ENVIRONMENTAL SOURCES OF NTM & REDUCING EXPOSURE

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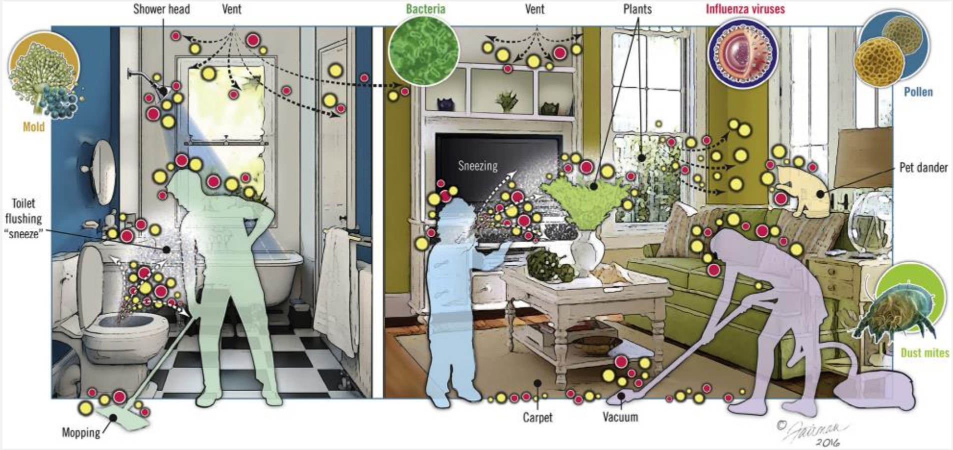
DISCLOSURES

- Advisory boards- Insmed, Savara
- Clinical trials – Insmed, Aradigm, BMS, Savara, ResTORbio, Zambon
- CME talks - Menarini, GSK, AstraZeneca

INTRODUCTION

- Nontuberculous mycobacteria are ubiquitous in the environment.
- Household and hospital tap water, bathrooms, potting soil, and garden soil are infection sources identified by matching genotypic profiles of clinical and environmental isolates.
- Mycobacterial transmission routes include water, soil and cough aerosols

S110 M.K. Ijaz et al. / American Journal of Infection Control 44 (2016) S109-S120

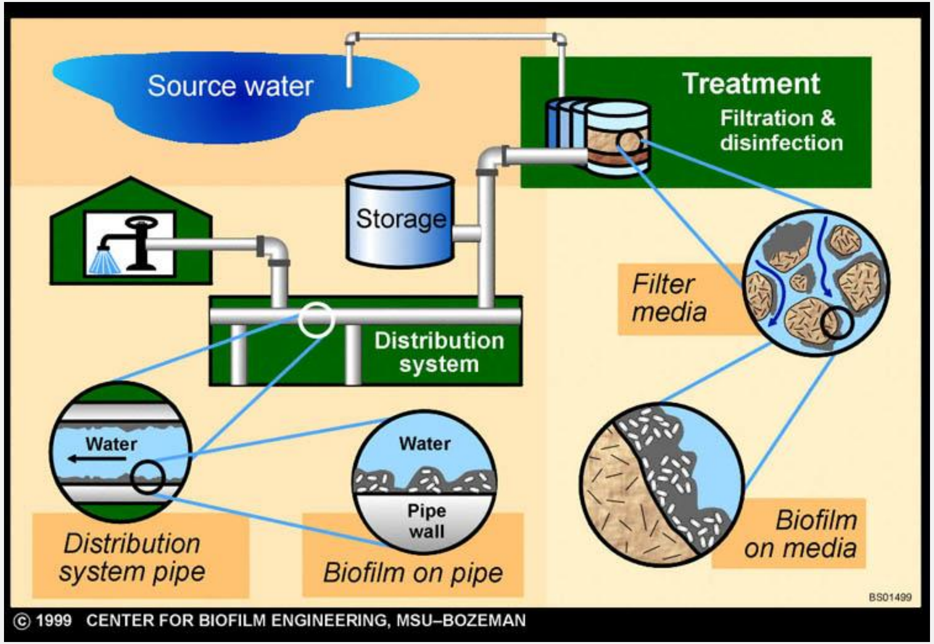


WATER

- Wide variety of NTM species identified in water samples – not all associated with disease
- Genotyping to match patient with water isolates
- Household/municipal water systems - ***M. avium, M. abscessus, M. kansasii, M. lentiflavum***
- Hospital water - ***M. porcinum, M. avium, M. abscessus, M. fortuitum, M. chimaera***

- not *M. intracellulare*

WHAT'S IN YOUR PIPES?



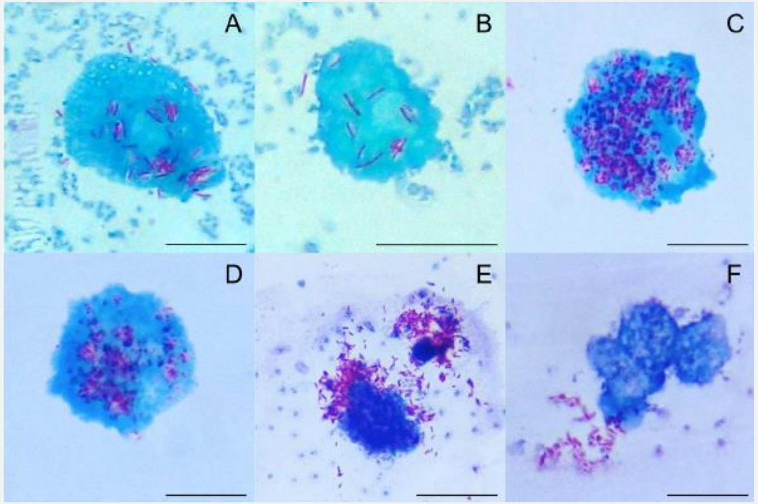
- organisms are many times more resistant to chlorine, chloramine, chlorine dioxide and ozone than other water borne micro-organisms such as *E. coli*.

