

Risks of prior trauma? Tuberculosis Resolution and Environmental Nontuberculous Mycobacterial Infections

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New Directions in TB Conference 2024

Texas Children's Hospital, Feigin Center
Houston, Texas

April 1, 2024



Beginnings in mycobacteria



University of Colorado Anschutz Medical Campus
Dept. of Microbiology
and
National Jewish Health

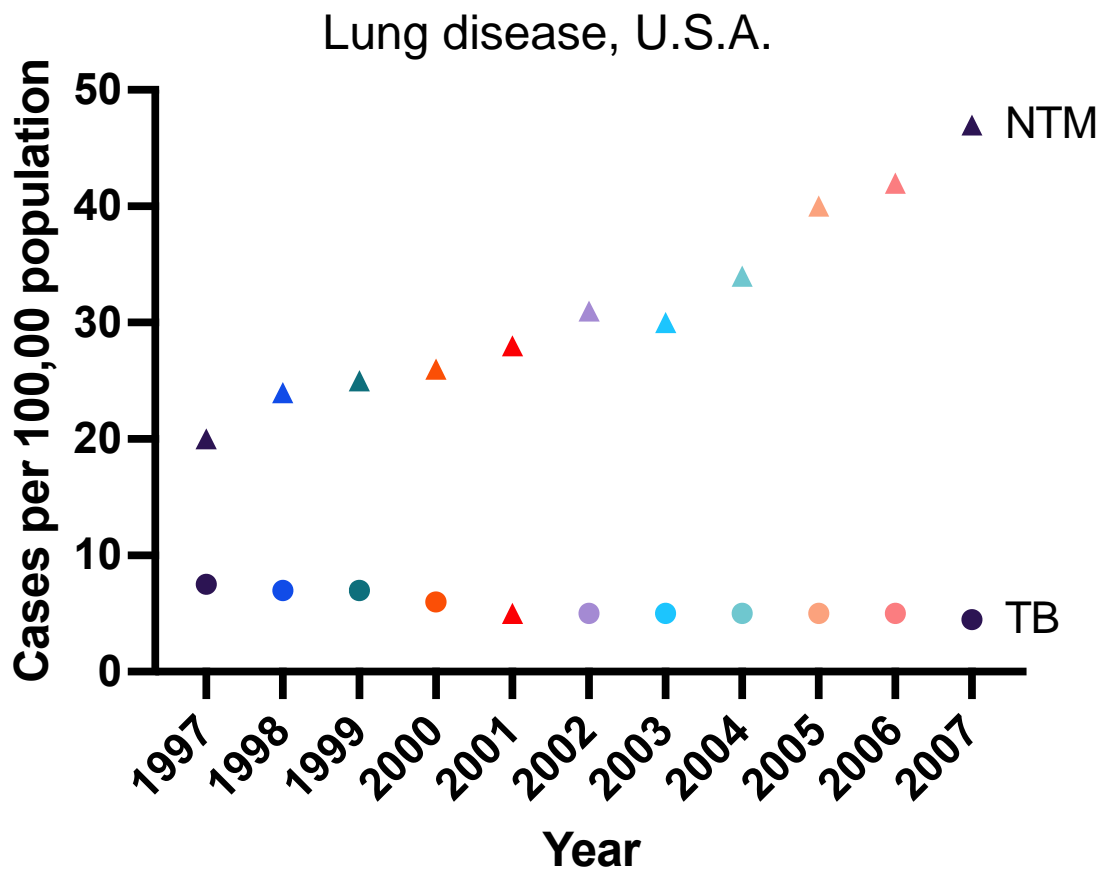
PhD Dissertation

IMMUNE RESPONSES TO MYCOBACTERIA IN THE CONTEXT OF HIV:
ROLE OF VITAMIN D AND CATHELICIDIN

JENNIFER REMI HONDA

Honda, *et al.*, 2015; Honda, *et al.*, 2014; Honda, *et al.*, 2011

Why study NTM



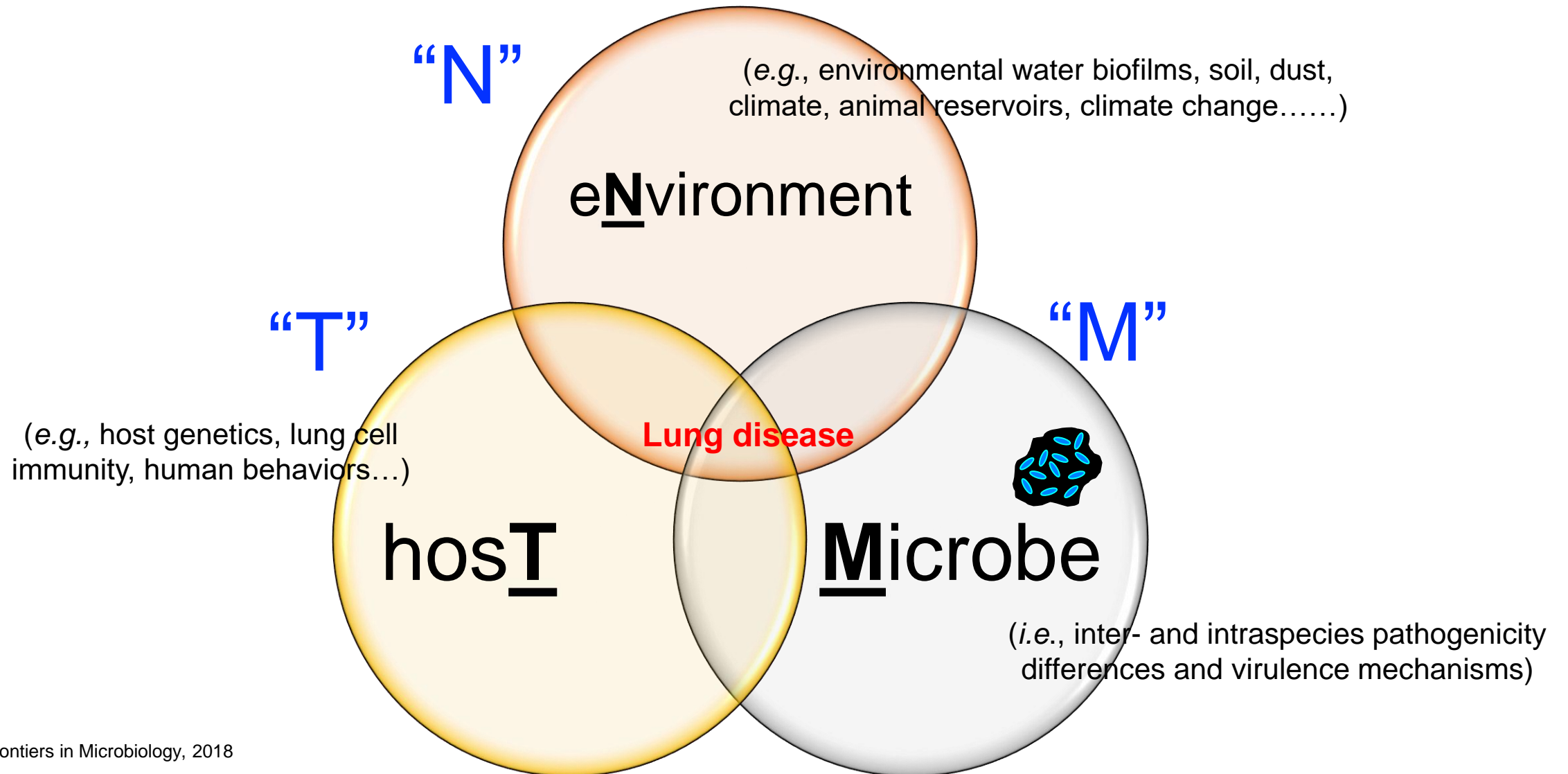
- Most common of the “rare” lung diseases.
 - > 180,000 infected
 - Prevalence is increasing at > 8.2% annually.
- Healthy, taller, slender, older Caucasian women.
- Typically, non-contagious.
 - Transmission “may” occur in people with cystic fibrosis (pwCF).
- Treatment is inadequate, lengthy (years), and expensive.
- Host-pathogen interactions driving disease have not been clearly defined.

