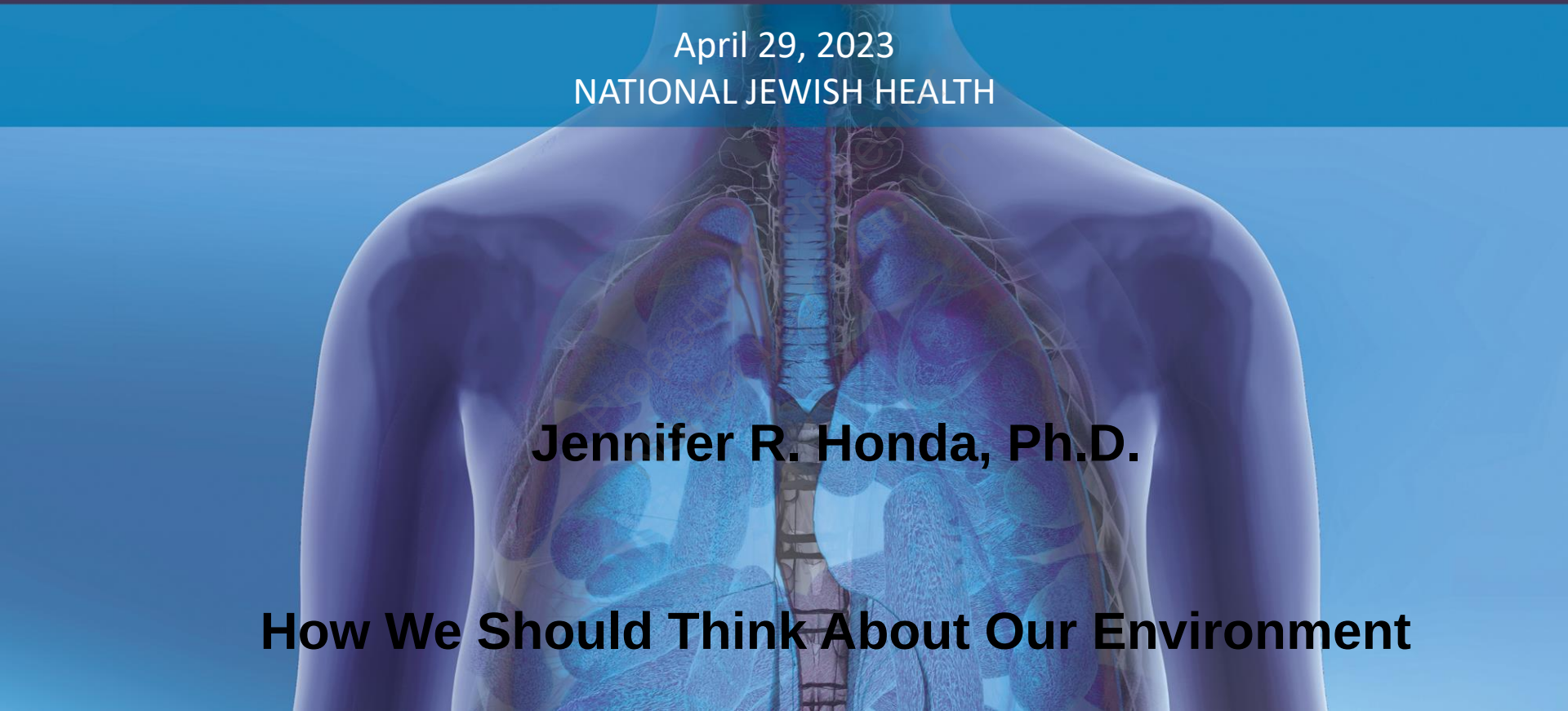
NTM Lecture Series for Patients

April 29, 2023
NATIONAL JEWISH HEALTH



Jennifer R. Honda, Ph.D.

How We Should Think About Our Environment

No disclosures.

Honda Lab Research Program

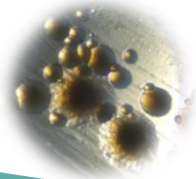
e”N”vironment

i.e., geography, water associated surface biofilms, soil, dust, animal reservoirs, climate, humidity, temperature, ash, etc…..

i.e., immune responses of macrophages and airway epithelial cells to NTM infection

hos”T”

“M”icrobe

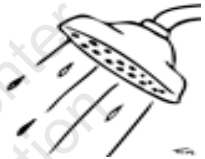


i.e., species of NTM matters, biofilm forming capacity, interaction with host and environment, pigment, virulence factors, etc…

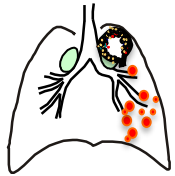
Honda, *et al.,* Frontiers in Microbiology, 2018

Do All *Mycobacteria* Cause Lung Disease?

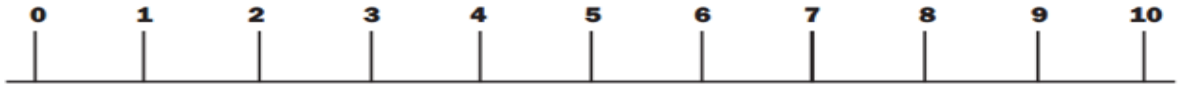
Mycobacterium gordonae
M. gilvum
M. smegmatis



Mycobacterium abscessus
***Mycobacterium avium* complex (MAC)**
(M. avium, M. intracellulare, M. chimaera)



Mycobacterium tuberculosis (TB)



Rarely causes lung disease

Causes true lung disease

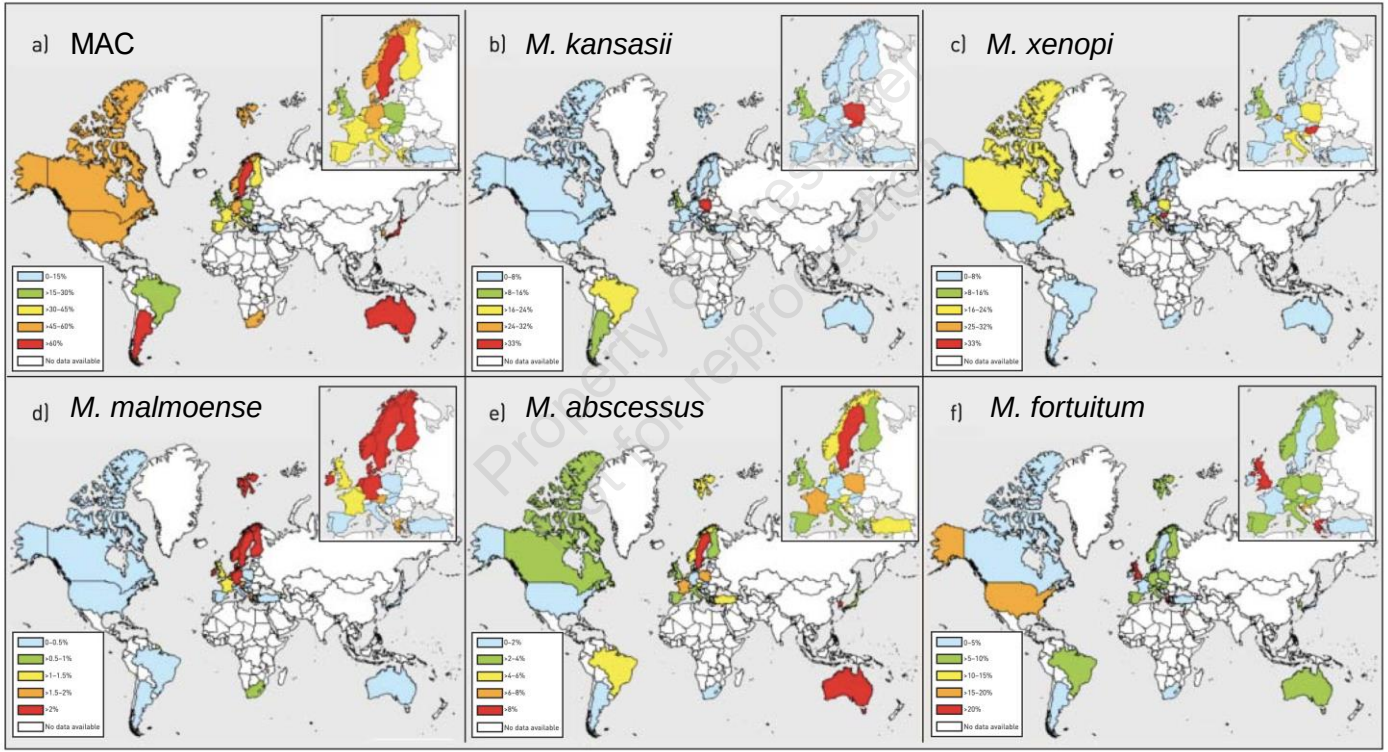
Learning Objectives

1). Become familiar with the varied environmental niches of NTM.