- disinfection may contribute in part to the persistence of MAC, as competition for growth is lacking.

- significantly higher mycobacterial numbers in distribution samples (average 25000 fold) than those collected immediately downstream from treatment plant

NTM SURVIVE WITHIN AMOEBAE

- vehicle for replication and transmission
- enhanced virulence

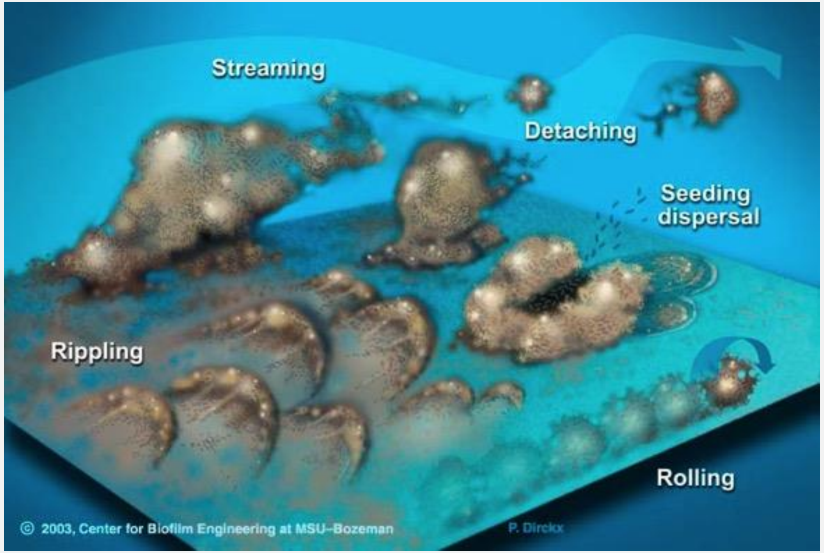


A,B Acanthomoeba spp
C,D Protacanthomoeba bohemica
E.F Vermamoeba vermiformis

Delafont Environ Sci Technol 2014

RELEASE FROM BIOFILMS

- **Transient pressure events**
- Rapid changes in water flow rate – increase the concentrations of bacteria in water.
- This occurs when we turn taps on and off
- Greater in smaller diameter pipes

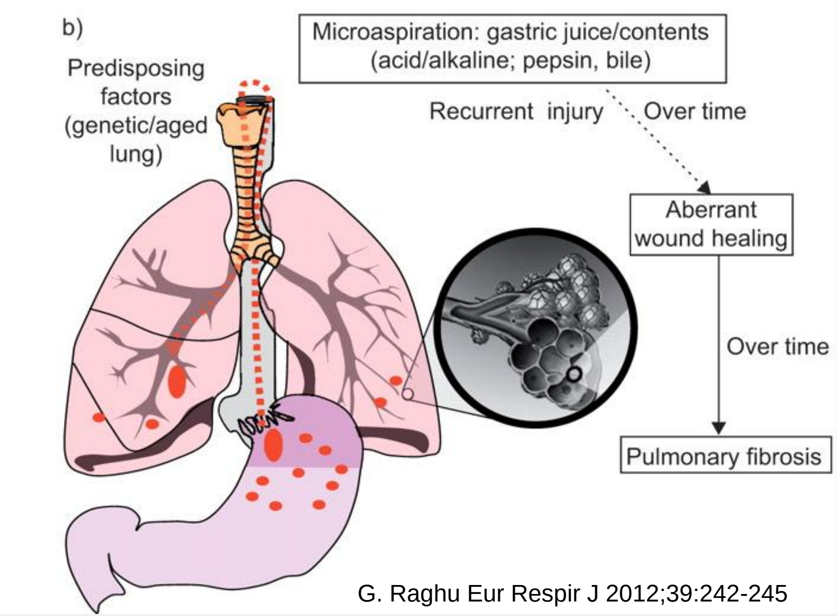


POINT OF USE CONNECTIONS

- POU connections and treatment devices promote biofilm formation, and amplify numbers of mycobacteria.

ASPIRATION OR INHALATION ?

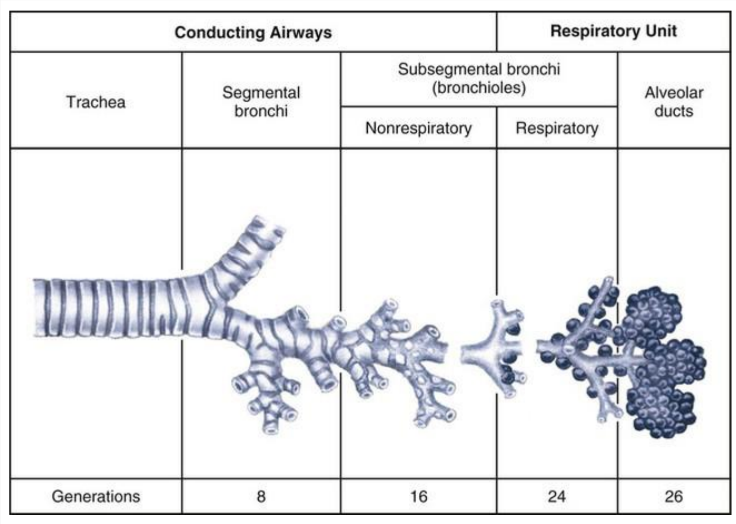
- Several studies associating NTM disease with GORD
- Deposition of relatively few mycobacteria can infect the host –2 to 3 bacteria, up to 50
- Aspiration of upper respiratory tract bacteria into the lungs -~̈ 50% of normal hosts during sleep
- 15.5% patients with MAC aspiration was a clinical problem



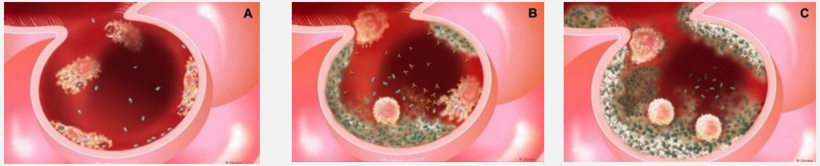
G. Raghu Eur Respir J 2012;39:242-245

Thomson *Chest* **2007**, *131*, 1166 - 1172.