Zheng, *et al.*, QJM Inter J of Med, 2013
Ryu, *et al.*, Tuberc Res Dis, 2016

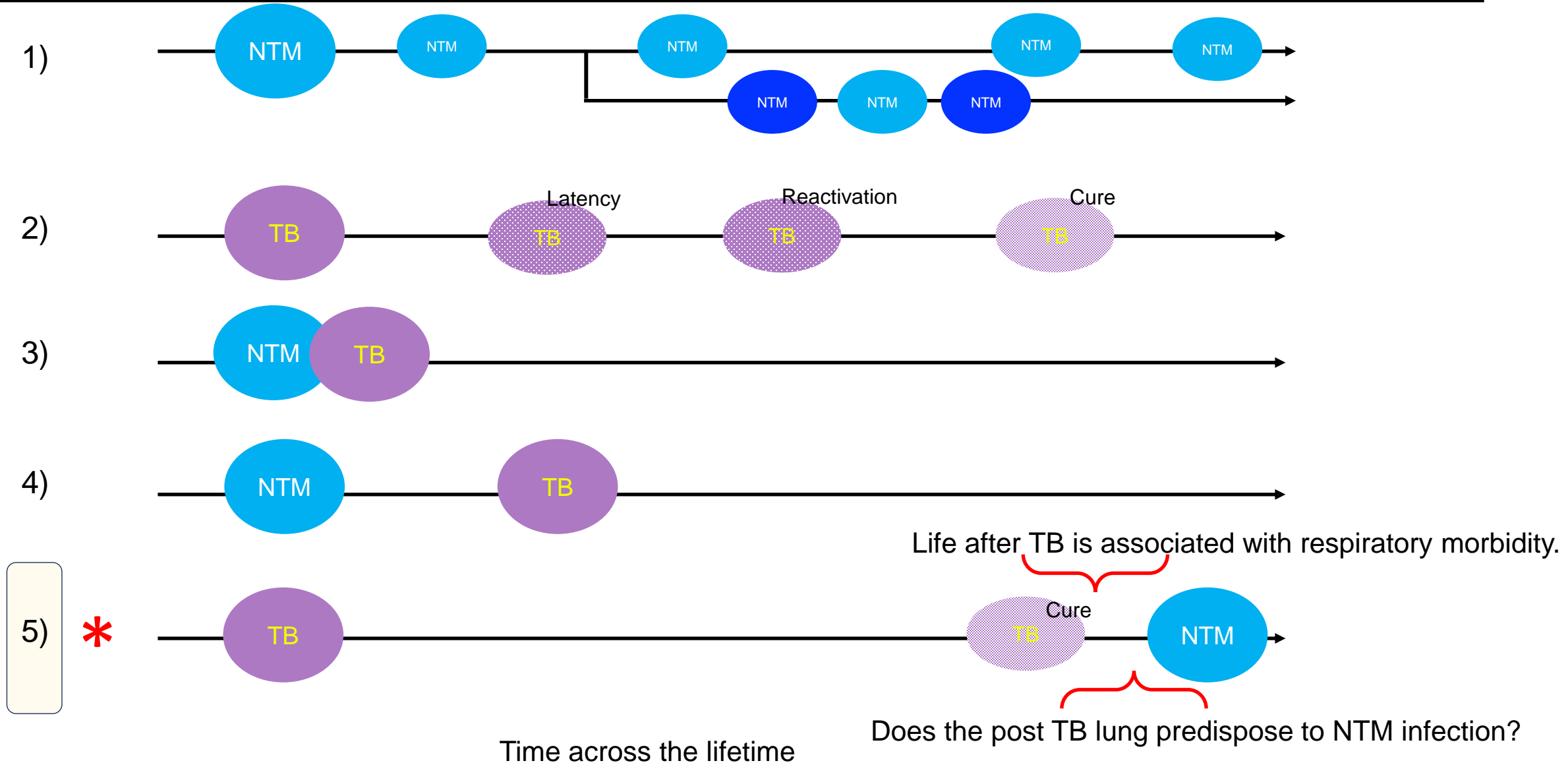
Aitken, *et al.*, AJRCCM, 2012
Bryant, *et al.*, Lancet, 2013

Sood *et al.*, Curr Opin Infect Dis, 2017
Strollo *et al.*, Ann Am Thor Soci, 2015
Adjemian, *et al.*, AJRCCM, 2012

Honda Lab Research Program

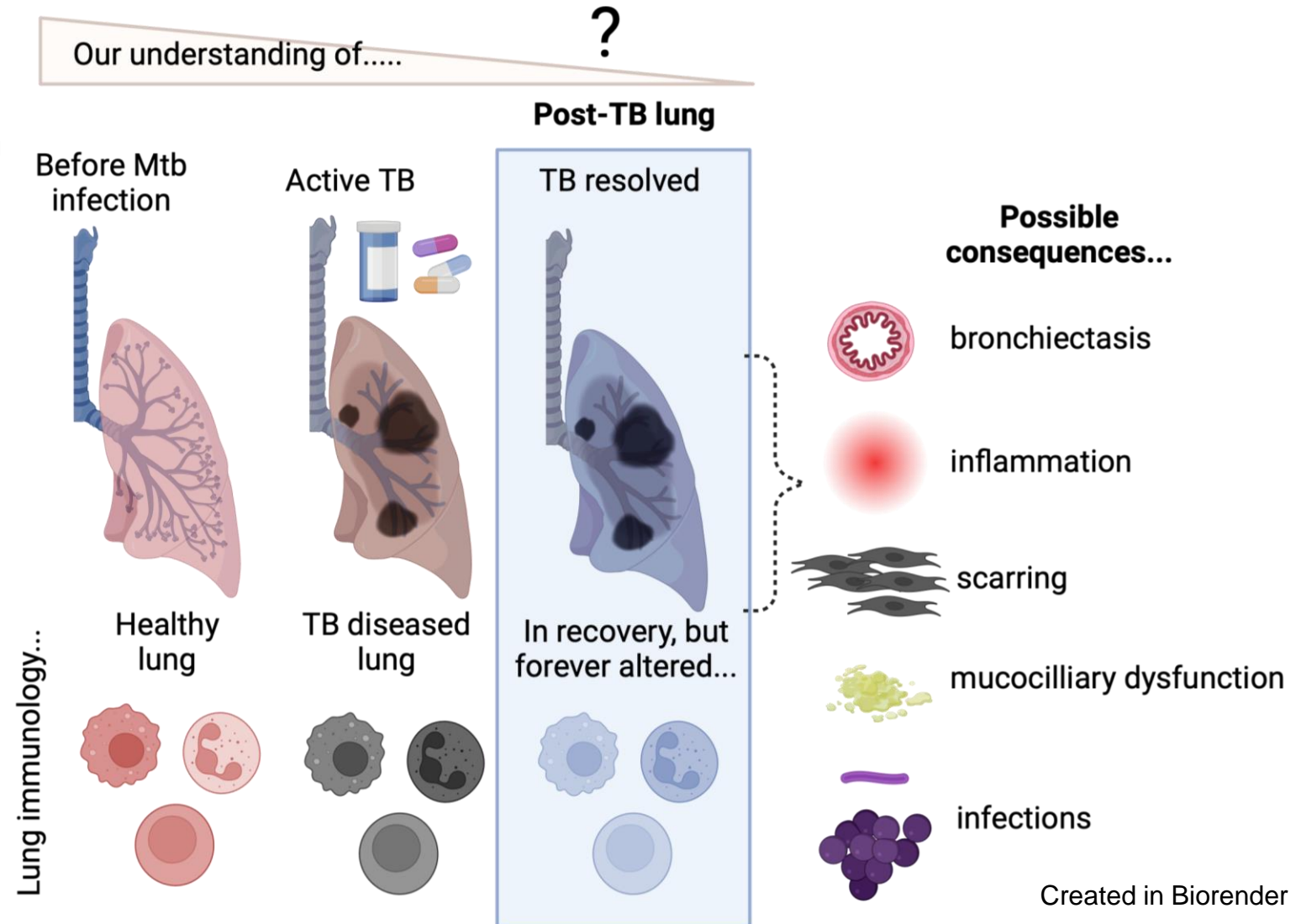


NTM and TB infections



Little is known about post TB lung disease

- TB treatment can achieve microbial cure, but over half of TB survivors have persistent pulmonary dysfunction (Pasipanodya *et al.*, 2007).
- The lung post-TB rarely returns to “normal” and often shows bronchiectasis and other consequential conditions (Meghji, *et al.*, 2016).
- Lack of evidence-based guidelines for managing post-TB lung disease.
- Care and information targeting patient needs after long term post-TB are lacking.