2). Recognize features that may promote NTM in the environment (*e.g.*, other studies and our work in Hawai'i).

3). Identify possible methods to reduce environmental NTM exposures.

Where You Live May Matter



Hoefsloot, *et al.,* ERS, 2013

NTM Identified From Drinking Water Systems Globally

Location:	% NTM recovery:	Species:	Reference:
Mexico	**16% (19/120)**	*M. mucogenicum* most common; ***M. avium*, no *M. abscessus***	Perez, *et al.,* BMC Res Notes, 2013
Greece	**22% (42/197)**	*M. chelonae* most common; **no *M. abscessus***	Tsintzou, et al., Water, Air, Soil Poll, 2000
USA	**33% (46/139)**	9 species, *M. mucogenicum* most common; **no *M. abscessus***	Covert, *et al.,* AEM 1999
Colombia	**50% (9/18)**	*M. mucogenicum* most common; **no *M. abscessus***	Dávalos, *et al.,* Env Res & Public Health, 2021
Argentina	**52% (64/124)**	*M. gordonae* most common	Oriani, *et al.,* Int J. Mycobacter, 2019
Australia	**62% (236/384)**	*M. gordonae* most common; ***M. abscessus* identified**	Thomson, *et al.,* BMC Microb, 2013
Paris, France	**72% (104/144)**	*M. gordonae* and *M. nonchromogenicum* most common; Potentially pathogenic, 16%; **no *M. abscessus*.**	Le Dantec, *et al.,* AEM, 2002

Which species of NTM is found, matters.

Environmental niches for NTM

Natural surface water

House dust

Ice machines

Air Humidifiers

Galvanized or iron pipes

Drinking water distribution systems

Hot tubs

Showerheads

Sink faucets

Soil

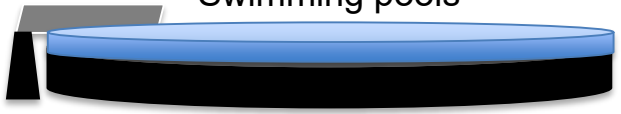
Aerators

Bronchoscopes

Cigarette paper

Footbaths

Swimming pools

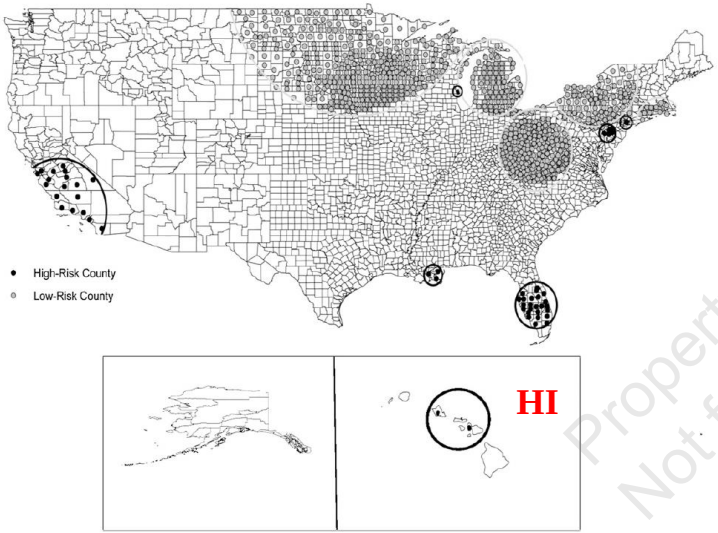


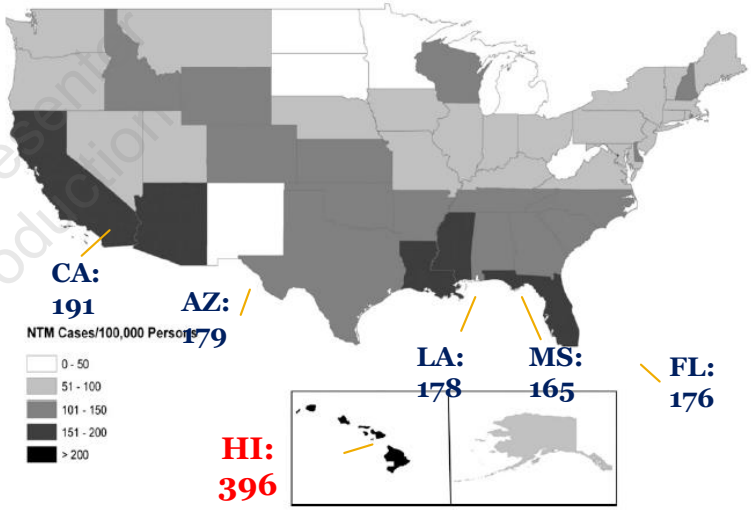
Chan, Breslawsky, NTMir, 2019
Honda, *et al,* PLOS Neg Trop, 2015
De Groote, *et al,* AEM, 2006

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

In the U.S., Hawai'i demonstrates the highest, national age-adjusted mortality rates

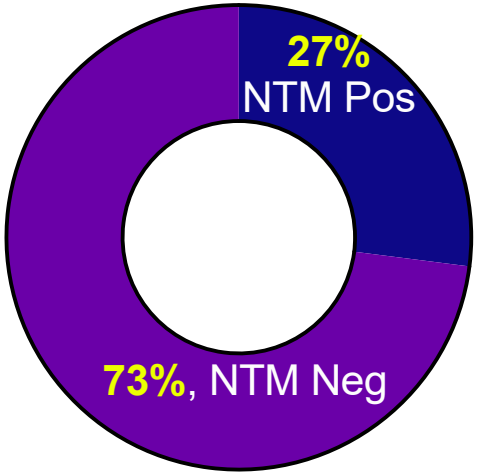




Adjemian, *et al*., AJRCCM, April 2012
Mirsaeidi, *et al.,* PLOS One, 2014
Honda, *et al*., Plos Neg Trop Dis, April 2016

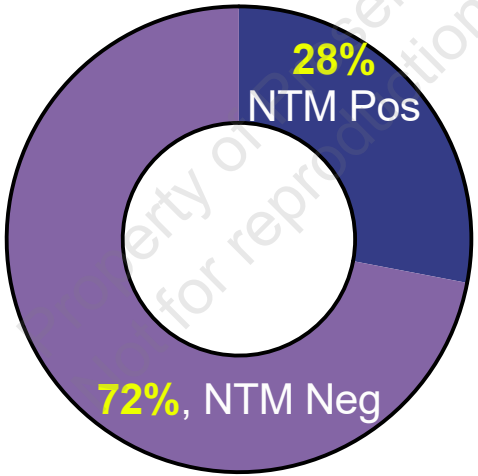
NTM may not be as “ubiquitous” as presumed

