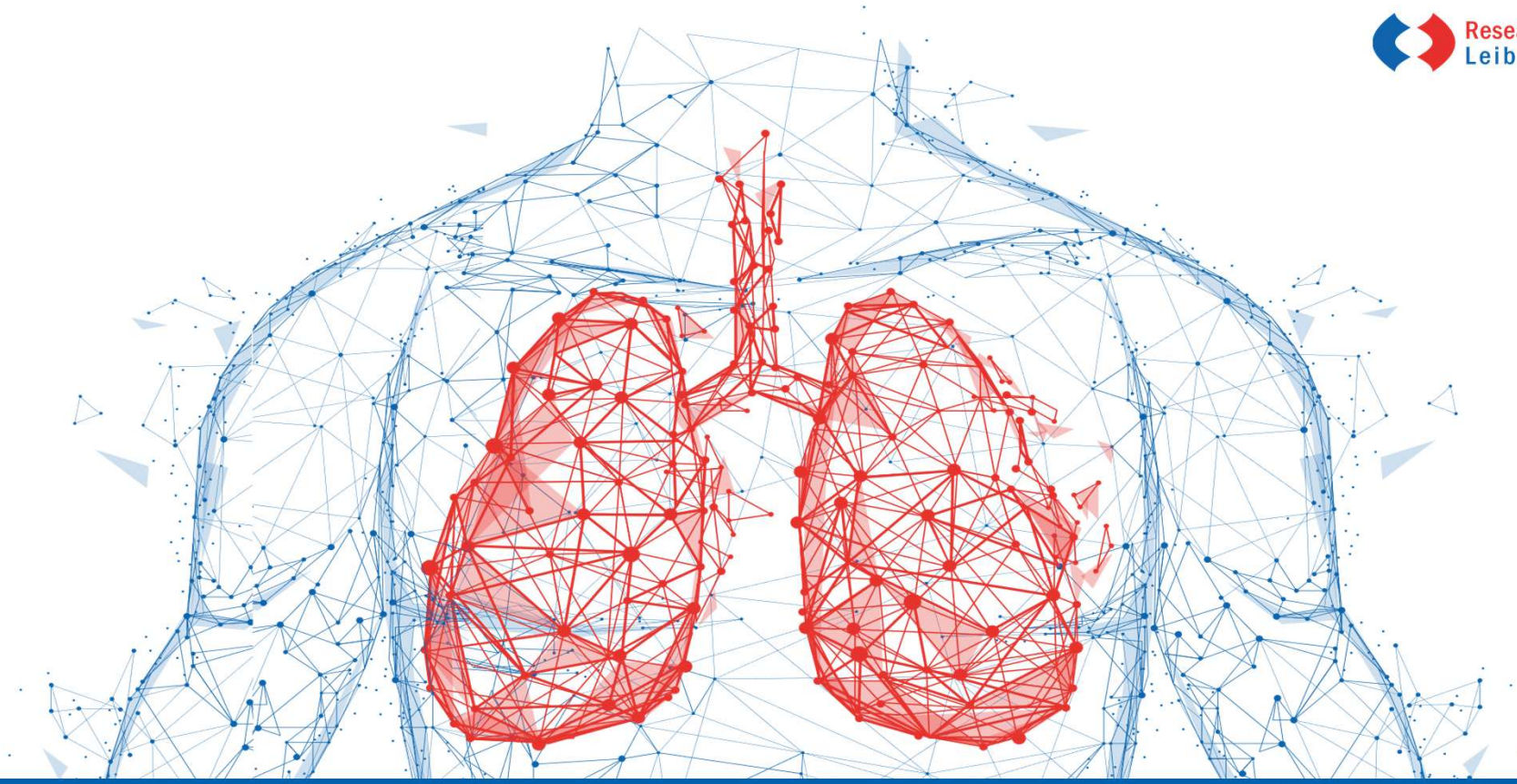
Leibniz Association

Research Center Borstel
Leibniz Lung Center



Introduction to non-tuberculous mycobacteria

INTRODUCTION TO NTM - OUTLINE

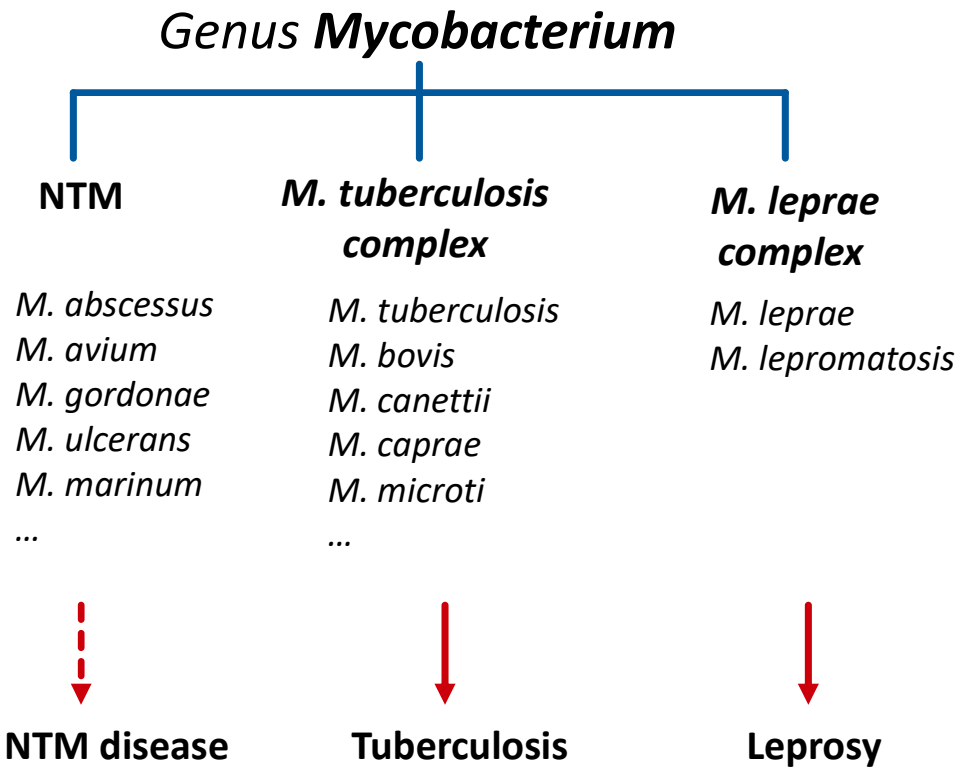
- Taxonomy
- Disease manifestation & risk factors
- Diagnosis of NTM
- NTM treatment and resistance
- Transmission
- Epidemiology
- Population structure of clinically relevant NTM

Taxonomy

TAXONOMY - WHERE ARE WE?

Research Center Borstel
Leibniz Lung Center

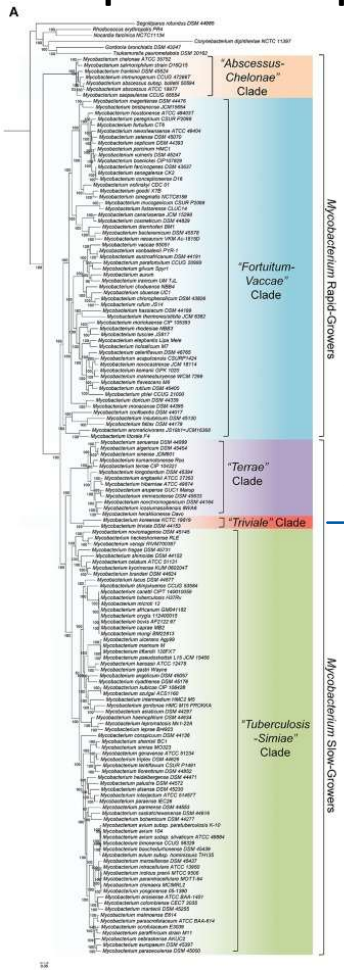
- Domain: Bacteria
- Kingdom: Bacillati
- Phylum: Actinomycetota
- Class: Actinomycetes
- Order: Mycobacteriales
- Family: Mycobacteriaceae
- **Genus: *Mycobacterium***



NTM: Non-tuberculous mycobacteria

TAXONOMY - DEBATE

Gupta 2018: Proposed split into 5 new genera



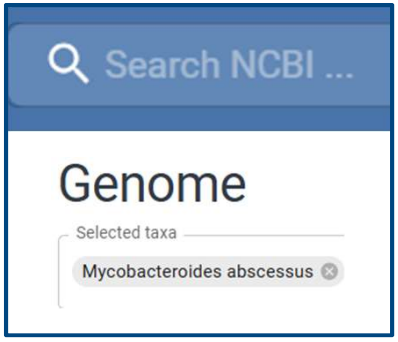
Mycobacteroides
M. abscessus, M. chelonae,…

Mycolicibacterium
M. fortuitum, M. gilvum,…

M. kumamotonense, M. terrae,…
Mycolicibacter
→ ***Mycolicibacillus***
M. koreense, M. triviale,…

Mycobacterium
M. xenopi, M. avium, M. tuberculosis, M. leprae, M. simiae,…

https://www.ncbi.nlm.nih.gov/



Genus
Mycobacterium

NTM	TB	Leprosy
M. abscessus	*M. tuberculosis*	*M. leprae*
M. avium	*M. bovis*	*M. lepromatosis*
M. chimaera	*M. canettii*	
(M. ulcerans)	*M. caprae*	
M. marinum	*M. microti*	
…	…	

Reconstituting the genus *Mycobacterium*

Conor J Meehan [1,2,*], Roman A Barco [3], Yong-Hwee E Loh [4], Sari Cogneau [1,5], Leen Rigouts [1,5,6]

▸ Author information ▸ Article notes ▸ Copyright and License information

PMCID: PMC8549266 PMID: 34554081

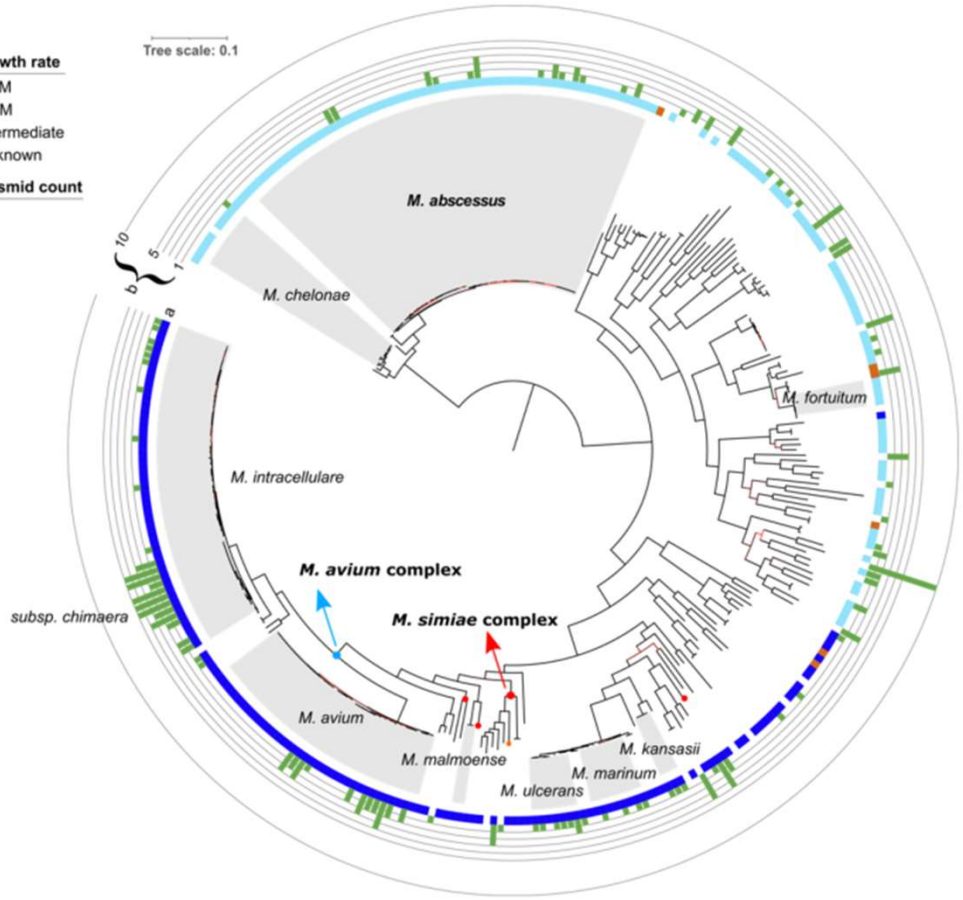
Abstract **2021**

The definition of a genus has wide-ranging implications both in terms of binomial species names and also evolutionary relationships. In recent years, the definition of the genus *Mycobacterium* has been debated due to the proposed split of this genus into five new genera (*Mycolicibacterium* , *Mycolicibacter* , *Mycolicibacillus* , *Mycobacteroides* and an emended *Mycobacterium*). Since this group of species contains many important obligate and opportunistic pathogens, it is important that any renaming of species does not cause confusion in clinical treatment as outlined by the *nomen periculosum* rule (56a) of the Prokaryotic Code. In this study, we evaluated the proposed and original genus boundaries for the mycobacteria, to determine if the split into five genera was warranted. By combining multiple approaches for defining genus boundaries (16S rRNA gene similarity, amino acid identity index, average nucleotide identity, alignment fraction and percentage of conserved proteins) we show that the original genus *Mycobacterium* is strongly supported over the proposed five-way split. Thus, we propose that the original genus label be reapplied to all species within this group, with the proposed five genera potentially used as sub-genus complex names.