AEROSOLS



- Mycobacteria can be aerosolized from natural waters and transferred from seawater to air by natural processes.
- **Aerosolisation-1000 fold increase** in the numbers of viable mycobacterial cells per ml of water
- Mycobacteria in natural aerosols found in particles and **droplets of a respirable size (ie <5μm**)



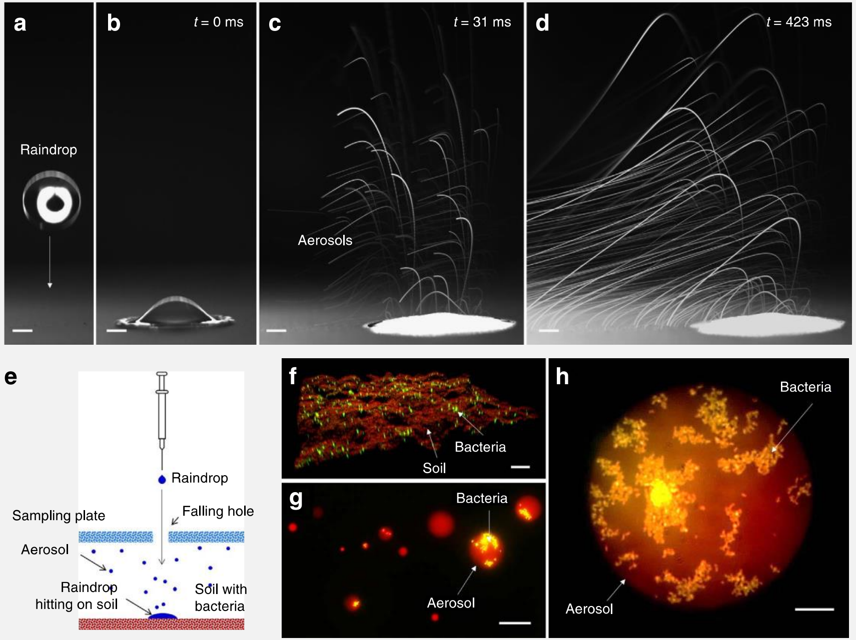
AEROSOLS

- Hypersensitivity pneumonitis – use of hot tubs, ***M. avium***
- reported in lifeguards and pool attendants, who worked in an indoor swimming pool that featured waterfalls and sprays.
- following disinfection of metalworking fluid ***M. immunogenum***

App Env Micro 2004;70:4906-10

BIOAEROSOL GENERATION BY RAINDROPS ON SOIL

- bioaerosols -aerosols containing microbes
- after a rainfall - rapid increase of bioaerosol concentration in the air
- hundreds of aerosols are generated from a single raindrop within a few microseconds
- estimate number of bacteria that can be transferred by aerosol as a function of soil type, bacterial surface density, rainfall velocity and soil surface temperature.



Bioaerosols transported by wind to other places much faster than other modes of transfer

NATURE COMMUNICATIONS | 8:14668 | DOI: 10.1038/ncomms14668 | www.nature.com/naturecommunications

SHOWERHEADS

- Culture-independent technology (rRNA **gene sequences**)
- Sequences representative of **nontuberculous mycobacteria (NTM)** and other opportunistic human pathogens are **enriched to high levels in many showerhead biofilms**, >100-fold above background water contents.

Feazel *PNAS* 2009, *106*, 16393-16399.

Journal of Clinical Microbiology

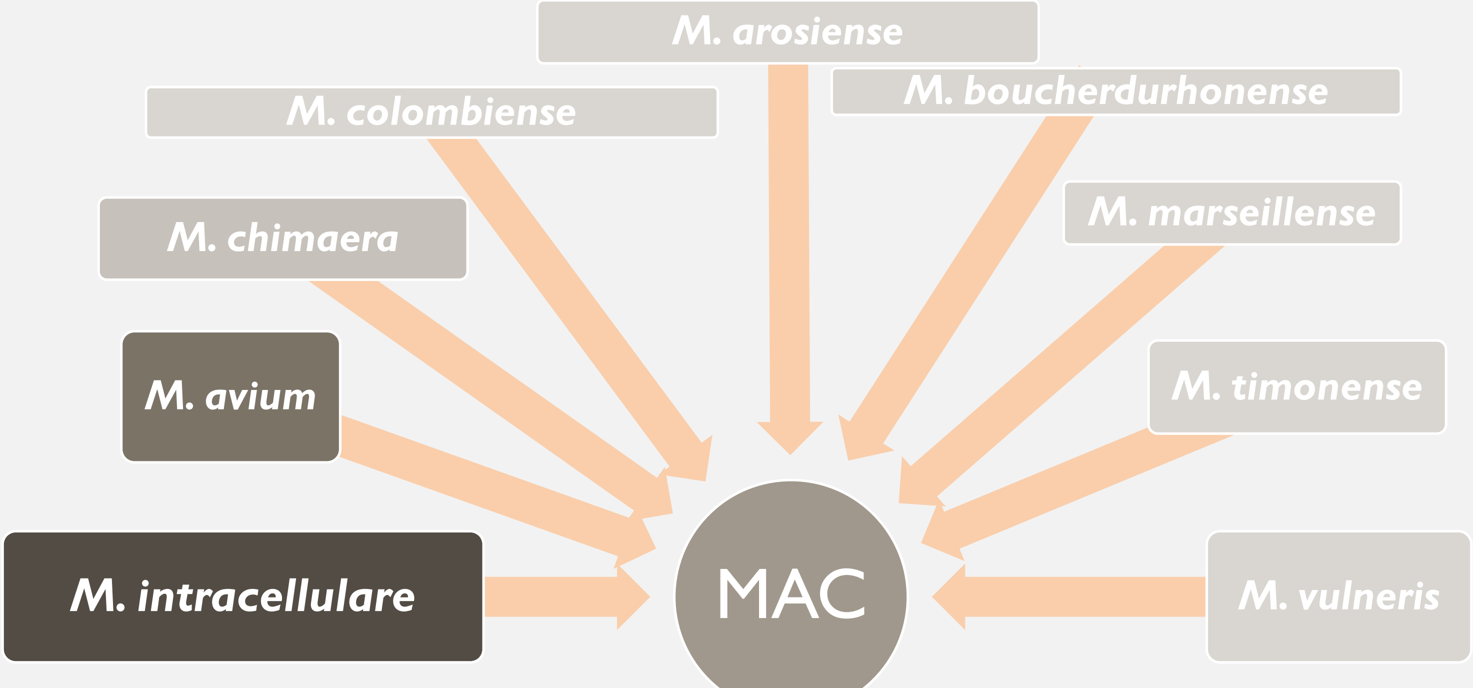
Isolation of Nontuberculous Mycobacteria (NTM) from Household Water and Shower Aerosols in Patients with Pulmonary Disease Caused by NTM