Hawai’i



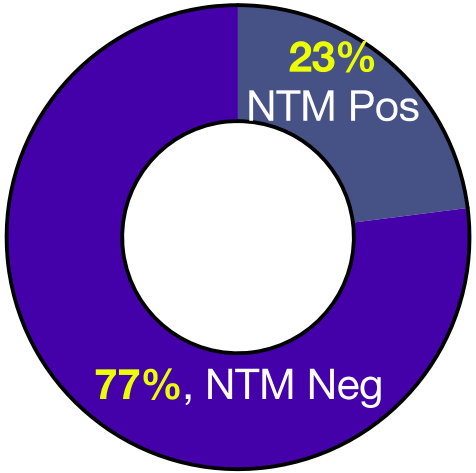
n = 2,831 samples

Falkinham, USA



n = 394 samples

non-Hawai’i, USA

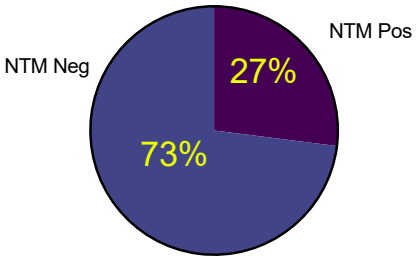


n = 525 samples

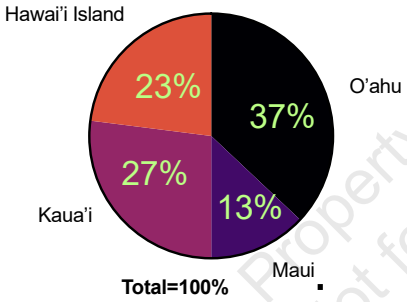
Falkinham, *et al.,* EID, 2011

Large Scale Environmental NTM Sampling, Hawai'i

All state (2,831 samples)



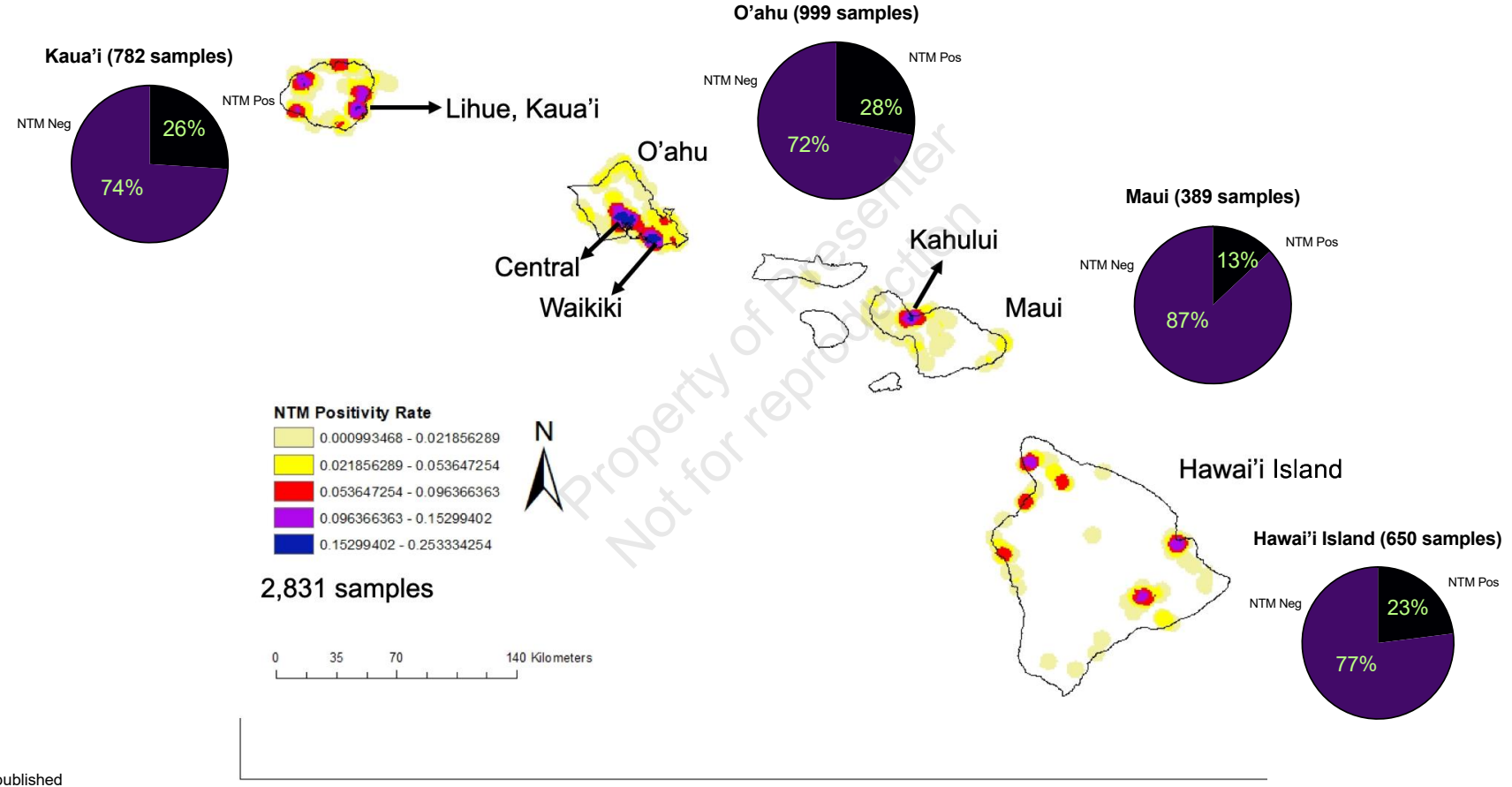
Island distribution
766 total NTM+ samples



Sample Type: NTM positive samples			
	Biofilm	***Soil***	***Dust***
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)

Unpublished
Falkinham, EID, 2011



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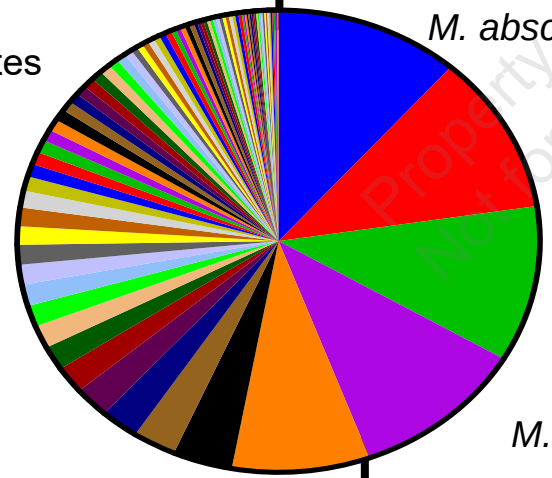
NTM species diversity in the Hawai'i environment

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

Of the NTM positive samples, which NTM species are represented?