TAXONOMY

- NTM = All mycobacteria except those causing tuberculosis or leprosy
  - Synonyms: anonymous or atypical mycobacteria; mycobacteria other than tuberculosis (MOTT)
- >200 species
  - Slow growers (SGM) and rapid growers (RGM)
  - Differences in pigmentation

Diricks et al. 2025



SGM = slowly growing mycobacteria; RGM = rapidly growing mycobacteria

RUNYON CLASSIFICATION

- **Slowly growing mycobacteria** (>7 days)
  - Runyon I: **Photochromogens**: yellow-orange when exposed to light
    - *E.g. M. kansasii, M. marinum, M. simiae*
  - Runyon II: **Scotochromogens**: yellow-orange
    - E.g. *M. scrofulaceum, M. gordonae, M. szulgai, M. xenopi*
  - Runyon III: **Nonchromogens**
    - E.g. *M. avium, M. ulcerans*
- **Rapidly growing mycobacteria** (<7 days)
  - *E.g. M. fortuitum, M. abscessus, M. chelonae, M. smegmatis*

M. marinum

M. kansasii

M. szulgai

M. gordonae

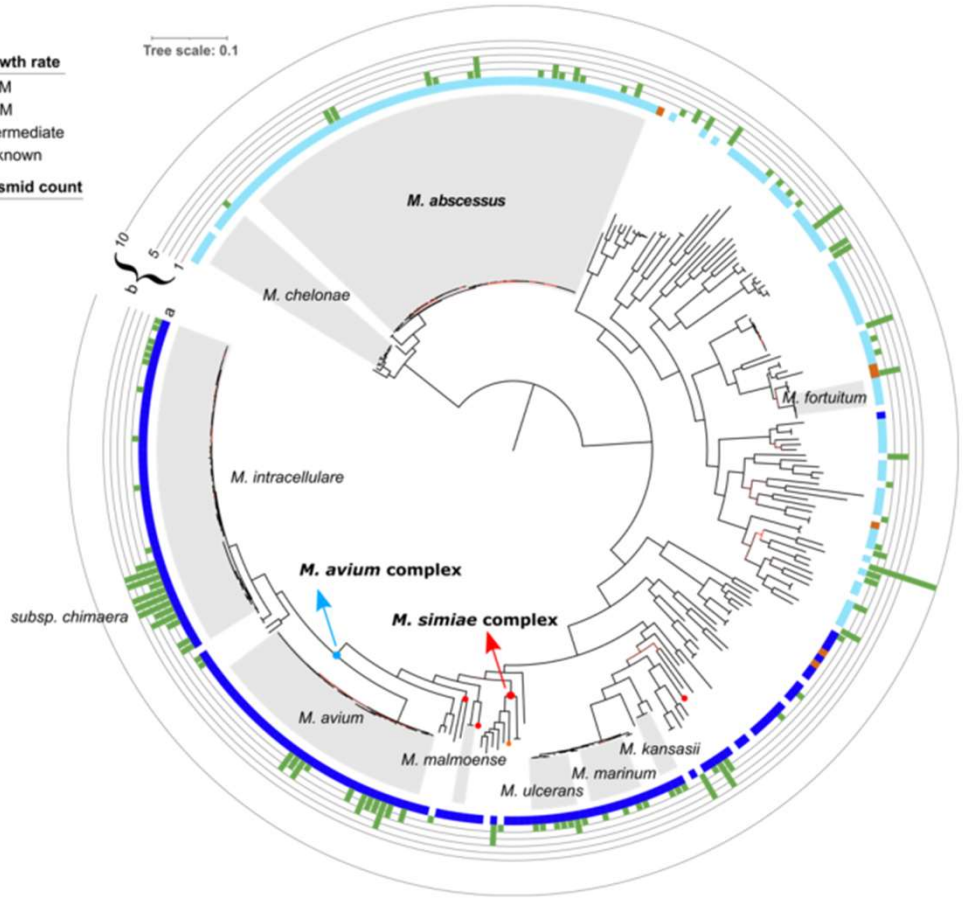
TB *MAC*

M. abscessus

TAXONOMY

- NTM = All mycobacteria except those causing tuberculosis or leprosy
  - Synonyms: anonymous or atypical mycobacteria; MOTT
- >200 species
  - Slow growers (SGM) and rapid growers (RGM)
  - Differences in pigmentation
  - Complex > species > subspecies > lineages/DCCs
  - Only few are clinically relevant

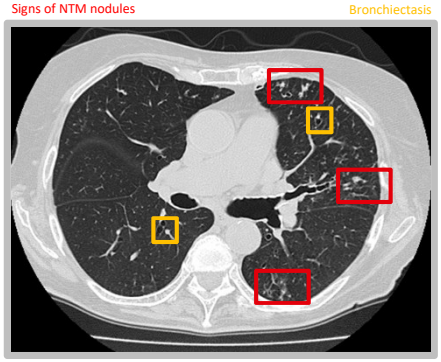
Diricks et al. 2025



SGM = slowly growing mycobacteria; RGM = rapidly growing mycobacteria

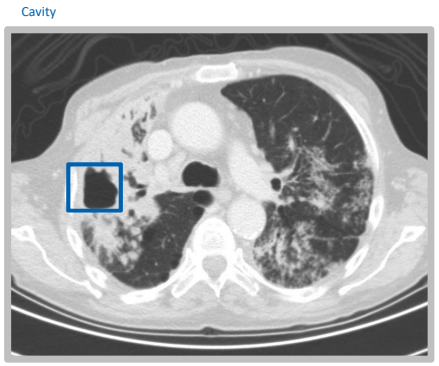
Disease manifestation & Risk factors

DISEASE MANIFESTATIONS OF NTM IN HUMANS



Nodular/bronchiectatic

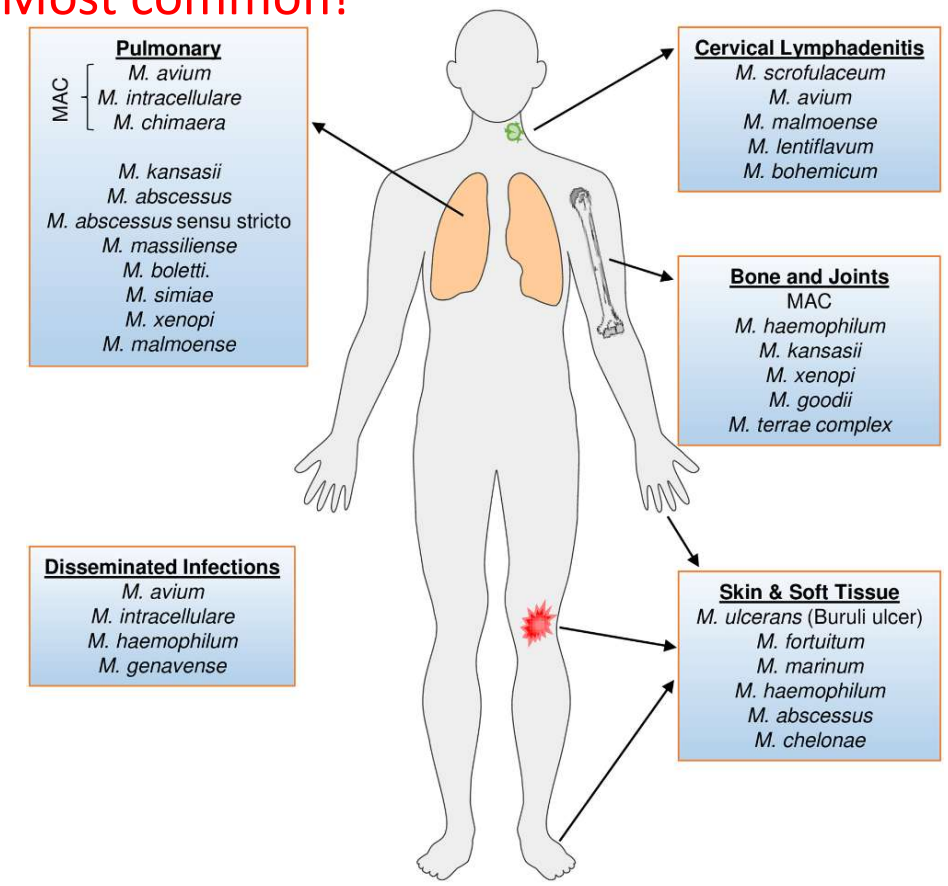
"Lady Windermere syndrome"



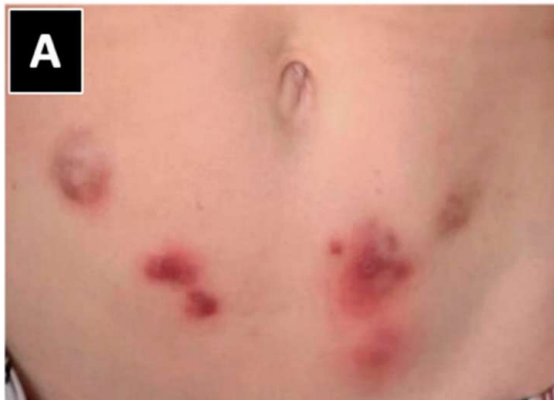
Fibrocavitary

(NTM slide repository)

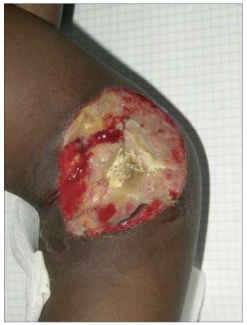
Most common!



Baldwin (2019)



M. abscessus (Carbonell 2024)



M. ulcerans

(Sizaire 2006)

M. chelonae

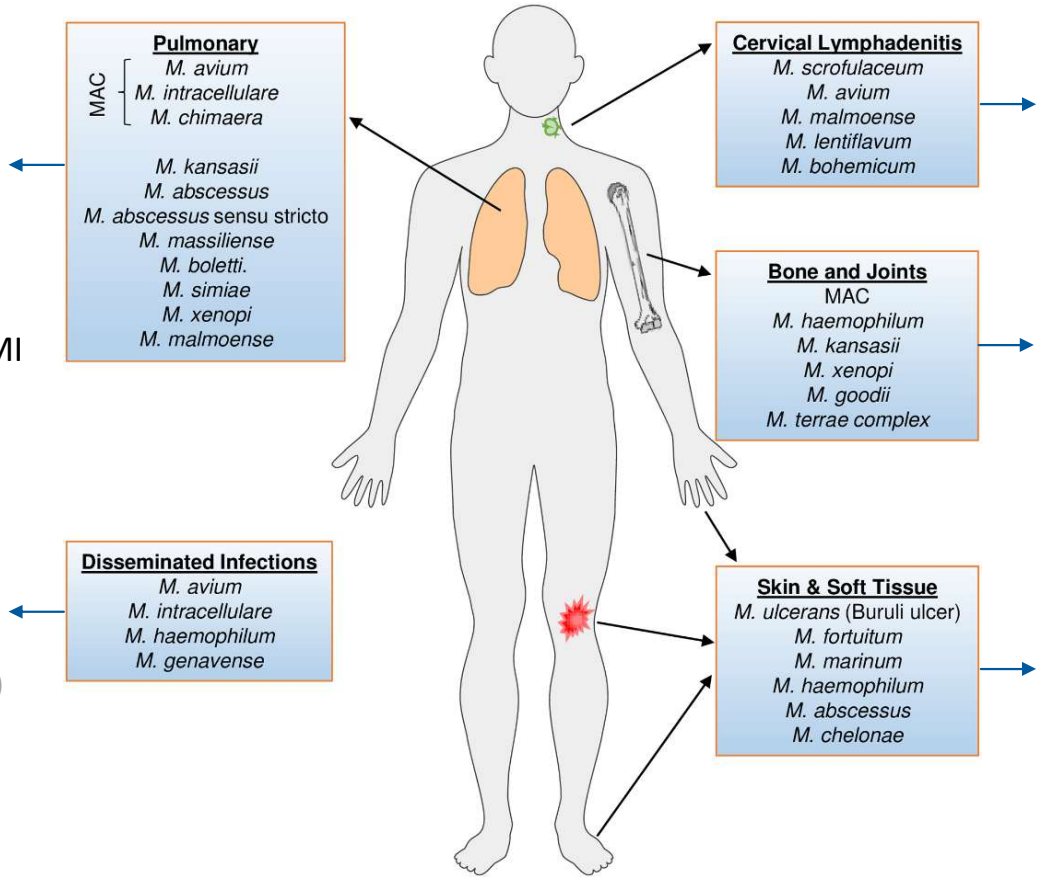
(Kennedy 2012)

HOST RISK FACTORS

Male/female ratio dependents on species, region, disease,…

- Prior or pre-existing lung disease
  - Bronchiectasis
  - Tuberculosis
  - Interstitial lung disease
  - COPD
  - Cystic fibrosis (~8-13%)
  - Asthma
- Postmenopausal women with low BMI (nodular)

- Immunocompromised
  - HIV
  - Immunosuppressive therapy (inhaled corticosteroids, anti-TNF-α)
  - Mutations in IFN-/-IL12 (Mendelian disease)



Mostly in children

Via Trauma

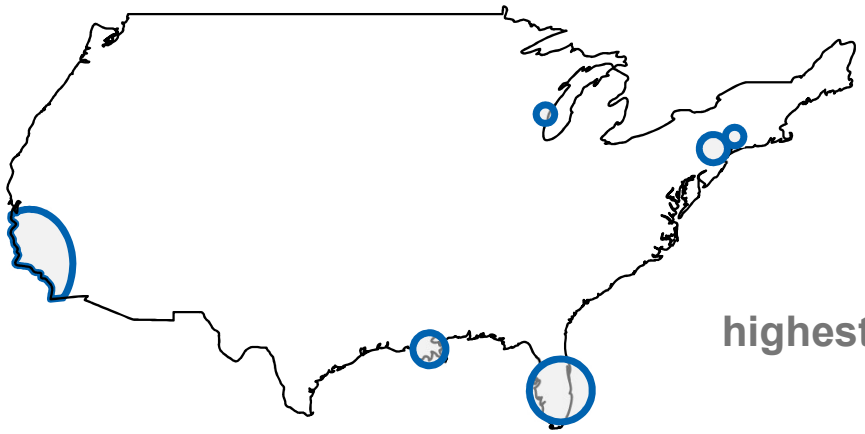
- Contact with contaminated water or infected fish
- Traumas and surgical wounds

Baldwin (2019)

OTHER RISK FACTORS FOR NTM PULMONARY DISEASE (NTM-PD)

Research Center Borstel
Leibniz Lung Center

Areas in the United States* with a high risk for a NTM-PD infection



highest incidence of NTM-PD

Environmental risk factors

- High evapotranspiration and percentages covered by surface water
- Greater precipitation
- Lower elevation
- Higher temperatures
- Lowever levels of aluminium and manganese in soils