Rachel Thomson, Carla Tolson, Robyn Carter, Chris Coulter, Flavia Huygens and Megan Hargreaves
***J. Clin. Microbiol.* 2013, 51(9):3006. DOI: 10.1128/JCM.00899-13.**
Published Ahead of Print 10 July 2013.

- NTM grown from shower aerosols: *M. avium, M. abscessus, M. kansasii*

Absence of *Mycobacterium intracellulare* and Presence of *Mycobacterium chimaera* in Household Water and Biofilm Samples of Patients in the United States with *Mycobacterium avium* Complex Respiratory Disease

Richard J. Wallace, Jr.,[a] Elena Iakhiaeva,[a] Myra D. Williams,[b] Barbara A. Brown-Elliott,[a] Sruthi Vasireddy,[a] Ravikiran Vasireddy,[a] Leah Lande,[c,d] Donald D. Peterson,[c,d] Janet Sawicki,[d] Rebecca Kwait,[c] Wellington S. Tichenor,[e] Christine Turenne,[f] Joseph O. Falkinham III[b]

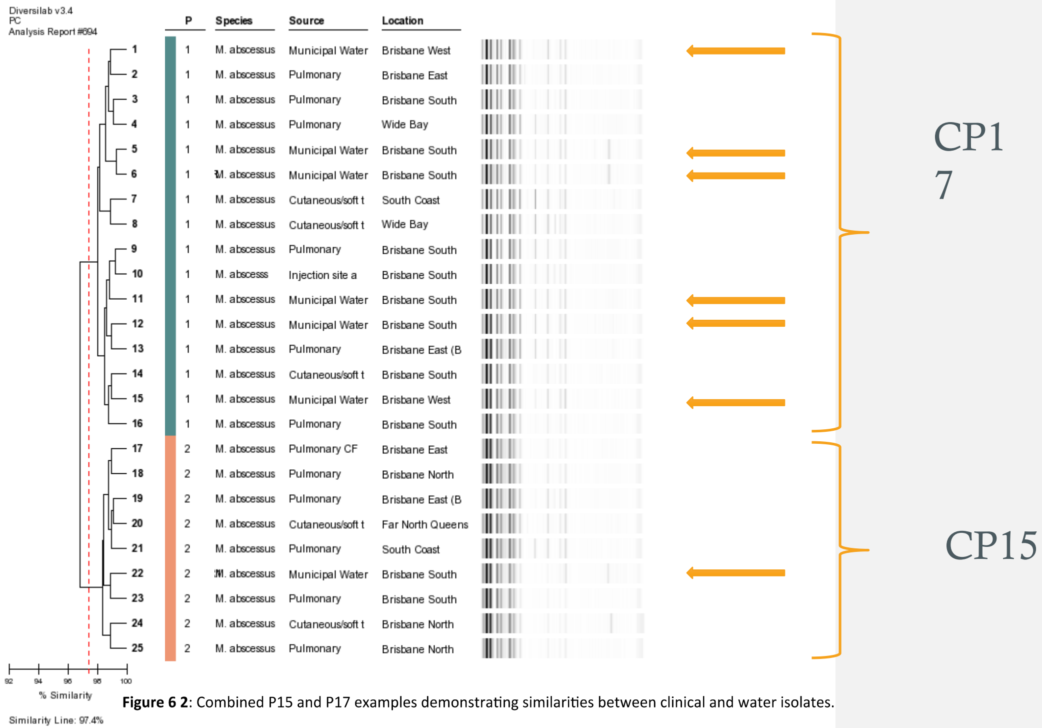


Genotyping of *Mycobacterium avium* complex organisms using multispacer sequence typing

Caroline Cayrou, Christine Turenne, Marcel A. Behr and Michel Drancourt

Microbiology (2010), 156, 687–694

GENOTYPIC MATCHING OF CLINICAL AND ENVIRONMENTAL ISOLATES



#	P	Species	Source	Location
1	1	M. abscessus	Municipal Water	Brisbane West
2	1	M. abscessus	Pulmonary	Brisbane East
3	1	M. abscessus	Pulmonary	Brisbane South
4	1	M. abscessus	Pulmonary	Wide Bay
5	1	M. abscessus	Municipal Water	Brisbane South
6	1	M. abscessus	Municipal Water	Brisbane South
7	1	M. abscessus	Cutaneous/soft t	South Coast
8	1	M. abscessus	Cutaneous/soft t	Wide Bay
9	1	M. abscessus	Pulmonary	Brisbane South
10	1	M. abscesss	Injection site a	Brisbane South
11	1	M. abscessus	Municipal Water	Brisbane South
12	1	M. abscessus	Municipal Water	Brisbane South
13	1	M. abscessus	Pulmonary	Brisbane East (B
14	1	M. abscessus	Cutaneous/soft t	Brisbane South
15	1	M. abscessus	Municipal Water	Brisbane West
16	1	M. abscessus	Pulmonary	Brisbane South
17	2	M. abscessus	Pulmonary CF	Brisbane East
18	2	M. abscessus	Pulmonary	Brisbane North
19	2	M. abscessus	Pulmonary	Brisbane East (B
20	2	M. abscessus	Cutaneous/soft t	Far North Queens
21	2	M. abscessus	Pulmonary	South Coast
22	2	M. abscessus	Municipal Water	Brisbane South
23	2	M. abscessus	Pulmonary	Brisbane South
24	2	M. abscessus	Cutaneous/soft t	Brisbane North
25	2	M. abscessus	Pulmonary	Brisbane North

