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Breathing Science is Life.®

Environmental Sources of NTM

NTM Lecture Series *for Providers*

April 25-26, 2024

Jennifer R. Honda, PhD, ATSF

Outline

- NTM microbiology and historical niches *
- What's new? Studies on environmental features that may impact NTM
- What's new? How to reduce exposures
- What's new? NTM in the hot spot of Hawai'i
  - Diversity and preferred niches
  - Volcanos
  - Wildfires
- The future – How climate change may impact environmental NTM distribution.

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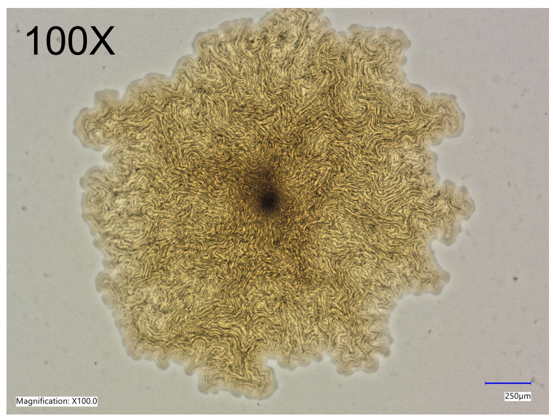
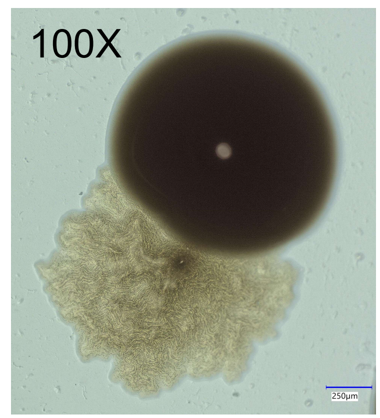
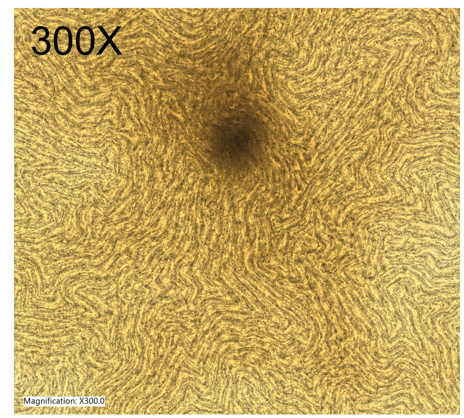
NTM - General Microbiology 101

- NTM have a thick outer membrane containing lipids, waxes, mycolic-acid → hydrophobic [1]
    - Adherence to plumbing pipe surfaces [2]
    - Broad resistance to disinfectants, chemicals, and antibiotics [3]
    - Can be biofilm pioneers [4]
- Resistant to low pH of stomach [5]
- Withstand exposure to high temperatures (50-60 ºC); *M. avium* tolerates 45℃ [4]
- Metal resistance [6].

Adaptable!







[1] Brennan, *et al*., Annu Rev Biochem, 1995; [2] Mullis, *et al.,* J Appl Micro, 2013; [3] Rastogi *et al.,* Antimicr Agents Chemo 1981; [4] [5] Falkinham *et al*., Clin Chest Med, 2002; [5] Portaels *et al.,* Ann Microb, 1992; [6] Falkinham *et al*., Antim Agents Chemo 1984.

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Generalized resistance of NTM to disinfection

TABLE 1 | Summary of relative susceptibility of NTM to chemicals used for disinfection.

Disinfectant chemicals	Relative susceptibility amongst mycobacterium species
Chlorine releasing compounds (including sodium hypochlorite and TC-101)	*M. fortuitum* and *M. chelonae* are more resistant than *M. gordonae* and *M. aurum*. *M. chelonei* subspecies *abscessus* is more resistant than *M. tuberculosis*.
Iodophor	*M. chelonei subspecies abscessus* and *M. tuberculosis* have similar susceptibility.
Phenol	*M. chelonae* and *M. terrae* are more resistant than *M. bovis*.
Silver nanoparticles	*M. smegmatis* is highly susceptible to silver nanoparticles (AgNP) compared to *M. avium* and *M. marinum*.
Glutaraldehyde	*M. tuberculosis*, *M. terrae*, *M. bovis*, *M. avium*, *M. abscessus*, and *M. chelonae* have similar susceptibility. However, glutaraldehyde-resistant clinical isolates have been identified for *M. abscessus* and *M. chelonae*. In a study of nine *Mycobacterium spp*., *M. smegmatis*, and *M. marinum* are highly susceptible to glutaraldehyde solutions; *M. avium*, *M. kansasii*, and *M. scrofulaceum* showed intermediate susceptibility; and *M. tuberculosis*, *M. bovis*, and *M. intracellular* were resistant, requiring higher concentrations and longer contact times to achieve reduction in counts.
Alcohol	*M. chelonei subspecies abscessus* and *M. tuberculosis* have similar susceptibility to alcohol. Resistance to glutaraldehyde does not alter resistance of *M. abscessus* to 15% isopropanol.
Hydrogen peroxide	*M. tuberculosis*, *M. terrae*, *M. bovis*, *M. avium*, *M. abscessus*, and *M. chelonae* have similar susceptibility.
Ortho-phthalaldehyde (OPA)	Glutaraldehyde-resistant strains of *M. abscessus* and *M. chelonae* are similarly susceptible to OPA as glutaraldehyde-sensitive strains. *M. terrae* is more resistant than *M. chelonea* and *M. bovis*.
Peracetic acid	*M. tuberculosis*, *M. terrae*, *M. bovis*, *M. avium*, *M. abscessus*, and *M. chelonae* have similar susceptibility.
Quaternary ammonium compounds	*M. chelonae* and *M. abscessus* are more resistant than *M. smegmatis*. *M. terrae* is more resistant than *M. bovis*.

Reviewed in Weeks *et al*., Frontiers in Public Health, 2020

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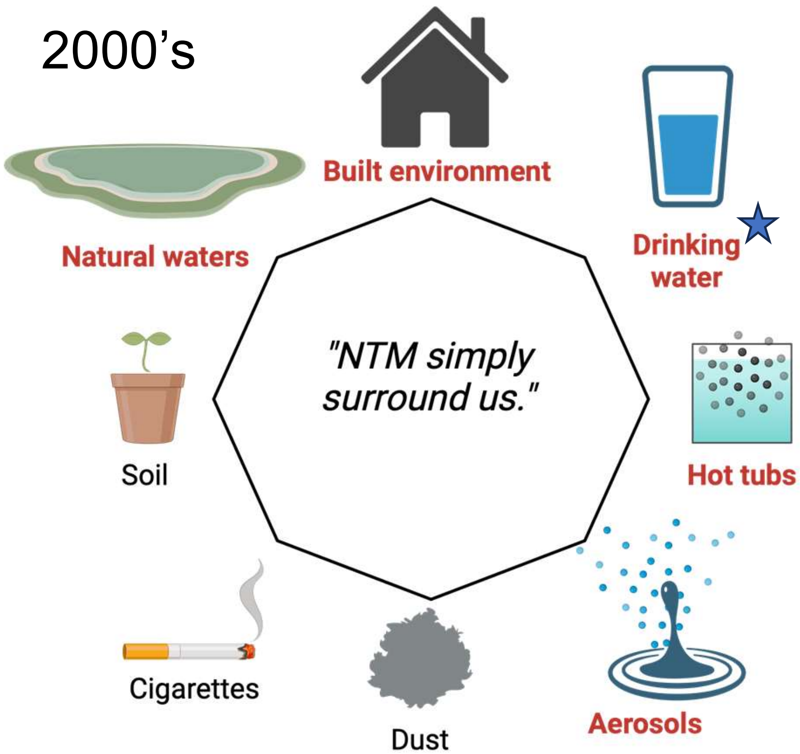
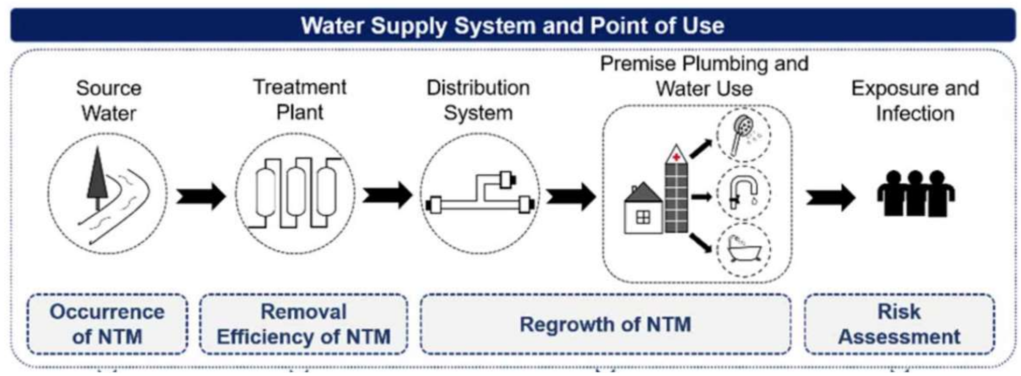
“Atypical” no longer

2000’s



One of the most serious waterborne infections. [1,2]



“We predict an increasing incidence of interactions between humans and mycobacteria in the coming years. [3]

[6] Faklinham et al., J Appl Micro, 2009; [1] Gan et al.. H2O Open Journal, 2022; [2] Collier, *et al.,* Estim Burden HealthCare, 2021; [3] Falkinham *et al*., Clin Chest Med, 2002; Primm *et al.,* 2004
Image created in BioRender

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“Anonymous” no longer

- Inhalation from the environment – shower water and soil aerosols; spa exposures [1,2 3,4]
- Oral ingestion – drinking water [5]
  - Survival in stomach acid and reflux into the lung
- Aerosols from ultrasonic humidifier use [6]
- Dermal contact [7]
- Hospital ice and ice machines [8]
- Heater-cooler devices [9] and bronchoscopes [10]
- Biofilms in water lines in dental drilling and cleaning devices [11,12]
- Glass, copper, galvanized steel, PVC [13, 14, 15]

[1] Thomason *et al.,* Appl Env Microi*,* 2013; [2] Gebert *et al*., mBio, 2018; [3]Uwamino, *et al.,* J Infect Chemoth; 2020; [4] Nakanaga, *et al.,* J Clin Micro, 201; [5] Hamilton, *et al.,* Water Research, 2017; [6] Hamilton *et al.,* J Med Microbio, 2018;[7] Patel *et al.,* Case Rep Dermatol Med, 2013; [8] Millar *et al.,* Int J Mycobacteria, 2020; [9] Sax *et al*., Clin Infect Dis, 2015; [10] Gubler et al., Chest, 1992; [11] Schulze-Robbecke, *et. al.,* Tubercle Lung Dis, 1995; [12] Wang *et al*., Eur Resp J, 1995; [13] Steed, *et al.,* Appl Env Micro*,* 2006; [14] du Moulin, *et al., JAMA*, 1988; [15] George, *et al.,* Am Rev Respir Dis 1980.

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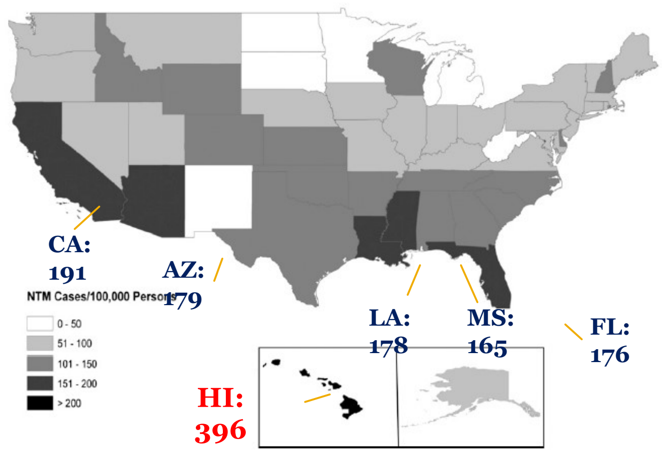
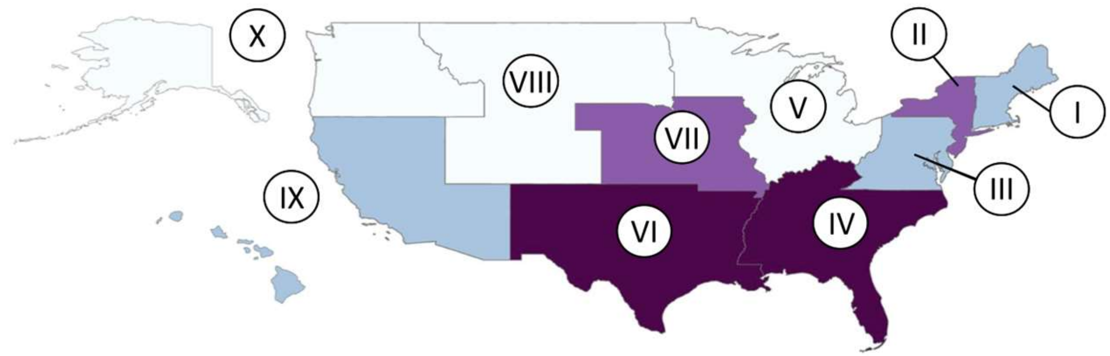
Geography to lung infections, U.S.