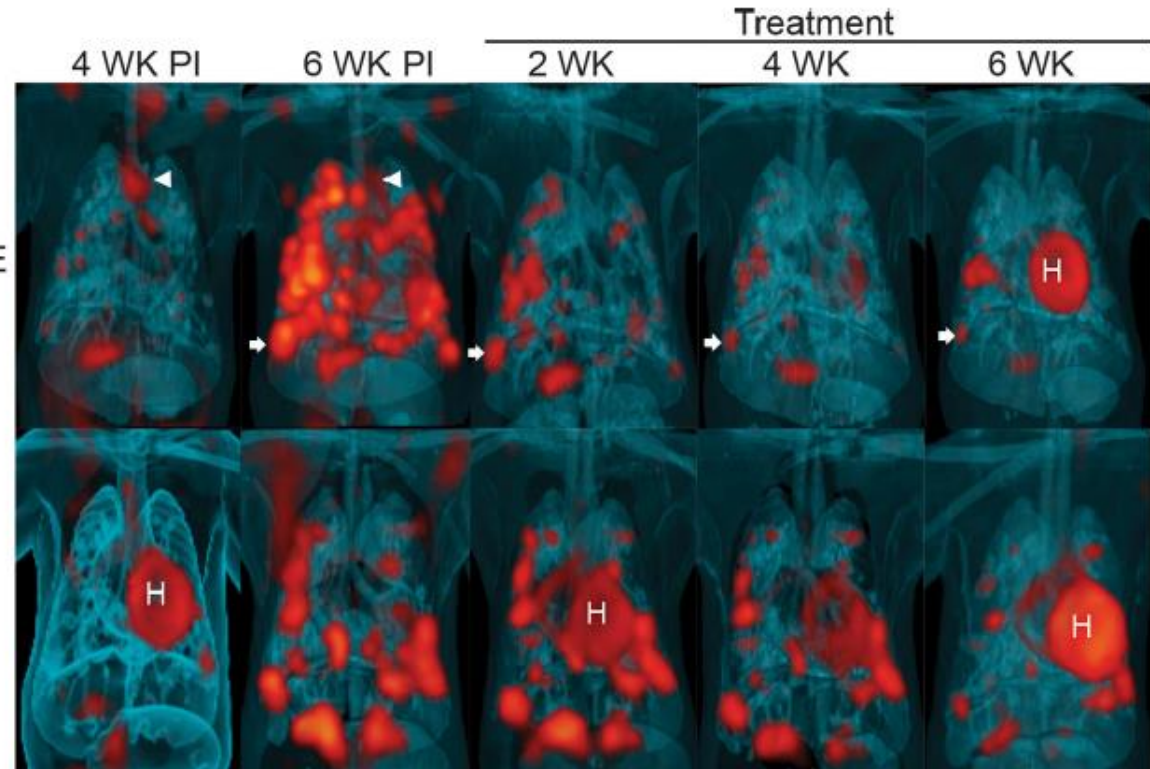
Lung after sterilizing TB treatment

Common marmoset
(*Callithrix jacchus*)



Sterilizing regime
HRZE - 4-drug combination of isoniazid, rifampin, pyrazinamide, and ethambutol

Non-sterilizing regime
HS - 2-drug combination INH and streptomycin



Risk Factors for NTM Lung Disease

Meta-analyses of Identified Attributable Risk Factors:
Overview of Outcomes (2011-2021; 99 studies met criteria)

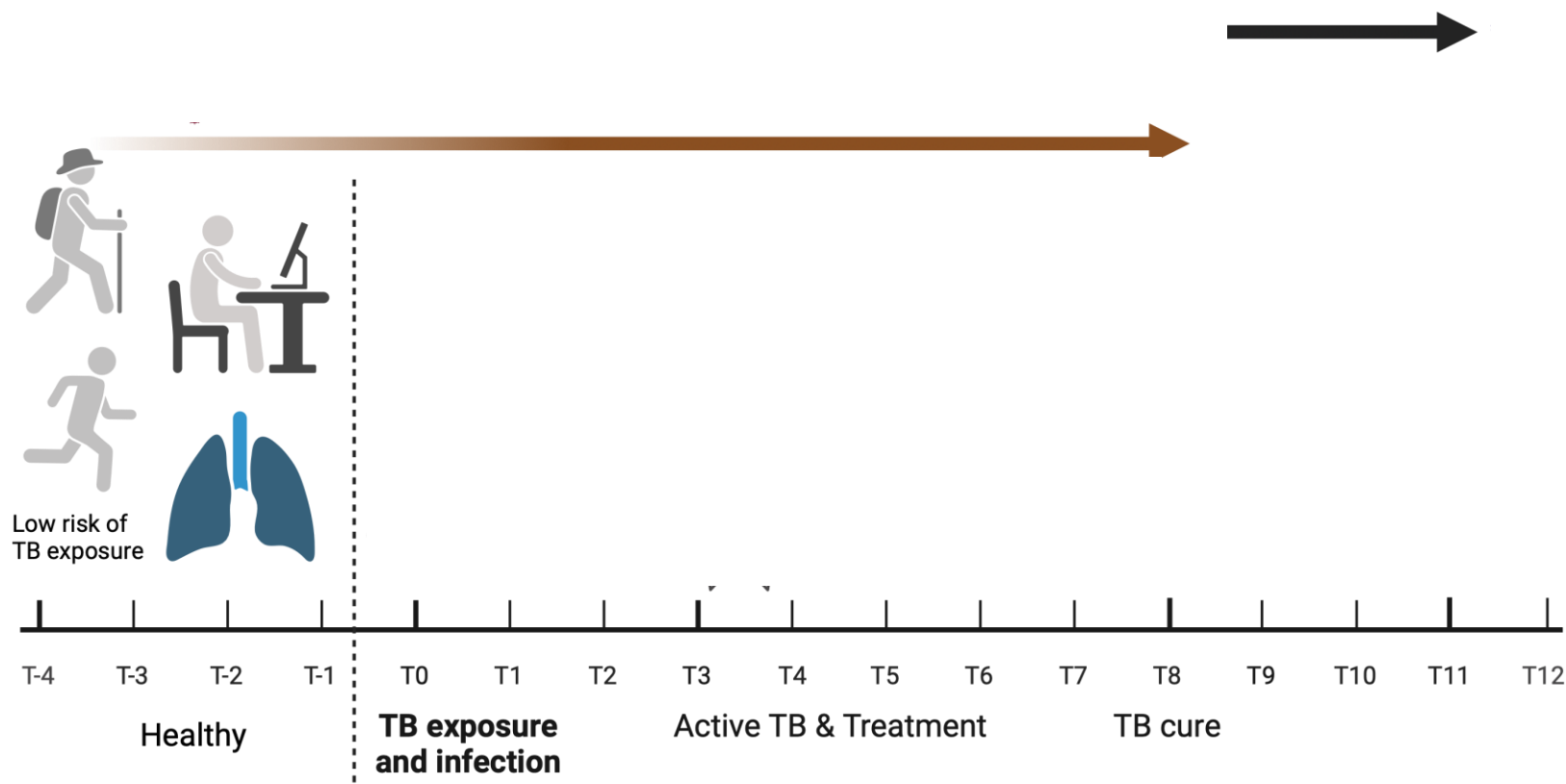
	Identified Risk Factor	No. of Studies (n)	Baseline Population	Combined OR	95% CI	I ² (%)
1	Non-cystic fibrosis bronchiectasis	4	General population; symptoms of TB	21.43	5.90-77.82	95
2	History of TB	7	General population; symptoms of TB; rheumatoid arthritis; COPD	12.69	2.39-67.26	99
3	Interstitial lung disease	4	General population; rheumatoid arthritis; COPD	6.39	2.65-15.37	97
4	COPD	9	General population; symptoms of TB; rheumatoid arthritis	6.63	4.57-9.63	96

How common are NTM and TB-coinfections?