Total = 766 isolates



M. abscessus (11.4%)

M. chelonae (11.1%)

M. chimaera (11.0%)

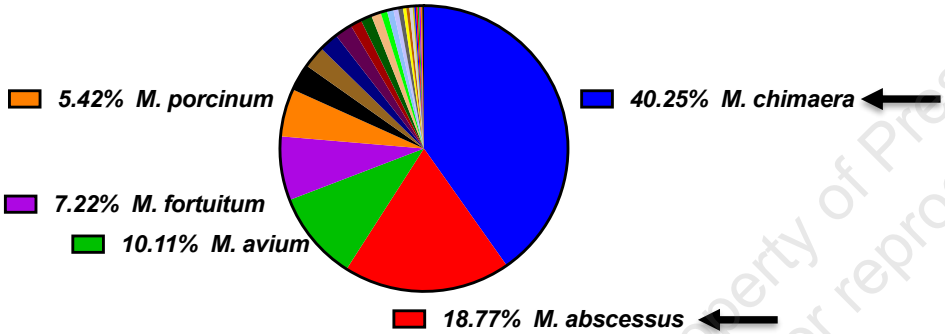
M. porcinum (11.0%)

Top 4 (44%) are also found in respiratory samples in Hawai'i

Respiratory NTM Isolate Diversity

Diagnostic Laboratory Services, Hawai'i

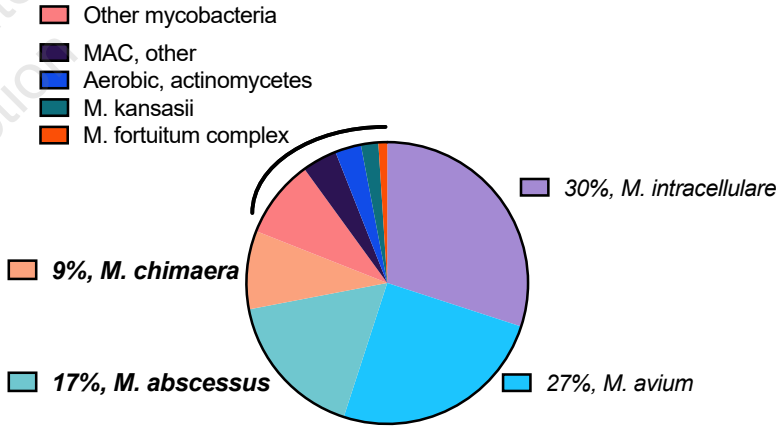
Total: 554 clinical isolates



- 3.07% Mycobacterium-intracellulare
- 2.53% Mycobacterium-yongonense
- 2.17% Novel/ un-speciated
- 1.99% Mycobacterium-timonense
- 1.26% Mycobacterium-chelonae
- 1.26% Mycobacterium-kubicae
- 1.08% Mycobacterium-simiae
- 0.72% Mycobacterium-gordonae
- 0.72% Mycobacterium-lentiflavum
- 0.54% Mycobacterium-conceptionense
- 0.54% Mycobacterium-senegalense
- 0.36% Mycobacterium-marseillense
- 0.36% Mycobacterium-paraintracellulare
- 0.36% Mycobacterium-parascrofulaceum
- 0.18% Mycobacterium-arosiense
- 0.18% Mycobacterium-canariasense
- 0.18% Mycobacterium-celatum
- 0.18% Mycobacterium-elephantis
- 0.18% Mycobacterium-phocaicum
- 0.18% Mycobacterium-scrofulaceum
- 0.18% Mycobacterium-shigaense

Unpublished

National Jewish Health



Total=100% (n=1,271 isolates)

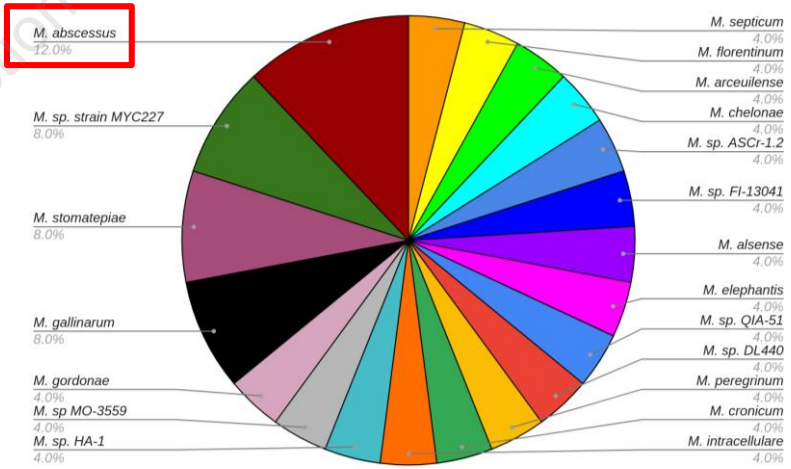
Acknowledgement: Dr. Reeti Khare; Director
NJH Mycobacterial Clinical Labs
Jan-Aug 2021

Awareness of possible NTM animal reservoirs

https://www.westhawaiitoday.com/2018/12/03/hawaii-news/problematic-park-pigs/

	Total number of NTM positives:	Total number sampled:	% positive:
Nasal Swabs	11	50	22%
Fecal Swabs	8	50	16%
All pigs	16	50	**32%**

Pig NTM isolate biodiversity, O'ahu

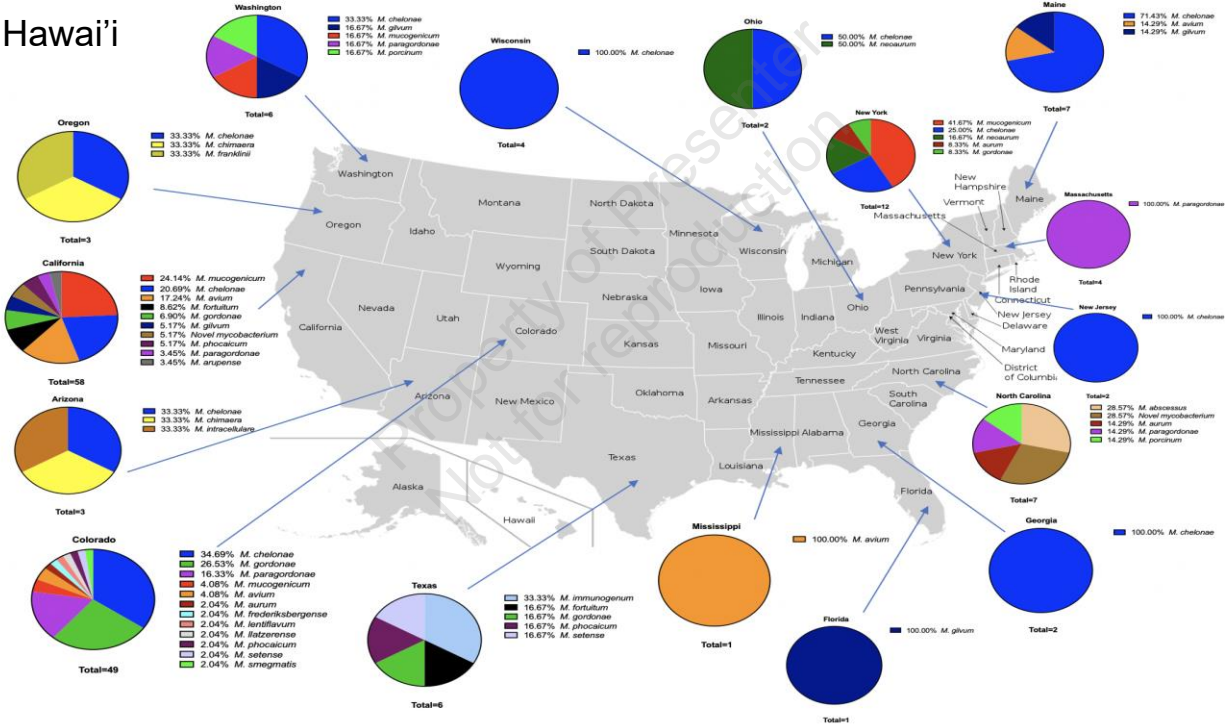


DOFW Permit #WL20-08; USDA Permit #134058; NJH IACUC Permit #AS2833-04-23

Unpublished

M. chelonae is seemingly widespread across the U.S.

Excluding Hawai'i



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Interim Conclusion 1

Q: How should we think about our environment?

A: Data suggests NTM species that cause opportunistic lung infections are not vastly widespread in the environment.

Maybe influenced by location.