Figure 6 2: Combined P15 and P17 examples demonstrating similarities between clinical and water isolates.

Thomson *et al. BMC Infectious Diseases* 2013, **13**:241
http://www.biomedcentral.com/1471-2334/13/241

BMC Infectious Diseases

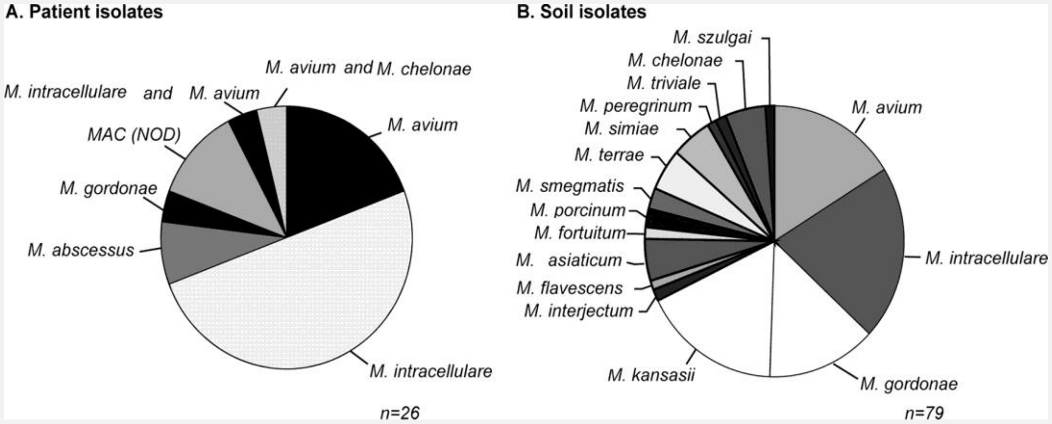
SOIL

TABLE 2.

Species isolated from soil	Mycobacterial species isolated from pulmonary MAC patients: *M. avium* (*n* = 67)	*M. intracellulare* (*n* = 26)	*M. avium* + *M. intracellulare* (*n* = 7)	p value
MAC	36 (53.7)[a]	10 (38.5)[a]	4 (57.1)	0.38
M. avium	23 (34.3)	4 (15.4)	1 (14.3)	0.19
M. intracellulare	17 (25.3)	7 (26.9)	3 (42.9)	0.36

Data show number (%) of samples positive for MAC strains.
[a]Both *M. avium* and *M. intracellulare* were detected in four soil samples from the residences of patients infected with *M. avium* and in one soil sample from the residence of a patient infected with *M. intracellulare*.

Fujita, K et al. *Clinical Microbiology and Infection* **2012**



De Groote, M. A. et al. 2006. Appl. Environ. Microbiol. 72(12):7602-7606

NTM grown from aerosols generated by pouring of potting mix and soil samples from patient homes (not speciated)

At least 3 studies that have correlated soil exposure with NTM risk

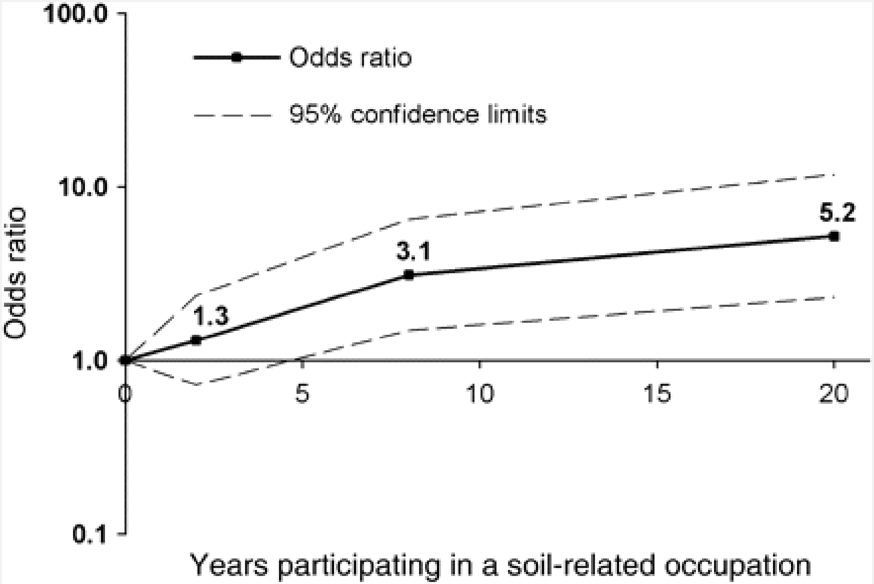
ENVIRONMENTAL RISK FACTORS FOR INFECTION WITH MYCOBACTERIUM AVIUM COMPLEX

Soil exposure						
Soil occupation, any	94/147	83/186	53.1	2.2	1.4, 3.4	<0.01
None	53/147	103/186	34.0	1.0		
Farm planting, ever‡	55/146	41/185	57.3	2.6	1.5, 4.4	<0.01
Farm truck driver, ever†,‡	33/139	25/172	56.9	2.6	1.4, 4.8	<0.01
Lawn/landscape service, ever‡	34/146	28/186	54.8	2.4	1.3, 4.3	<0.01
Other soil occupations, ever‡	33/145	26/185	55.9	2.5	1.3, 4.5	<0.01