Socioeconomic risk factors

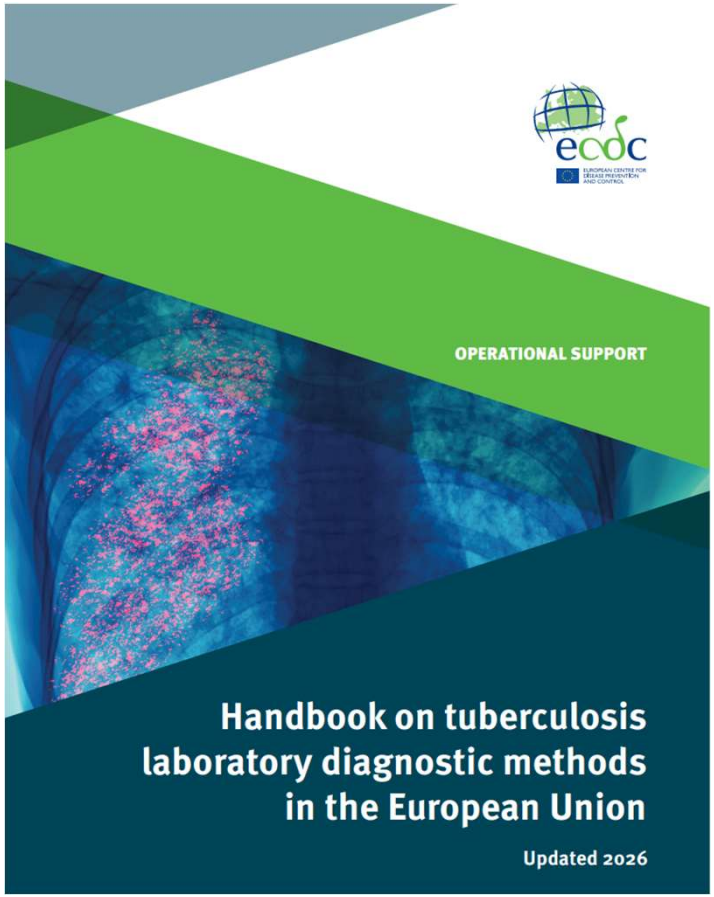
- Greater population density
- Higher education and income

*US study chosen due to high number of unique cases: Nearly 2.3 million individuals from all 50 states and the District of Columbia were included, from which 16,508 NTM-LD claims representing 2,548 unique cases were identified. Data are representative but not directly applicable to the European situation. NTM-LD, non-tuberculous mycobacterial lung disease. Adapted from Adjemian J, et al. Am J Respir Crit Care Med 2012; 186:553-8.

Diagnosis of NTM disease

DIAGNOSIS OF NTM DISEASE

https://www.ecdc.europa.eu/sites/default/files/documents/handbook-tuberculosis-lab-diagnostics-2026.pdf



DIAGNOSIS OF NTM-PD (ATS CRITERIA)

NTM pulmonary isolation from clinical sample ≠ NTM pulmonary disease (NTM-PD)!

Clinical criteria

- Bronchopulmonary or systemic symptoms (chronic cough, fatigue, weight loss, fever,…)

and

- Exclusion of other lung diseases (difficult!)

Radiological criteria

- Nodular or cavitary structures on chest radiograph

or

- Multifocal bronchiectasis with multiple small nodules on HRCT scan

and

- Exclusion of other causes

Microbiological criteria

- At least 2 positive separate sputum cultures

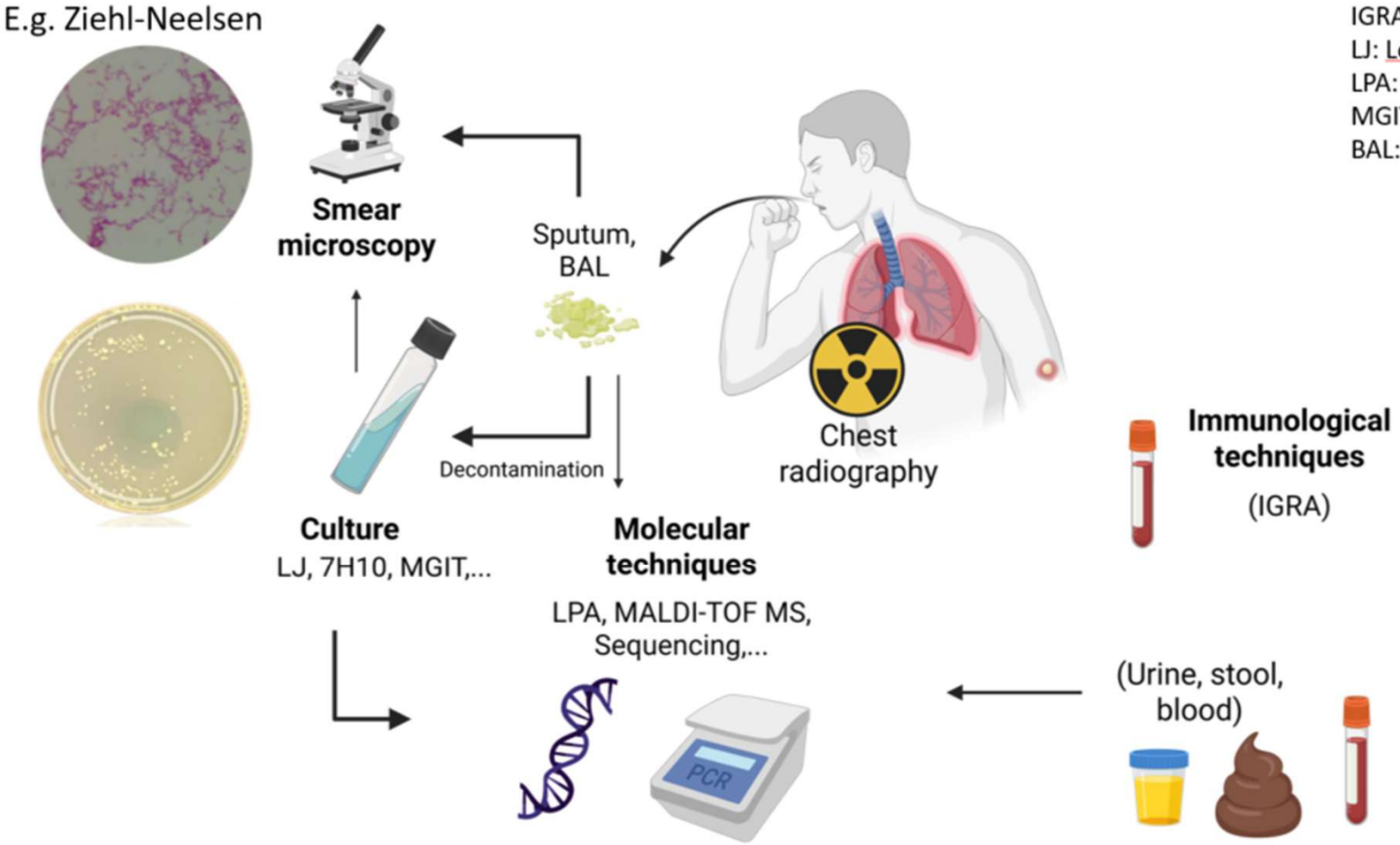
or

- 1 positive culture from bronchoalveolar wash/lavage or lung biopsy with mycobacterial features

Last updated with data from Lange 2022

HRCT, high resolution computed tomography; NTM-LD, non-tuberculous mycobacterial lung disease.
ATS = American Thoracic Society

DIAGNOSIS OF NTM DISEASE

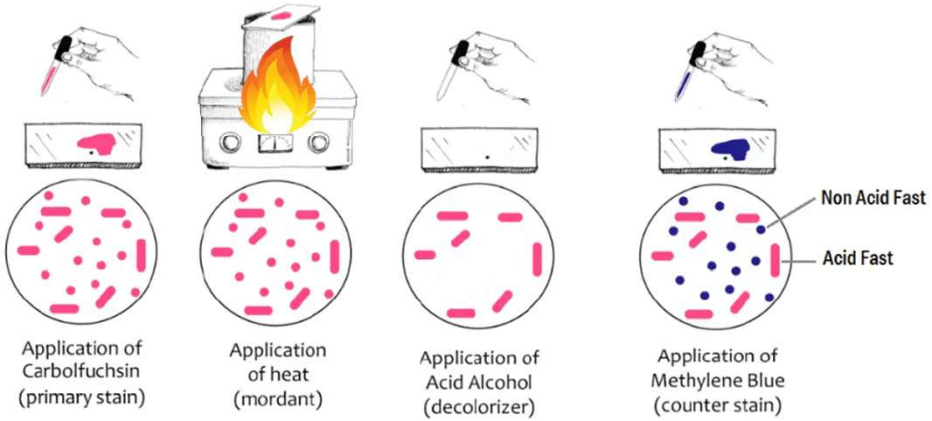


IGRA: Interferon-Gamma Release Assay
LJ: Löwenstein-Jensen
LPA: line probe assay
MGIT: mycobacterial growth indicator tube
BAL: bronchoalveolar lavage

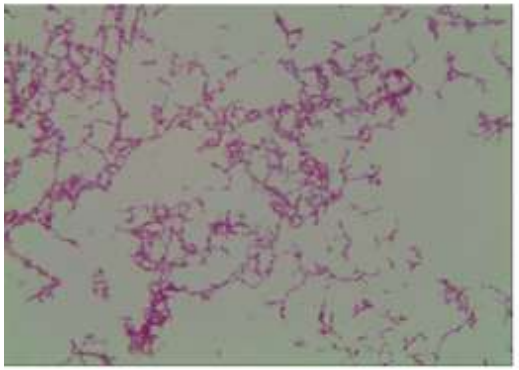
DIAGNOSIS (MICROBIOLOGICAL)

- Smear microscopy: acid-fast staining

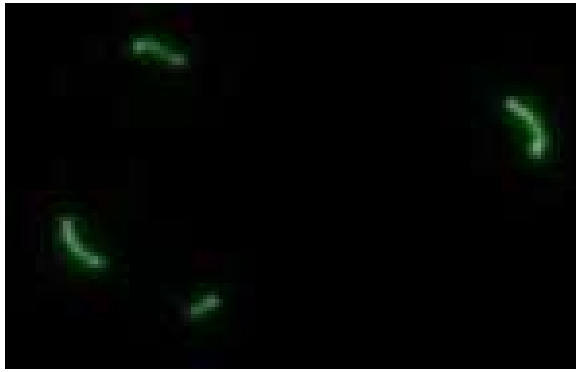
	Ziehl-Neelsen	Kinyoun	Auramine
Stain	Carbol fuchsin	Carbol fuchsin (higher conc.)	Auramine O or Auramine/Rhodamine mix
Decolorizer	Acid-alcohol	Acid-alcohol	Acid-alcohol
Counterstain	Methylene blue	Methylene blue	Potassium permanganate
Microscopy	Bright-field	Bright-field	Fluorescence
Heat	Yes	No	No



https://laboratoryinfo.com/zn-stain/



ZN/Kinyoun staining



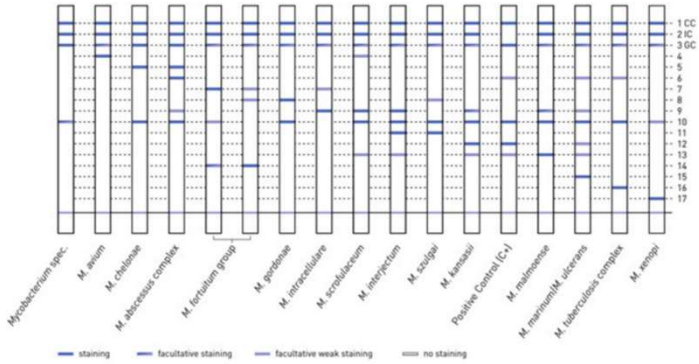
auramine staining

Zou 2014

MOLECULAR IN-VITRO DIAGNOSTICS

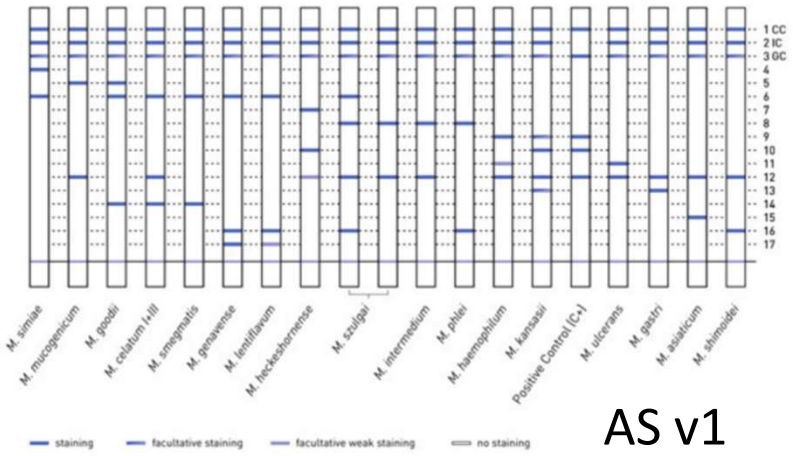
- Line probe assay
  - E.g. Hain LifeScience
    - Genotype CM (common mycobacteria)
    - Genotype CMdirect (on sputum samples)
    - Genotype AS (additional species)
    - Genotype NTM-DR (with drug resistance)

Species-specific probes

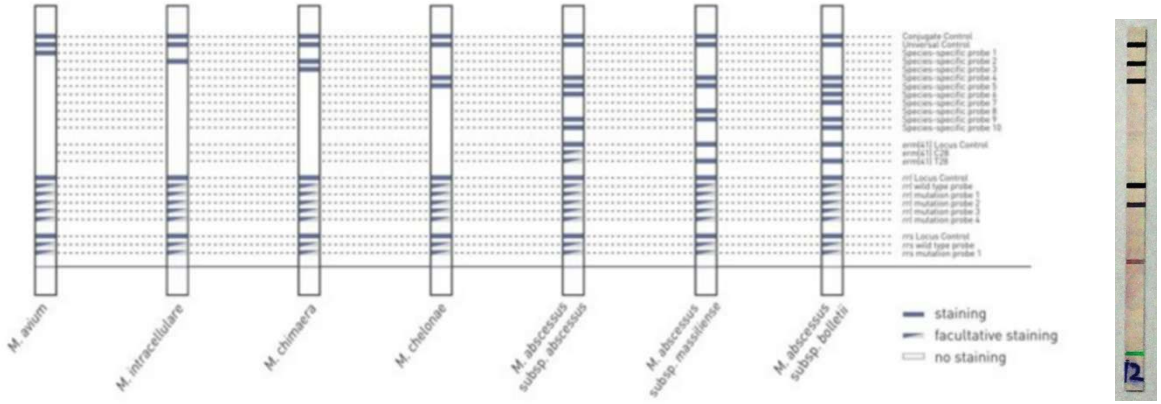


CM v2

No identification/misclassifications can occur!!