NTM national prevalence – 1997-2007 [1]



396 cases/100,000 population
among persons > 65 years-old

NTM culture positivity (%); 2019-2022
National Commercial Lab [2]



[1] Adjemian, *et al.,* AJRCCM, 2012; [2] Marshall *et al.*, BMC infectious Disease, 2002

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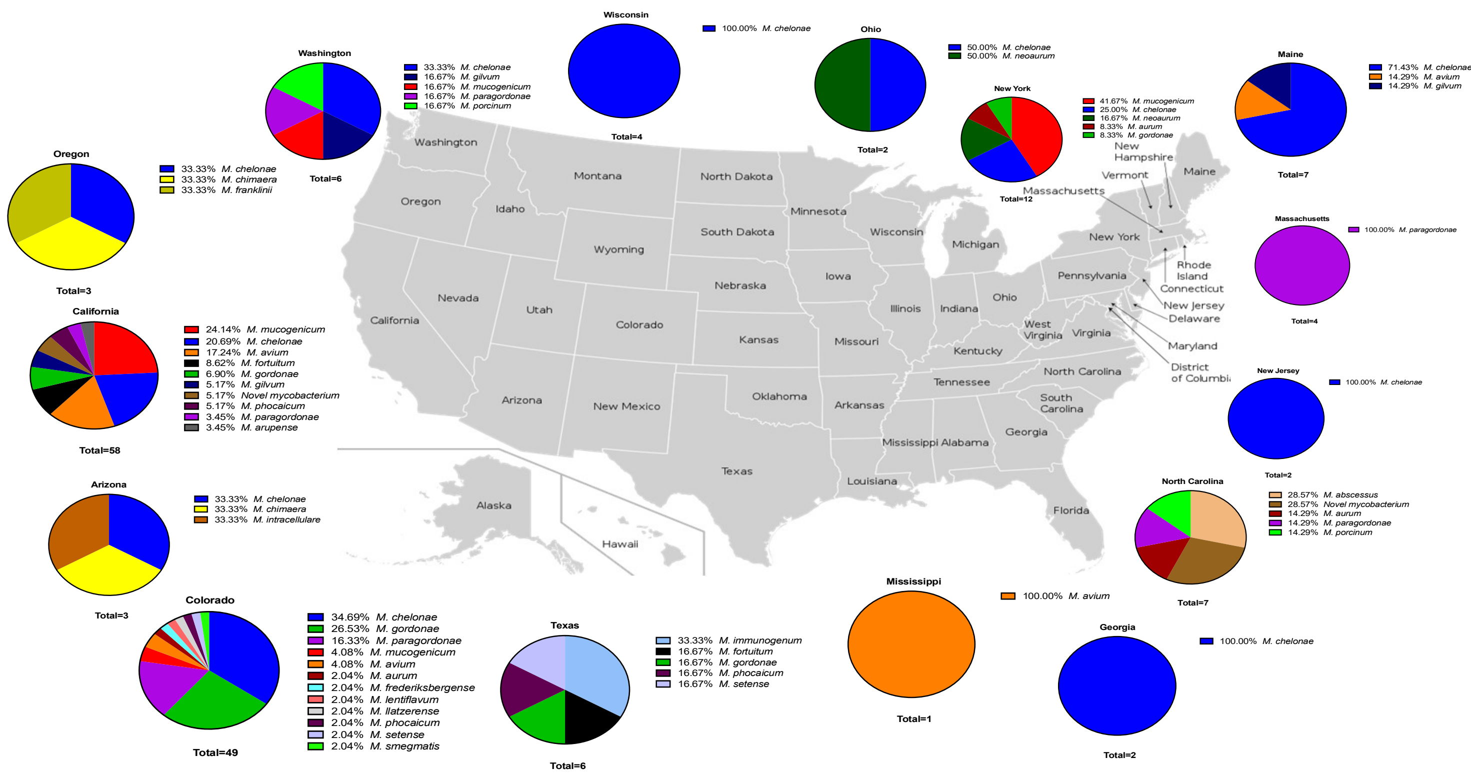
M. chelonae, the environmental generalist



Unpublished

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Water age impacts *M. avium* in drinking water

AMERICAN SOCIETY FOR MICROBIOLOGY | mBio®

RESEARCH ARTICLE

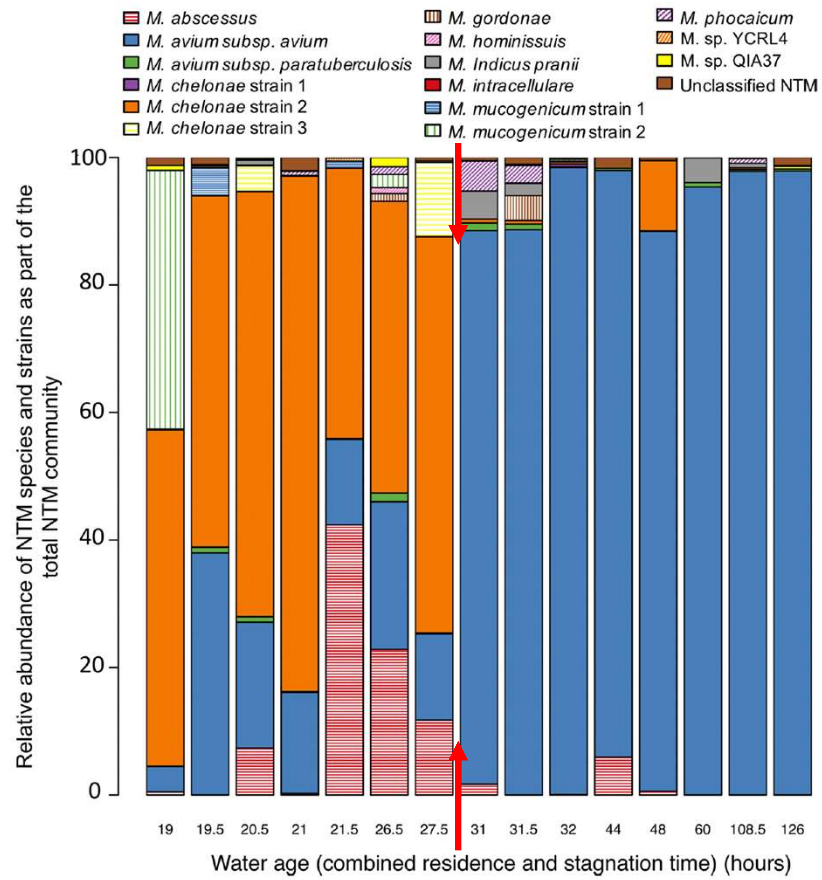
Check for updates

A High-Throughput Approach for Identification of Nontuberculous Mycobacteria in Drinking Water Reveals Relationship between Water Age and *Mycobacterium avium*

Sarah-Jane Haig,[a] Nadine Kotlarz,[a*] John J. LiPuma,[b] Lutgarde Raskin[a]

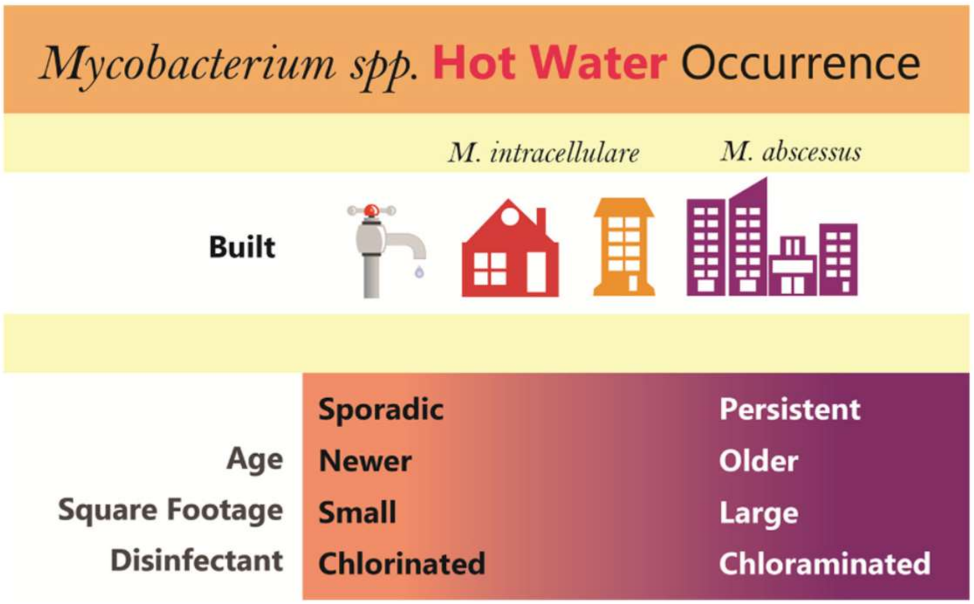
- 15 home kitchen faucets with chloraminated distribution systems (Michigan)
- Multivariate statistical analyses show greater water age (combined time in distribution system and home plumbing stagnation time) promotes *M. avium.*

Haig *et al.*, mBio, 2018



Building size and disinfectant type drives NTM in hot water plumbing

Residences vs office buildings



- *M. abscessus* hot water persistence is higher at residences than office buildings.
- *M. intracellulare* hot water occurrence is influenced by age and square footage.
- *M. avium's* hot water occurrence is affected by distances between tank and tap.

Each NTM shows different trends associated with structure and disinfectant.

[1] Donohue, *et al.,* Science Total Environment, 2022

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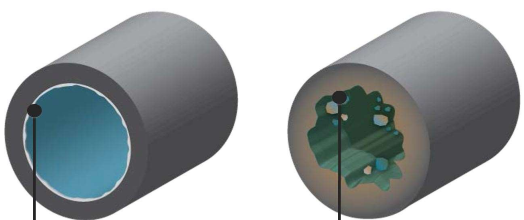
Freshwater features that may contribute to NTM

***Mycobacterium avium* in Community and Household Water, Suburban Philadelphia, Pennsylvania, USA, 2010–2012**

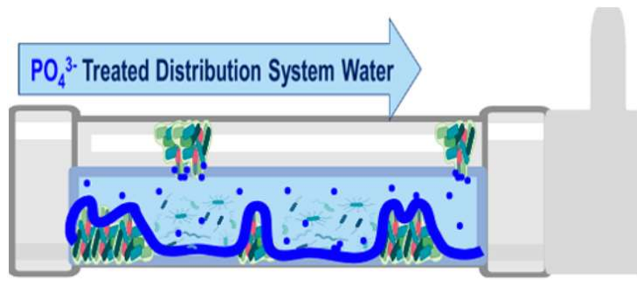
Leah Lande, David C. Alexander, Richard J. Wallace, Jr., Rebecca Kwait, Elena Iakhiaeva, Myra Williams, Andrew D.S. Cameron, Stephen Olshefsky, Ronit Devon, Ravikiran Vasireddy, Donald D. Peterson, Joseph O. Falkinham, III

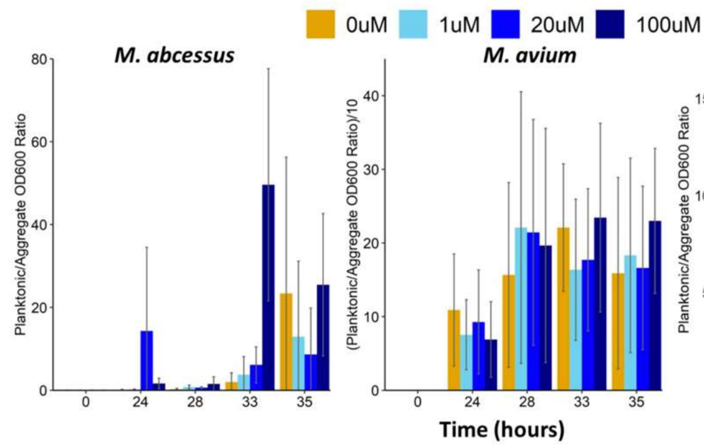
Many drinking water systems commonly add orthophosphates to reduce the release of metals and control for lead and copper in pipes. [1]

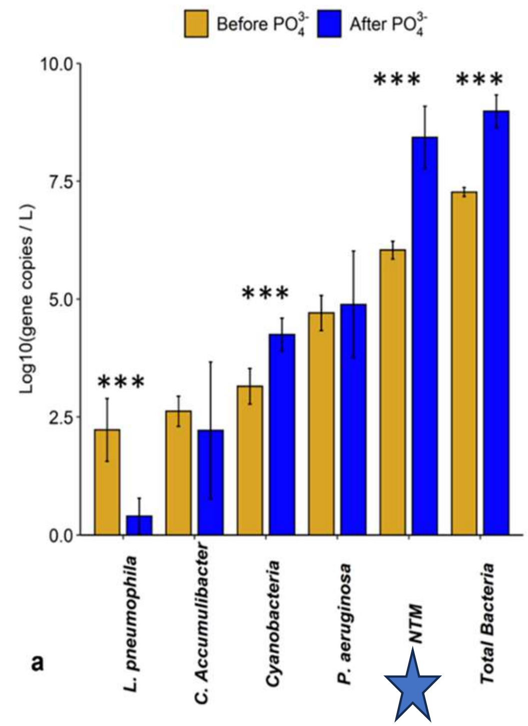


A protective layer of *Orthophosphate* forms to prevent pipe corrosion.

Lack of corrosion control allows lead to leach from pipes into water.







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Lande *et al.*, EID, 2019; [1] Pittsburgh Water and Sewer Authority, 2019; [2] Spencer-Williams, et al., Env Science and Tech., 2023

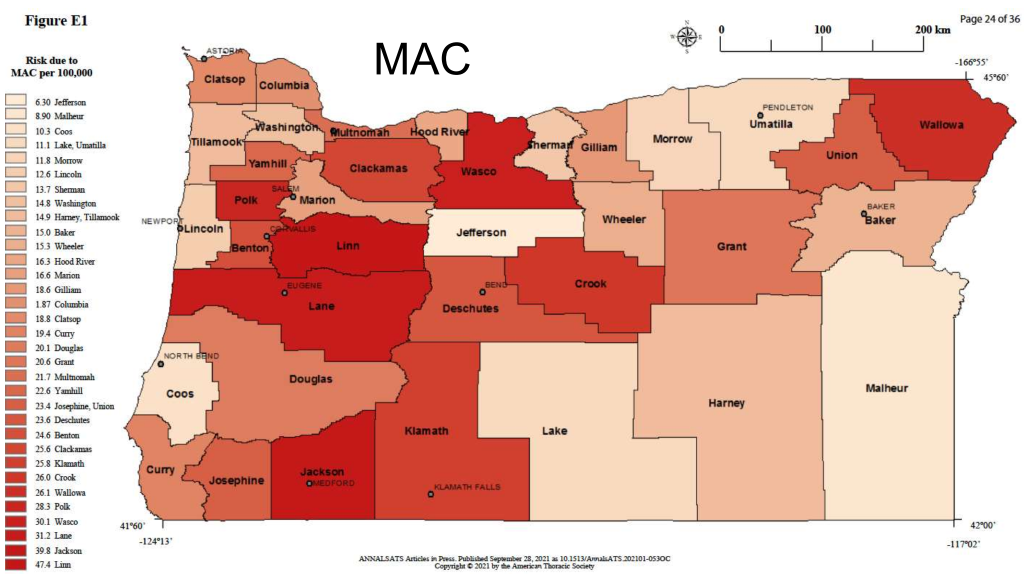
Certain metals as predictors – location dependent

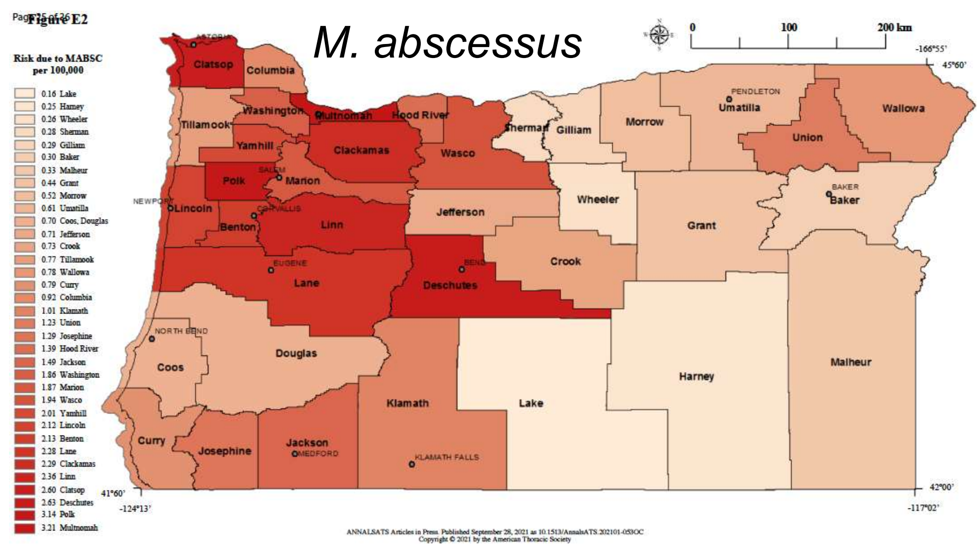
Oregon

As molybdenum increases, MAC infections increase by 45%.