NTM and TB co-infection:		Study site:	Reference:
18%	11 / 61	Mali	Maiga <i>et al.</i> , 2012
11%	40 / 369; MAC (55%)	Canada	Damaraju <i>et al.</i> , 2013
10%	Meta-analyses; 95% CI 6.3-15.9	Iran	Nasiri <i>et al.</i> , 2015
3%	22 / 837; MDR-TB; <i>M. intracellulare</i>	China	Huang <i>et al.</i> , 2022
2.8%	87 / 3148	Taiwan	Lin <i>et al.</i> , 2020
0.7%	31 / 4327	South India	Thangavelu <i>et al.</i> , 2021
0.2%	13 / 6123	Africa	Chanda-Kapata <i>et al.</i> , 2015

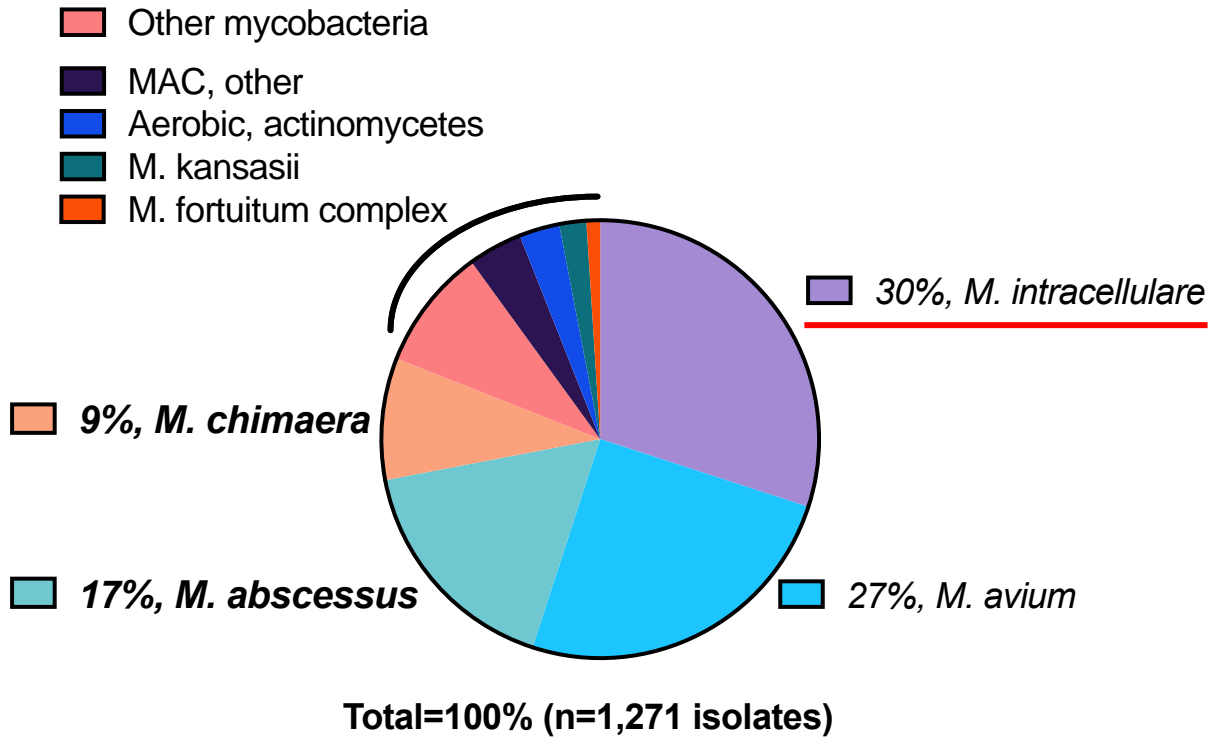
NTM and TB co-infection risk factors include advanced age and living in urban communities (Lin, *et al.*, 2020).

Gradual increase in susceptibility to NTM after TB



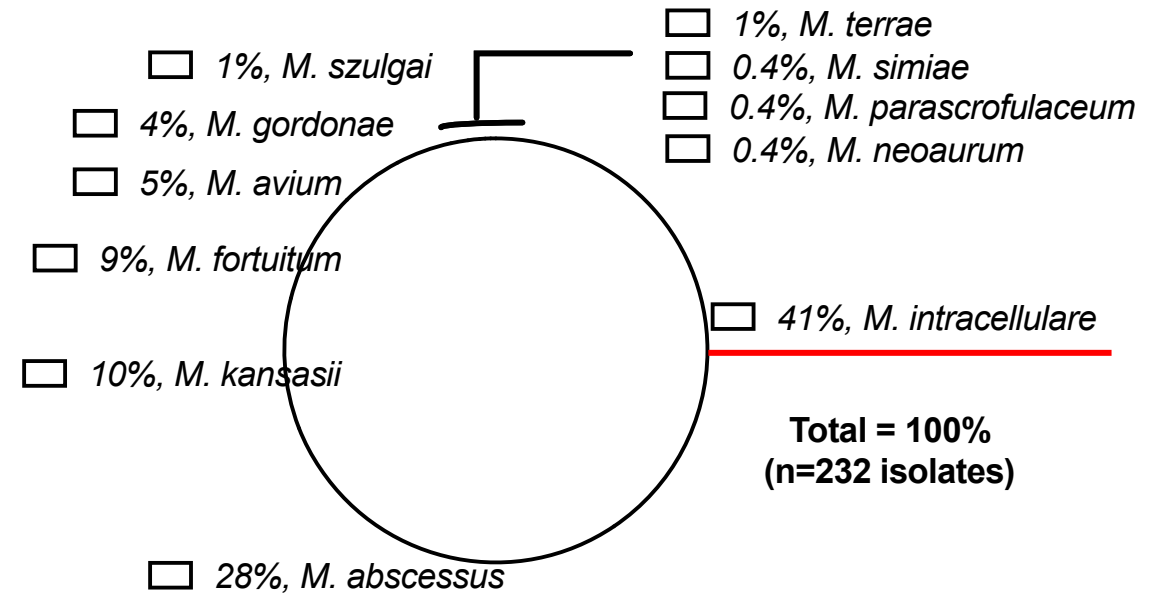
Respiratory relevant NTM species

U.S.



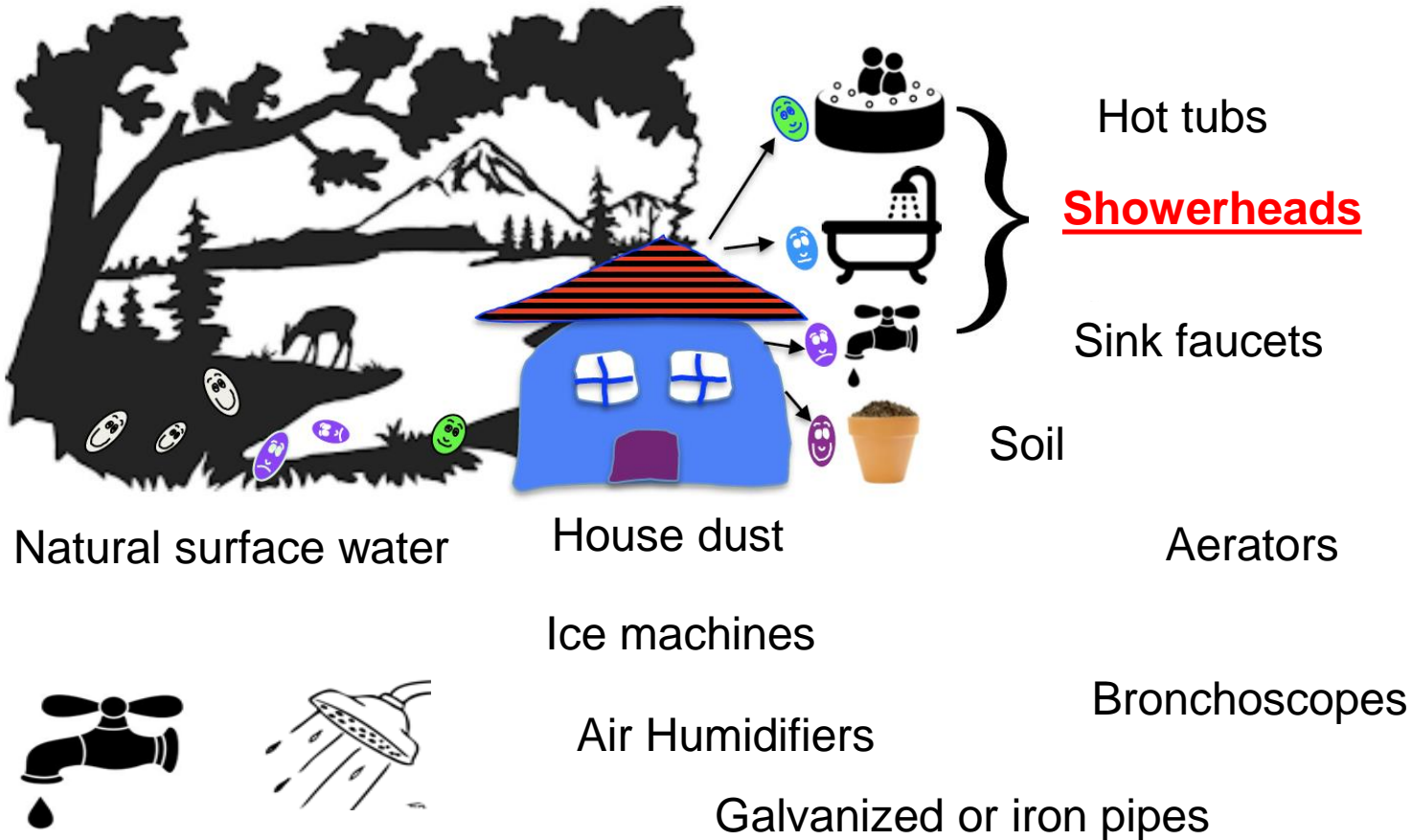
Acknowledgement: Dr. Reeti Khare; Director
 NJH Mycobacterial Clinical Labs
 Jan-Aug 2021