Learning Objectives

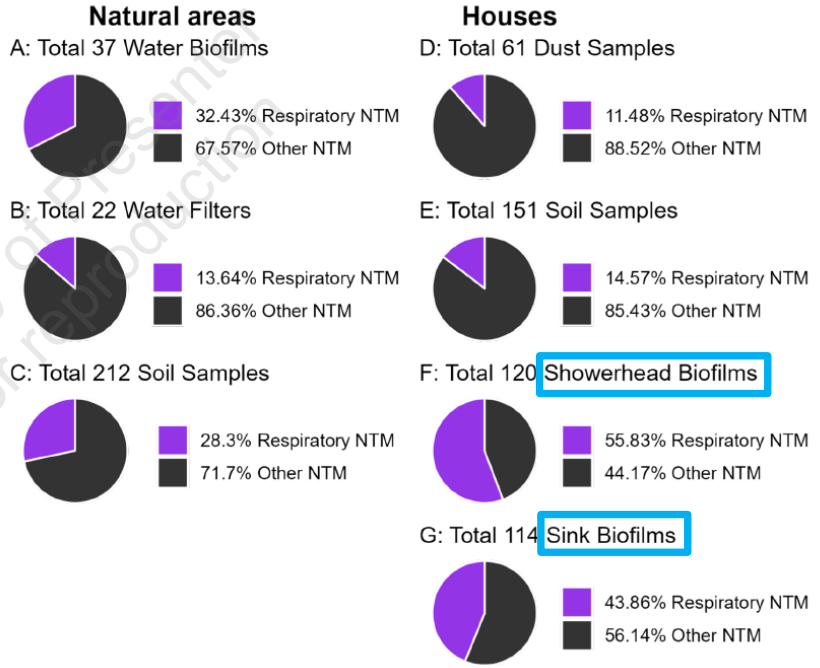
1). Become familiar with the varied environmental niches of NTM.

2). Recognize features that may promote NTM in the environment (*e.g.*, other studies and our work in Hawai'i).

3). Identify possible methods to reduce environmental NTM exposures.

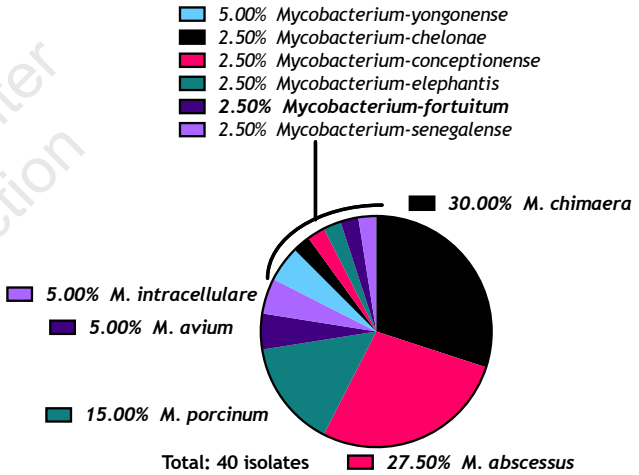
Possible significance of NTM for people in Hawai'i

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



NTM in Hawai'i – A Matched Study

	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

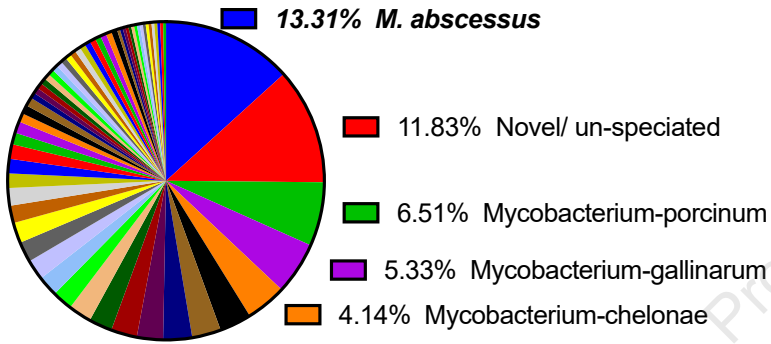


	Kitchen Faucet	Showerhead	Soil
M. abscessus	5/5 (100%)	0/7 (0%)	N/A
M. chimaera	0/7 (0%)	4/4 (100%)	0/2 (0%)

Unpublished

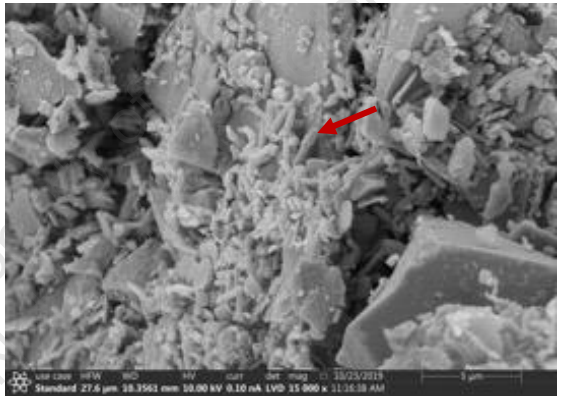
Soil minerals contribute to NTM in Hawai'i

Total: 251 soil samples



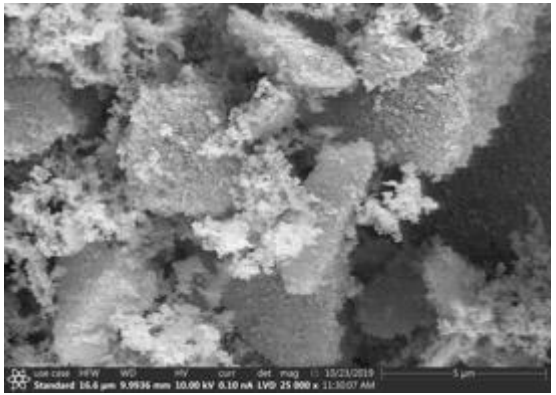
Iron minerals

More *M. abscessus* with *hematite*



Clay minerals

Less with *gibbsite*



NTM probability highest in:

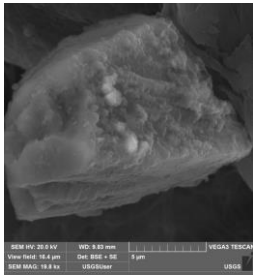
- Rich in ferric oxide.
- Expansive soils with a high-water balance.

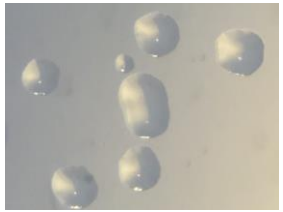
Unpublished
Glickman and Virdi *et al.*, AEM, 2020

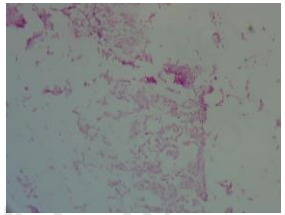
Volcanic ash harbors pathogenic NTM

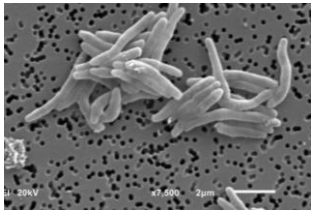
Kilauea Volcano
Hawai'i Island

Kilauea ash, May 2018



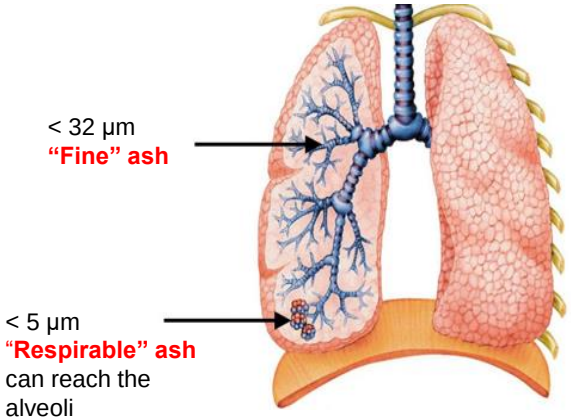






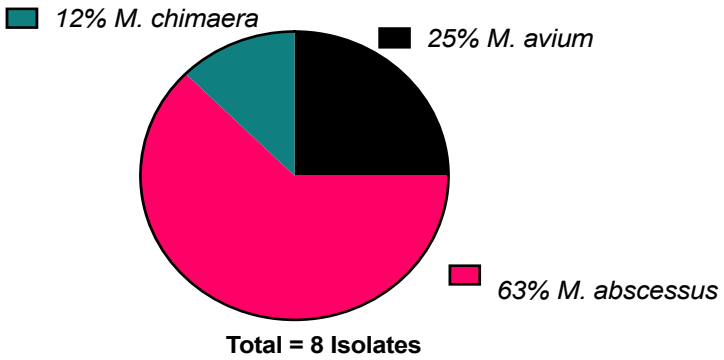
rpoB Taxa ID	BLAST ID
Mycobacterium avium	99.2%