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

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





Lipner *et al.,* Env Epi, 2023
Lipner *et al.,* Env Epi, 2022
Lipner et al., J Expo Sci Env Epi, 2021
Lipner et al., In J Env Res Pub Health, 2020

Lipner, *et al*., Annals ATS, 2021

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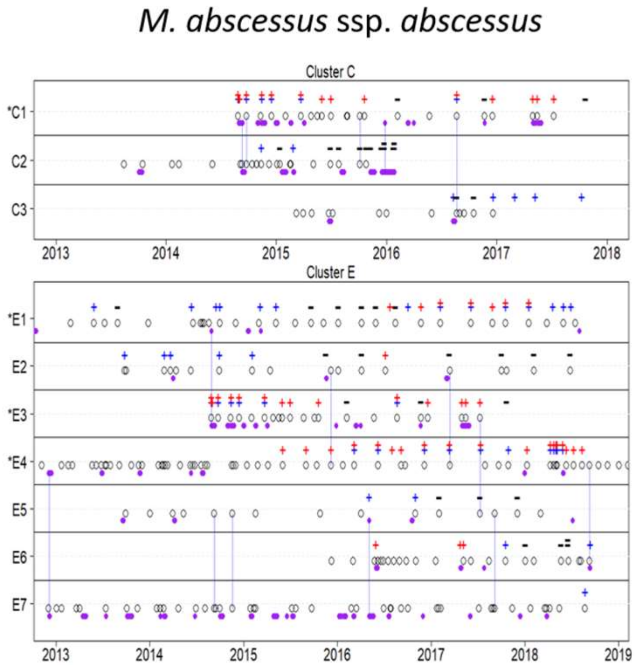
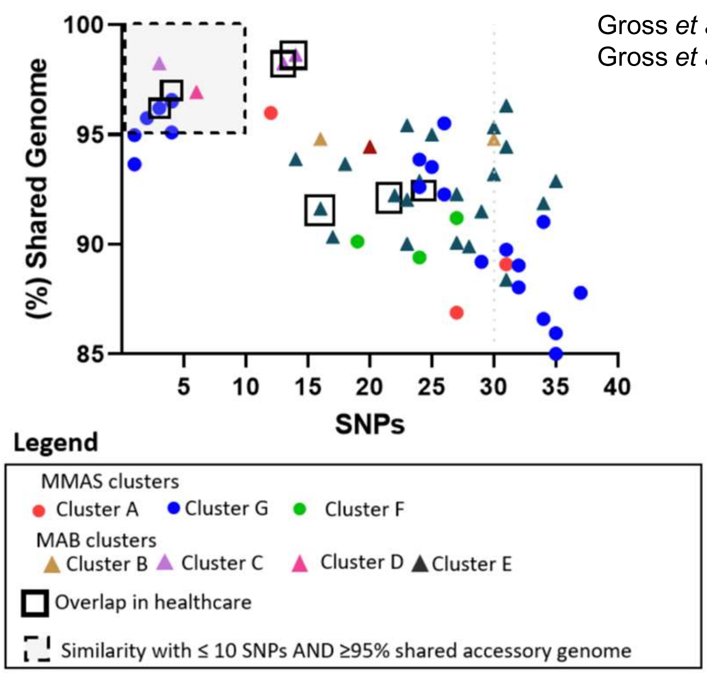
Risk for healthcare NTM acquisition

Genomic Epidemiology of ***Mycobacterium abscessus*** at an Adult Cystic Fibrosis Program Reveals Low Potential for Healthcare-Associated Transmission



Gross *et al.,* Ann Am Thorac Soc, 2023
Gross *et al*., Am J Resp CCCM, 2022



Gross et al., ERJ, 2024 (In press);

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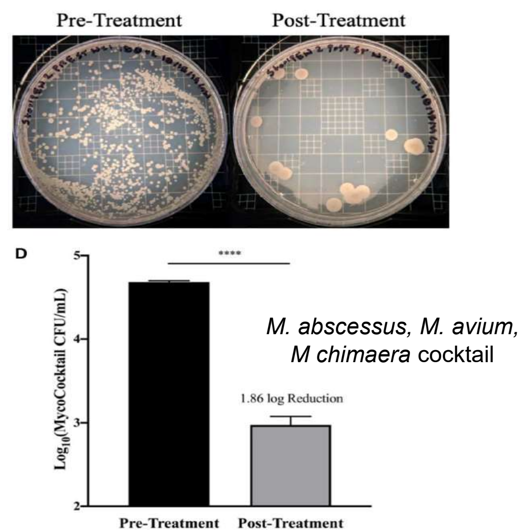
Longstanding suggestions on how to reduce exposures

- ○ Clean showerheads and faucet taps regularly.
- ○ Avoid misting showerheads
- ○ Ventilate bathrooms, showers, other steam areas.
- ○ Use a water filter.
- ○ Raise the temperature of household water heater and drain.
- ○ Avoid humidifiers.
- ○ Wear dust mask.
- ○ Reduce acid reflux.
- ○ Self-supplied water (*e.g*., wells, collected rainwater) is a protective factor, Virginia [5]

- ○ Avoid dusts from soil * [1, 2]
- ○ Boil water for 10min before use [3].
- ○ Use of UV water bottles [4]

UV Water Bottles reduce NTM from drinking water



Falkinham, Clin Chest Med, 2015; Honda, Clin Chest Med, 2023; [1] Hamada *et al.,* Int J Myco 2016; [2], Reed *et al,* Am J Epidem, 2006; [3] Falkinham, WhiteJ, 2013; [5] Norton, *et al.,* Frontiers in Public Health*,* 2020; [5] Mullen, *et al*, EID, 2024.

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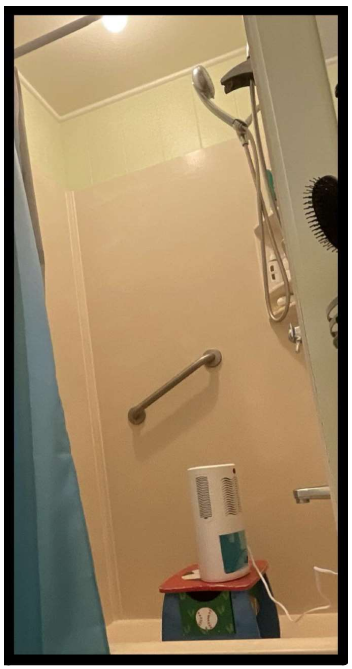
Reducing shower humidity reduces aerosolized NTM

Saturated vapor pressure is a climate variable that affects NTM prevalence [1,2,3]



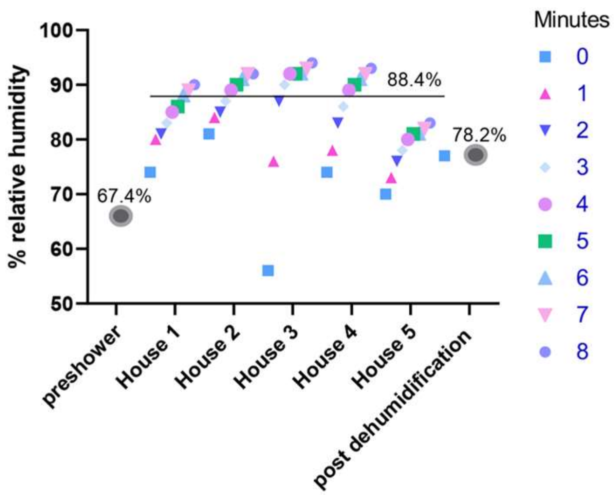


Table 1 Dehumidification reduced *Mycobacterium chelonae* aerosolization, sampling round 1 (37 °C)

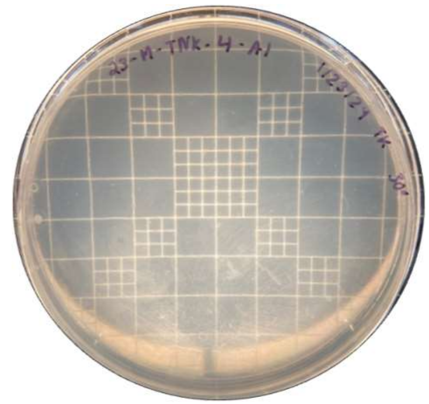
	Biofilm		**Air**		
House:	**Showerhead biofilm (swab):**	**Showerhead biofilm (swab), post- disinfection**	**Pre shower air (SAS):**	**Post shower air (SAS):**	**Post de-humidi-fication (SAS):**
1	***M. chelonae***	No NTM	No NTM	***M. chelonae***	No NTM
2	No NTM	No NTM	No NTM*	No NTM*	No NTM*
3	No NTM	No NTM	No NTM	No NTM	No NTM
4	No NTM	No NTM	No NTM*	No NTM*	No NTM
5	No NTM	No NTM	No NTM*	No NTM*	No NTM

(*) Limitation - indicates instances where mold overgrowth likely reduced NTM detection

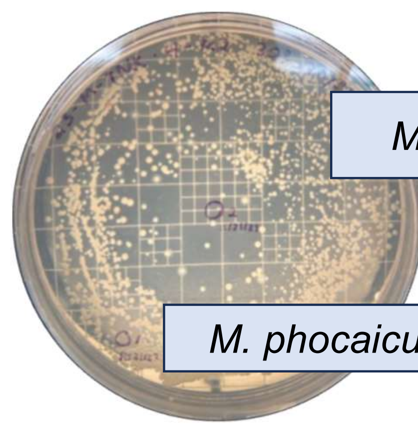
Kostecki, *et al.*, BMC Research Notes, 2024

Showerhead filters do not reduce NTM, a pilot

	Biofilm		Water
House:	Pre-intervention Showerhead biofilm (swab):	Post-intervention Showerhead biofilm (filter):	Post-intervention Showerhead water:
1	No NTM		*M. gordonae*
4	No NTM	Pending	*M. phocaicum, M. chelonae*
5	No NTM		*M. porcinum*
6	No NTM		No NTM



Showerhead, pre-intervention



Showerhead, post-intervention

Unpublished

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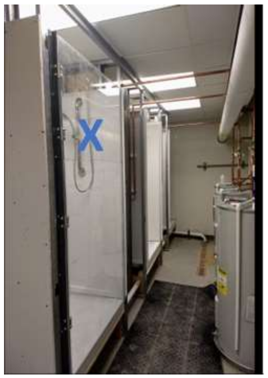
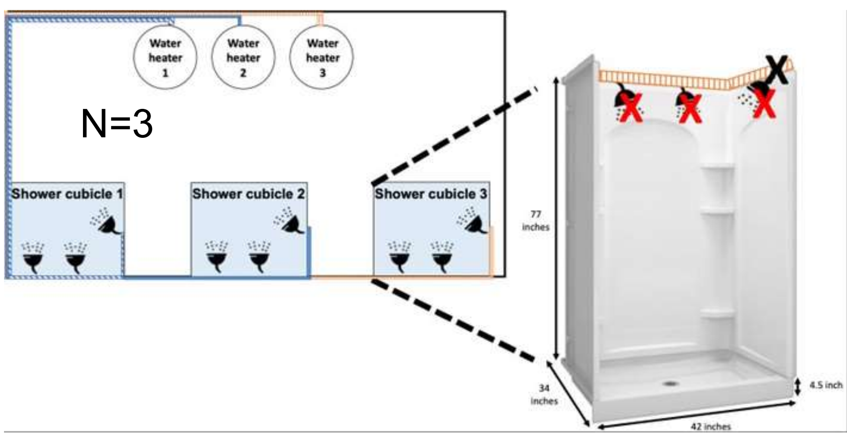
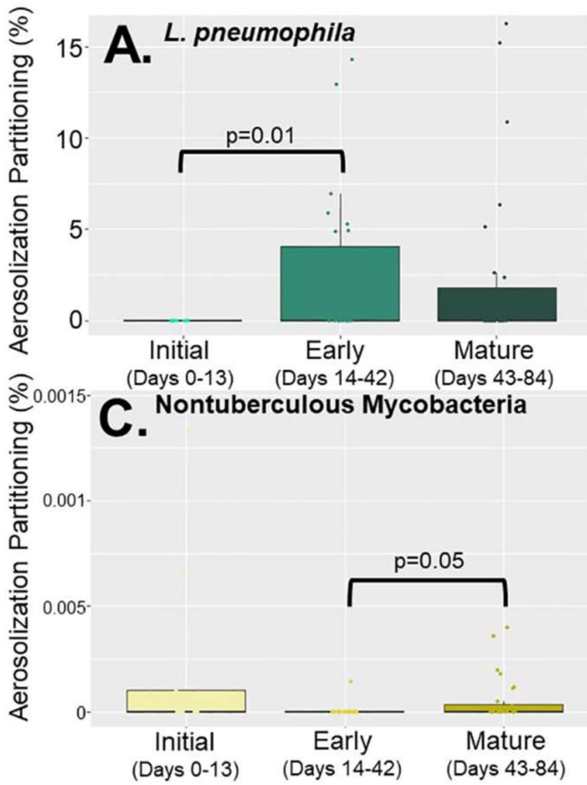
Antimicrobial showerheads do not impact aerosolization



1. Proprietary multistage antimicrobial filter
2. Antimicrobial silver-embedded
3. Conventional plastic





Drinking water associated pathogens did not differ between showerhead type

Each peaked as showerhead aged

# of days of showerhead operation important.

Pitell and Haig, Fronters in Microbiome, 2024;

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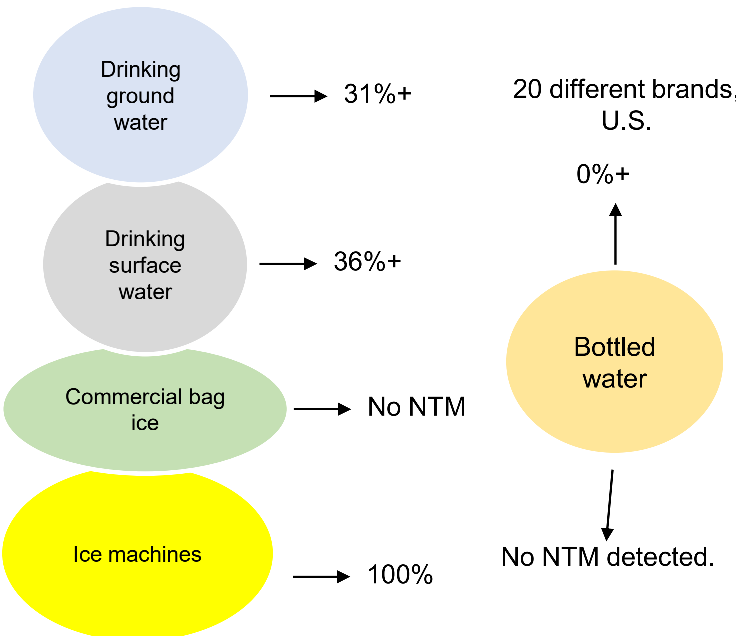
Expand Drinking Water Awareness



Bottled Water (Honda Lab)

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.