AS v1



NTM-DR v1

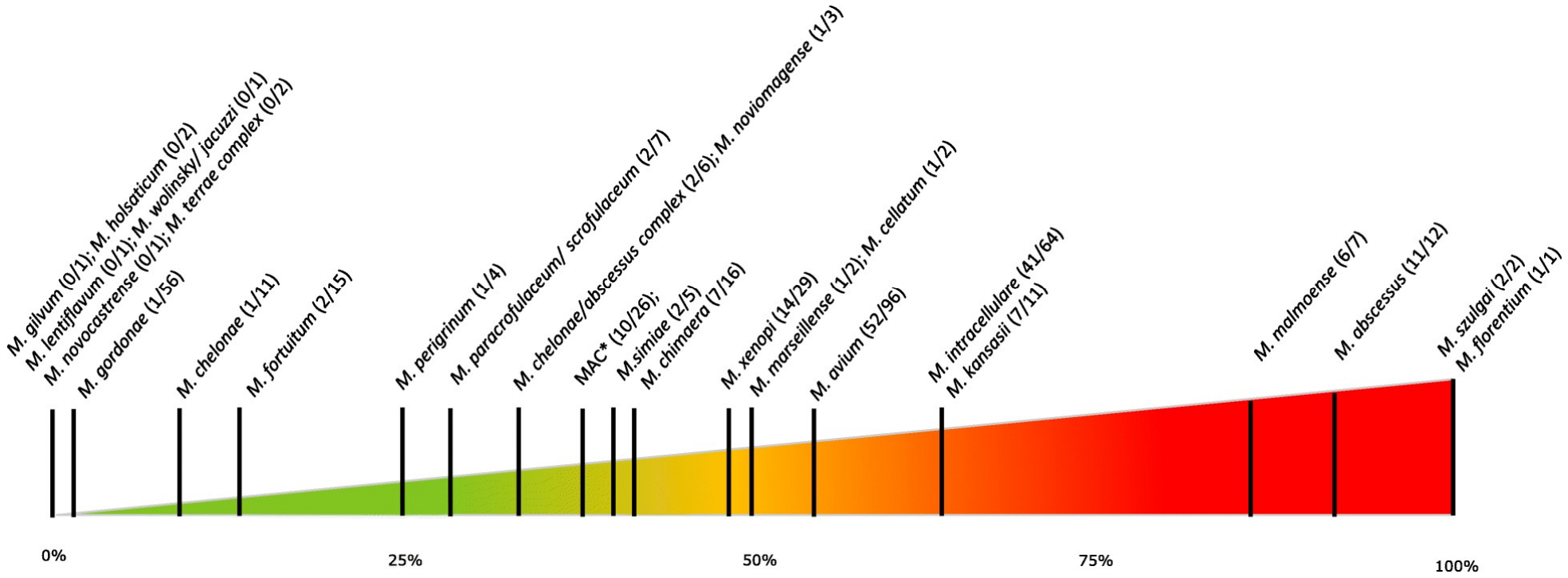
CE
IVD

CLINICAL RELEVANCE OF NTM

Research Center Borstel
Leibniz Lung Center

~1/3 of isolations from respiratory tract are clinically relevant

Vande Weygaerde 2019



Data from three reference centres in Belgium 2010-2017

percentage based on the number of cases meeting ATS/IDSA criteria for NTM-PD

NTM treatment and resistance

NTM TREATMENT

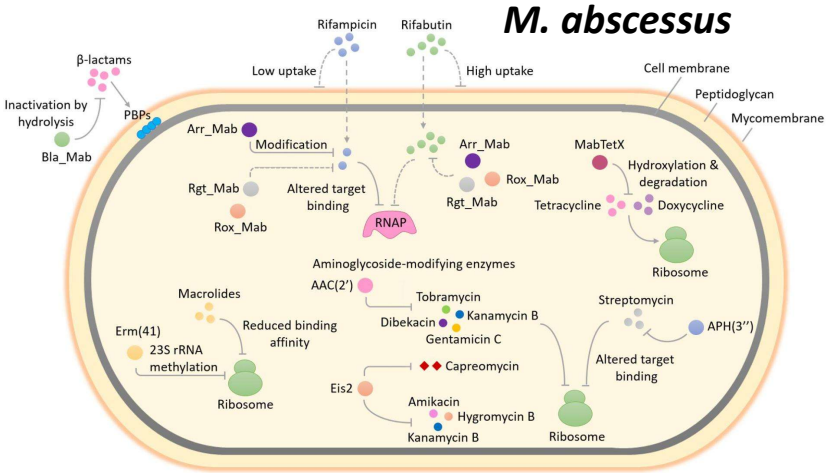
- Combination therapy (≥ 3 active drugs): long, costly, serious side effects
  - E.g. Macrolides, aminoglycosides, ethambutol, rifampicin, clofazimine
- Effective antibiotics depend on species → species-specific guidelines
- Duration/amount: >2 years depending on severity, patient tolerance, response
- Should be guided by in vitro pDST
- Cure rates depend on species
  - *M. abscessus* : 30-50%
  - *M. avium complex*: 50-70%
  - *M. malmoense* and *M. kansasii* : 80-90%

	No. of drugs	Macrolides	Rifamycins	Ethambutol	Aminoglycosides	Isoniazid	B-lactams	Tetracycline	Pyrazinamide	Dapsone	Fluoroquinolones	Bedaquiline	Clofazimine	Oxazolidinones	Nitroimidazoles	Ethionamide	Co-trimoxazole
*Mode of action**																	
M. leprae	3																
M. tuberculosis complex	3-4																
M. abscessus (macrolide susceptible)	≥3, ≥2																
M. abscessus (macrolide resistant)	≥4, ≥2																
MAC: nodular-bronchiectatic	3																
MAC: cavitary	≥3																
MAC: refractory	≥4																
M. kansasii	3																
M. xenopi	≥3																
M. simiae	≥3																
M. simiae: cavitary or severe disease	≥3																

pDST = phenotypic drug susceptibility testing

ANTIBIOTIC RESISTANCE

- Intrinsic resistance
  - Biofilm formation
  - Cell wall impermeability and efflux pumps
  - Enzymes that modify antibiotics (e.g. bla_Mab, arr_Mab,…)
  - Enzymes that modify targets (e.g. erm(41))
- Acquired resistance
  - Macrolides: rrl (23S rRNA) mutations
  - Amikacin: rrs (16S rRNA) mutation
  - Fluoroquinolones: gyrA/B
  - Rifampicin: rpoB
  - …



Luthra 2018

→ **Differs between NTM species and even subspecies!**

HOW TO DETECT ANTIBIOTIC RESISTANCE?

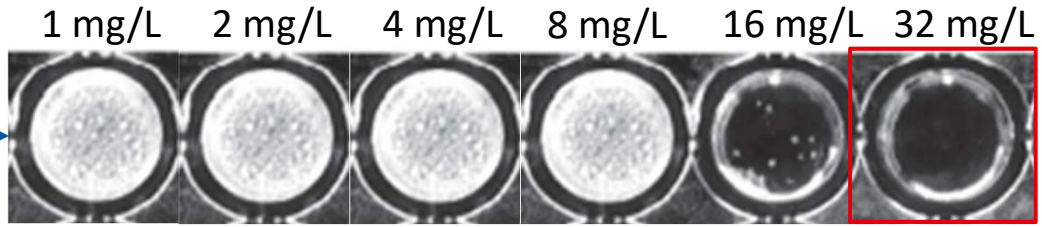
1. In vitro drug susceptibility testing (pDST)
(e.g. Sensititre plates RAPMYCOI, SLOMYCOI)

Antibiotic concentration (mg/L)

RAPMYCO I

	1	2	3	4	5	6	7	8	9	10	11	12
A	SXT 0,25/4,75 - S	SXT 0,5/9,5 - S	SXT 1/19 - S	SXT 2/38 - S	SXT 4/76 R	SXT 8/152 - R	LZD 1 - S	LZD 2 - S	LZD 4 - S	LZD 8 - S	LZD 16 - I	LZD 32 - R
B	CIP 0,12 - S	CIP 0,25 - S	CIP 0,5 - S	CIP 1 - S	CIP 2 - I	CIP 4 - R	IMI 2 - S	IMI 4 - S	IMI 8 - I	IMI 16 - I	IMI 32 - R	IMI 64 - R
C	MXF 0,25 - S	MXF 0,5 - S	MXF 1 - S	MXF 2 - I	MXF 4 - R	MXF 8 - R	FEP 1	FEP 2	FEP 4	FEP 8	FEP 16	FEP 32
D	FOX 4 - S	FOX 8 - S	FOX 16 - S	FOX 32 - I	FOX 64 - I	FOX 128 - R	AUG2 2/1	AUG2 4/2	AUG2 8/4	AUG2 16/8	AUG2 32/16	AUG2 64/32
E	AMI 1 - S	AMI 2 - S	AMI 4 - S	AMI 8 - S	AMI 16 - S	AMI 32 - I	AMI 64 - R	AXO 4	AXO 8	AXO 16	AXO 32	AXO 64
F	DOX 0,12 - S	DOX 0,25 - S	DOX 0,5 - S	DOX 1 - S	DOX 2 - I	DOX 4 - I	DOX 8 - R	DOX 16 - R	MIN 1	MIN 2	MIN 4	MIN 8
G	TGC 0,015	TGC 0,03	TGC 0,06	TGC 0,12	TGC 0,25	TGC 0,5	TGC 1	TGC 2	TGC 4	TOB 1	TOB 2	TOB 4
	CLA	CLA	CLA	CLA 0,5	CLA 1 - S	CLA 2 - S	CLA 4 - I	CLA 8 - R	CLA 16 - R	TOB 8	TOB 16	POS
				A 0,5	CLA 1 - S	CLA 2 - S	CLA 4 - I	CLA 8 - R	CLA 16 - R			POS
				A 0,5	CLA 1 - S	CLA 2 - S	CLA 4 - I	CLA 8 - R	CLA 16 - R			POS

Linezolid (LZD)



M24 Ed3

Growth | Growth | Growth | Growth | Minimal growth | No Growth = MIC!

Minimum inhibitory concentration (MIC) = lowest concentration of antibiotic that inhibits visible growth

Antibiotic will probably not cure patients

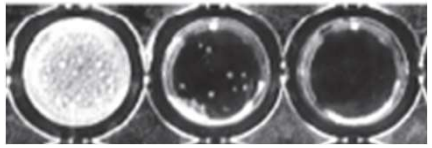
Higher chance on good treatment outcomes

Antimicrobial Agent	MIC, µg/mL		
	S	I	R
Amikacin (IV)	≤16	32	≥64

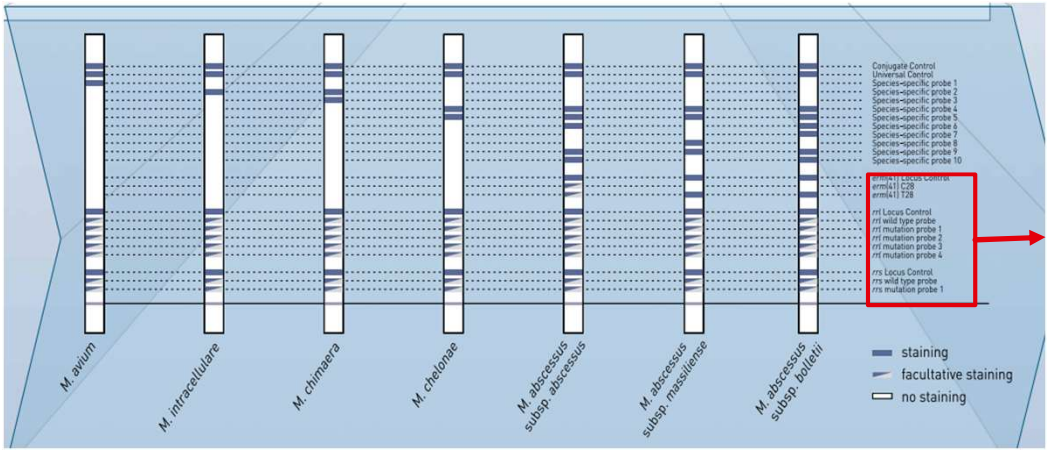
Antibiotic and species-specific clinical breakpoints

HOW TO DETECT ANTIBIOTIC RESISTANCE?

