval; NTMLD=nontuberculous mycobacterial lung disease.

Sensitivity analysis: ***propensity score matching, difference reduced to an average of $5,296 per year (averaged over both follow-up years)***

Marras et al. J Manag Care Spec Pharm 2018


O U T C O M E S

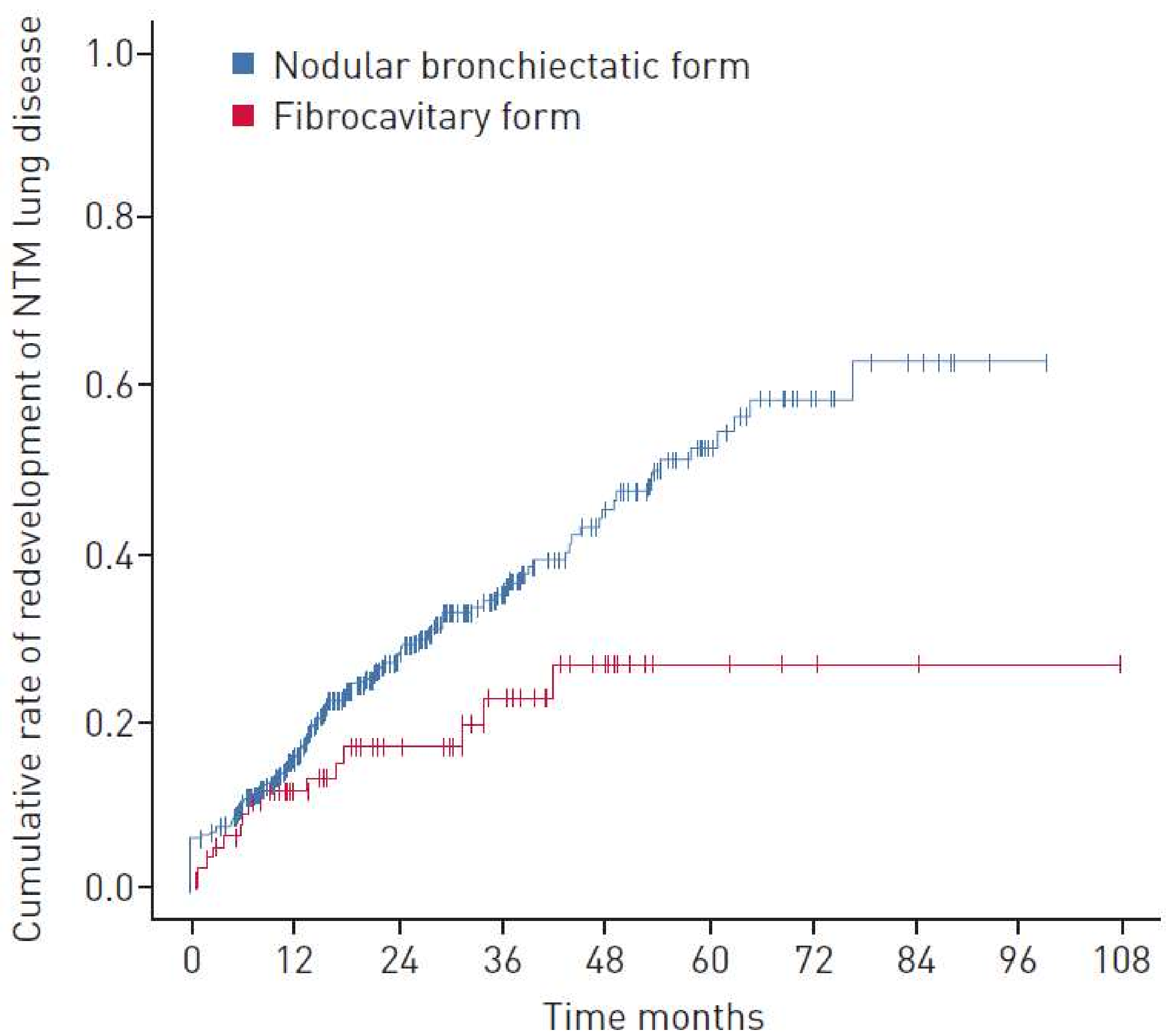
NTM outcomes

- Chronic disease

- Minority treated
  - 18% US HMO study (*Prevots, AJRCCM 2010)*
  - 20-24% ON population *(Brode, ATS meeting 2018)*
- Treatment "success" (MAC)
  - 52-66% - systematic review *(Diel et al. Chest 2018)*
  - 60% - systematic review and meta-analysis *(Kwak et al. Clin Infect Dis 2017)*
- Recurrence
  - 14 months – 30% *(Koh et al. Eur Respir J 2017)*
  - 48 mo – 50% *(Wallace et al. Chest 2014)*