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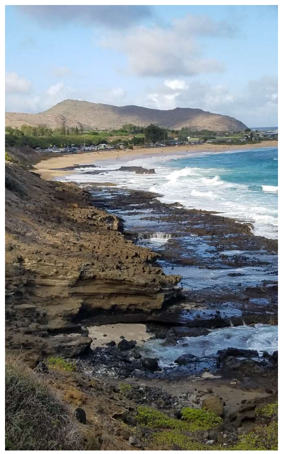
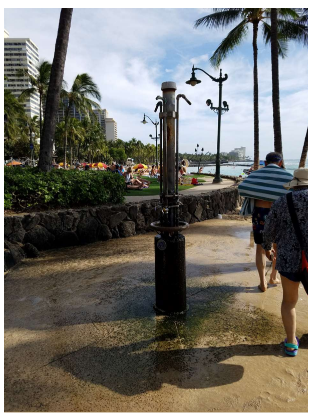
Aloha Hawai'i – Teaching us about NTM





1. Enrichment in the built environment (Honda *et al*., Plos Neg Trop 2016; Virdi, *et al*, Microorganisms, 2020)

2. Preference for iron minerals, hematite in soil and aversion to gibbsite (Glickman *et al*., App Env Micro, 2020)

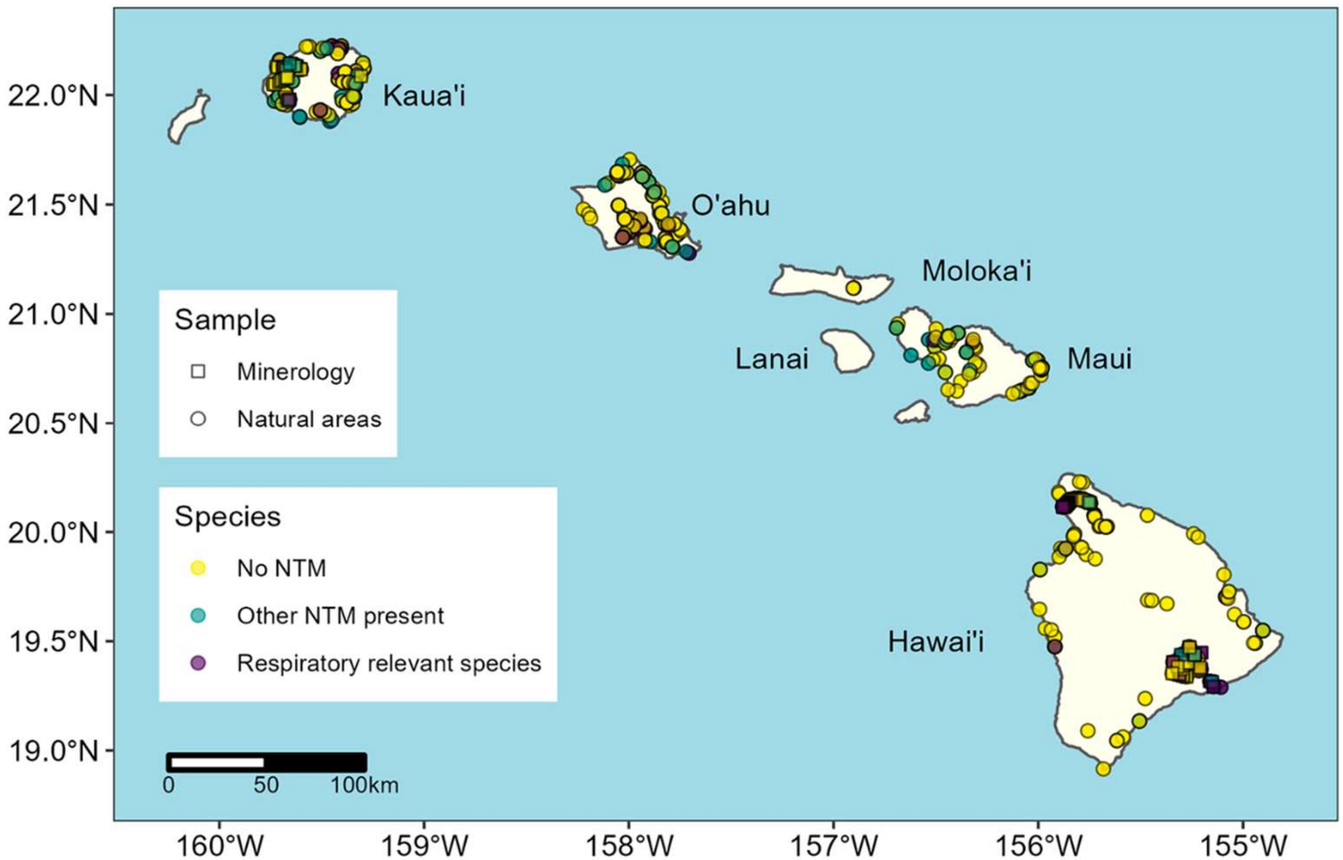
3. Like highly expansive, moist soils containing high iron oxides and hydroxides (Parsons *et al*., Appl Env Micro, 2022)

4. Vanadium in groundwater increases MAC lung disease risk (Lipner *et al*., Env Epi, 2022)

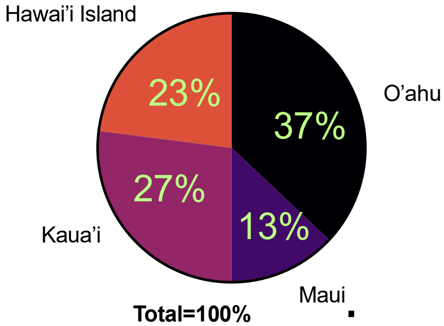
5. Water transport from riparian zones into losing stream stretches, aquifers, and into homes (Nelson *et al*., Geohealth, 2021).

6. Local feral pigs harbor pathogenic NTM species. (Hendrick, et al, in preparation.)

Larger cities are NTM hot spots



Island distribution
766 total NTM+ samples



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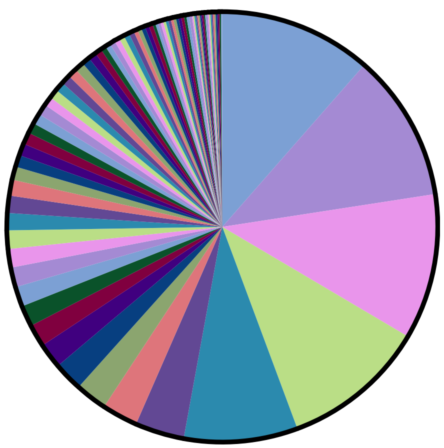
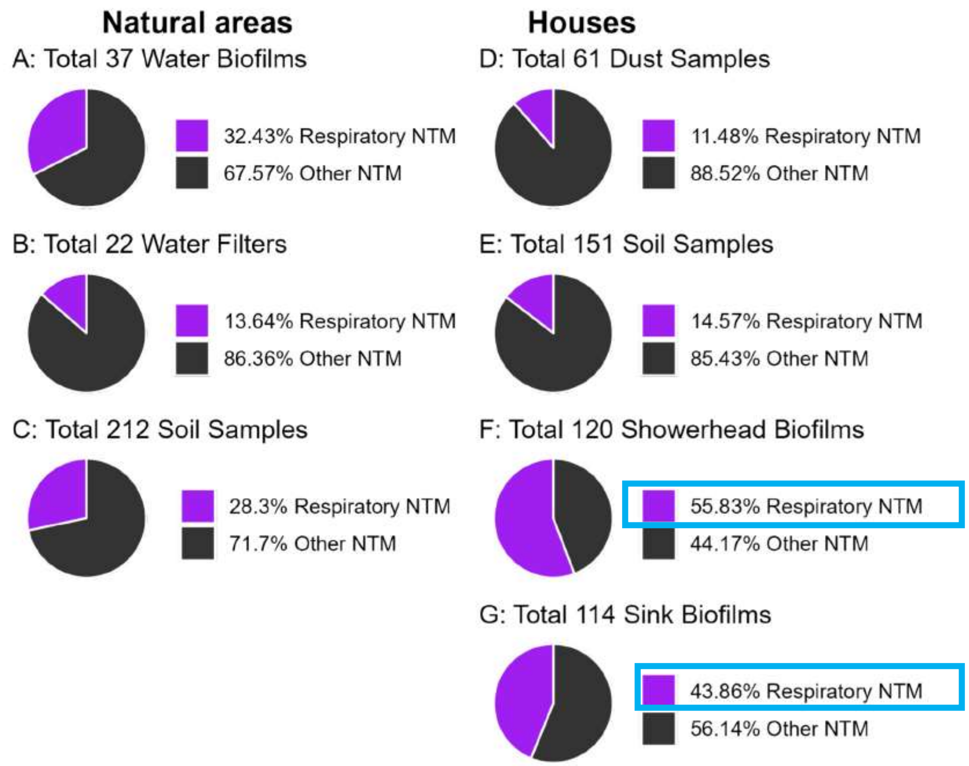
Environmental NTM species diversity

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



Total: 766 samples

- 11.43% *Mycobacterium-abscessus*
- 11.13% *Mycobacterium-chelonae*
- 10.93% *Mycobacterium-chimaera*
- 10.83% *Mycobacterium-porcinum*
- 8.55% *Novel/ un-speciated*
- 3.68% *Mycobacterium-gordonae*
- 2.68% *Mycobacterium-mucogenicum*
- 2.39% *Mycobacterium-avium*
- 2.19% *Mycobacterium-iranicum*
- 1.89% *Mycobacterium-gallinarum*
- 1.69% *Mycobacterium-paragordonae*
- 1.59% *Mycobacterium-peregrinum*
- 1.49% *Mycobacterium-neoaurum*
- 1.49% *Mycobacterium-phocaicum*
- 1.39% *Mycobacterium-flavescens*
- 1.39% *Mycobacterium-litorale*
- 1.29% *Mycobacterium-fortuitum*
- 1.29% *Mycobacterium-rhodesiae*
- 1.19% *Mycobacterium-timonense*
- 0.99% *Mycobacterium-septicum*
- 0.89% *Mycobacterium-florentinum*
- 0.89% *Mycobacterium-triplex*
- 0.89% *Mycobacterium-stomatepiae*
- 0.80% *Mycobacterium-conceptionense*
- 0.80% *Mycobacterium-gilvum*
- 0.80% *Mycobacterium-wolinskyi*
- 0.70% *Mycobacterium-boenickei*
- 0.70% *Mycobacterium-frederiksbergense*
- 0.70% *Mycobacterium-intracellulare*



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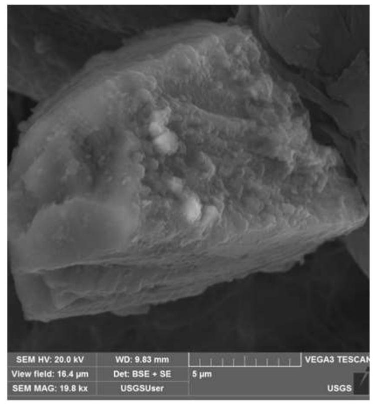
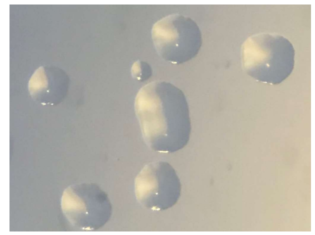
Active volcanism contributes to NTM

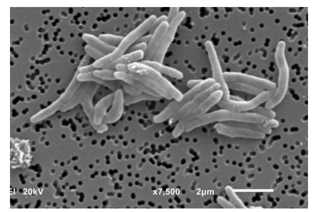
Kīlauea volcano, Hawai'i Island, 2018

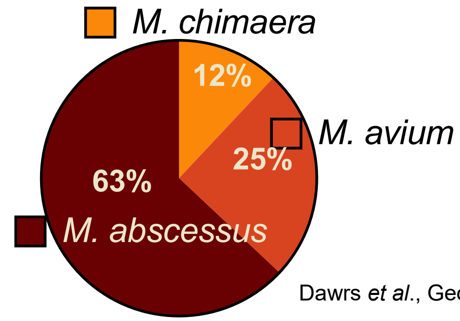
Photo credit: USGS

Kīlauea ash, SEM





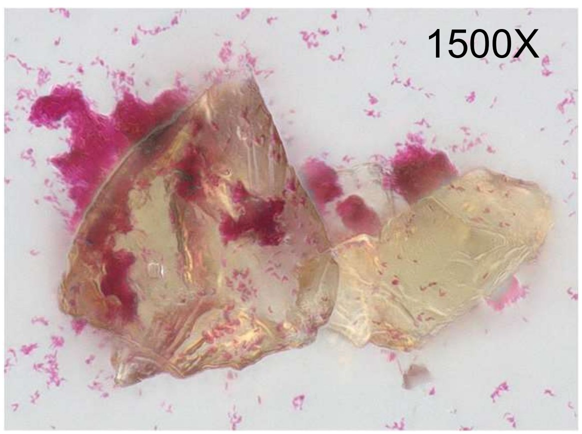


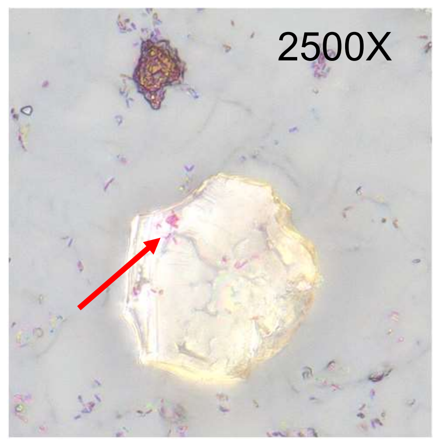


Dawrs *et al.*, GeoHealth, 2023

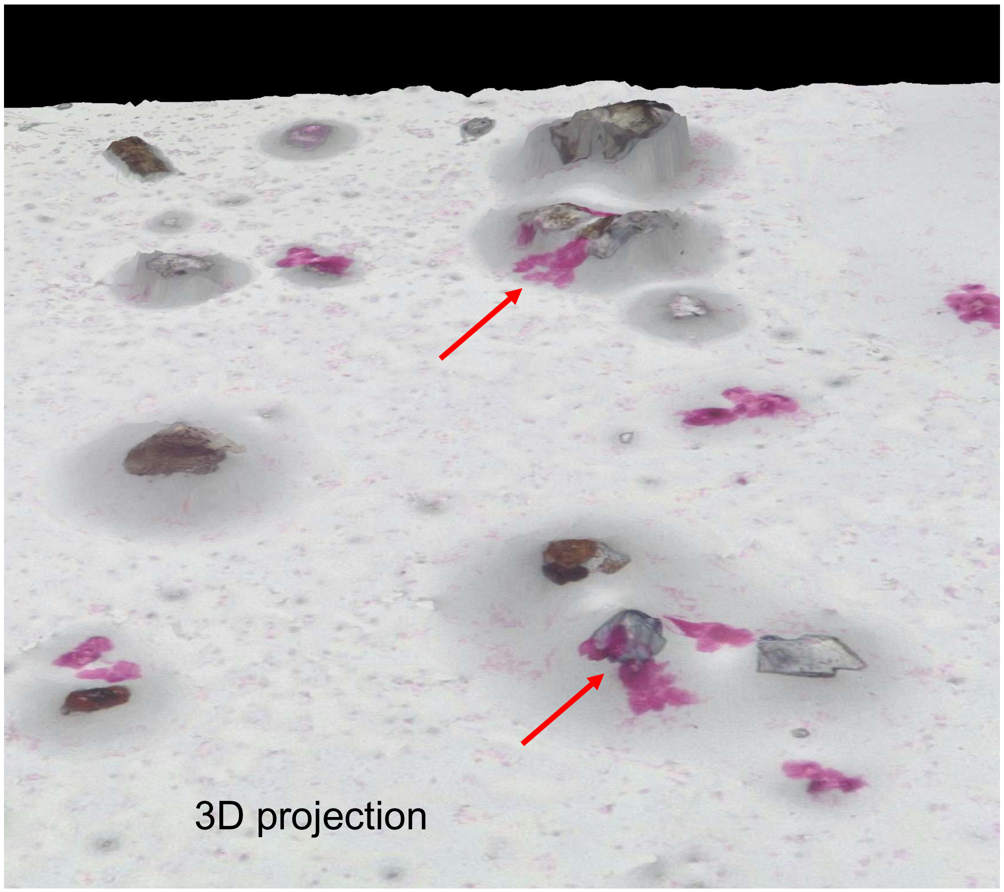
Total = 8 NTM recovered from Kilauea ash