Water exposures						
Shower/bath >once/day	59/147	63/186	48.4	1.3	0.8, 2.0	0.24
Does dishes by hand >once/day	42/123	56/145	42.9	0.8	0.5, 1.4	0.45
Drinks bottled water >once/day	28/136	38/163	42.4	0.9	0.5, 1.5	0.57
Ever swims, any	107/147	145/186	42.5	0.8	0.5, 1.6	0.28
Ever, pool	73/141	109/183	40.1	0.7	0.5, 1.1	0.16
Ever, lake	31/138	48/179	39.2	0.8	0.5, 1.6	0.37
Ever, ocean	91/144	119/181	43.3	0.9	0.6, 1.4	0.63

Reed C Am. J. Epidemiol. **2006**, 164, 32-40.

ENVIRONMENTAL RISK FACTORS FOR INFECTION WITH *MYCOBACTERIUM AVIUM* COMPLEX



Reed C Am. J. Epidemiol. **2006**, 164, 32-40.

HOUSE-DUST

Dust particles are commonly suspended in the air

120 strains NTM isolated from vacuum cleaner dust collected in SE QLD

50 strains of *M. intracellulare* – 44% belonged to serotypes that were recognized as disease associated strains

Dawson MJA 1971

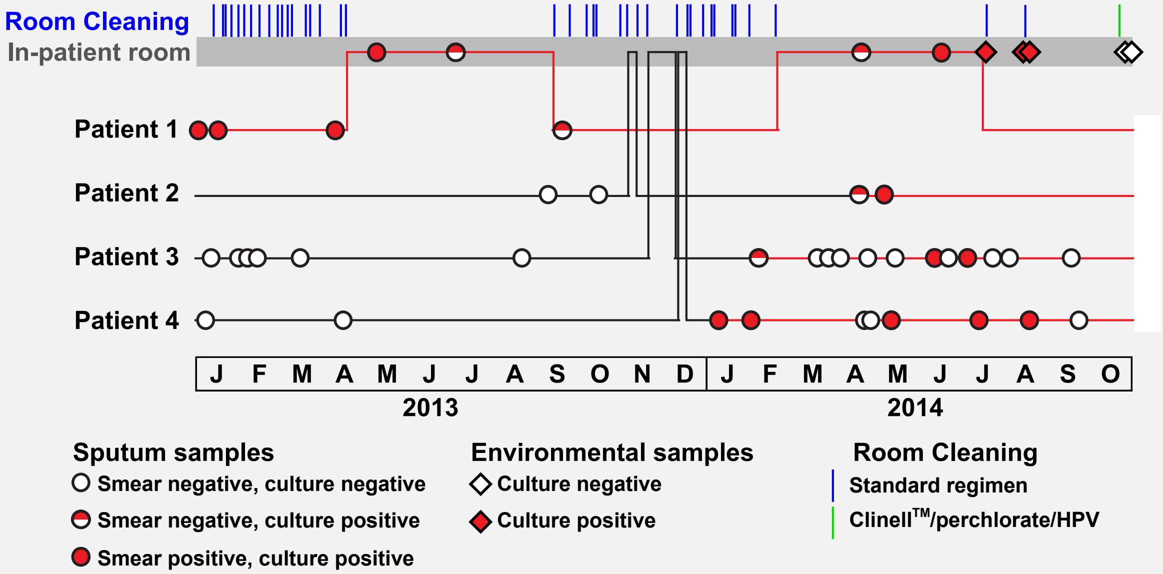
NTM IN HOUSE DUST

Mycobacterial species isolated from the dust samples. Combined data of the GLC and 16 S rDNA sequence analyses.

Species or groups	N	%
M. terrae complex (*M. noncromogenicum* or *M. arupense*, *M. kumamotonense*, and *M. terrae*)	43	31
M. avium. intracellulare, scrofulaceum complex (*M. colombiense*, *M. intracellulare*, *M. avium*, and *M. scrofulaceum*)	38	27
M. gordonae	22	16
M. lentiflavum	7	5
M. triviale	5	4
M. asiaticum	3	2
M. "*aquaeductus*"	3	2
M. bohemicum	2	1
M. interjectum	2	1
M. malmoense	2	1
M. palustre	1	1
M. "*savoniense*"	1	1
M. tusciae	1	1
Non-identifiable	10	7

E. Torvinen et al. / Journal of Microbiological Methods 82 (2010) 78–84

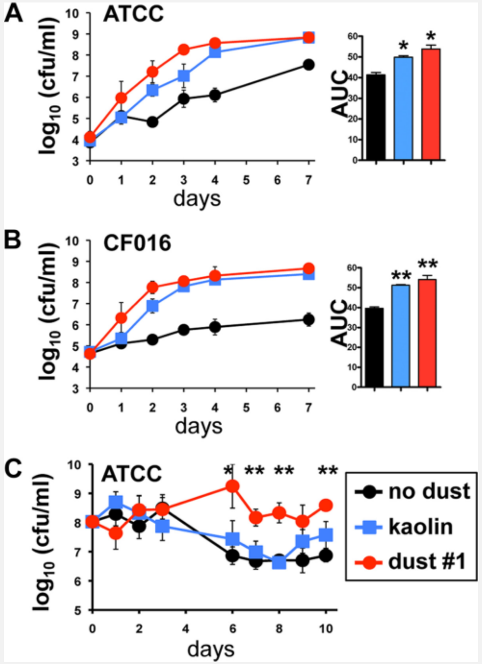
FOMITE SPREAD



Josephine M. Bryant et al. Science 2016;354:751-757

FOMITES – NON LIVING CARRIERS OF INFECTIOUS AGENTS

- *M. abscessus* displays fitness for fomite transmission
- *M. abscessus* physically associated with particulates
- Growth enhanced in the presence of both kaolin and house dust
- Survived desiccation for 2 weeks, but not viable after 3 weeks
- Rate of decline of *M. abscessus* viability during desiccation was reduced in the presence of house dust
- Evidence for enhanced growth and survival of *M. abscessus* during alternating growth and drying periods



Malcolm 2017 AEM

REDUCING EXPOSURE – WHY?