NTM-PD outcomes

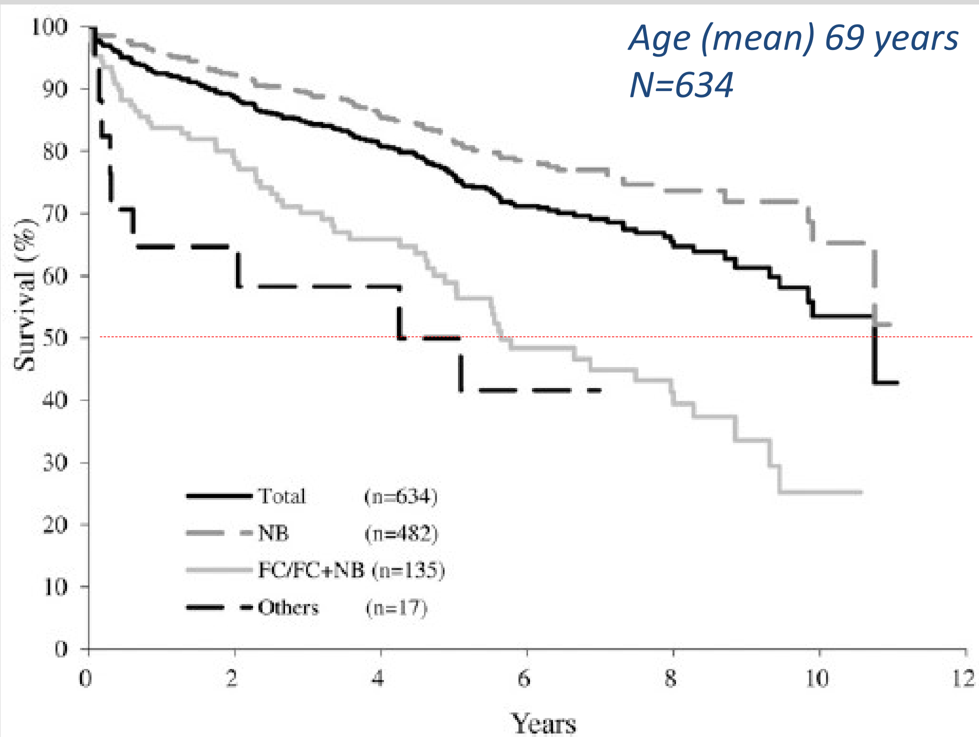
- Recurrence



Koh et al. Eur Respir J 2017

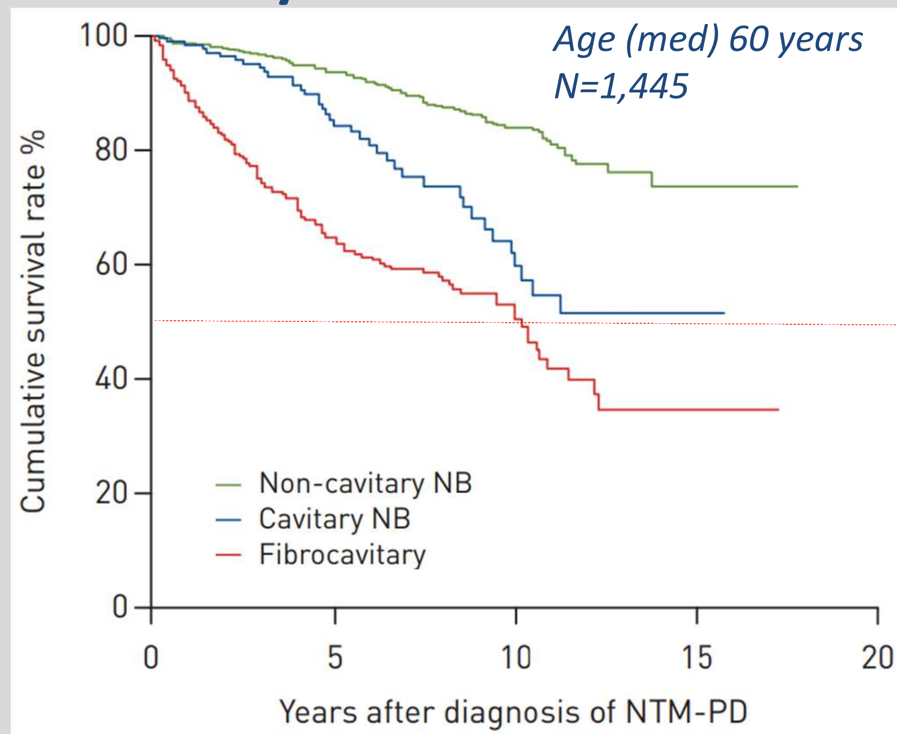
All Cause Mortality

MAC



Hayashi et al. AJRCCM 2012

MAC / *M. abscessus*

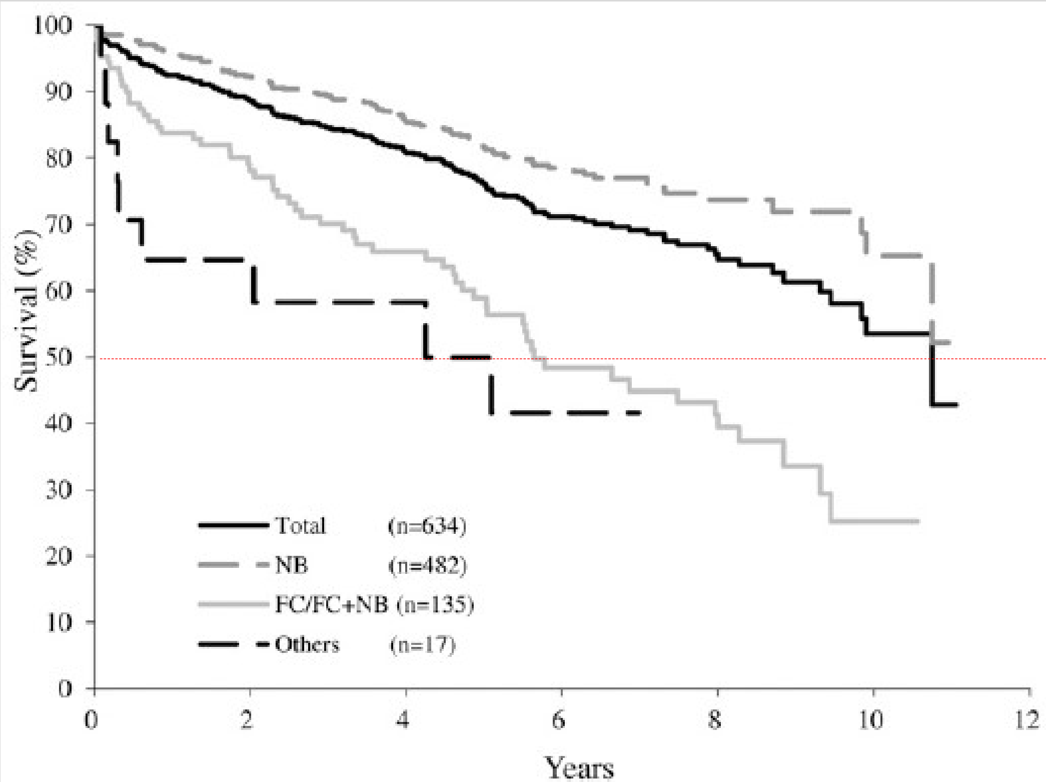


Jhun et al. Eur Resp J 2020

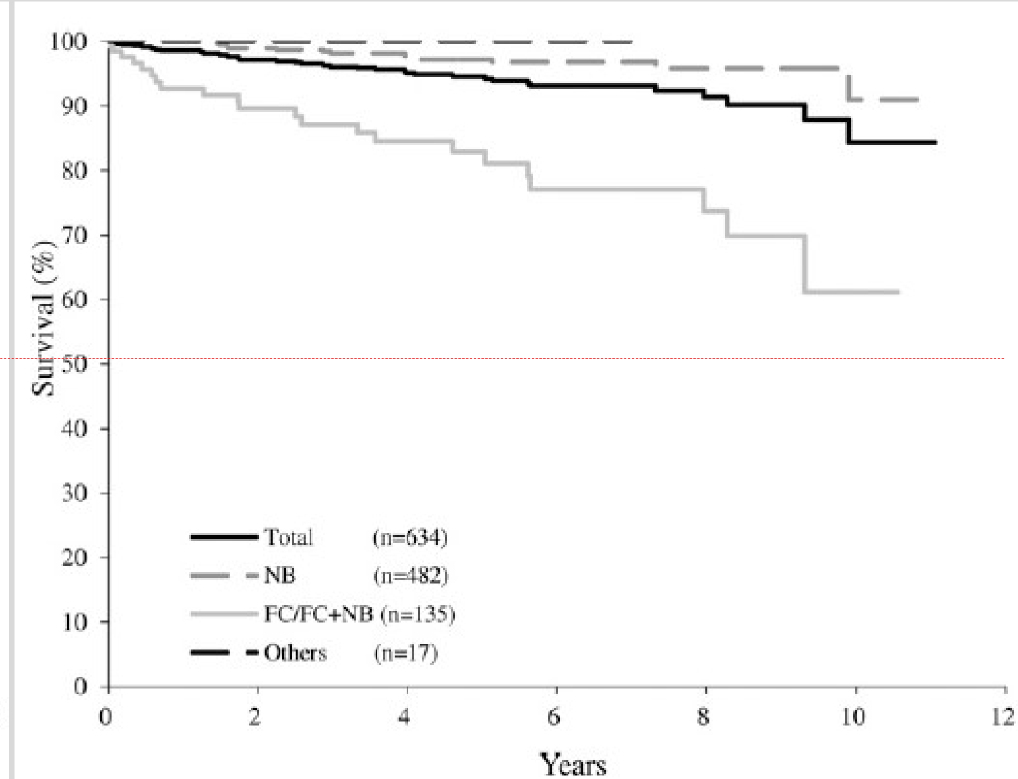
	Median Survival	
~ 11 years	**NB**	> 15 years
~ 5.5 years	**Cavitary (FC / cavitary NB)**	~ 12 years

MAC-PD

All cause mortality



MAC-PD mortality



N=634, mean age 69 years