AFB





Active volcanism contributes to NTM



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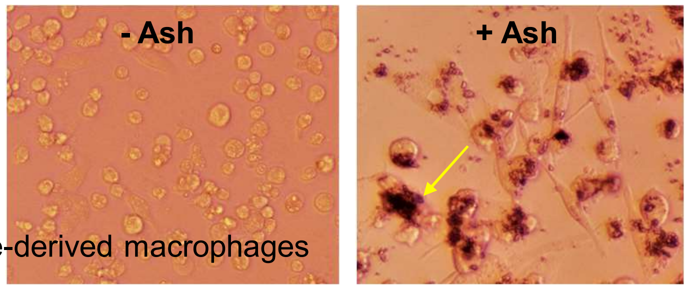
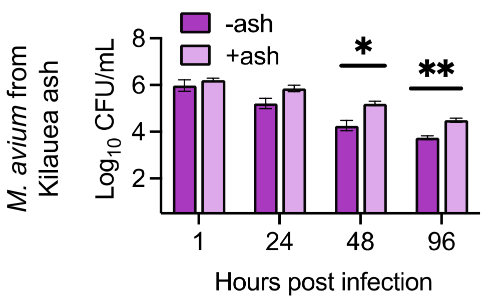
NTM, volcanic ash, and the inflammasome

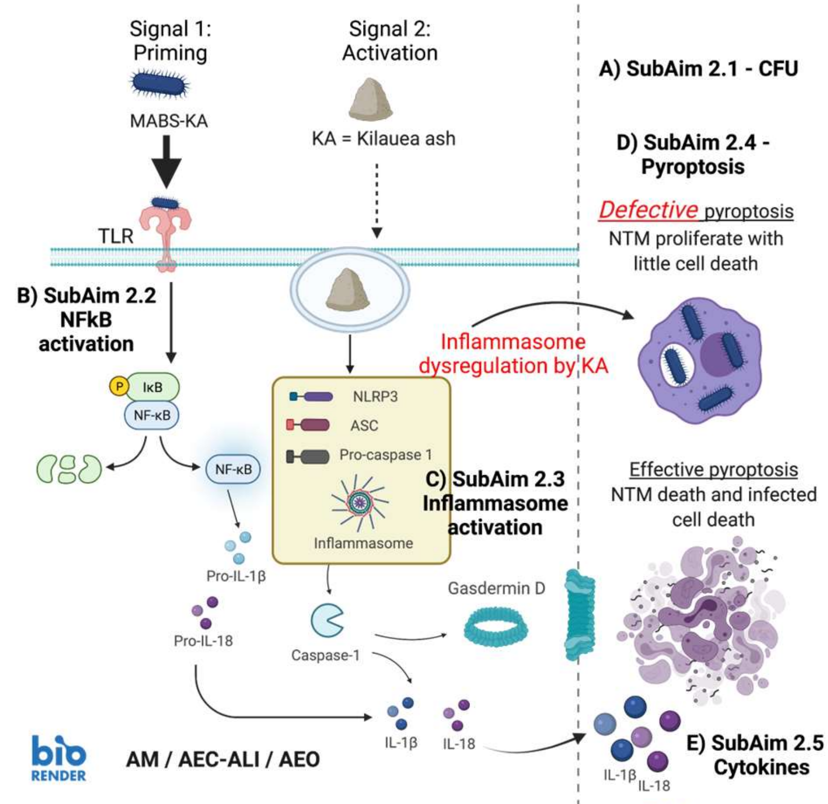


Monocyte-derived macrophages



Alveolar macrophages (n=5 donors)

Air-liquid interface cultures (n=5 donors)

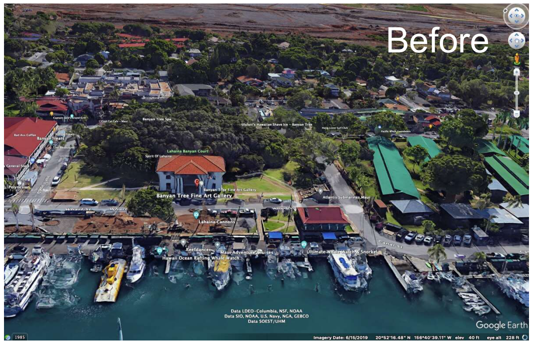


NTM and the Lāhainā wildfire

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.*

August 2023

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



February, 2024, Lāhainā

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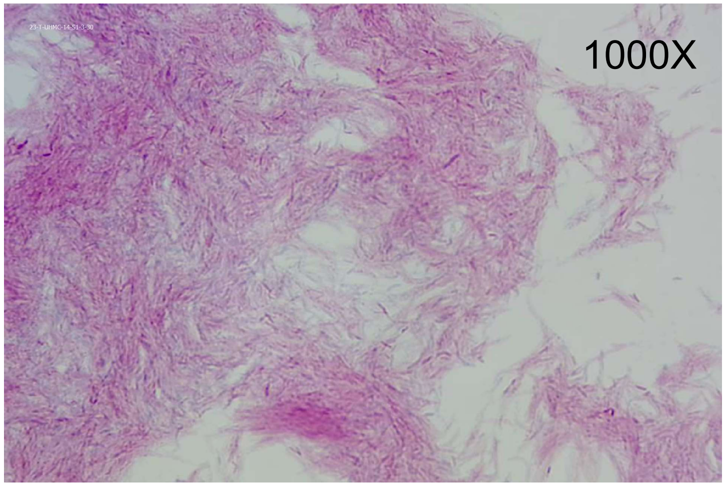
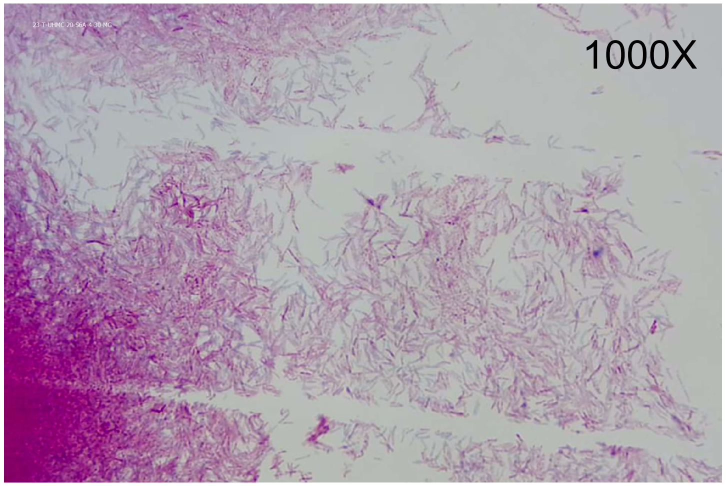
NTM and the Lāhainā wildfire

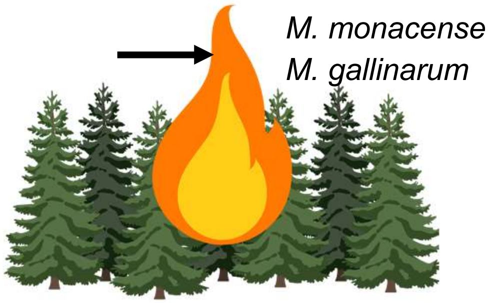
Soil and ash (burnt ground)
Non-household



Soil and ash (burnt ground)
Household



Wildfire ash, Kansas



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Outline

- NTM microbiology and historical niches
- What's new? Studies on environmental features that may impact NTM
- What's new? How to reduce exposures
- What's new? NTM in the hot spot of Hawai'i
  - Diversity and preferred niches
  - Volcanos
  - Wildfires
- The future – How climate change may impact environmental NTM distribution.

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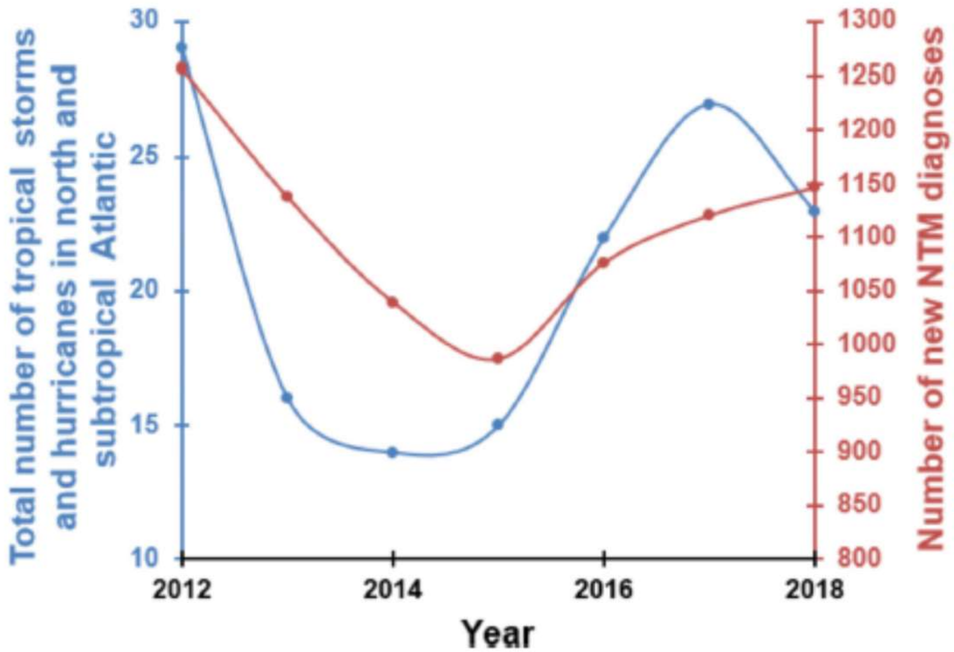
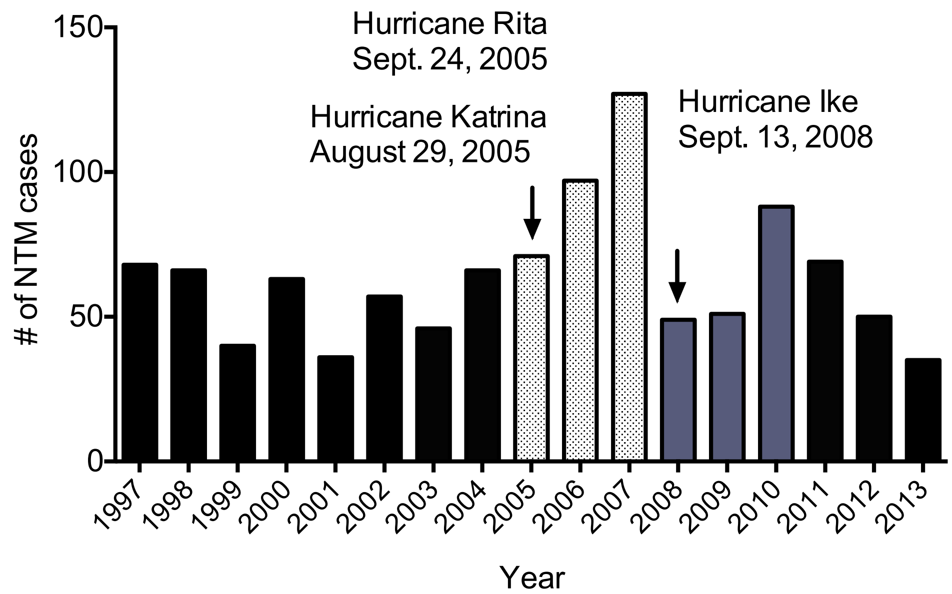
In addition to volcanic eruptions and wildfires…..

Tropical storms



Hurricanes



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

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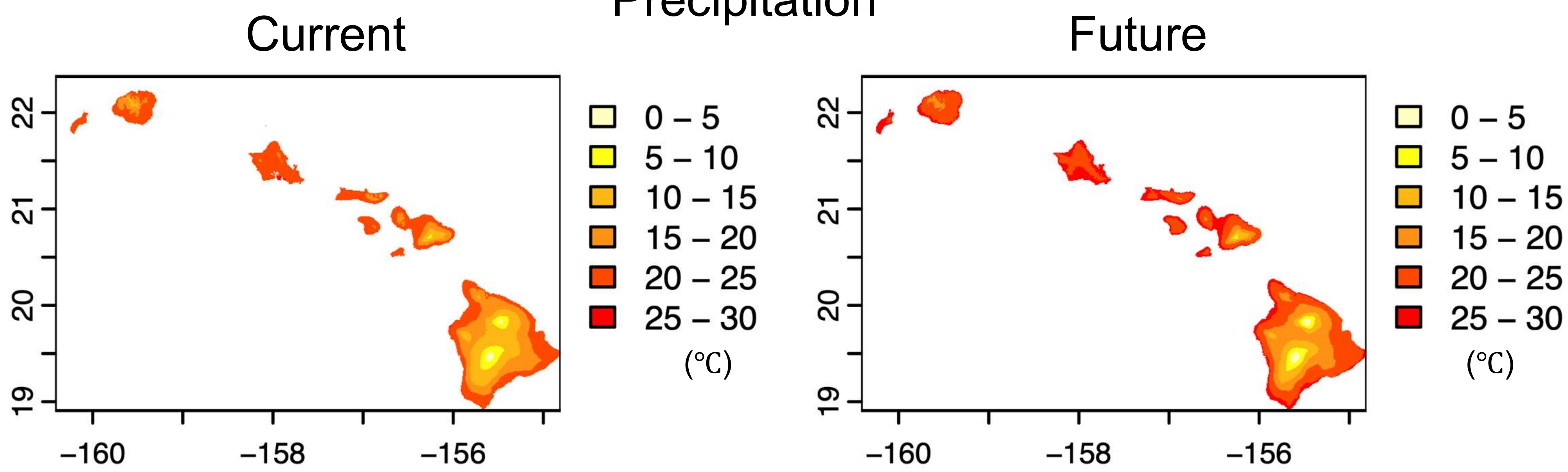
Our environments will likely get warmer

Precipitation



Ecological niche modeling

Unpublished
** Joshua Banta, PhD, University of Texas Health Science Center at Tyler
Jim Crooks, PhD, National Jewish Health