1. In vitro drug susceptibility testing (pDST)
(e.g. Sensititre plates RAPMYCOI, SLOMYCOI)



2. Molecular tests
(e.g. LPA: Line probe assays NTM-DR)



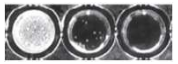
Only for *M. avium* complex, the *M. abscessus* complex, and *M. chelonae*

Resistance genes and mutations
Erm(41)
rrl
rrs

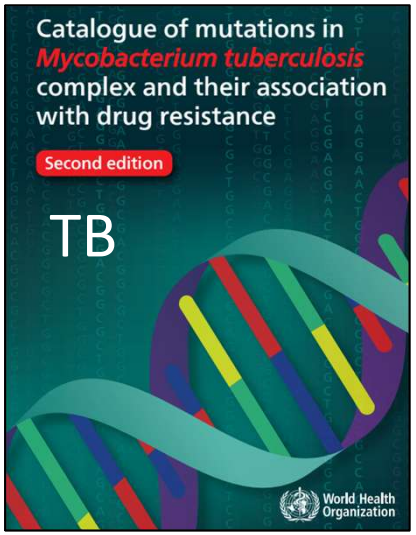
2. Molecular tests
(e.g. whole genome sequencing)

Bioinformatic pipelines → search for known resistance-associated mutations

Translate mutations in phenotypes (S/I/R)



RESISTANCE CATALOGUES FOR MYCOBACTERIA

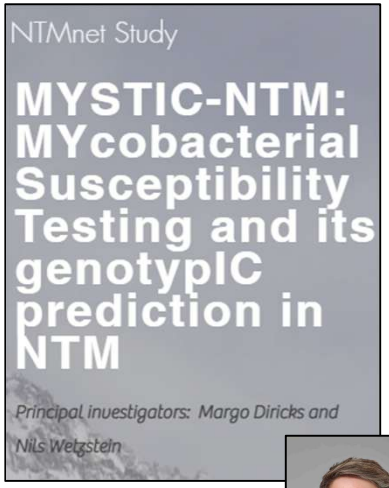


Drug	Variant	MUT Present_pheno S	MUT Absent_pheno S	MUT Present_pheno R	MUT Absent_pheno R	Sensitivity	Specificity	Grading
RIF	rpoB_p.Ser450Leu	226	30643	10859	6002	64.4%	99.3%	R
RIF	rpoB_p.Asp435Val	17	30515	1154	15656	6.9%	99.9%	R
RIF	rpoB_p.His445Asp	10	30522	608	16202	3.6%	100.0%	R
RIF	Rv1129c_c.-46C>G	49	23658	14	11488	0.1%	99.8%	S

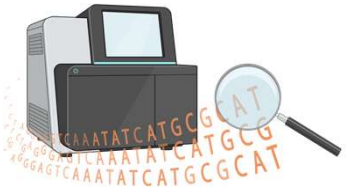
Associated with resistance
Or not associated with resistance

MYSTIC NTM

https://www.ntmnet.org/mystic-ntm



pDST

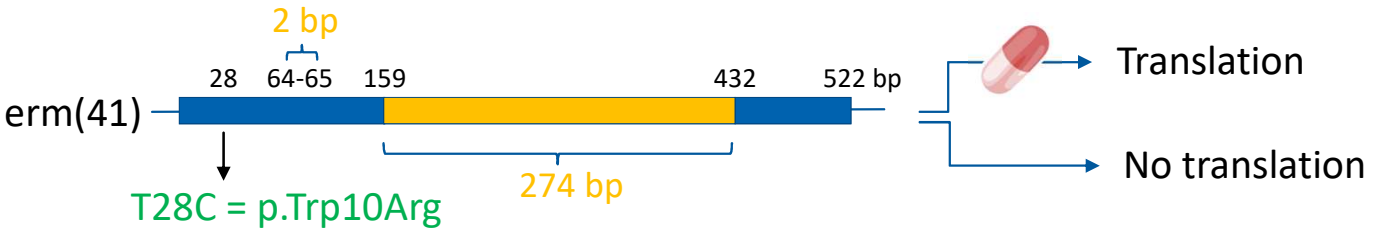


WGS

- Build resistance catalogues for NTM
  - Using isolates for which we both have pDST and sequencing data
- > 17 institutions across 13 countries expressed interest
  - Data sharing (preparations) have already begun for a few of them

MACROLIDE RESISTANCE (M. ABSCESSUS)

Erm methylates 23S rRNA (*rrl*) = target of macrolides → inducible resistance



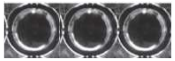
Full length erm(41) with T28
(most subsp. abscessus/bolletii)

→ Inducible macrolide resistance (iR)

e.g. 8 mg/L

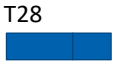
Full length erm(41) with C28
(some subsp. abscessus)

→ Susceptible to macrolides (S)

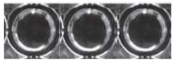


e.g. 8 mg/L

Truncated erm(41)
(Δ2bp + 274 bp del.)
(most subsp. massiliense)



→ Susceptible to macrolides (S)

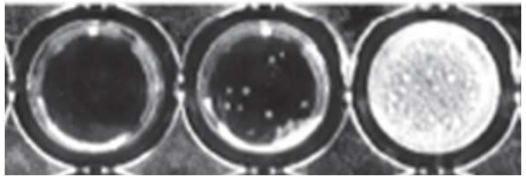


e.g. 8 mg/L

→ Constitutive macrolide resistance (R)

e.g. 8 mg/L

3 days 7 days 14 days



Macrolides (e.g. clarithromycin)
Incubate for 14 days!

↓

MIC ≥ 8 after day 3-5 =
constitutive resistance
(rrl mutations)
MIC ≥ 8 only after 14 days =
inducible resistance (erm)

↓

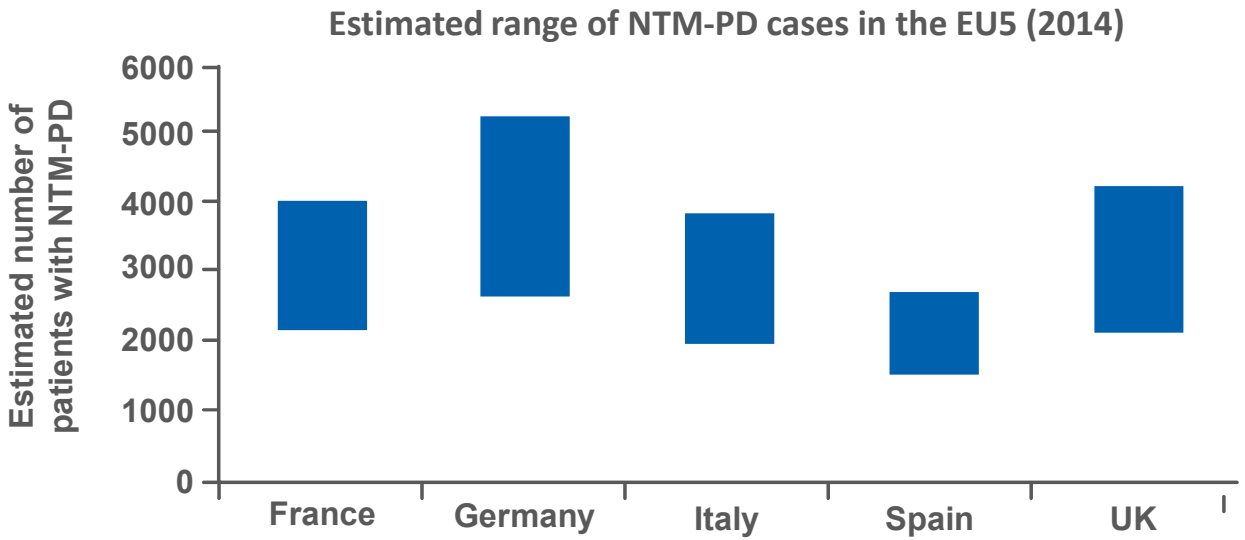
Worse treatment outcomes

MACROLIDE RESISTANCE

- Chromosomal *erm* genes found in
  - *Slow growing mycobacteria*
    - *Erm(37): M. tuberculosis complex*
  - *Rapidly growing mycobacteria*
    - *Erm(41)*: *M. abscessus*
    - *Erm(38)*: *M. smegmatis* and other *M. smegmatis* complex species (e.g. *M. goodii*)
    - *Erm(39):* in *M. fortuitum* and other *M. fortuitum* complex species (e.g. *M. boenickei, M. houstonense, M. neworleansense* and *M. porcinum*)
    - *Erm(40)*: *in M. mageritense and other M. neoaurum complex species (e.g. M. wolinskyi)*
- Plasmid associated *erm* gene found in RGM
  - Erm(55): in *M. chelonae*
  - *M. bacteremicum, M. grossiae, M. iranicum, M. neoaurum* and *M. obuense*

Epidemiology

PREVALENCE OF NTM



Annual prevalence of NTM-PD is 3–6 per 100,000 inhabitants in EU5 countries (2014) → Below threshold for orphan disease

Difficult to assess!

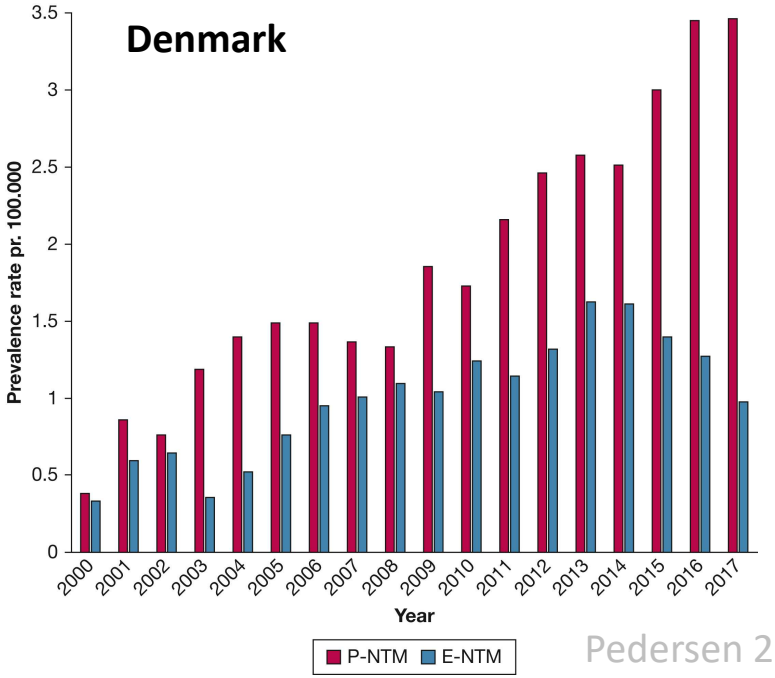
- **NTM is not a notifiable disease in Europe (and many other countries).**
  Exception: Australia
- **Awareness of NTM varies between countries**
- **Difficult diagnosis**
- **NTM detection ≠ disease**

Likely underestimated!

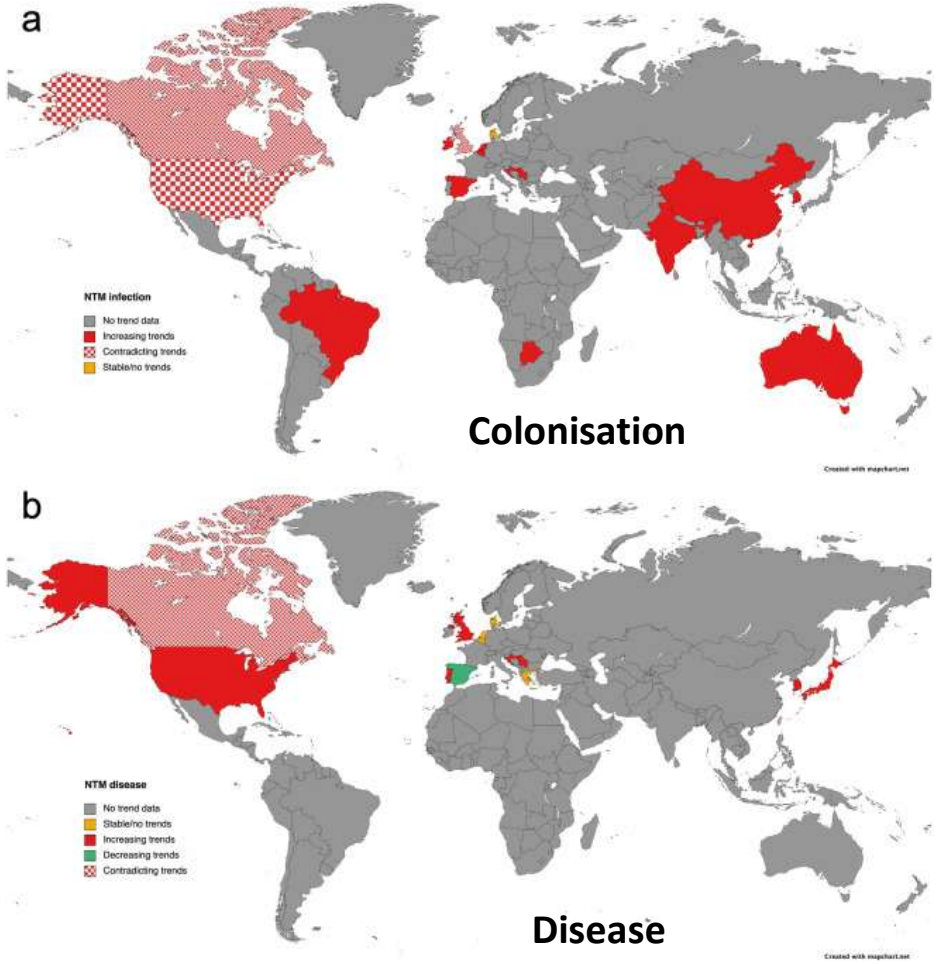
NTM-PD, non-tuberculous mycobacterial pulmonary disease.

GLOBAL TRENDS OF INFECTIONS WITH NTM

- Most studies report increasing trends of pulmonary NTM isolation (82%) and disease (67%)
  - Depends on species and country