Hayashi et al. AJRCCM 2012

NTM-PD Survival, Ontario, Canada

Group	Total	1-year Survival	5-year Survival	Hazard ratio (95% CI)
NTM	**8469**	**85.8%**	**65.6%**	**1.63 (1.56-1.70)**
Control	8469	95.0%	78.7%	
MAC	**5543**	**86.6%**	**66.7%**	**1.57 (1.48-1.66)**
Control	5543	94.8%	78.5%	
M. xenopi	**1975**	**82.3%**	**59.9%**	**1.84 (1.69-2.01)**
Control	1975	95.0%	77.7%	
M. abscessus	**201**	**92.0%**	**79.2%**	**1.49 (1.00-2.21)**
Control	201	95.5%	87.3%	

Population-based, incident NTM, matched by age, sex, index date, propensity score

Marras et al. Emerg Infect Dis 2017

Studying survival, predicting mortality

Prognostic indices

Study	Patients (mean age)	Variables (1 point each)	5-year mortality (derivation / validation)
Kumagai et al. BMC Infect Dis 2017 Japan **MAC**	Derivation n=368 (72 yrs) Validation n=118 (70 yrs)	• Male sex • Age ≥70 • Malignancy • BMI <18.5 • Lymphocytes <1 • Albumin <35 • FC pattern	Low risk (0-1 pts) - 2.3 / 2.8% Int risk (2-3 pts) - 23.4 / 17.7% High risk (≥4 pts) – 69.2 / 54.6%