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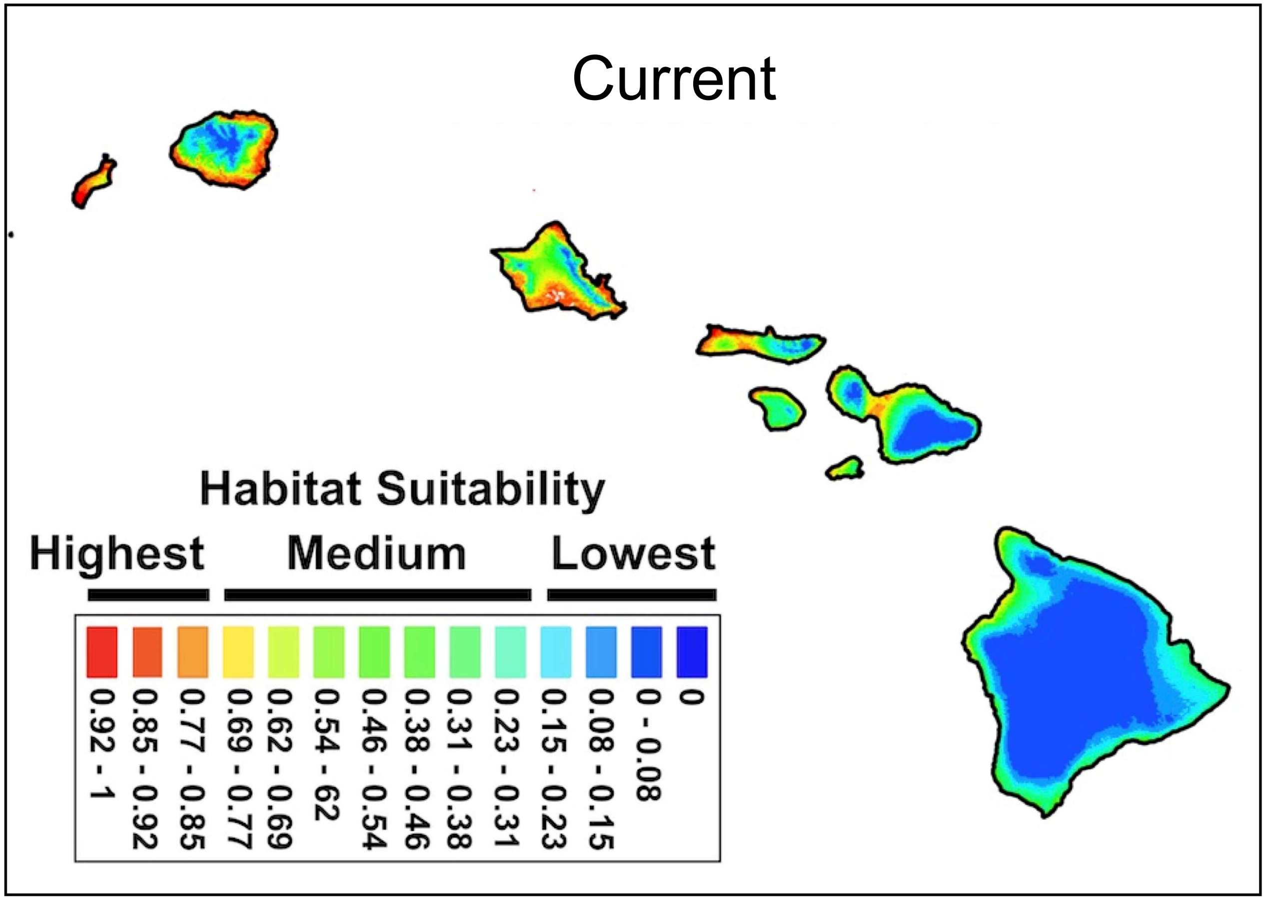
M. abscessus in Hawai'i



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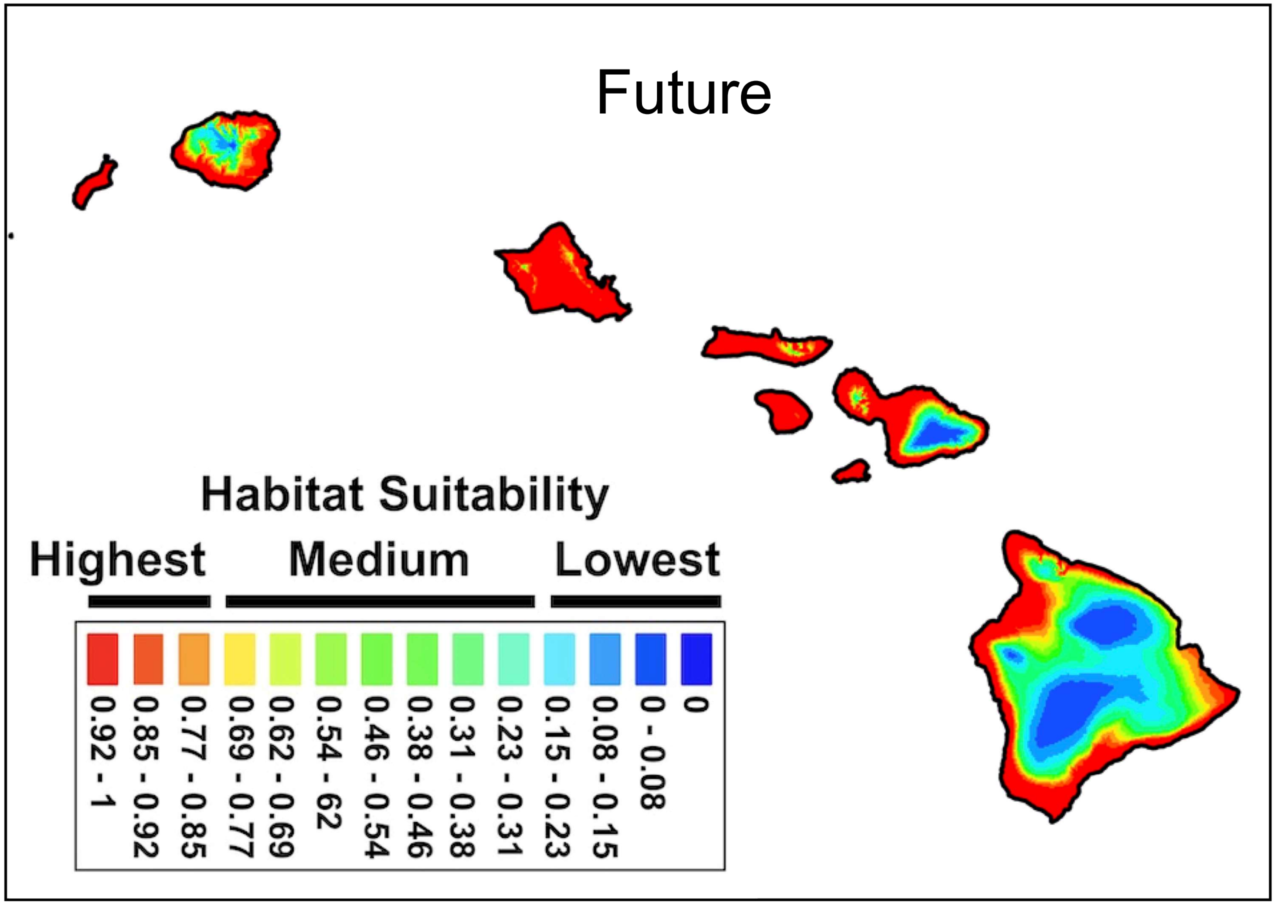
M. abscessus in Hawai'i



Future climate data from the years 2041 - 2070 based on the IPSL-CM6A-LR climate model and a shared socioeconomic pathway

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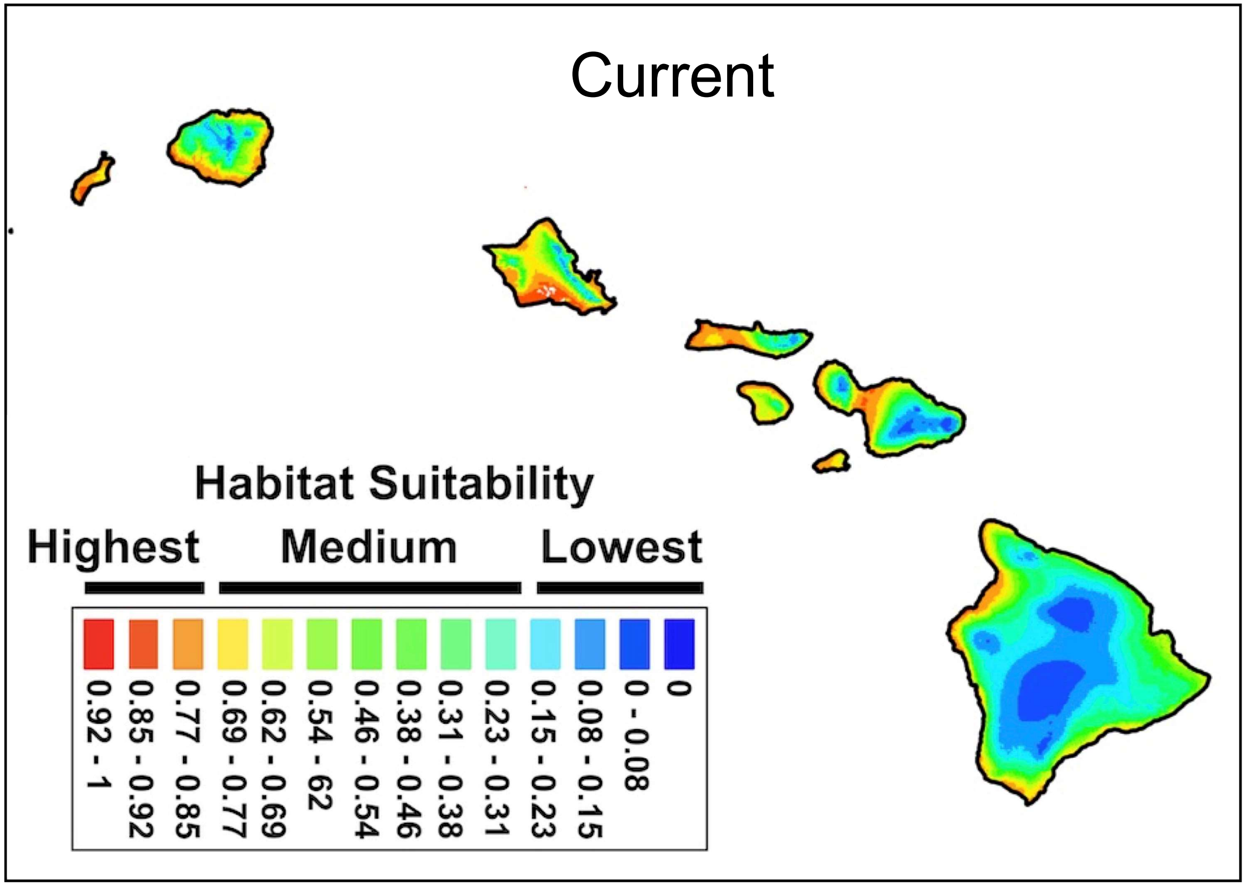
M. gordonae in Hawai'i



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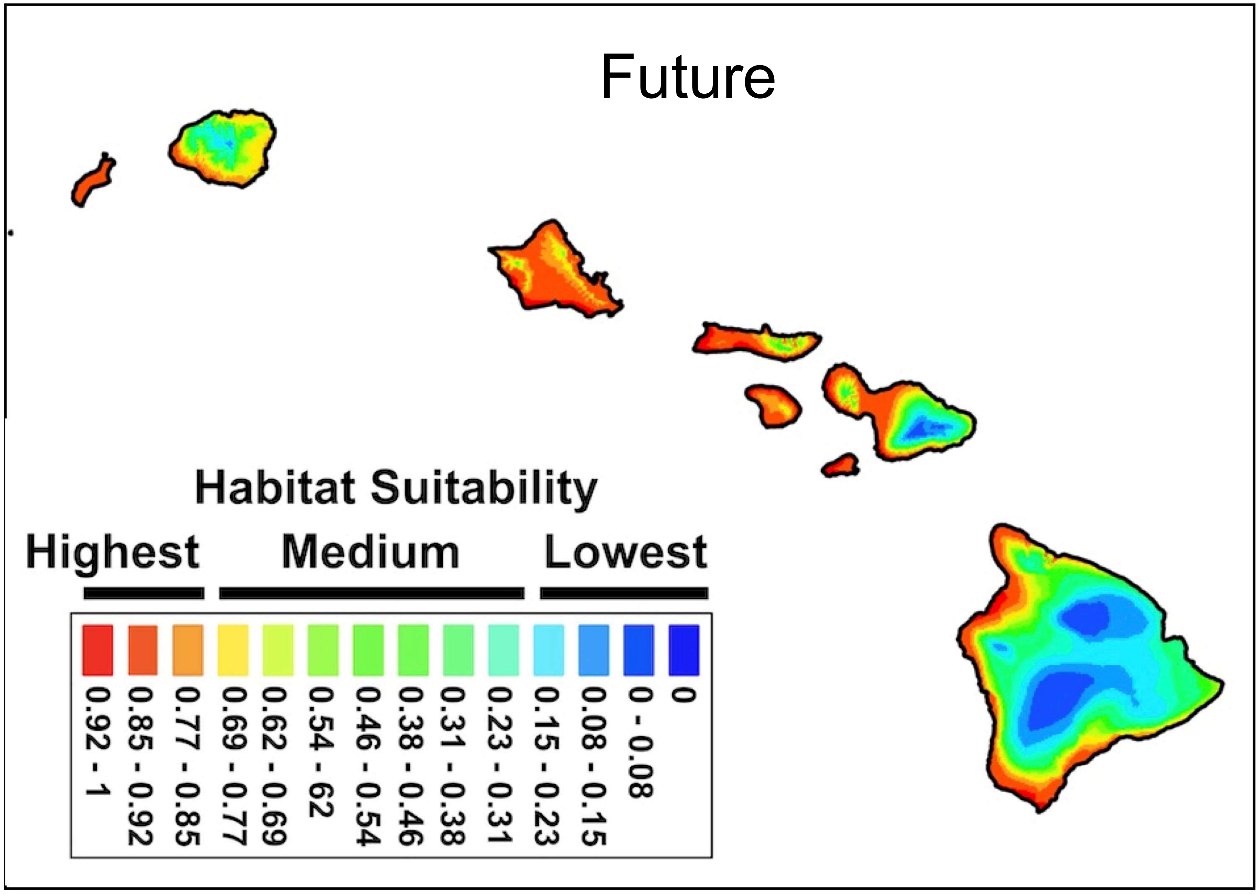
M. gordonae in Hawai'i



Future climate data from the years 2041 - 2070 based on the IPSL-CM6A-LR climate model and a shared socioeconomic pathway