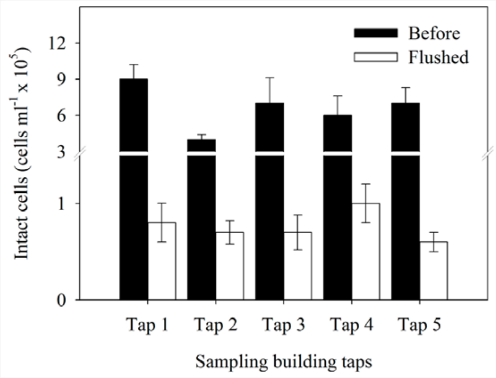
- Prevent new infections in susceptible patients
- Prevent re-infection whilst on treatment and after completion of treatment
- Recurrence rates as high as 30-48% after apparently successful treatment
- Most recurrences are new infections with a different strain type of the same species or a different species
- Many patients with nodular bronchiectasis can have different strains present in the airways at the same time, that appear to come and go over time

EVIDENCE

- The exact route of acquisition in the individual patient – e.g dust v shower aerosol v soil v aspiration
- How much exposure is necessary- i.e. what dose of organism is needed?
- Single vs repetitive exposures
- Impact of climate and industry on background environmental levels of NTM
- No formal studies of any intervention to reduce NTM exposure
- These studies are difficult to conduct and common sense should prevail
- Any intervention that is simple, cost effective and and easy to implement and that has some evidence base in theory should be considered

FLUSHING OF TAPS

- Stagnation of water in pipes leading to taps that are infrequently used has been shown to increase NTM in 'first catch' samples
- Can simply be overnight stagnation
- For taps used infrequently, a **5 minute flush** is recommended before use of the water from that tap
- For taps used on a daily basis, a **shorter flush on first use for the day** is recommended (e.g. 200ml)



Lautenschlager K, Water Research 2010; 44(17): 4868-77
Zhang, Int J Environ Res Public Health 2015 12(10):13649-61

REMOVAL OF MESH AERATORS

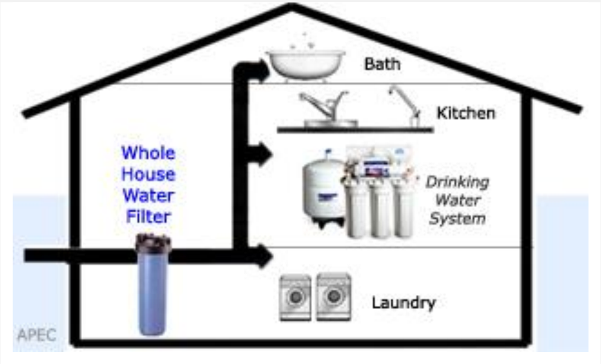
- Mycobacteria attach to the large surface area provided by the mesh, form biofilm in which they can then proliferate
- Numbers of mycobacteria coming through taps with them attached are greater than taps without
- Their removal may help to reduce exposure from water

Chaidez, Gerba. Int J Env Health Res 2004; 14:253

POINT OF USE FILTERS

- NTM can multiply within carbon filters, even those impregnated with silver
- NTM are released into the water passing through
- Avoid
- If they are to be used, they need to be changed every 2 weeks

UNDERBENCH/PRE-TAP WATER FILTRATION



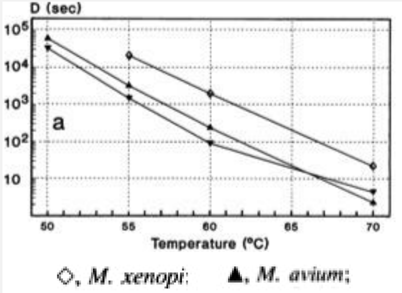
- Cartridge based systems installed under kitchen benches or anywhere after the main supply of water enters the premises
- Microfiltered water dispensers (MWDs) with composite filters
- Reverse-osmosis water dispensers (ROWDs)
- Adequate and continuous maintenance is crucial
- May filter other bacteria, chemicals and sediment
- Have been shown to increase the numbers of mycobacteria in tap water

Zhou, Clinical microbiology and infection. 2014;20:310-4

TURN UP THE HEAT

- Hot water should be stored at 60°C (140°F) minimum
- many can heat up to 75-80°C

- A tempering device or thermostatic mixing valve can be installed at the tap to ensure the maximum temperature of water deliver from the tap is 50°C to reduce scalding risk (45° is recommended for children and the elderly)

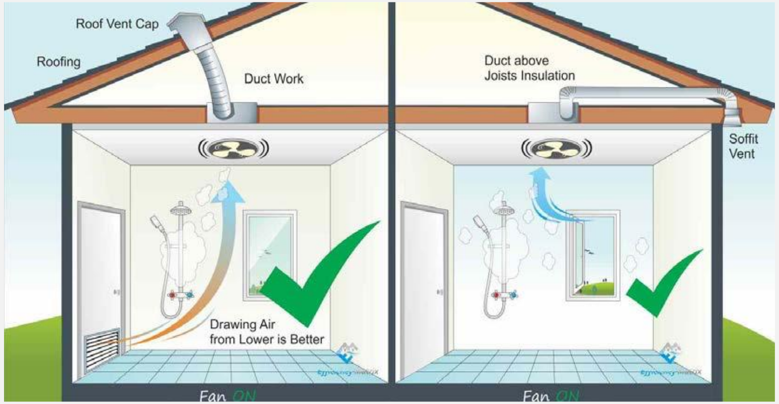


Du Moulin JAMA 1988
Schulz-Robbecke 1992 AEM

SHOWERS

- Replace plastic showerheads with metal ones (less likely to harbor biofilm where NTM grow)
- Soaking shower heads in vinegar for 60 minutes has been recommended as a means of cleaning
- Needs to be repeated at least every 6 months (probably more often)
- Household bleach has been recommended as an alternative - however suggestion of regrowth of NTM with increased resistance to chlorine