rpoB Taxa ID	BLAST ID
Mycobacterium abscessus	99.7%



8 NTM-like colonies were isolated

Viable NTM recovered from ash



Unpublished

Certain metals as NTM predictors – location dependent

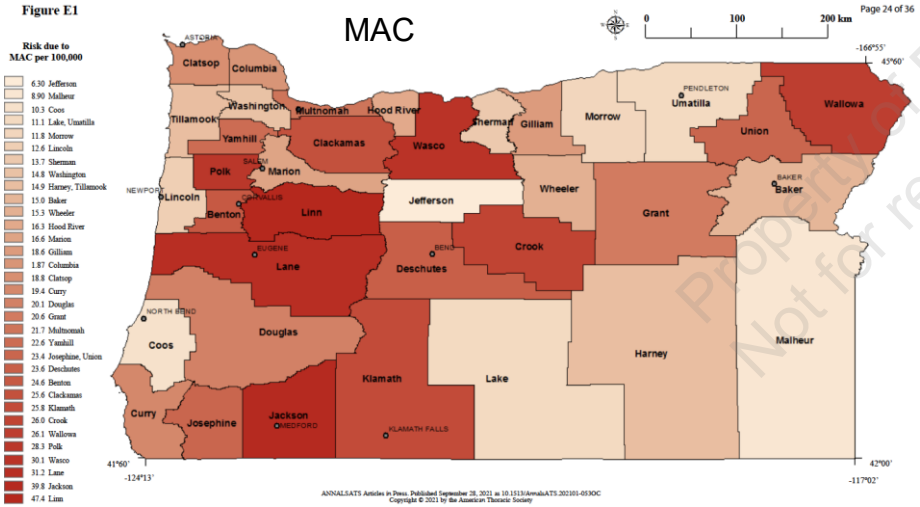
Oregon

As molybdenum increases, MAC infections increase by 45%.

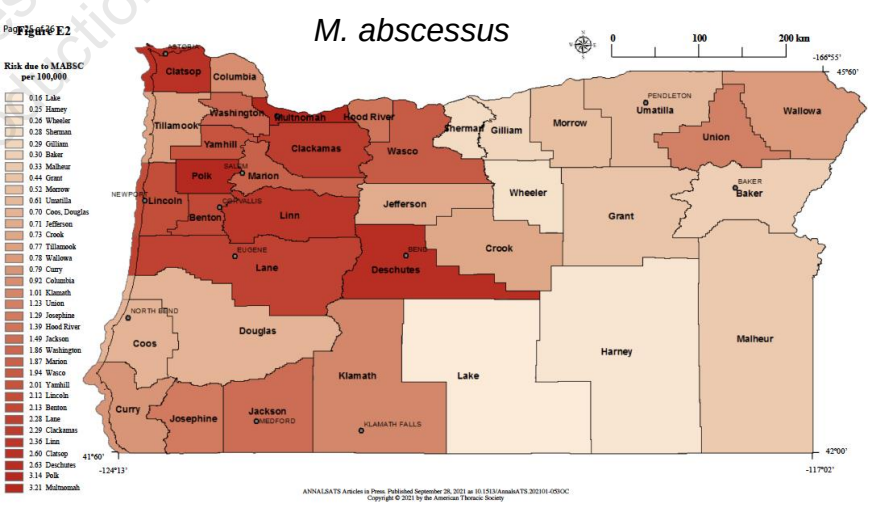
((Molybdenum associated with disease rink in Colorado)).

As vanadium increases, *M. abscessus* infections increase by 41%.

MAC



M. abscessus



Lipner, *et al.,* Int J Env Res Pulb Health, 2020; Lipner, *et al*., Annals ATS, 2021

Interim Conclusion 2

Q: How should we think about our environment?

A: Certain environmental features promote or inhibit NTM.
Maybe influenced by location.

Learning Objectives

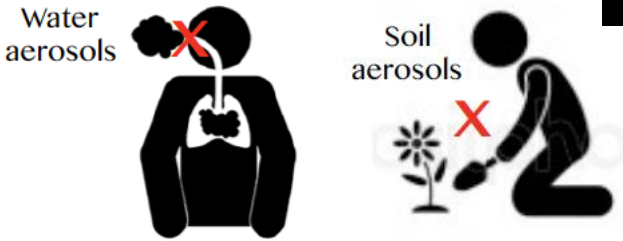
1). Become familiar with the varied environmental niches of NTM.

2). Recognize features that may promote NTM in the environment (*e.g.*, other studies and our work in Hawai'i).

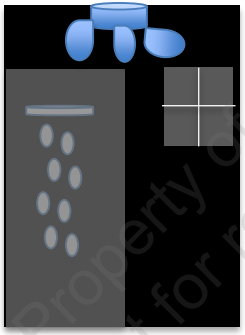
3). Identify possible methods to reduce environmental NTM exposures.

Proposed methods to reduce exposures

Avoid aerosol generating activities



Use fans or open windows in shower area

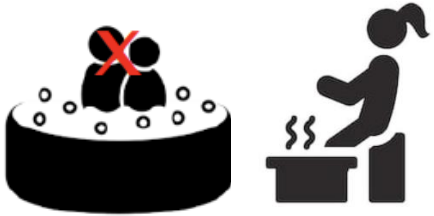


preferred

Replace or clean showerheads regularly
Avoid fine mist showerheads

NOT recommended

Avoid bubbling water (*i.e.*, hot tubs, nail foot baths, humidifiers)



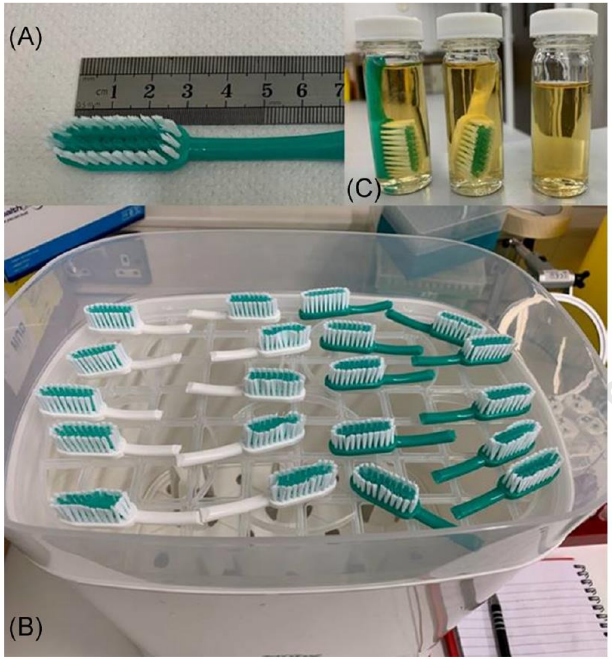
Avoid smoking

Flush water heater frequently
Increase hot water heater temperature

Avoid using tap water for nasal irrigations

Falkinham, *et al,* Ann Am Thor Soc, 2013
Chan, Breslawsky, NTMiR, 2019

Steam disinfection of toothbrushes reduces NTM



M. abscessus subsp. *abscessus* (n=2)
M. abscessus subsp. *bolletii* (n=2)
M. abscessus subsp. *massiliense* (n=2)

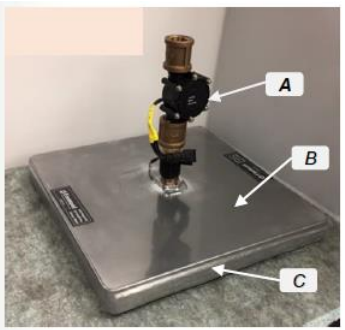
None of the 80 isolates examined survived at 91℃ for 4 min. [1]