Studying survival, predicting mortality

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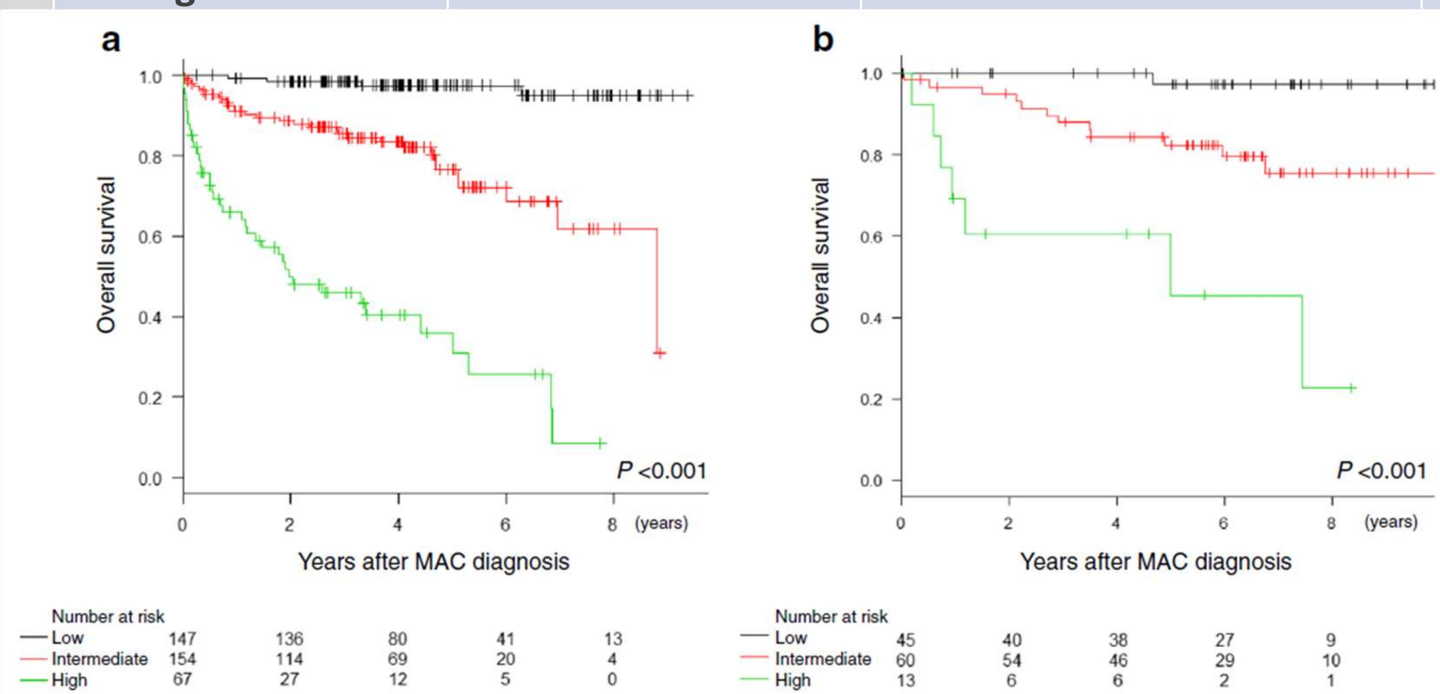

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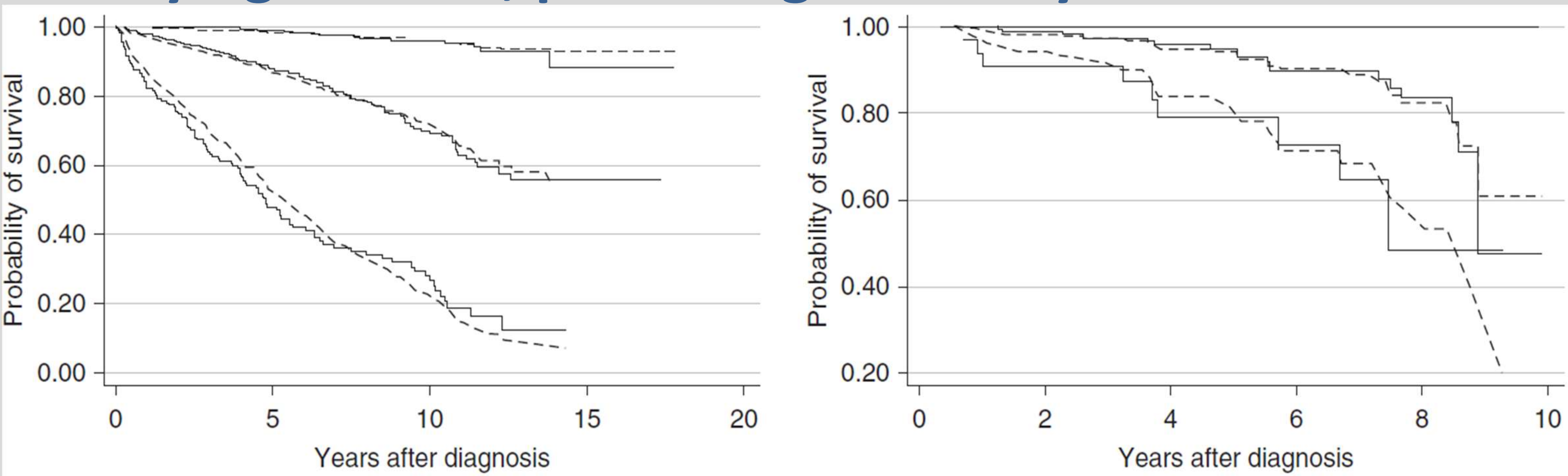
Kim et al. Am J Respir Crit Care Med 2021 Korea **MAC 78%** **Mabs 22%**	Derivation n=1,181 (60 yrs) Validation n=377 (63 yrs)	• BMI <18.5 • Age≥65 • Cavitation • ESR elevated (>15 M / 20 F) • Sex – male	Low risk (0-1 pts) – ~2 / 0% Int risk (2-3 pts) - ~12 / ~ 5% High risk (4-5 pts) – ~50 / 20%