China

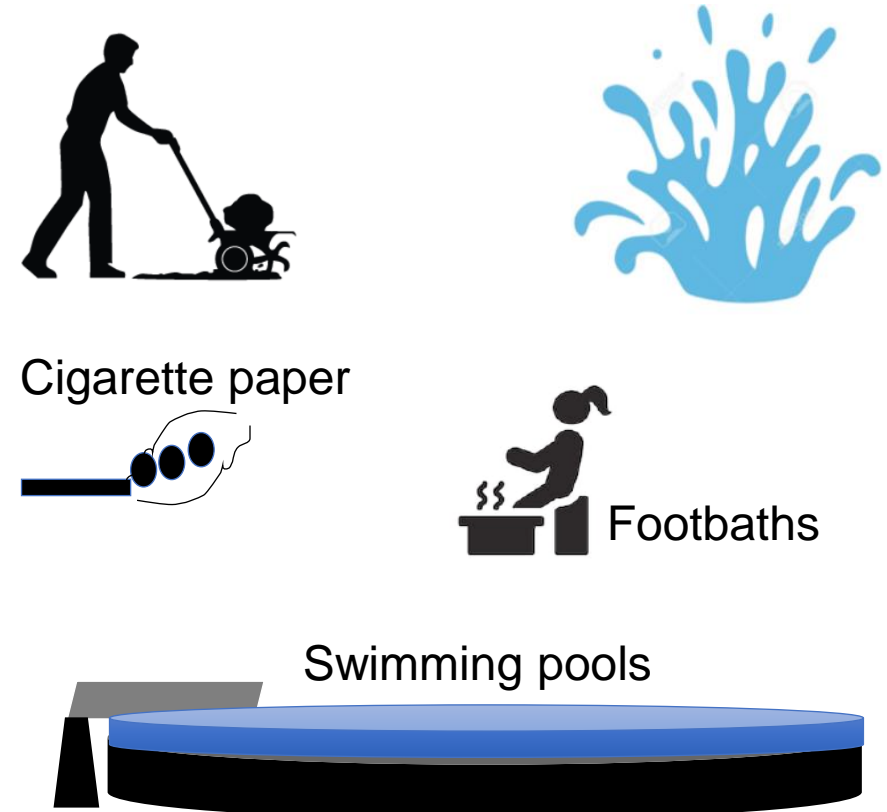


Duan *et al.*, 2016

Exposure niches for NTM



Drinking water distribution systems



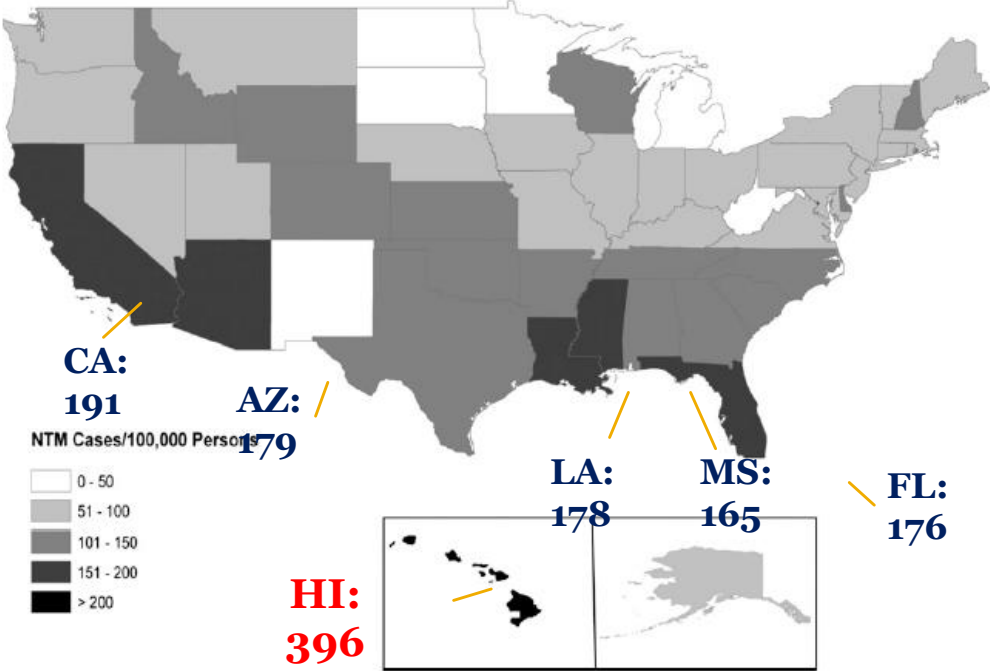
Chan, Breslawsky, NTMiR, 2019
 Honda, *et al*, PLOS Neg Trop, 2015
 De Groote, *et al*, AEM, 2006

Guimaraes, *et al*, Am J Infect Con, 2016
 Martin, *et al*, Am Rev Resp Dis 1987
 Briancesco, *et al*, Microchem J, 2014

Falkinham, *et al*, J Clin Micro, 1995
 Falkinham, *et al*, Sem Resp Crit Care Med, 2013
 Falkinham, *et al*, J Water Health, 2007

Our model system

Geography to NTM infections in the U.S.



Hawai'i demonstrates the highest, national age-adjusted mortality rates from NTM lung disease.

Adjemian, *et al.*, 2012; Mirsaeidi, *et al.*, 2014; Thomson, *et al.*, 2007

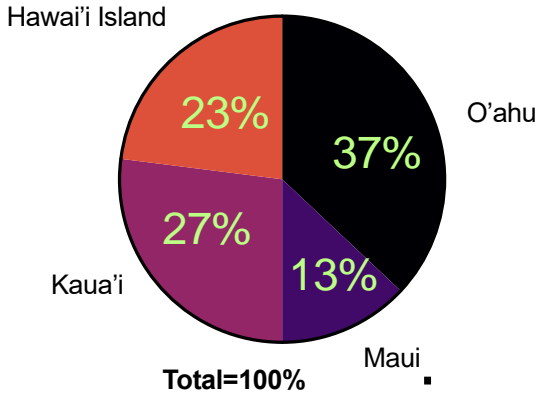
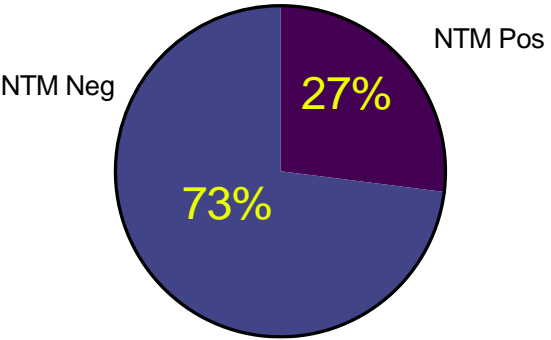
Hawai'i