** Boiling water for 10-15min reduces NTM. [2]

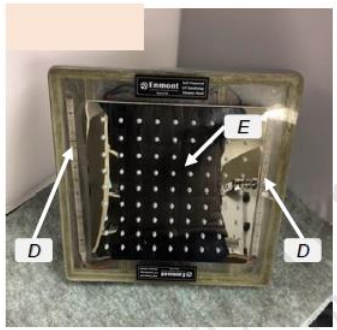
[1] Millar, *et al*., Pediatric Pulmonology, 2020
[2] Falkinham, WhiteJ, 2013

UV disinfection to reduce NTM in freshwater

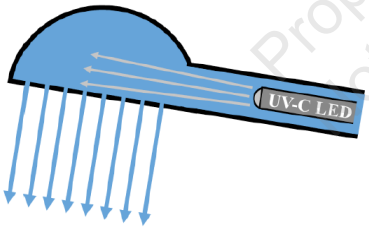
UV-LED adapted showerhead reduces *Legionella* (EPA)



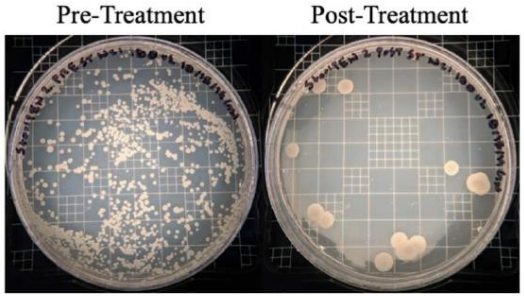
Top View

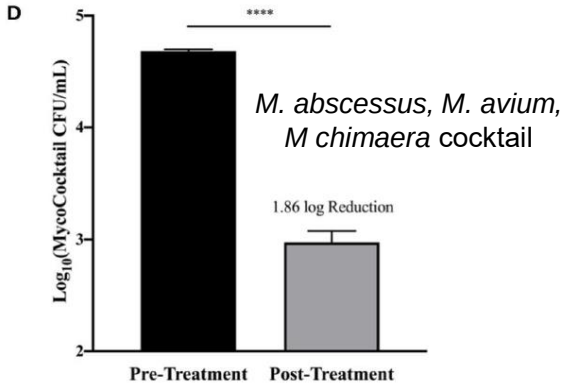


Bottom View



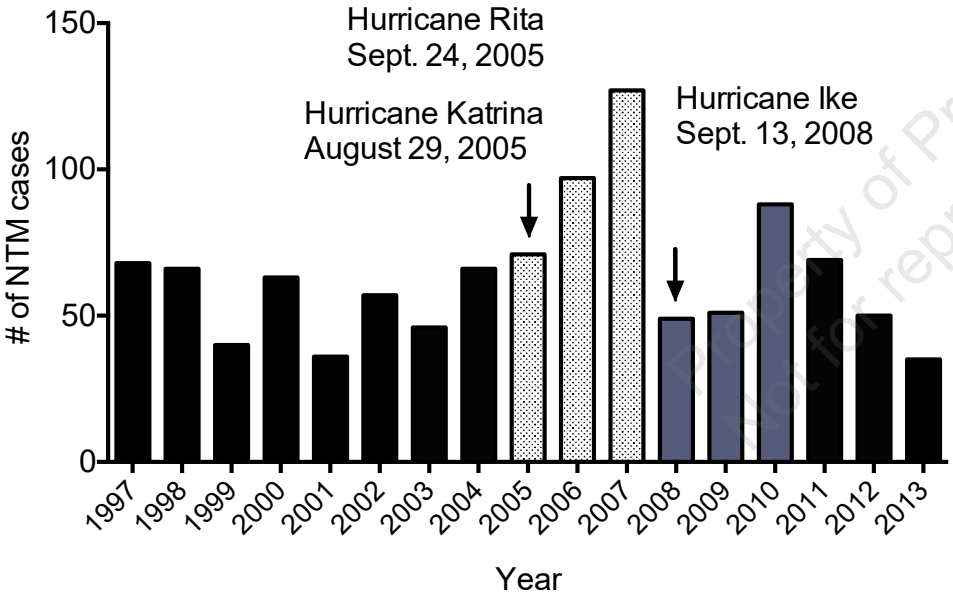
UV Water Bottles reduce NTM from drinking water





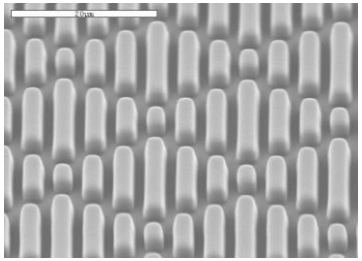
Norton, *et al.,* Frontiers in Public Health, 2020
https://www.epa.gov/sciencematters/uv-led-showerhead-invention-reduces-risk-legionella-contamination
Hessling, *et al.,* Hosp Pract Res, 2018

Reduce exposure to aerosol generating events



Honda, *et al*, Chest, 2015
Image: https://www.usgs.gov/special-topic/fire
Image: https://volcanoes.usgs.gov/volcanic_ash/ash_gas.html

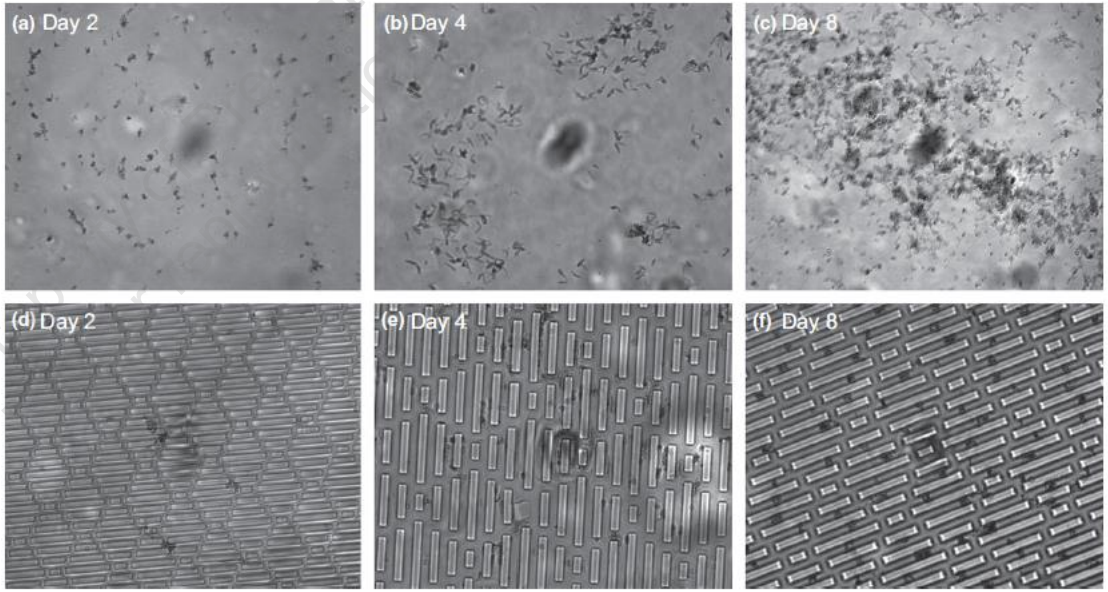
Novel applications to reduce surface NTM adherence