Studying survival, predicting mortality



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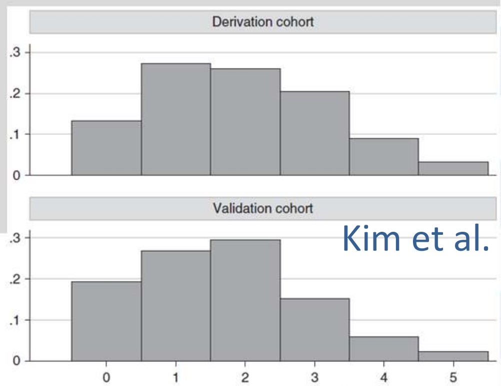
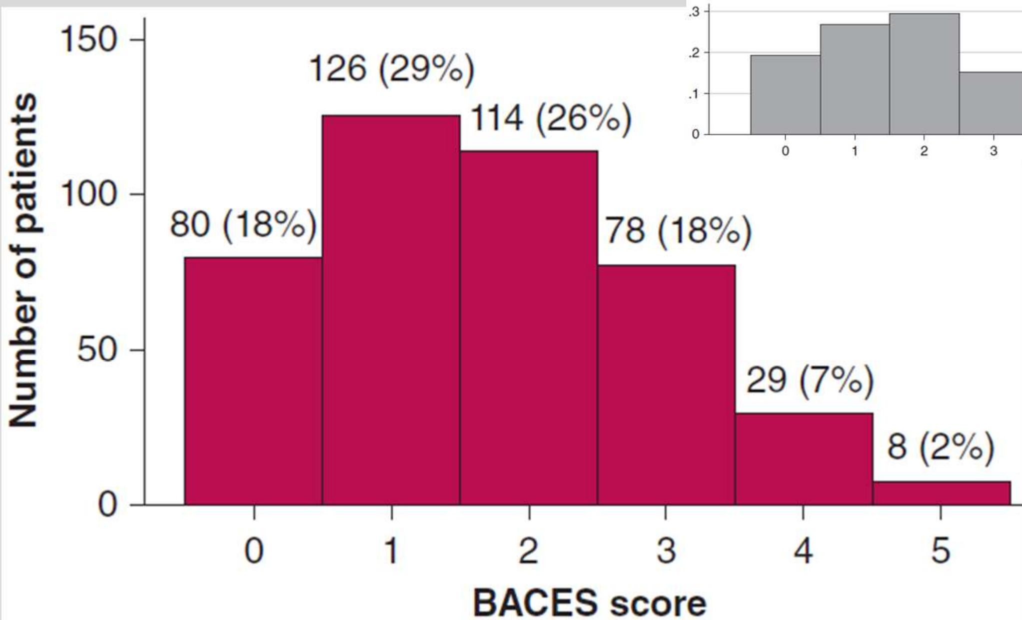
BACES International Validation

Toronto, Canada



Kim et al.