NTM "ubiquity" is not that ubiquitous

Island distribution
766 total NTM+ samples

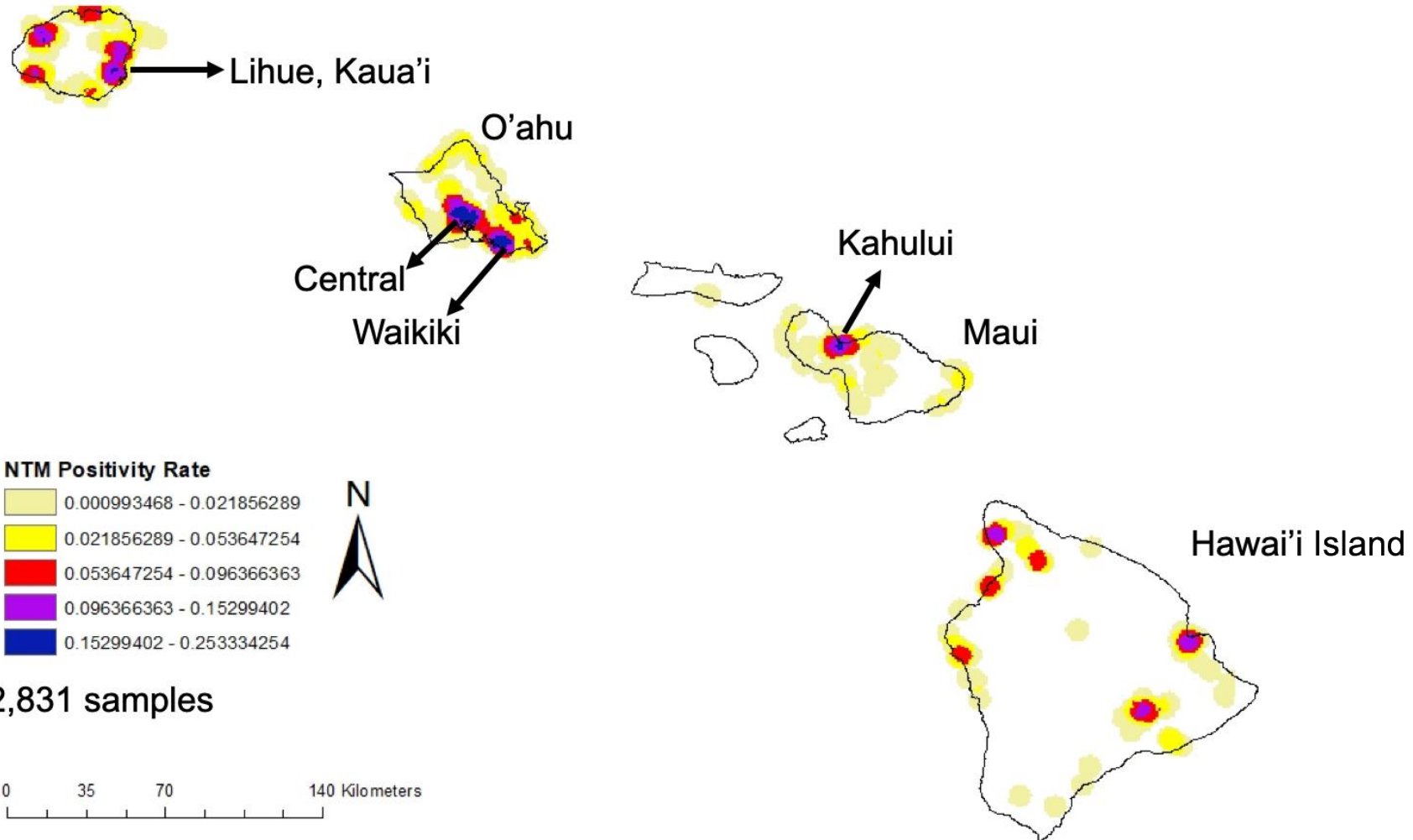
All state (2,831 samples)



	Sample Type: NTM positive samples		
	<i>Biofilm</i>	<i>Soil</i>	<i>Dust</i>
Entire State	458/1779 (26%)	251/728 (35%)	34/279 (12%)
O'ahu	175/642 (27%)	79/213 (37%)	14/110 (13%)
Hawai'i Island	108/362 (30%)	59/230 (27%)	5/53 (9%)
Maui	50/265 (19%)	38/76 (50%)	9/48 (19%)
Kaua'i	123/499 (25%)	75/209 (35%)	6/68 (9%)

Similar to Falkinham 2011 US samples
28% (109/394)
(biofilm, soil, filters)

Larger cities are NTM hot spots



Environmental NTM species diversity

82 known NTM species identified
39 "Novel" NTM were also identified



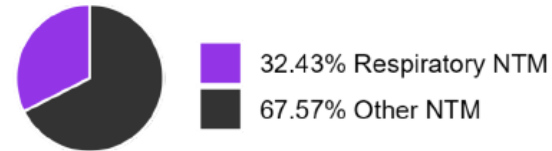
What's in the environment, mirrors the host

Summary from Hawai'i

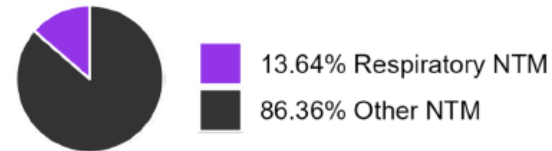
Ranking	Top Environmental:	Top Respiratory:
1	<i>M. abscessus</i>	<i>M. chimaera</i>
2	<i>M. chelonae</i>	<i>M. abscessus</i>
3	<i>M. chimaera</i>	<i>M. avium</i>
4	<i>M. porcinum</i>	<i>M. fortuitum</i>
5	Novel/un-specified	<i>M. porcinum</i>
6	<i>M. gordonae</i>	<i>M. intracellulare</i>
7	<i>M. mucogenicum</i>	<i>M. yongonense</i>
8	<i>M. avium</i>	Novel/un-specified
9	<i>M. iranicum</i>	<i>M. timonense</i>
10	<i>M. gallinarum</i>	<i>M. chelonae</i>

Natural areas

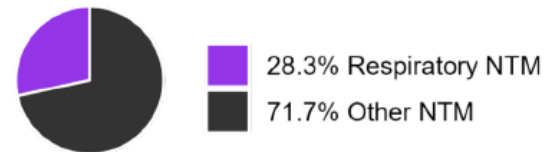
A: Total 37 Water Biofilms



B: Total 22 Water Filters

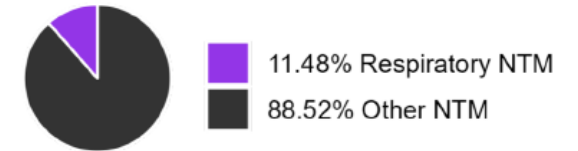


C: Total 212 Soil Samples

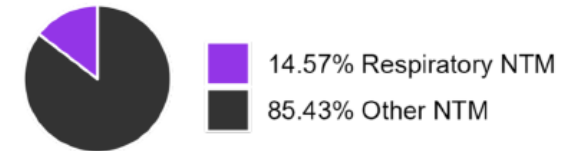


Houses

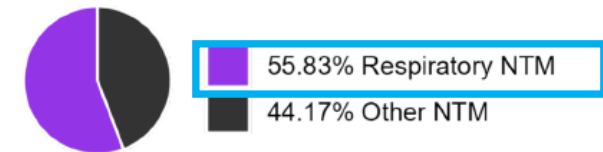
D: Total 61 Dust Samples



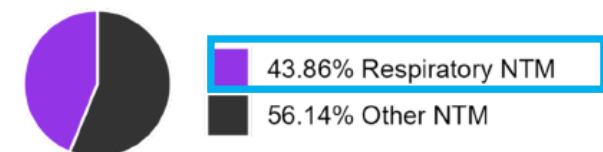
E: Total 151 Soil Samples



F: Total 120 Showerhead Biofilms

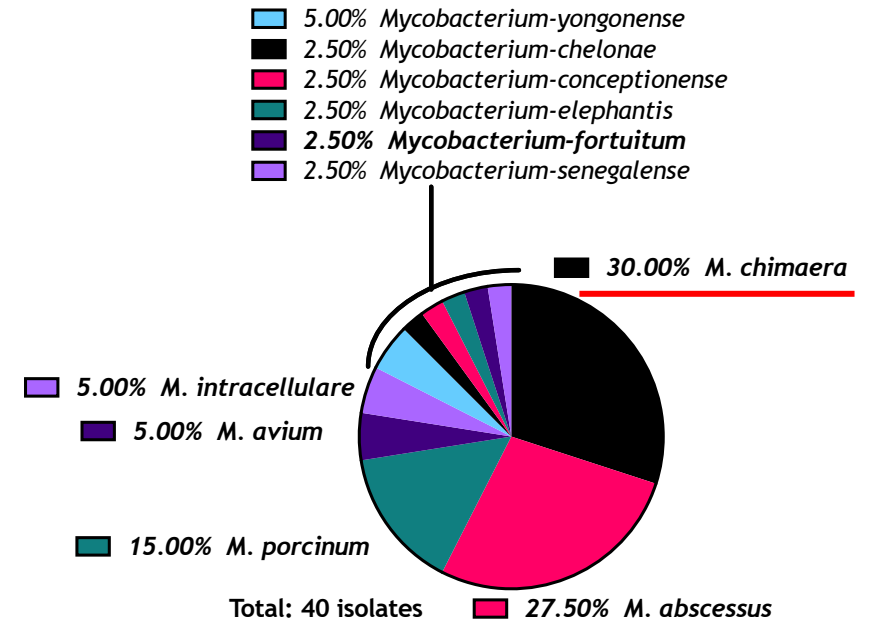


G: Total 114 Sink Biofilms



Hot spot niches for NTM in the home

	Cases (n=35)	Controls (n=28)	p-value
Gender			
Female	18 (51.4%)	15 (53.6%)	1
Male	17 (48.6%)	13 (46.4%)	1
Age			
40-50	21 (60.0%)	14 (50.0%)	0.59
51-60	2 (5.7%)	1 (3.6%)	1
61-70	4 (11.4%)	4 (14.3%)	1
71-80	7 (20%)	7 (25%)	0.89
81-90	1 (2.9%)	2 (7.1%)	0.58
Race/Ethnicity			
Asian	13 (37.1%)	4 (14.3%)	0.08
Native Hawaiian and Pacific Islander	2 (5.7%)	2 (7.1%)	1
White	15 (42.9%)	12 (42.9%)	1
Other	5 (14.3%)	10 (35.7%)	0.09