VENTILATION



- Ensure adequate bathroom ventilation to clear contaminated shower aerosols and steam
- The use of exhaust fans, and leaving windows open with help alleviate steam build up
- Replace/clean filters on exhaust fans as per manufacturers instructions (usually every 6 mths)

NEBULIZERS AND AIRWAY CLEARANCE DEVICES

- Nebulizers should be cleaned after each use
- The use of unit dose vials for medication is recommended (rather than a larger volume that is repeatedly accessed, when contamination can occur)
- Heat methods:
  - Steam sterilizer marketed for baby bottles
  - Place in boiling water and boil for 5 minutes
  - Place in microwave- safe container submerged in water and microwave for 5 min
  - Use dishwasher if temp >70°C (158°F) for 30 min

OTHER DEVICES

- CPAP humidifiers, neti pots/nasal rinse devices, humidifiers and other devices that require water for humidification/aerosolization, should be used with sterile/boiled water only

OTHER WATER RELATED EXPOSURES

- Indoor pools, hot tubs, steam saunas, hydrotherapy pools and other leisure activities that involve aerosolization of water should be avoided

REFLUX AND NOCTURNAL MICRO-ASPIRATION

- Maintain healthy weight, avoid tight fitting clothing
- Avoid foods and drinks that trigger heartburn
- Eat smaller meals more frequently (to maintain caloric requirements)
- Don’t lie down after a meal. Wait at least 3 hours after eating before lying down or going to bed
- Use a foam wedge to elevate the head of the bed

SOIL

- No studies examining the effectiveness of masks
- Reasonable for high risk patients to use personal-protection whilst engaging in dusty activities
- Moistening soil/potting mix prior to use may reduce the aerosolization and subsequent inhalation of contaminated soil particles

SUMMARY

- NTM causing human infections can be found in a wide variety of environmental sources, but environmental niche can be species specific – eg *M. avium* vs *M. intracellulare*
- Geographic variation in species distribution in both patients and the environment
- Human activities may influence the numbers of mycobacteria in the environment (e.g agriculture, water disinfection practices) and increase exposure (e.g hot tub use, soil related activities, house dust)
- Aerosols of a respirable particle size generated by showering and the pouring of potting mix/soil can be inhaled
- *M. intracellulare* – the main pathogen responsible for NTM disease in most parts of the world is not found in water/showerheads
- No evidence that showering frequency is associated with NTM infection
- Climate and natural events likely to influence mycobacterial numbers in the environment and more work is need in this space

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Finding cures. Saving lives.

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Flavia Huygens

SAHMRI

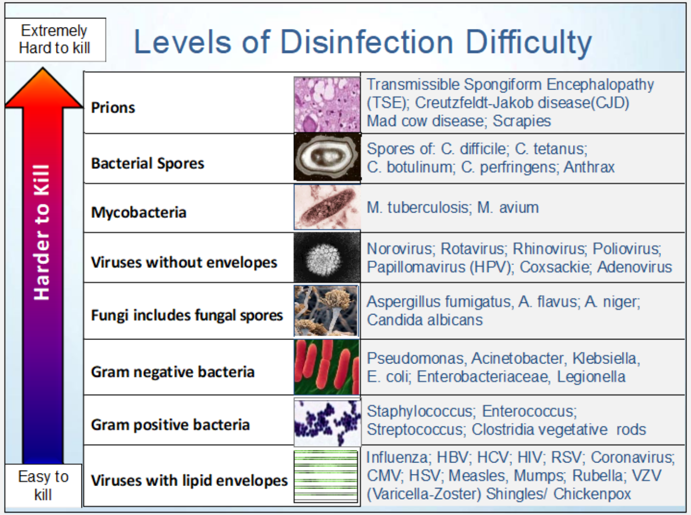
Geraint Rogers
Lex Leong

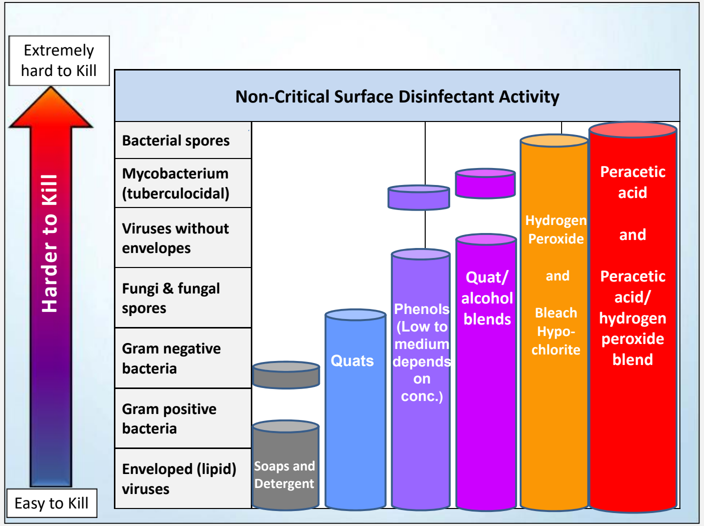
University of Cambridge

Andres Floto
Dorothy Grogono
Nicole Wheeler

SURVIVAL OF NTM ON SURFACES

- MTB can survive on dry inanimate surfaces 1day- 4mths





Kramer A. (A Review) BMC Infect Dis 2006;6:130//(2) Bonilla H F, Zervos M J, Kauffman C A. Infect Control Hosp Epidemiol. 1996;17: 770-71