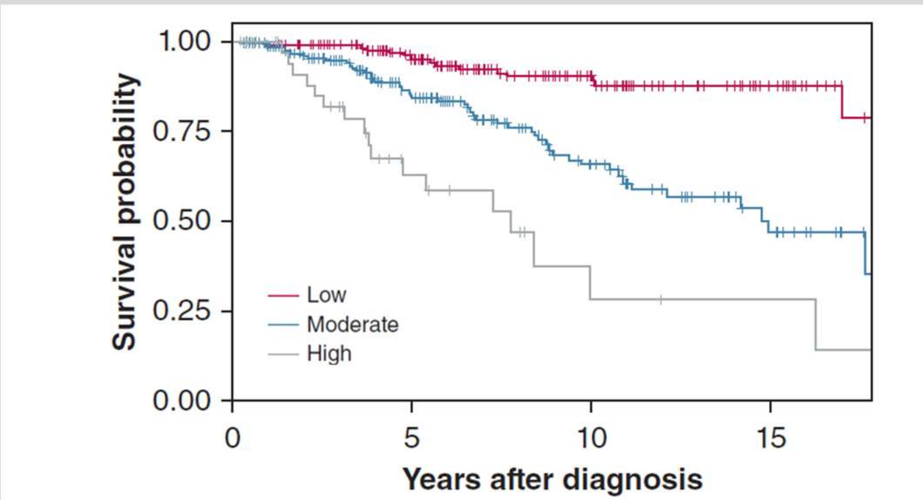
Yan et al. Chest 2024

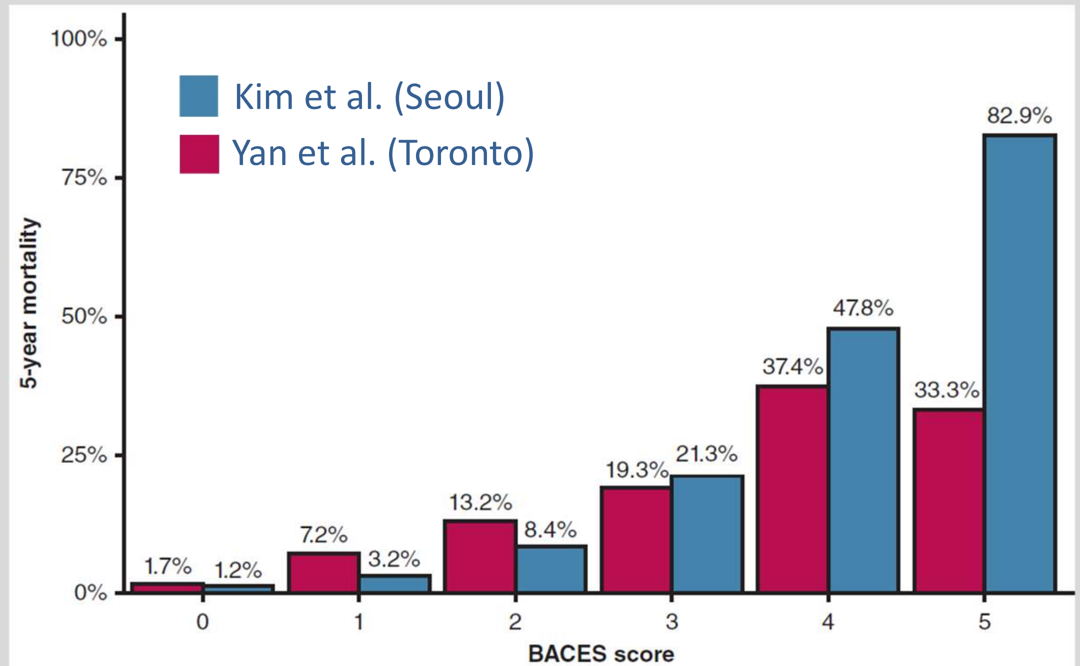


Characteristic	Overall (N = 435)
Age, y	64 (55-71)
Sex	
Male	113 (26)
Female	322 (74)
Ethnicity	
White	297 (68)
East Asian	95 (22)
South Asian	28 (6.4)
Other[b]	6 (1.4)
Missing	9 (2.1)
BMI, kg/m^2	21.5 (19.0-24.6)
History of tuberculosis	42 (9.7)
NTM species	
MAC	60 (14)
M avium	288 (66)
M intracellulare	44 (10)
M abscessus	43 (9.9)

BACES International Validation

Toronto, Canada





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THANK
YOU