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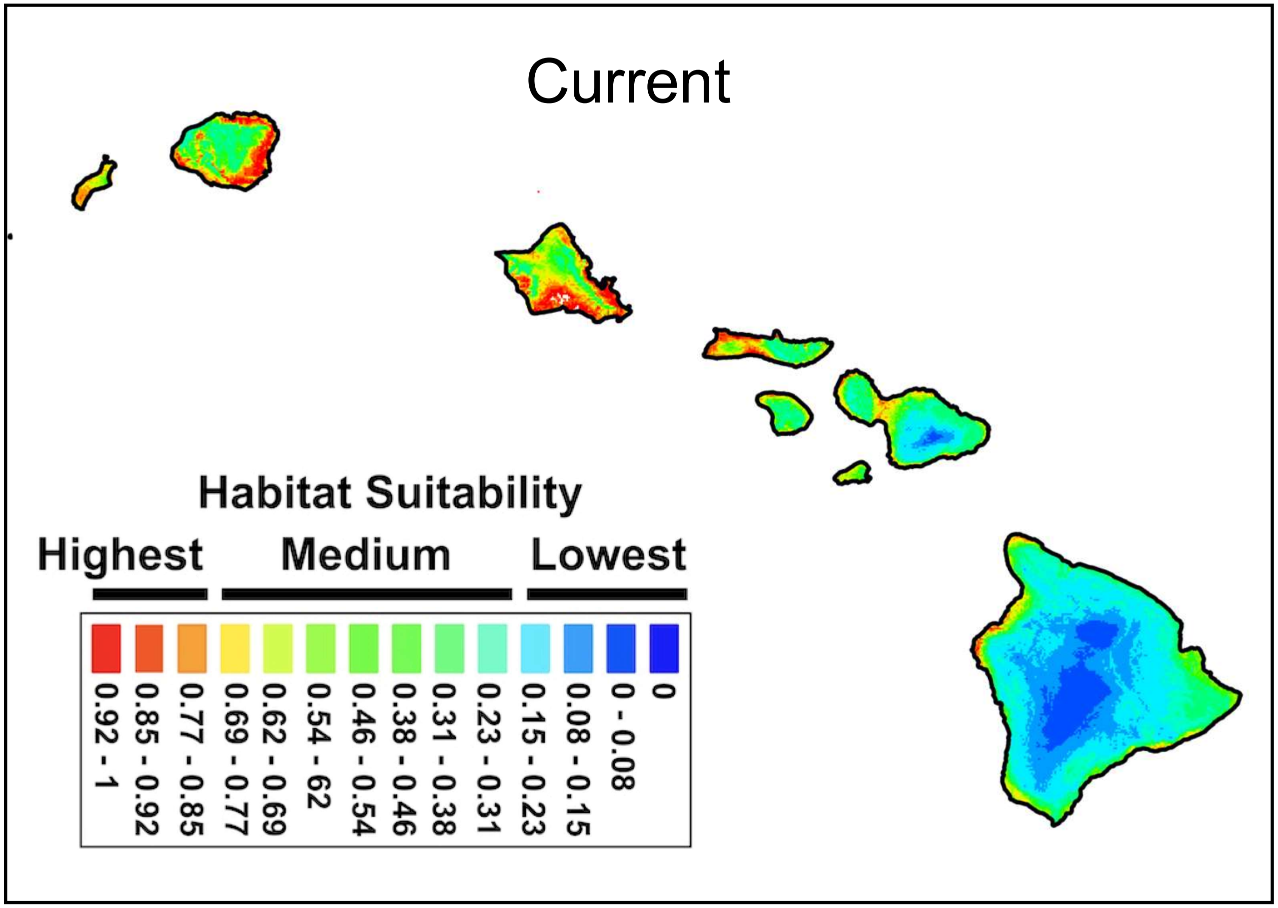
M. chelonae in Hawai'i



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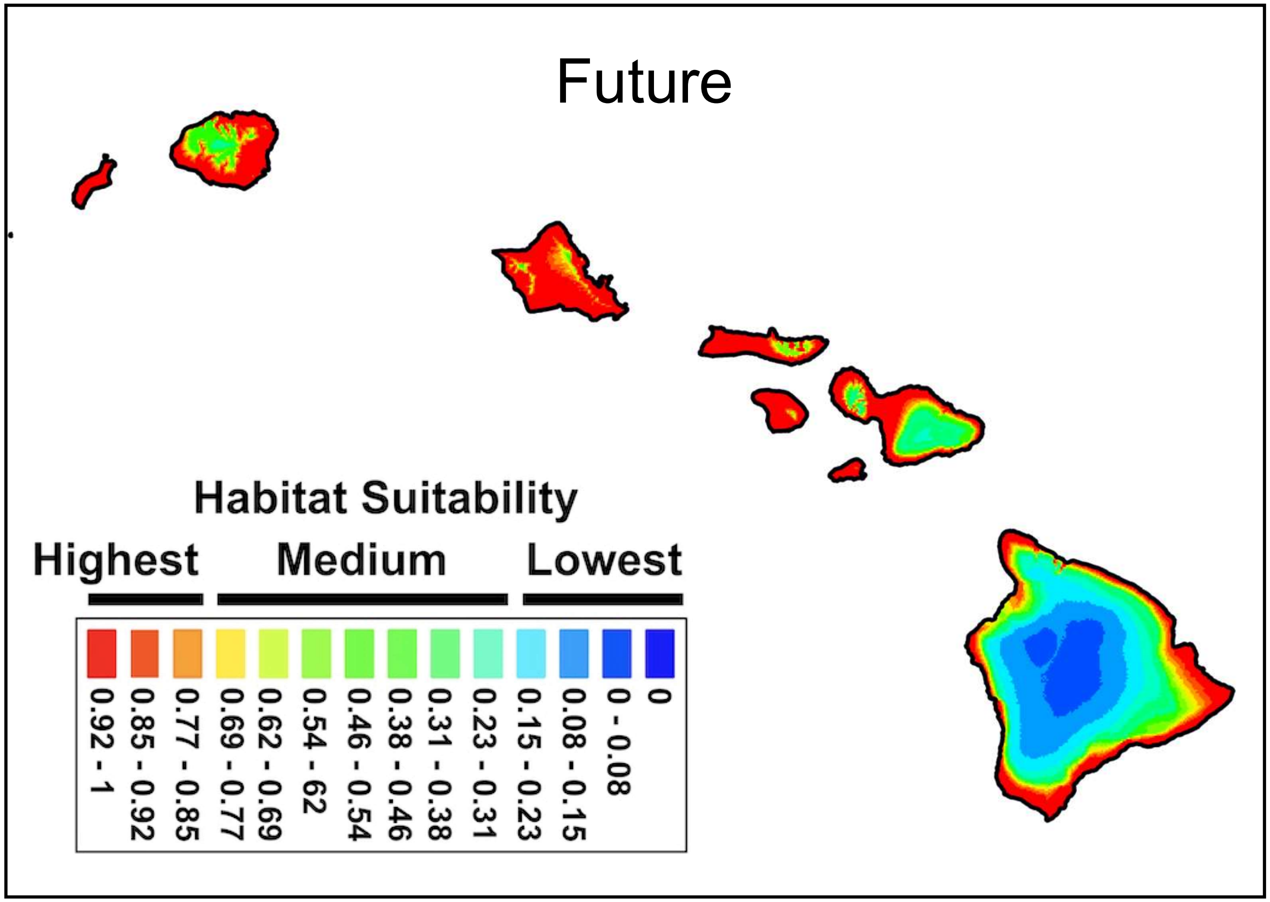
M. chelonae in Hawai'i



Future climate data from the years 2041 - 2070 based on the IPSL-CM6A-LR climate model and a shared socioeconomic pathway

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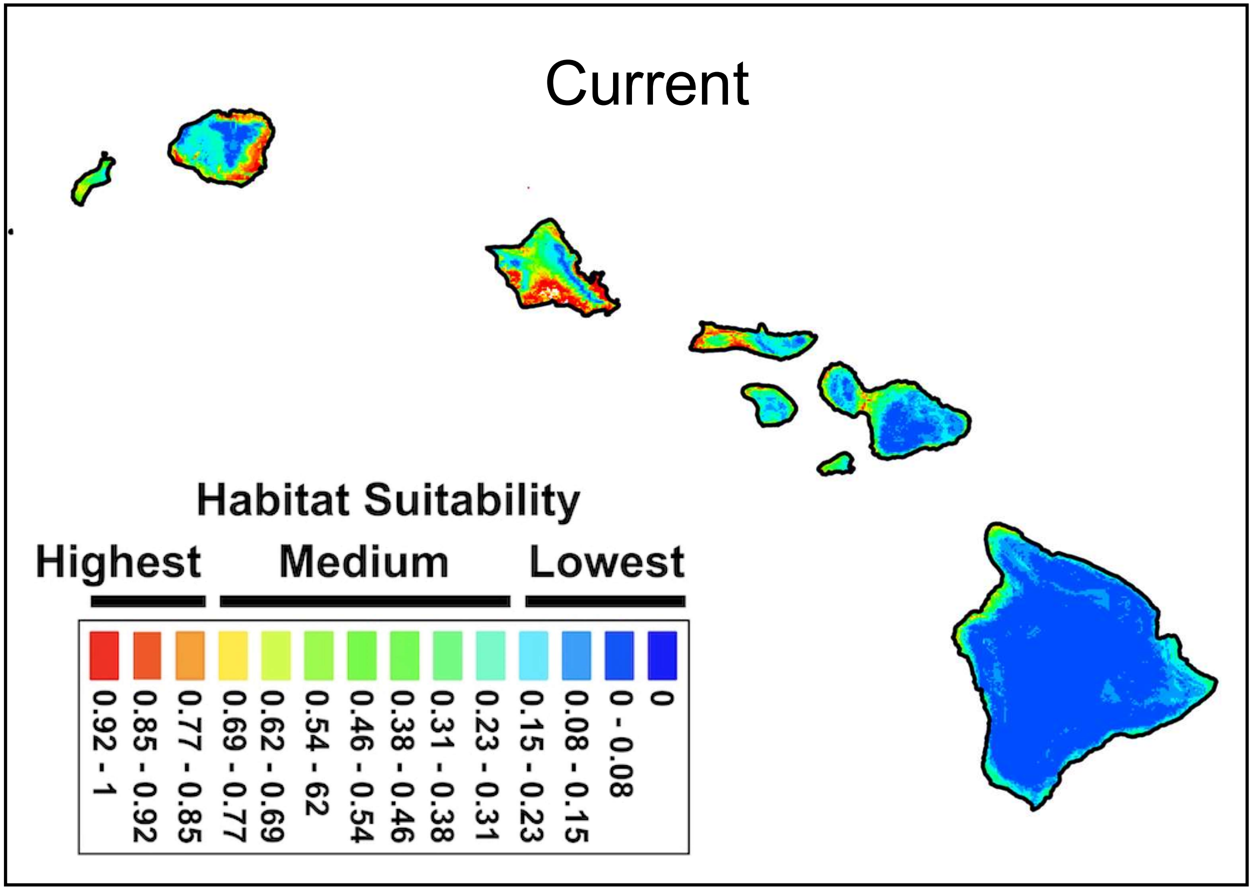
M. chimaera in Hawai'i



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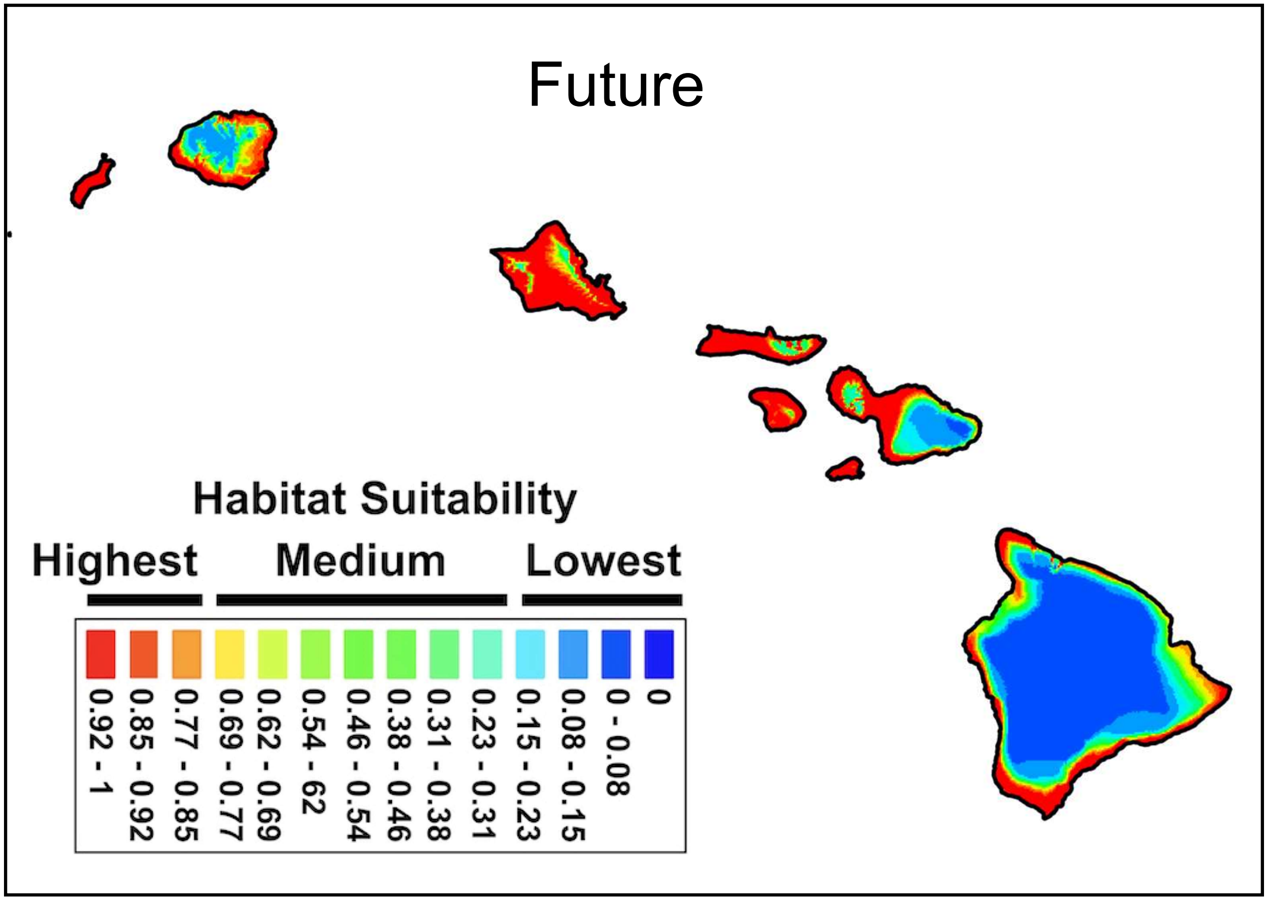
M. chimaera in Hawai'i



Future climate data from the years 2041 - 2070 based on the IPSL-CM6A-LR climate model and a shared socioeconomic pathway

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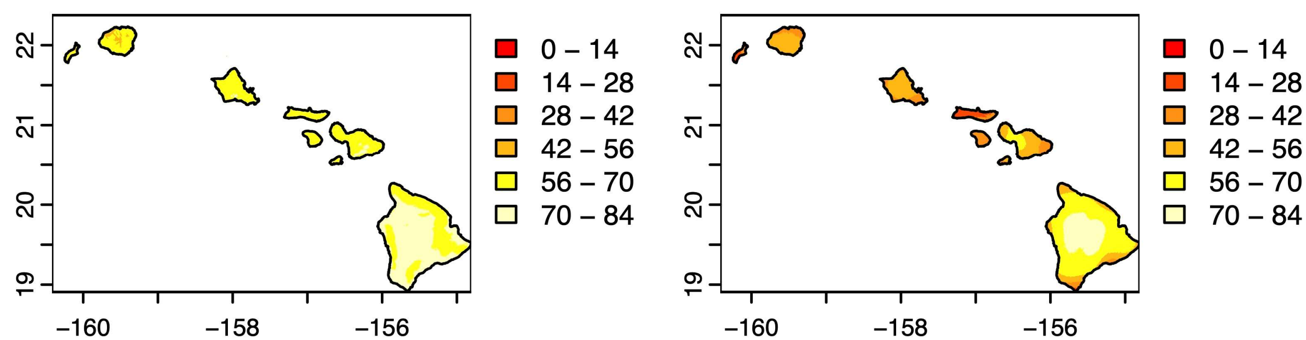
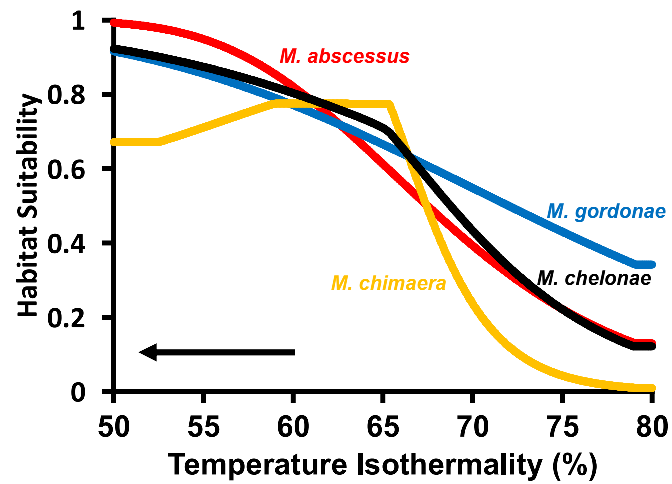
Predicted tolerance of *M. chimaera* to future increases in nighttime temperatures