Whole genome sequencing analyses

	<i>M. abscessus</i>	<i>M. chimaera</i>
Kitchen faucet	5/5 (100%)	0/7 (0%)
Showerhead	0/7 (0%)	4/4 (100%)
Soil	N/A	0/2 (0%)

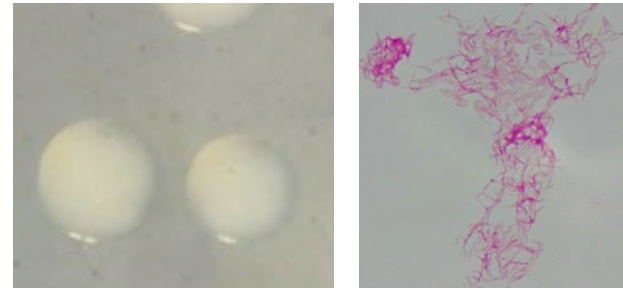
Point source for *M. abscessus* in the home are **kitchen faucets**.
 Point source for *M. chimaera* in the home are **showerheads**.

Other sources of exposure for NTM

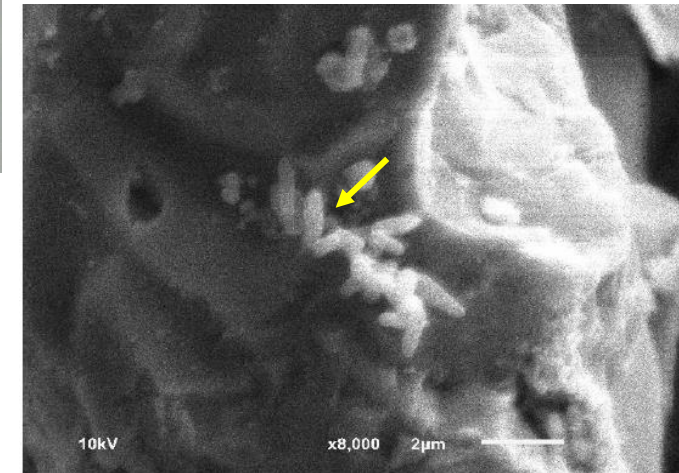
Kīlauea volcano, Hawai'i Island, 2018



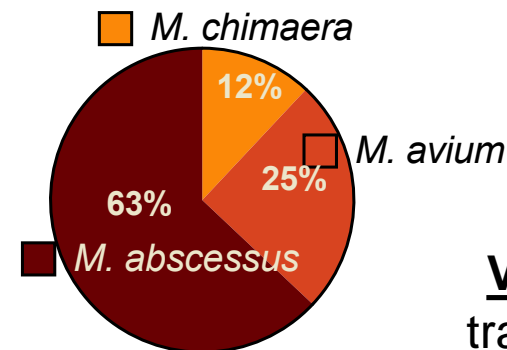
Kīlauea ash harbors AFB



M. abscessus from Kīlauea ash
+
Kīlauea ash



Viable NTM recovered from Kīlauea ash



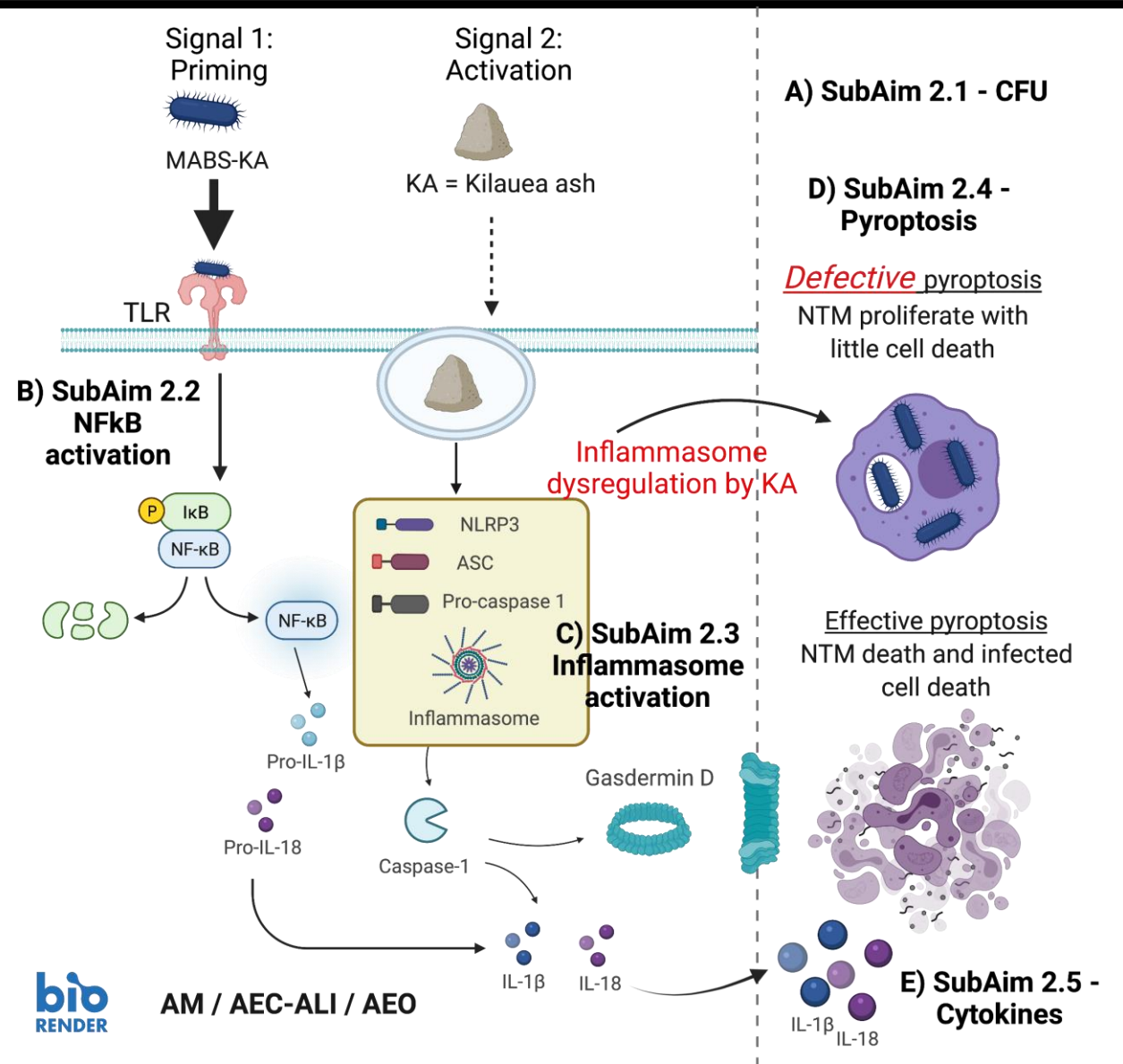
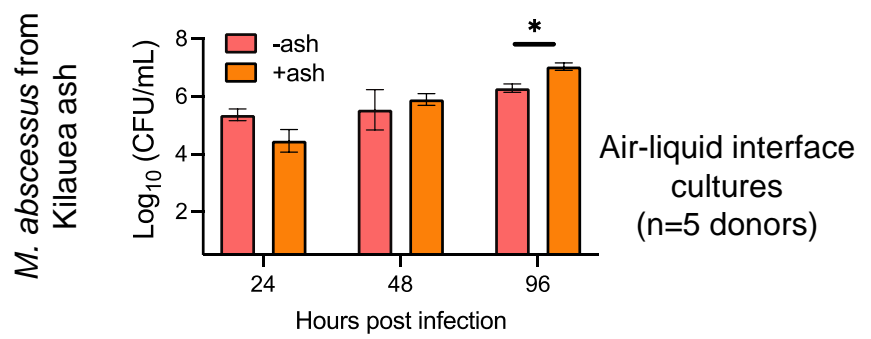
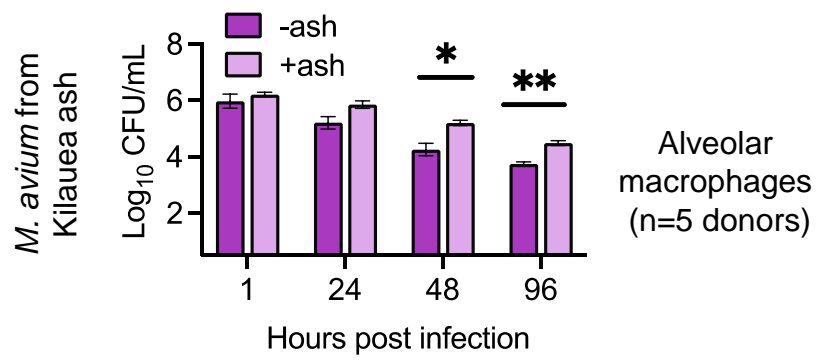
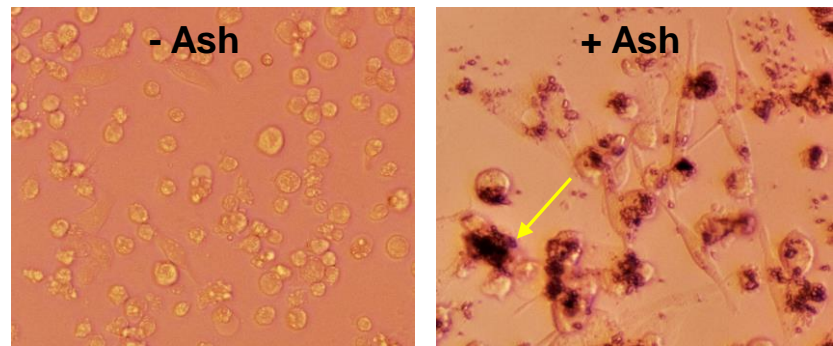
Total = 8 NTM recovered from Kilauea ash