Pedersen 2024

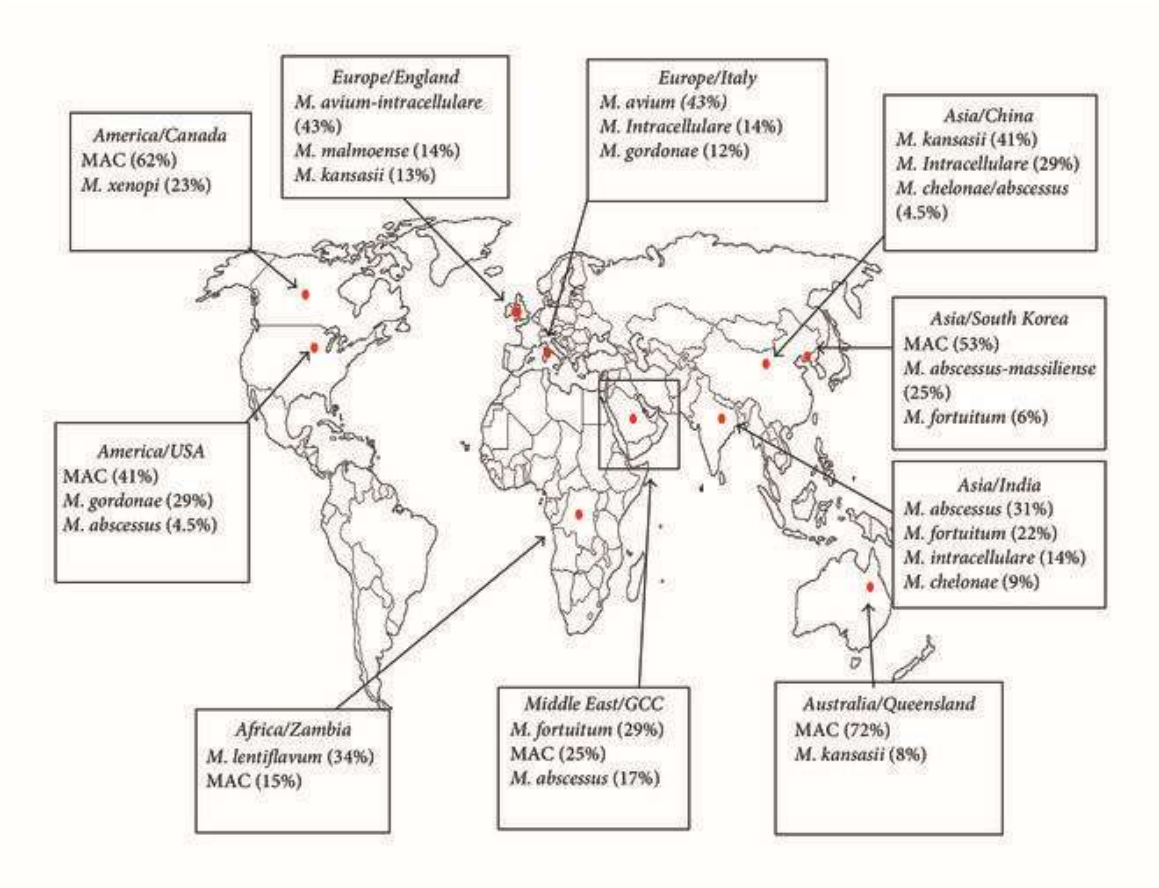


Dahl 2022

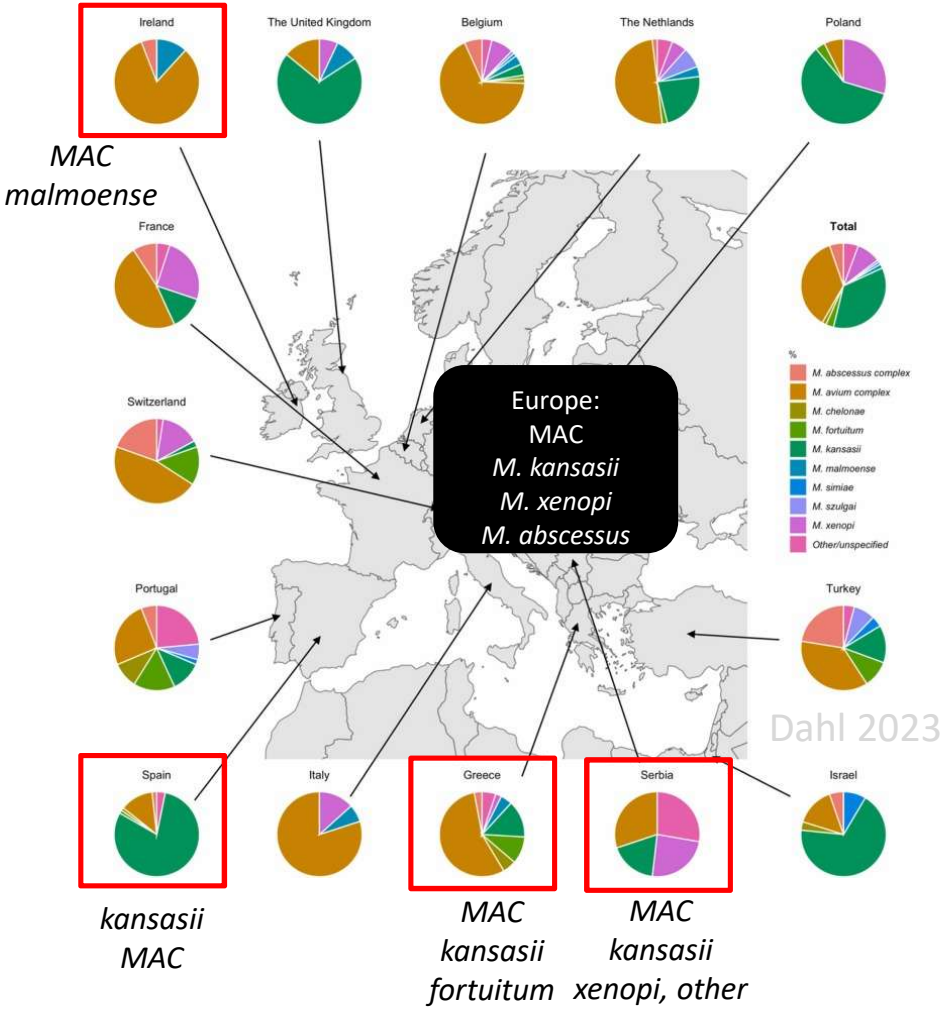
WHY ARE THE RATES OF INFECTIONS RISING?

- **Improved quality of diagnostic methods e.g. microbiological detection techniques**
- **Ageing population with an increase in the prevalence of COPD[2] and other co-morbidities**
- **Increased disease awareness**
- **Decreased rates of Tuberculosis (infection with TB can result in cross-protection against NTM)**
- **Climate change?**

GLOBAL TRENDS - SPECIES DISTRIBUTION



Al-Ghafli 2017



TRANSMISSION OF NTM

Research Center Borstel
Leibniz Lung Center

HABITAT

Lakes
Oceans
Rivers

Hot tubs
Swimming pools
Showers

Potable water
Dust
Soil

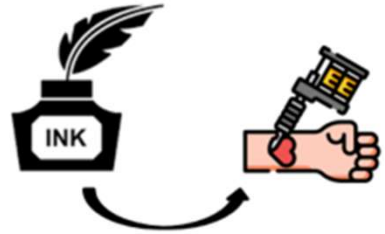
Tattoo ink
Medical devices

inhalation, ingestion and introduction into wounds

Mab in CF community

(Patient-to-patient transmission)

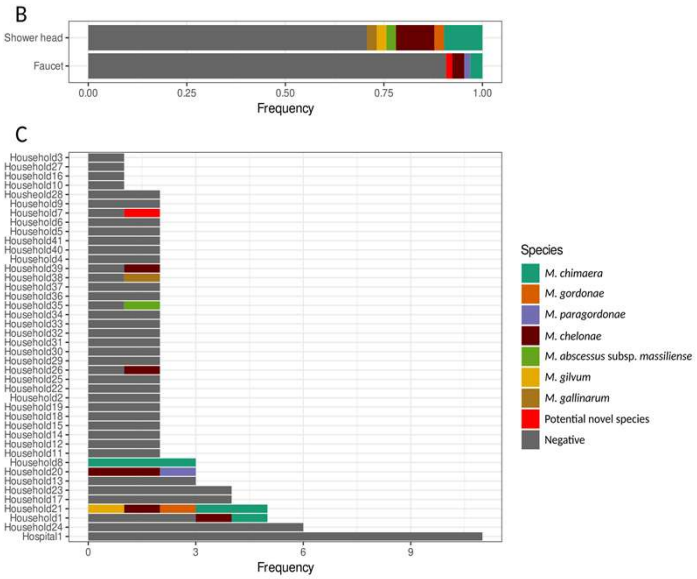
e.g. *M. chelonae*



e.g. national outbreak of post-surgical Mab wound infections in Brasil

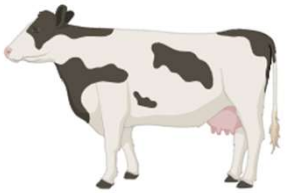
PREVALENCE OF MYCOBACTERIA IN THE ENVIRONMENT

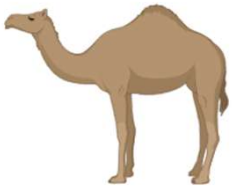
- NTM are frequently found in household water systems
  - Prevalence varies widely by setting and country
  - NTM positivity rate typically between 15-50%; can be up to 95% (Virdi 2021, Diricks 2025, Lande 2019, Thomson 2013)
    - Differs between regions and can depend on isolation protocol
  - Also potentially pathogenic species
  - Partial overlap between environmental and clinical isolates (35-50%) → environmental exposure at home might be an important transmission route

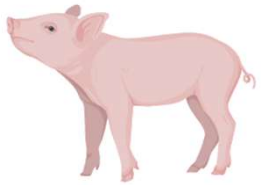


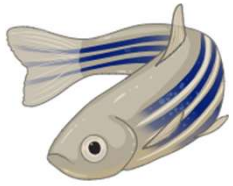
NTM IN ANIMAL

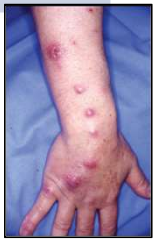
Cows (Gomez-Buendia 2024)	Camel milk (Asaava 2020)	**Amphibians** (Komine 2023)	**Pigs** (Gcebe 2023)	**Fish** (Yazdanmanesh 2024)
M. avium (131)	*M. fortuitum* (3)	*M. marinum*	*M. avium (122)*	*M. marinum (6)*
M. nonchromogenicum (85)	*M. szulgai* (20)	*M. chelonae*	*M. lentiflavum (1)*	*M. fortuitum (3)*
M. bourgelatii (11)	*M. monacense* (5)	*M. fortuitum*	*M. novocastrense (4)*	*M. chelonae* (3)
M. intracellulare (7)	*M. lehmanni* (4)	*M. xenopi*	*M. intracellulare (2)*	*M. parascrofulaceum (1)*
M. kansasii (7)	*M. litorale* (4)	*M. liflandii*		
M. smegmatis (5)	*M. elephantis* (3)			
M. xenopi (4)	*M. duvalii* (3)	*M. montefiorense*		*M. montefiorense*
M. abscessus (3)	*M. brasiliensis* (1)			*M. abscessus*
…	…	…	…	…







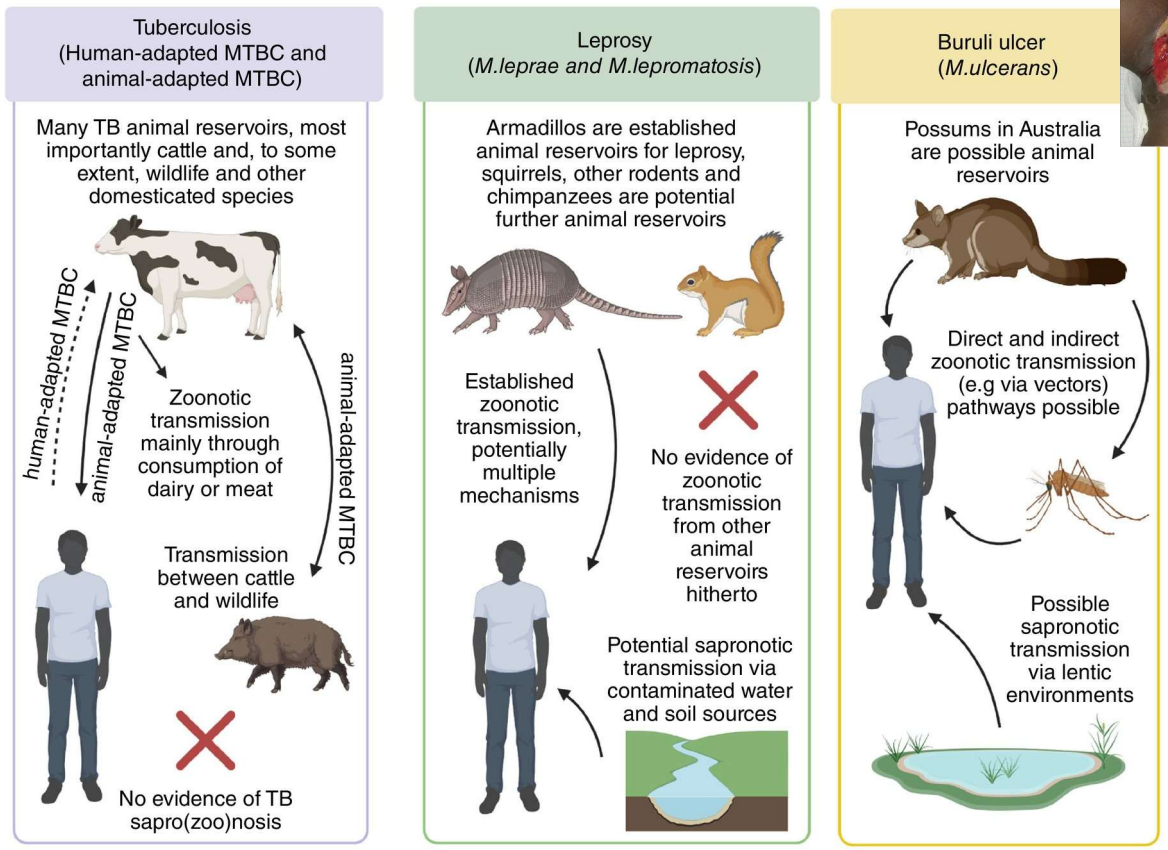




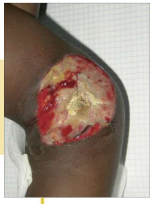
M. avium subsp. paratuberculosis!