Current

Future



Warmer colors = warmer nights relative to days
(less isothermality)



How large the day to night temperatures oscillate relative to summer-to winter

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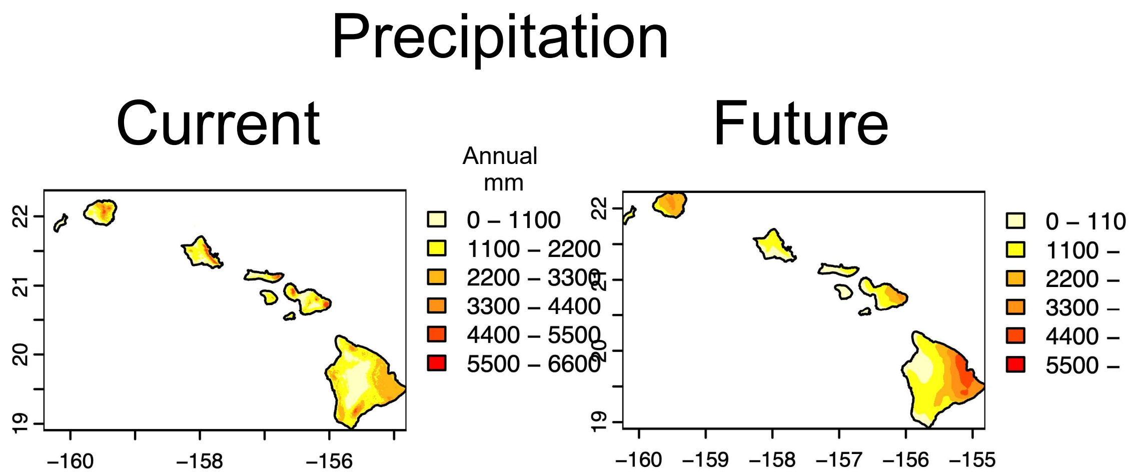
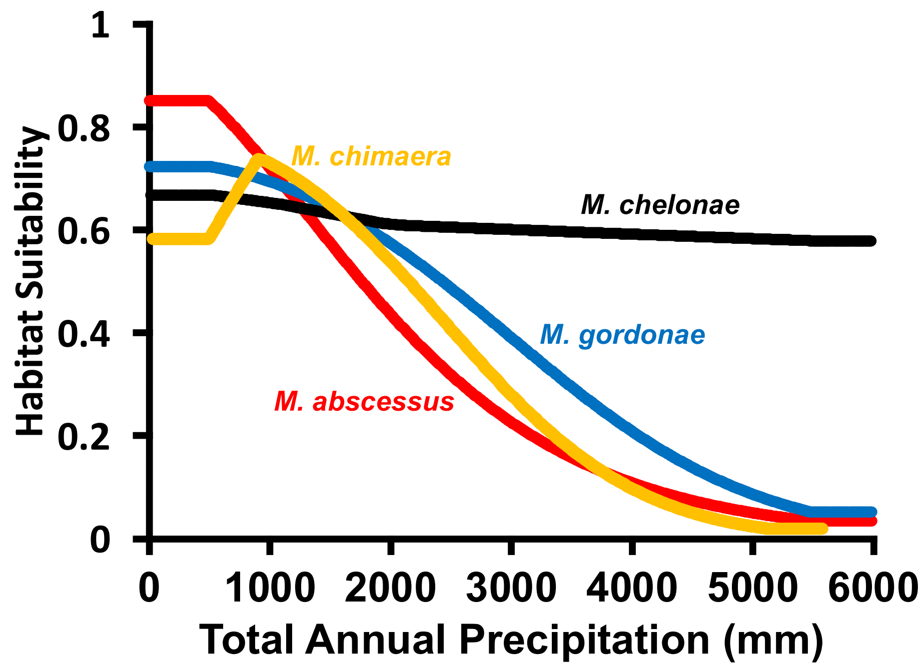
Colonization of *M. chelonae* across areas with wide ranges of precipitation





Among people with CF in FL: Precipitation and NTM
(Foote, *et al.*, PloS One, 2021)

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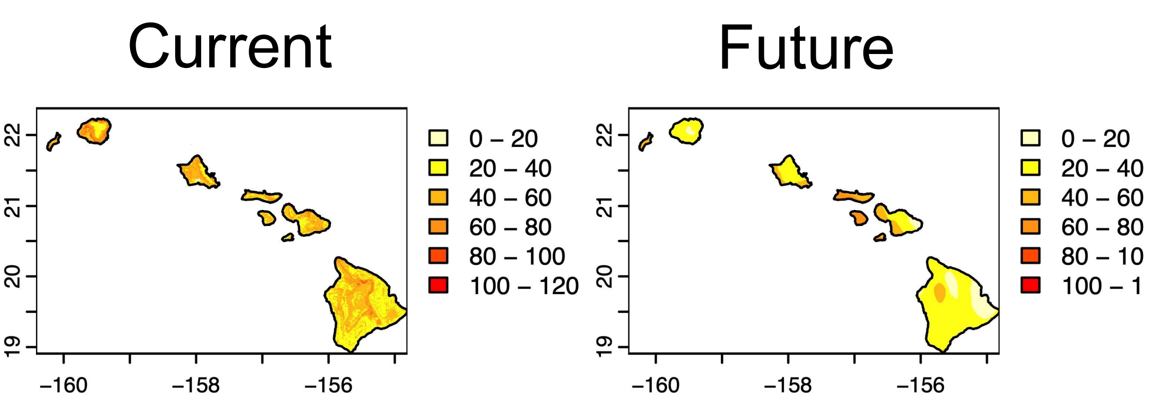
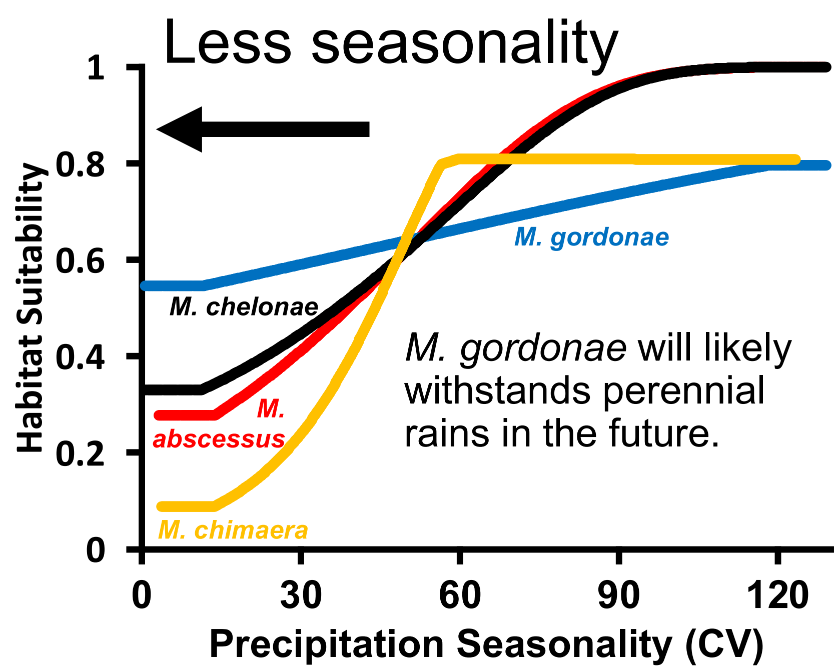
Precipitation will become less seasonal and more perennial in the future, impacting NTM



Warmer colors = more seasonal precipitation



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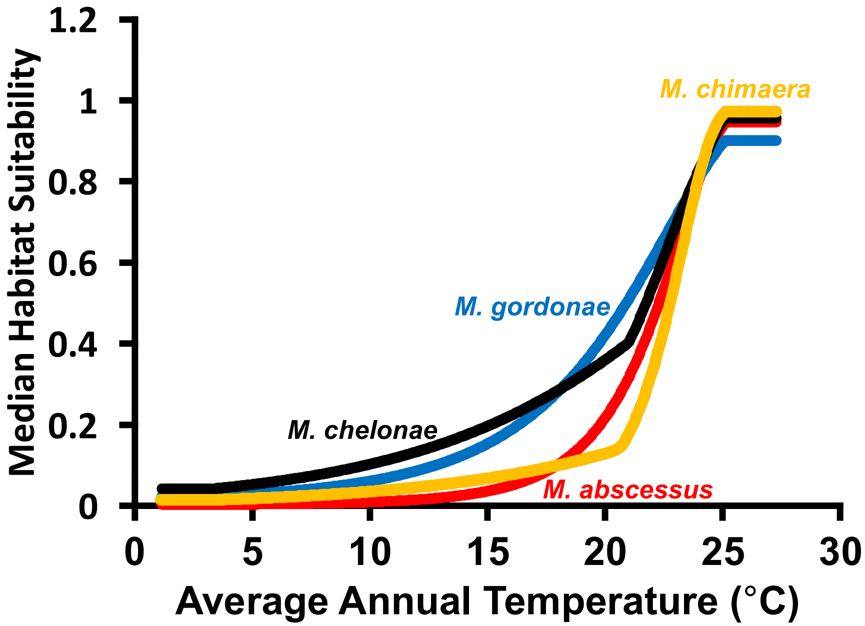
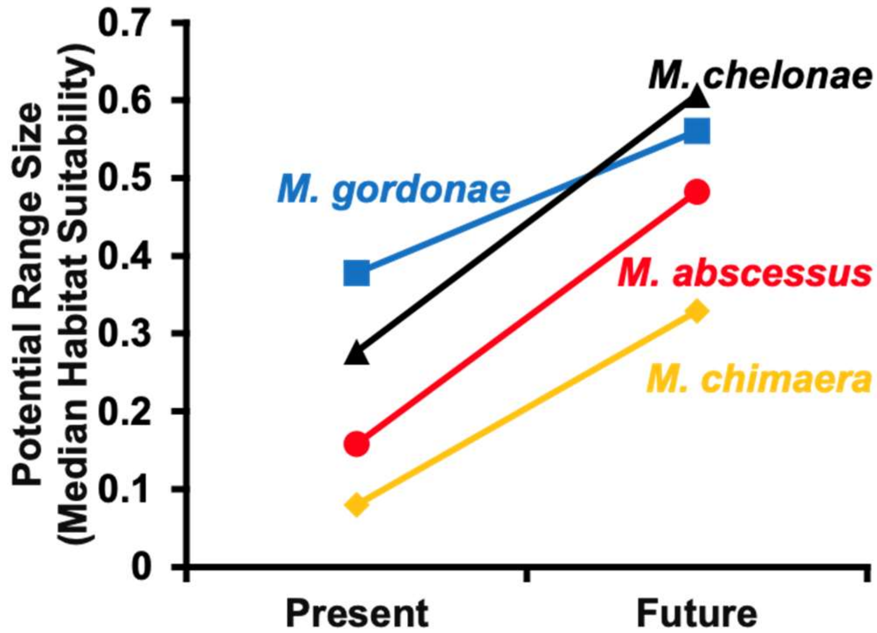
Emergence of NTM under future climates

M. chimaera will thrive in hotter climates.



Greater NTM emergence under future climates.



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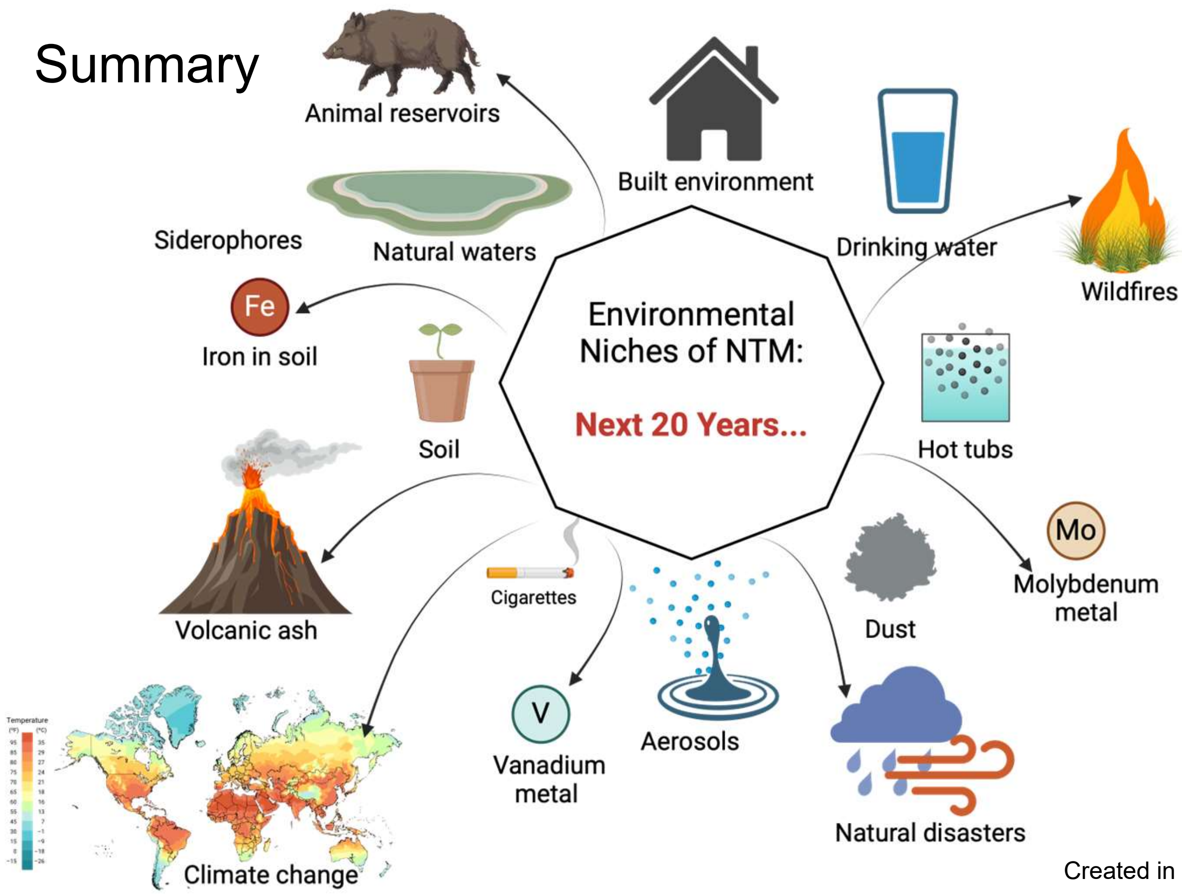
Conclusions

Summary



Created in BioRender

Future directions

"We predict an increasing incidence of interactions between humans and mycobacteria in the coming years.

↓

Climate changes may be increasingly recognized pressures for the emergence of environmentally acquired NTM.

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"Flat Stanley" Travels with our "Flat Stanley"

Ho'okipa Beach Park , Maui

Waipuilani Park, Maui

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