Volcanic ash is a fomite for NTM transmission and a possible source of infection.

<https://www.usgs.gov/media/before-after/recent-changes-k-lauea-volcano-october-4-2021>
Photo credit: <https://www.usgs.gov/center-news/photo-and-video-chronology-k-lauea-may-29-2018>

NTM, volcanic ash, and the inflammasome

Monocyte-derived macrophages



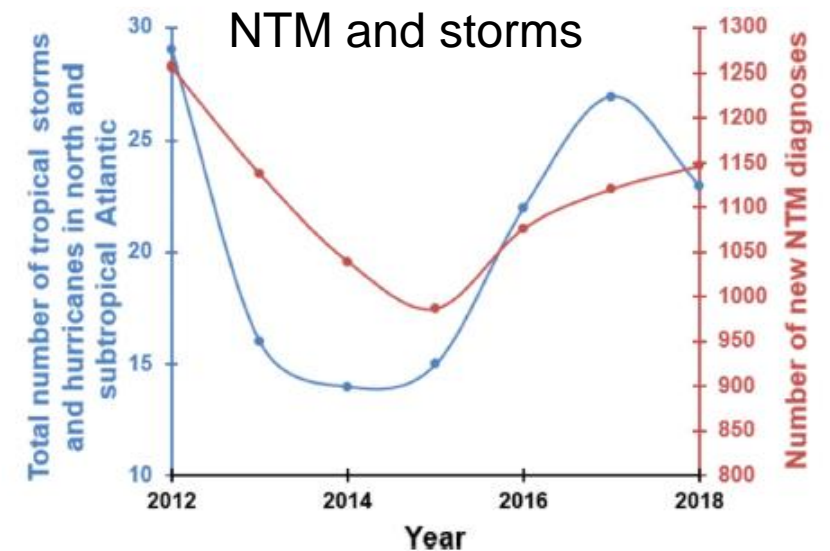
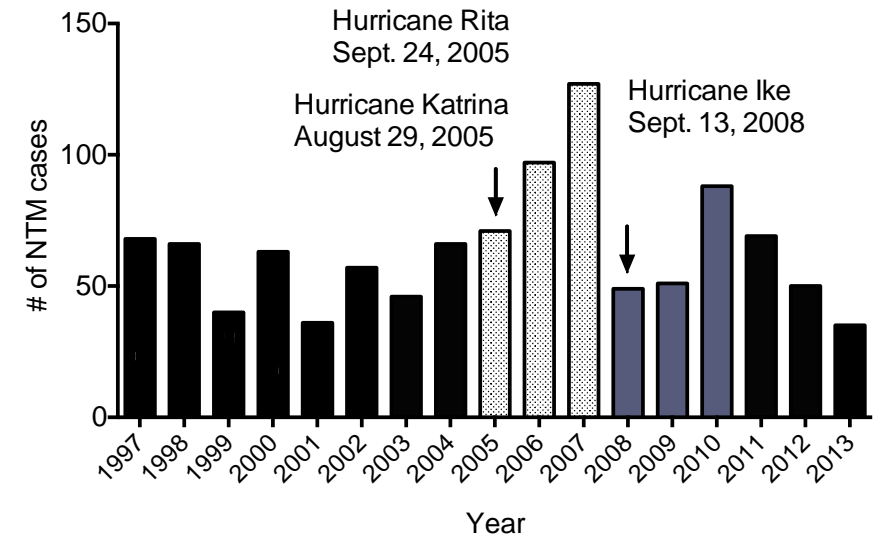
NTM and climate change



Global climate changes are here
(Image credit: NOAA)

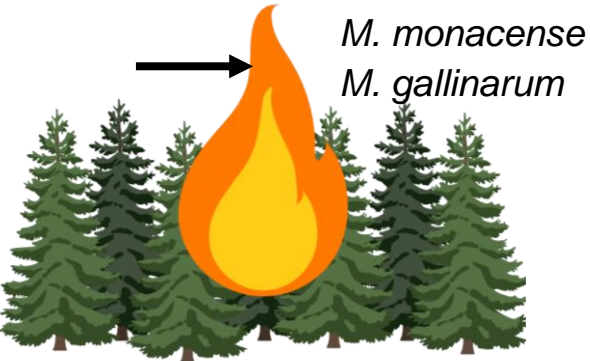
Honda *et al*, 2015; Kambali, *et al.*, 2021

NTM and hurricanes



Other environmental hazards – wildfires

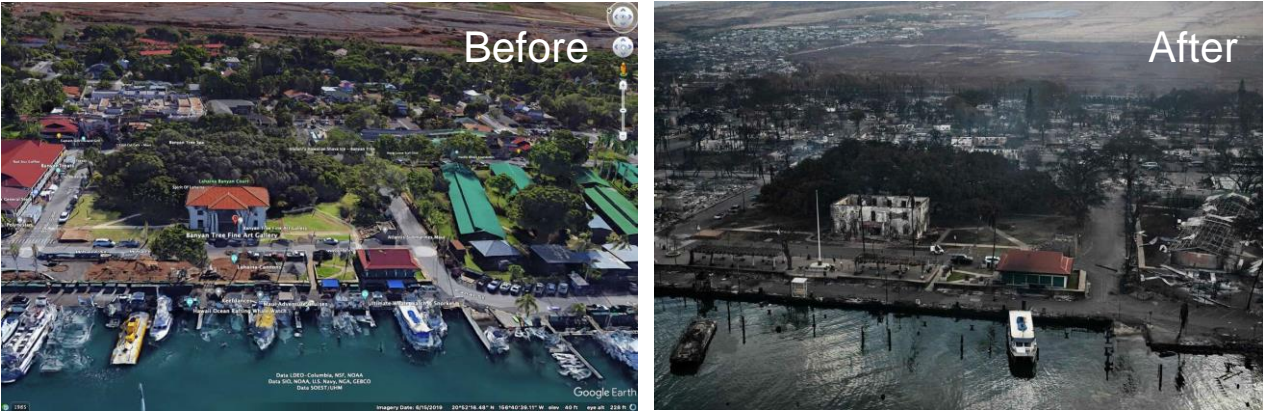
Wildfire ash, Kansas



August 2023, Lāhainā



The Lāhainā Maui wildfire is earmarked both as the worst natural disaster in Hawai'i history and the deadliest U.S. wildfire in over 100 years.



February, 2024, Lāhainā



<https://www.sfchronicle.com/climate/article/maui-fire-before-after-photos-18290051.php>

Conclusions

- > 50% of TB survivors develop bronchiectasis after completing treatment (Martinez-Garcia *et al*, 2023).
 - Prevalence of post-TB bronchiectasis varies by country and data is scant for the U.S.
- Overall, the full spectrum of complications after TB resolution including immunology and cellular functions are significantly understudied.
- Untouched here are other TB sequelae (depression, greater disability, and economic burden).
- Bronchiectasis is a predisposing factor for NTM lung infections. **NTM show a myriad of environmental niches.**
- *In vitro* and *in vivo* studies are needed to understand how the post TB lung may predispose to later infections *e.g.*, NTM.

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Our NTM “Flat Stanley”

Waipuilani Park , Maui



Haleakalā , Maui