Fish tank granuloma

ZOONOTIC TRANSMISSION VIA (IN)DIRECT CONTACT



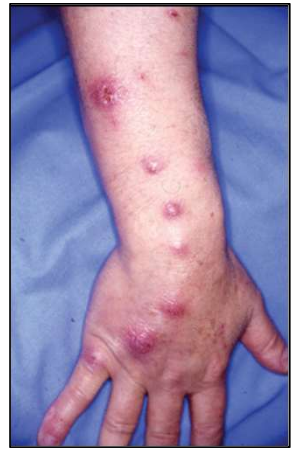
Spiliopoulos 2024



(Sizaire 2006)

M. marinum and M. abscessus: in fishes and humans

- Fish tank granuloma/Swimming pool granuloma



(Hervé Darie, France)

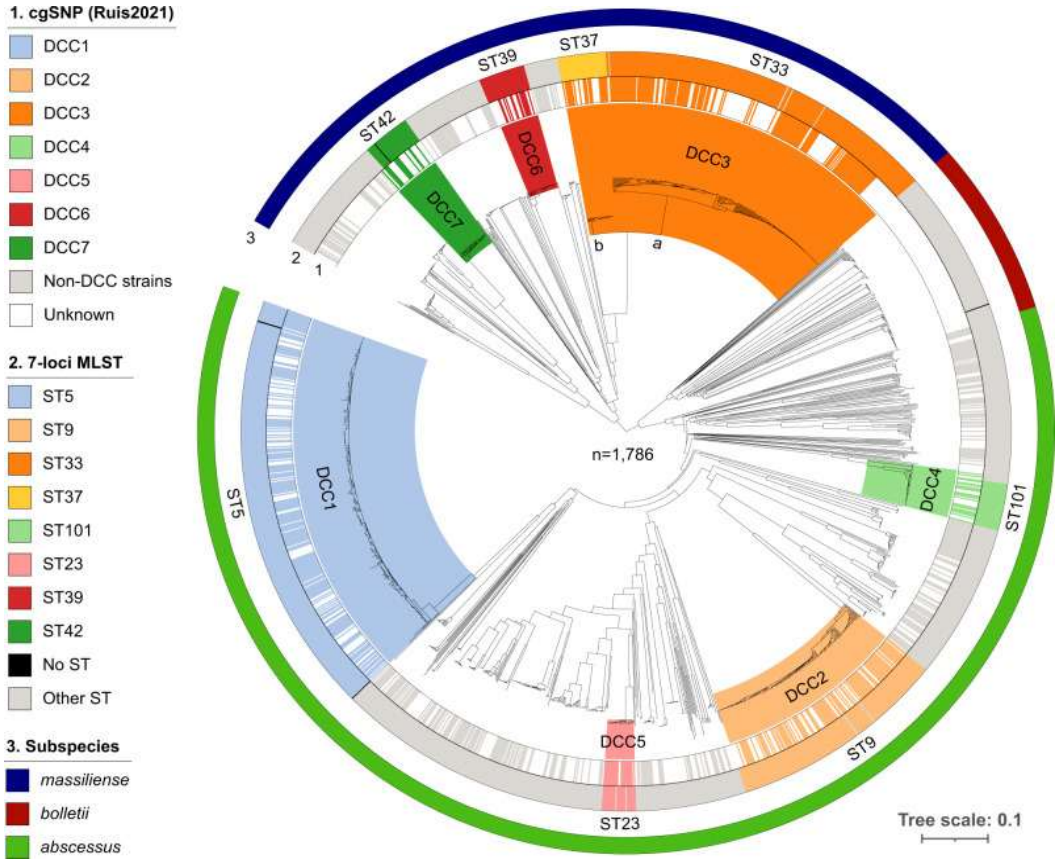
TRANSMISSION OF NTM VIA FOOD

- Mycobacteria can contaminate various food sources: e.g. unpasteurized milk or dairy products (e.g. MAP), vegetables, seafood
- In pubmed: no reports of mycobacteria connected to foodborne illness
- Transmission via food underestimated?
  - Challenge in detection: slow growth and special media required

Population structure of clinically relevant NTM

M. ABSCESSUS

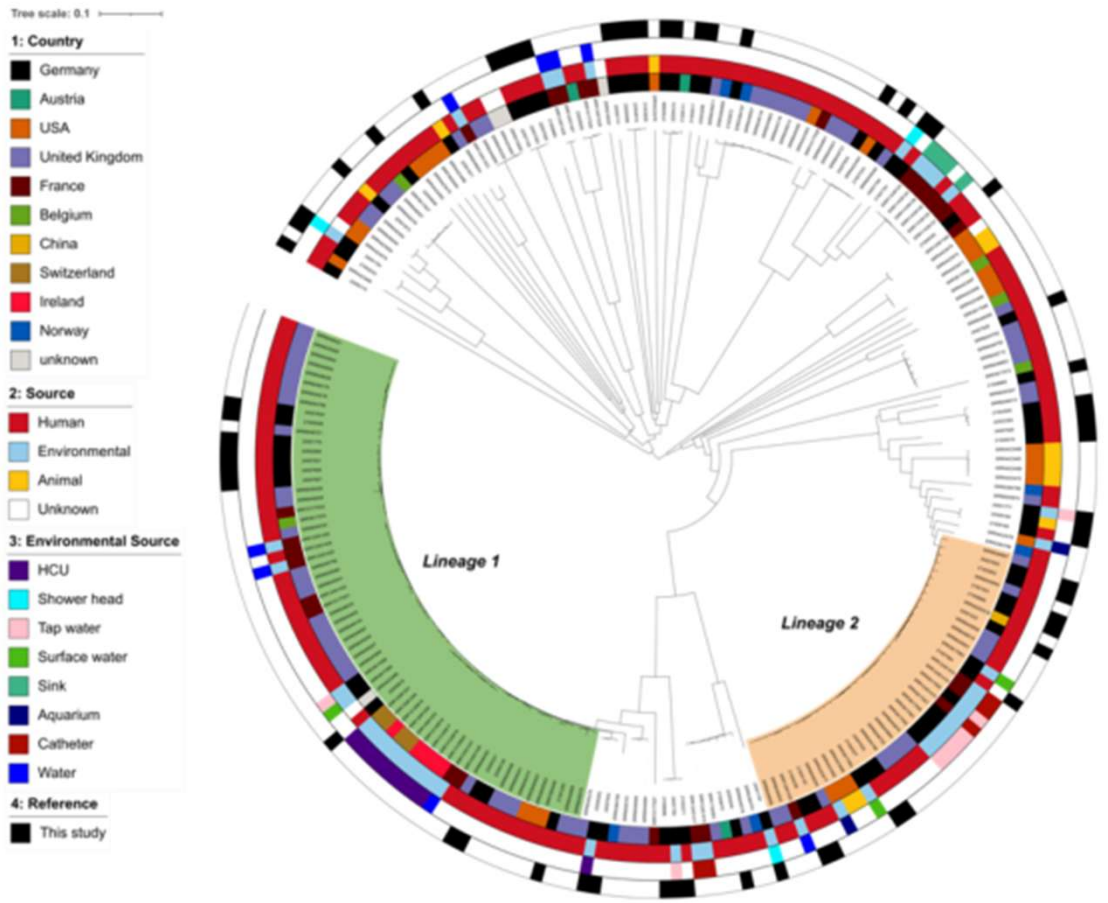
- Rapidly growing NTM
- 3 subspecies
  - *abscessus* → *typically macrolide iR*
  - *massiliense* → *typically macrolide S*
  - *bolletii* → *typically macrolide iR*
- 7 dominant circulating clones (DCCs)
  - Most prevalent
  - Found gobally
  - More virulent
  - Higher resistance rates
  - Worse clinical outcomes
  - Lower mutation rate



Diricks et al. 2022

M. CHELONAE

- Subspecies (e.g. gwanakae) not supported by WGS data
- Dominant circulating clones



Diricks et al. 2025

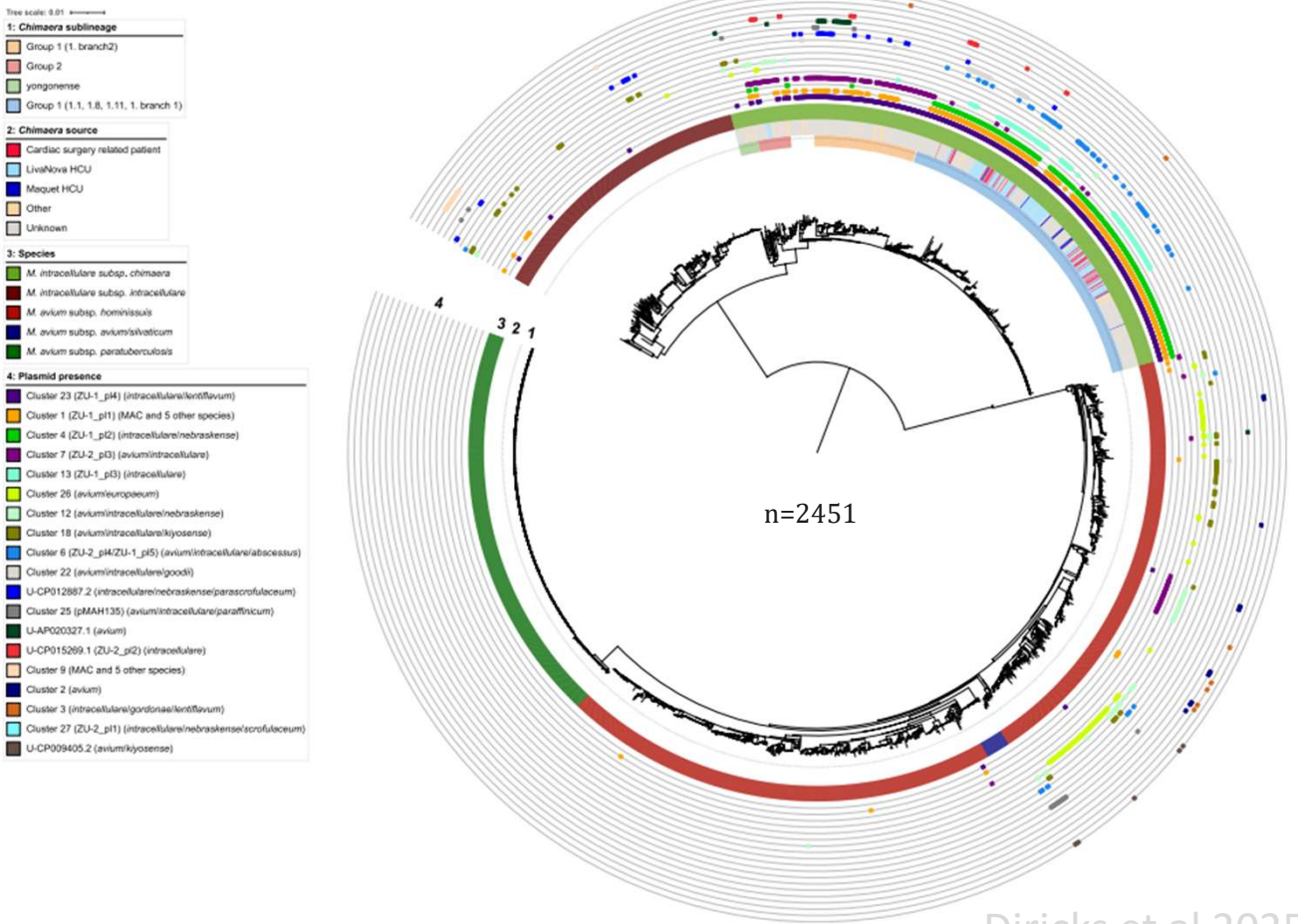
M. AVIUM COMPLEX

- **12 species**
  - ***M. intracellulare*** *(Tortoli 2019)*
    - subsp. *intracellulare*

      (containing former *M. intracellulare* and M. *paraintracellulare*)
    - subsp. *chimaera*

      (containing former *M. chimaera* and *M. yongonense*)
  - ***M. avium***
    - subsp. *hominisuis*

      (No official standing in nomenclature)
    - subsp. *avium/silvaticum*
    - subsp. *paratuberculosis*
  - Other
    - *M. colombiense, arosiense, vulneris, bouchedurhonense*, timonense*, marseillense, yongonense, lepraemurium**



Diricks et al 2025

M. AVIUM COMPLEX

- Co-infections (33% of patients)

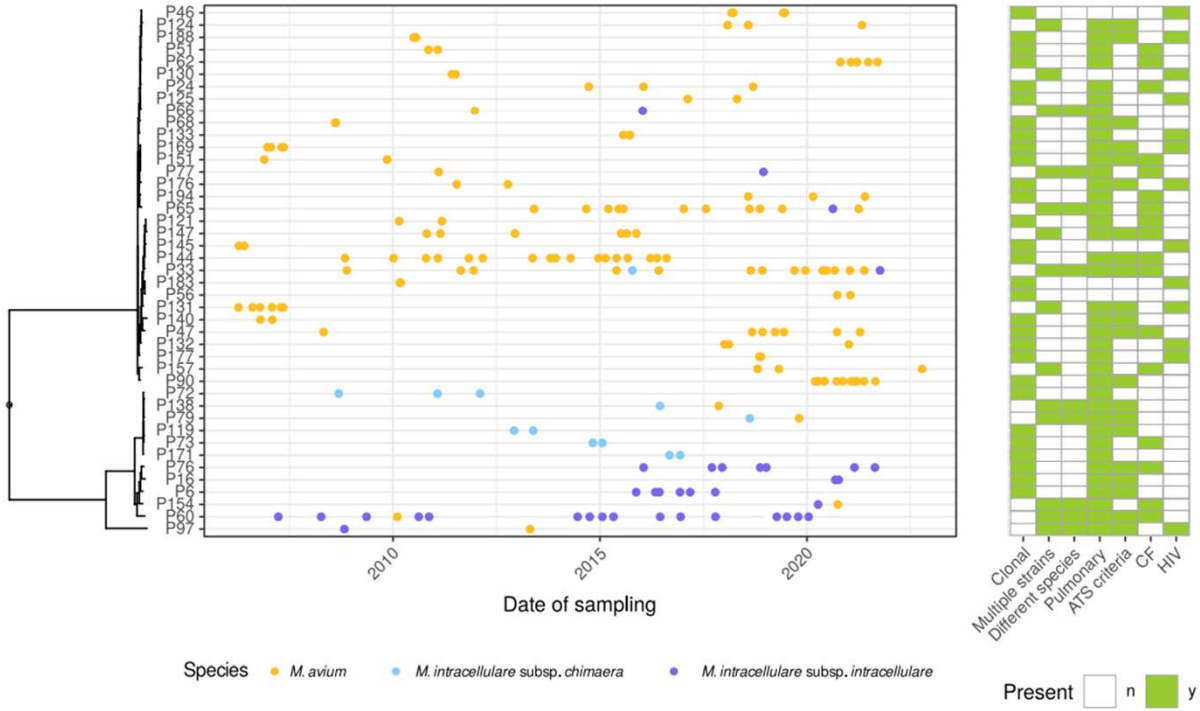
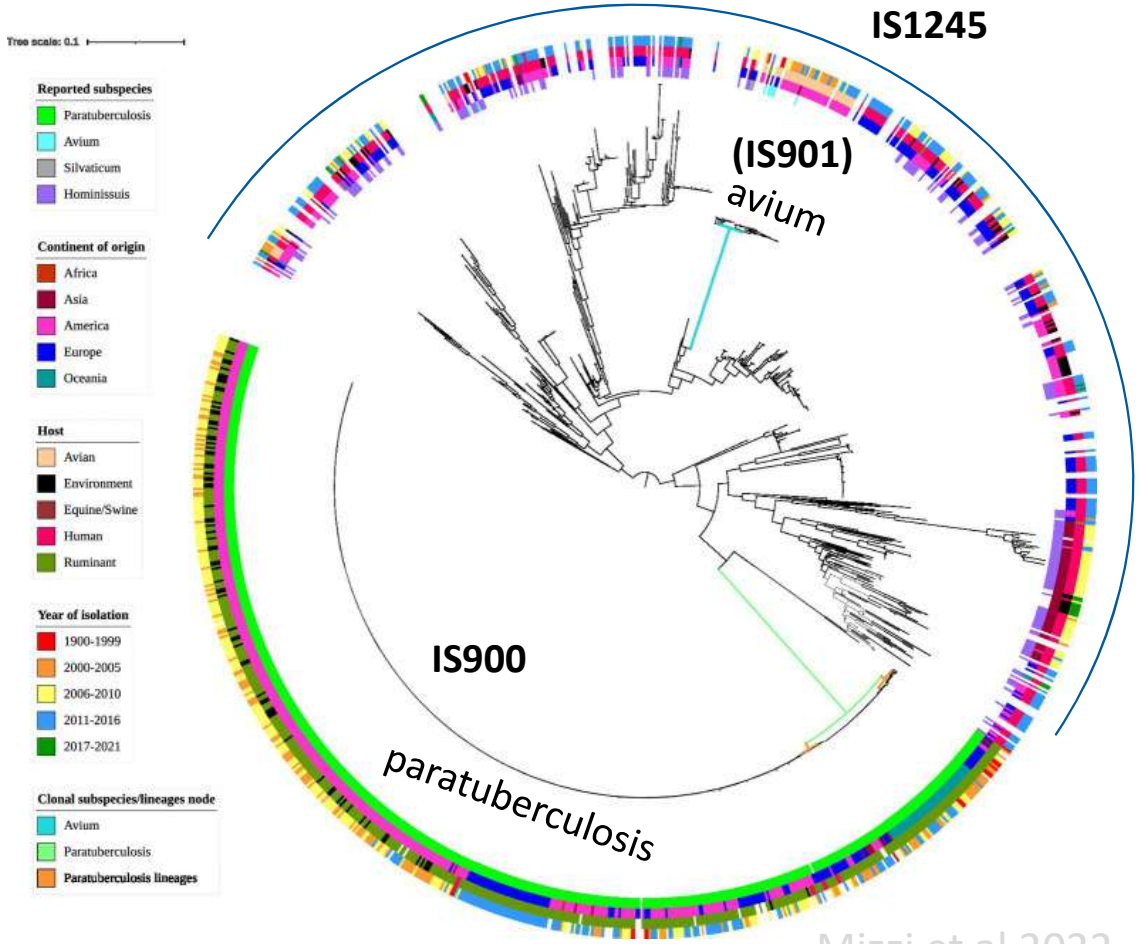