Sharklet(-)

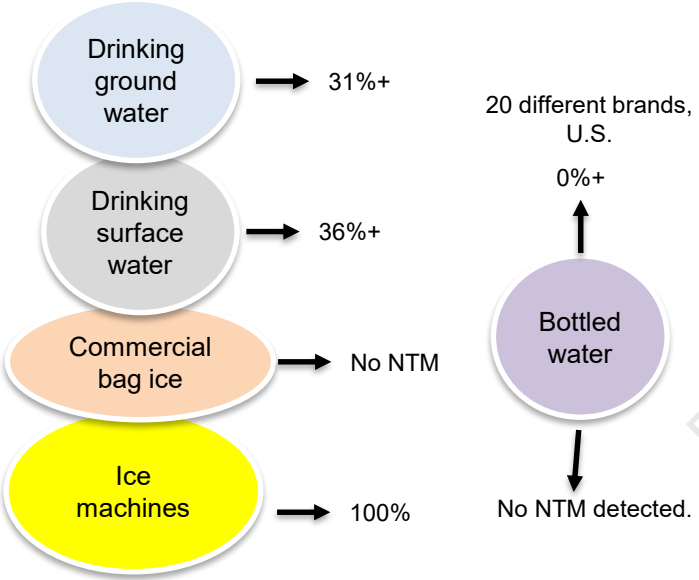
Sharklet(+)

M. abscessus



Kim *et al*., FEMS Microb Letters, 2014

Expand Drinking Water Awareness



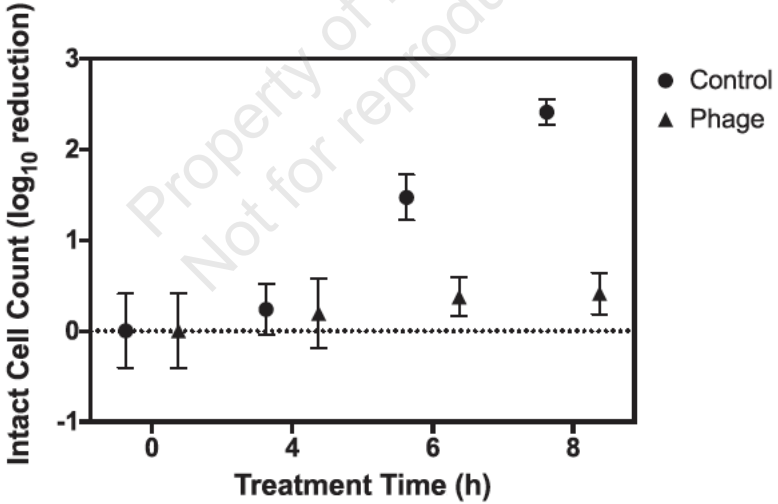
Bottled Water (Honda Lab, 2021):

Water Tested:	Type of water (Source = U.S.A.) unless noted:	Characteristic:	Results:
1	Bottled Water, Brand 1	Natural spring water	None
2	Bottled Water, Brand 2	Purified water	None
3	Bottled Water, Brand 3	Natural spring water	None
4	Bottled Water, Brand 4	Water from snow	None
5	Bottled Water, Brand 5	Volcanic rock filtered water	*Mycobacterium neoaurum* *Mycobacterium phocaicum*
6	Bottled Water, Brand 6	Volcanic rock filtered water	None
7	Bottled Water, Brand (non-U.S.A)	Volcanic rock filtered water	None
8	Distilled water	Commercially available	None
9	Sink faucet 1	Municipal water, Colorado	*Mycobacterium abscessus*
10	Sink faucet 2	Municipal water, Colorado	None
11	Sink faucet 3	Municipal water, Colorado	None
12	Water fountain	Municipal water, Colorado	None
13	Wall mounted water bottle filling station	Municipal water, Colorado	None

Holtzman, *et al,* J Food Protect 1997
Covert, *et al,* AEM, 1999
Totaro, *et al,* J Water Health, 2018
https://www.bottledwater.org/public/CCL4%20Microbes%20of%20Interest%20in%20Drinking%20Water_0.pdf0
Honda Lab, unpublished.

Phages as possible sanitizers to prevent NTM in the built environment

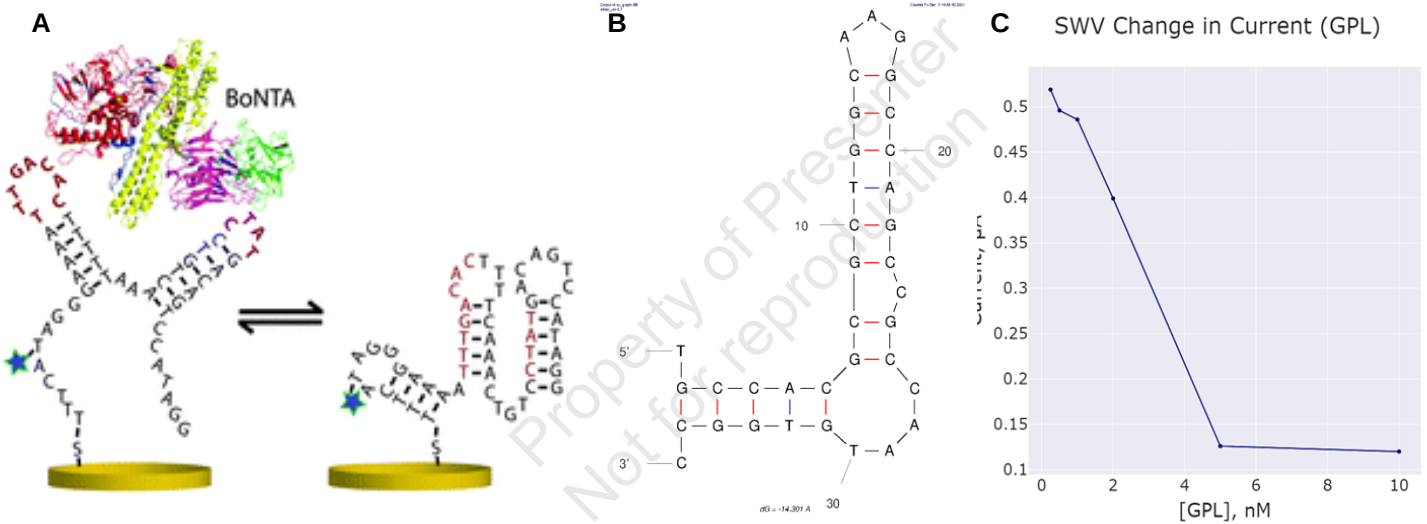
Bacteriophage Treatment before Chemical Disinfection Can Enhance Removal of Plastic-Surface-Associated *Pseudomonas aeruginosa*



Stachler *et al*., AEM, 2021

Developing new point of use DNA biosensors to detect environmental NTM

(Andrew Bonham, PhD, Metro State University)



Electrochemical DNA-based biosensor for GPL. A) Schematic of the general biosensor approach, wherein a DNA aptamer selected to bind to a target, in this example Botulinum neurotoxin A (BoNTA), is attached to a gold electrode with a redox-active tag (blue star). Binding of the target changes DNA conformation and generates a specific, reproducible change in electrical current. **B)** SELEX-evolved DNA aptamer specific to GPL. **C)** Preliminary graph of electrical current response change when tested against purified GPL.

Poch, *et al.,* Rowdy Scholar, 2020

Interim Conclusion 3

Q: How should we think about our environment?

A: Large scale environmental intervention studies are needed to provide essential data that is currently missing.

Sensors are needed to quickly and accurately determine which environments harbor pathogenic NTM.

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