Fig. 4 Timeline of serial isolates in 43 patients treated at Frankfurt University hospital (left panel) and associated clinical characteristics (right panel). Clonal—same strain during the whole observation period, multiple strains—different strains of the same species or different species within the MAC, different species—different species within the MAC. CF—cystic fibrosis, HIV—human immunodeficiency virus, n—no, y—yes

Wetzstein-Diricks et al 2024

M. AVIUM

- subsp. **paratuberculosis**
  - Ruminants
  - Enteritis (Johne`s disease!)
  - Chrohn‘s disease in humans?
  - Highly clonal
- subsp. **avium/silvaticum**
  - Birds
  - Avian tuberculosis (systemic)
- subsp. **hominissuis**
  - Pigs/humans
  - Lymfadenitis, pulmonary disease,…
  - More diverse, many small regional as well as global clusters

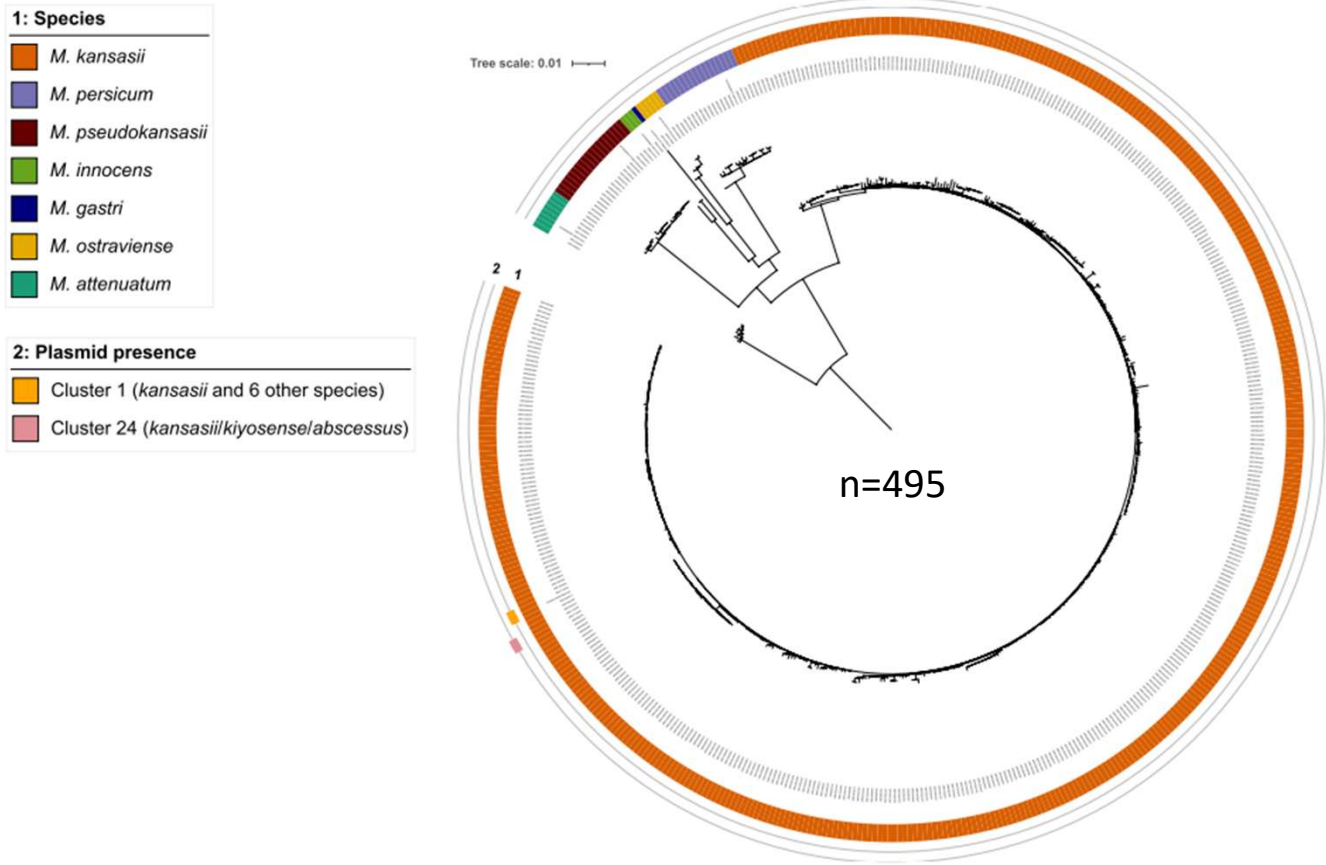


Mizzi et al 2022

M. KANSASII COMPLEX

- **7 species (previous subtypes)**
  - (I) *M. kansasii* sensu stricto

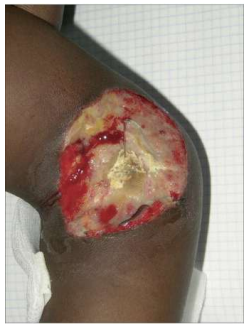
  (most pathogenic and frequently infecting humans)
  - (II) *M. persicum*
  - (III) *M. pseudokansasii*
  - (IV) *M. ostraviense*
  - (V) *M. innocens*
  - (VI) *M. attenuatum*
  - *M. gastri*



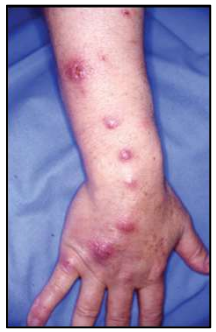
Diricks et al 2025

M. ULCERANS COMPLEX

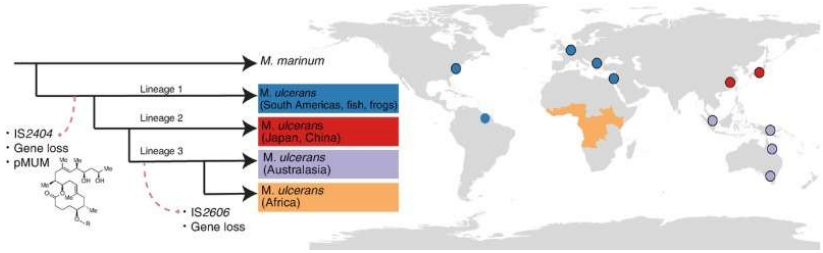
- **5 species**
  - *M. ulcerans* sensu stricto
  - *M. liflandii*
    (ecovar of *M. ulcerans; lineage 1*)
  - *M. pseudoshottsii*
    (ecovar of *M. ulcerans, lineage 1*)
  - *M. shottsii*
  - *M. marinum*



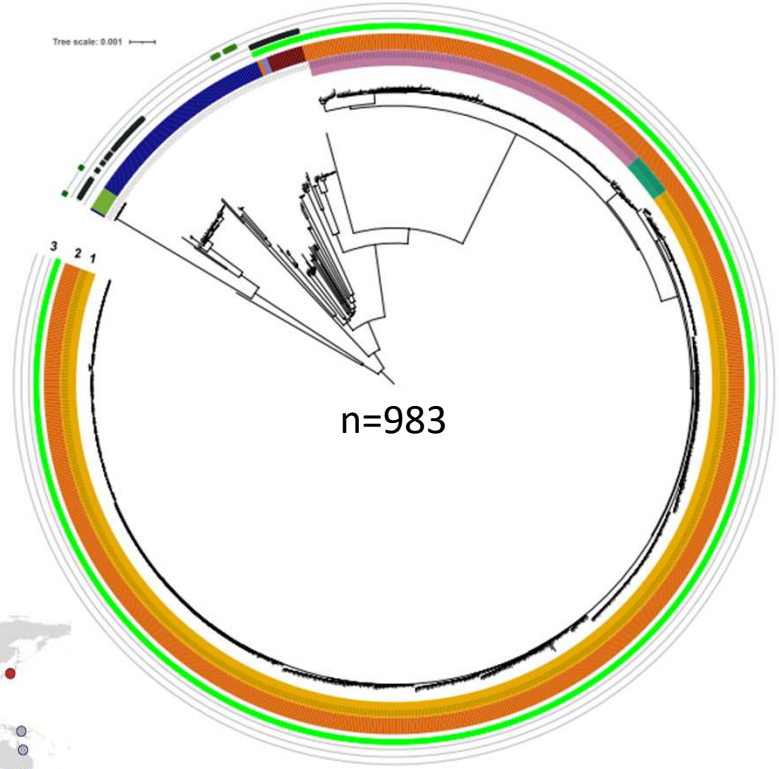
M. ulcerans
(Sizaire 2006)



M. marinum
(Hervé Darie)



Vandelannoote 2019

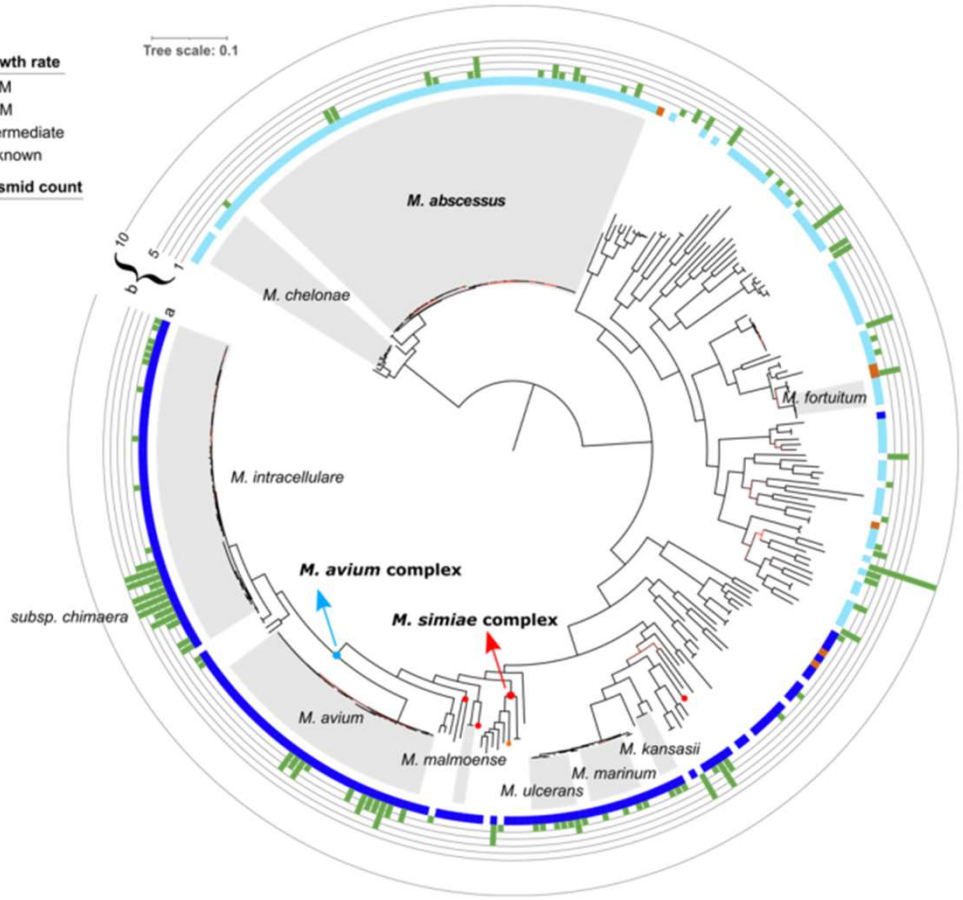


Diricks et al 2025

CONCLUSION

- NTM = All mycobacteria except those causing tuberculosis or leprosy
- >200 species
  - Slow growers (SGM) and rapid growers (RGM)
  - Differences in pigmentation
  - Complex > species > subspecies > dominant circulating clones/lineages (regional or global)
- Environmental organisms
- Few clinically relevant: opportunistic pathogens
  - Pulmonary and extrapulmonary infections
- Difficult to diagnose and treat
- Number of infections/isolations increasing globally

Diricks et al. 2025



SGM = slowly growing mycobacteria; RGM = rapidly growing mycobacteria