Pathogenesis and risk factors for NTM pulmonary disease

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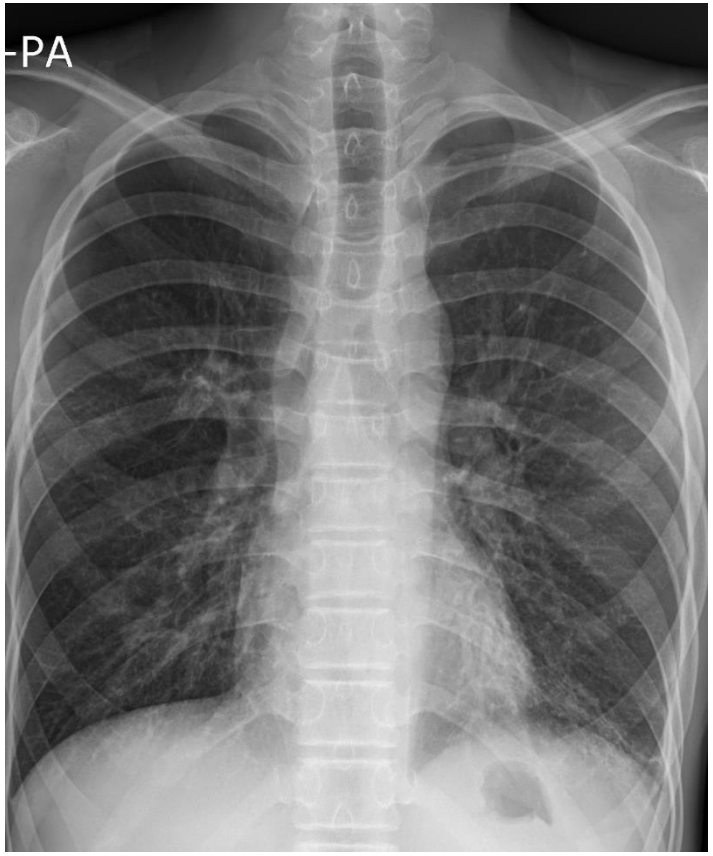
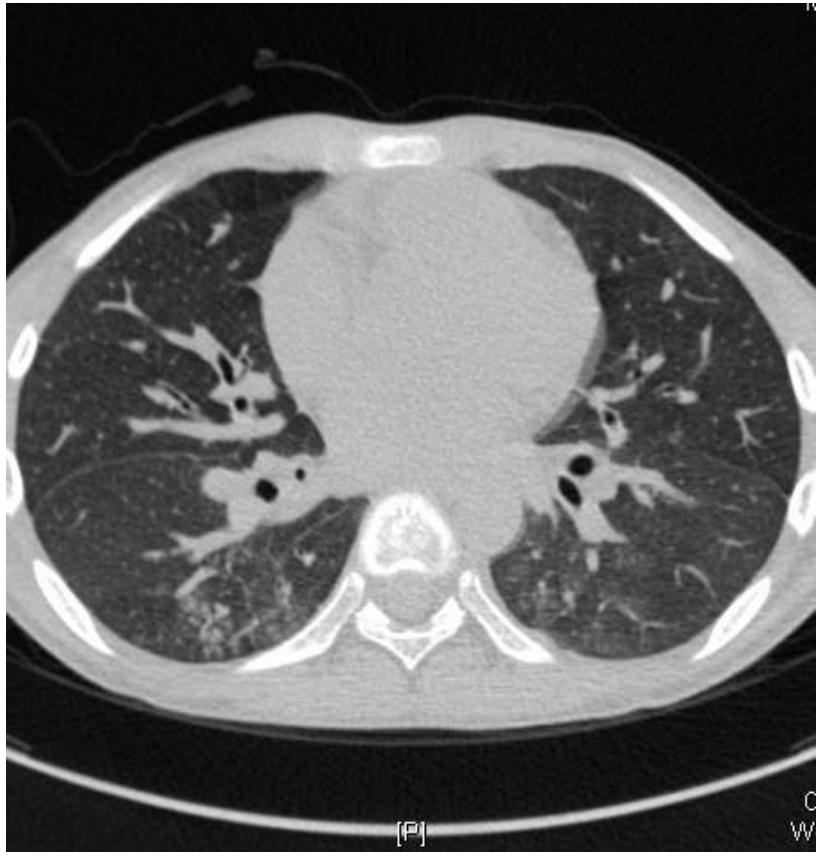
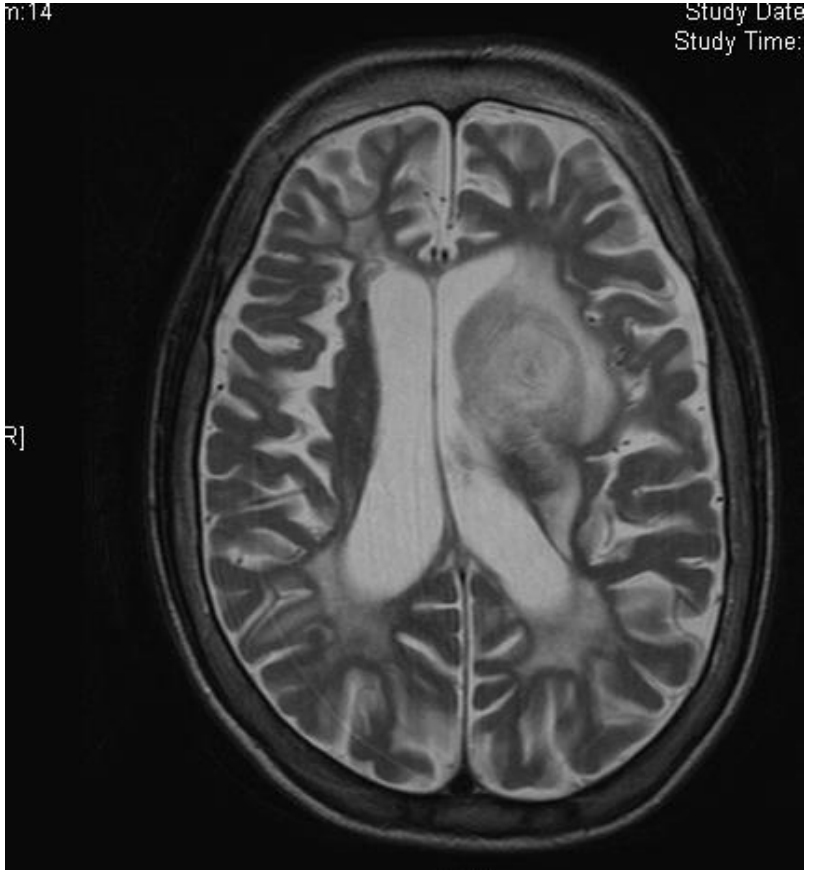
M/17







Cough and sputum
Frequent seizure during treatment of CNS TB

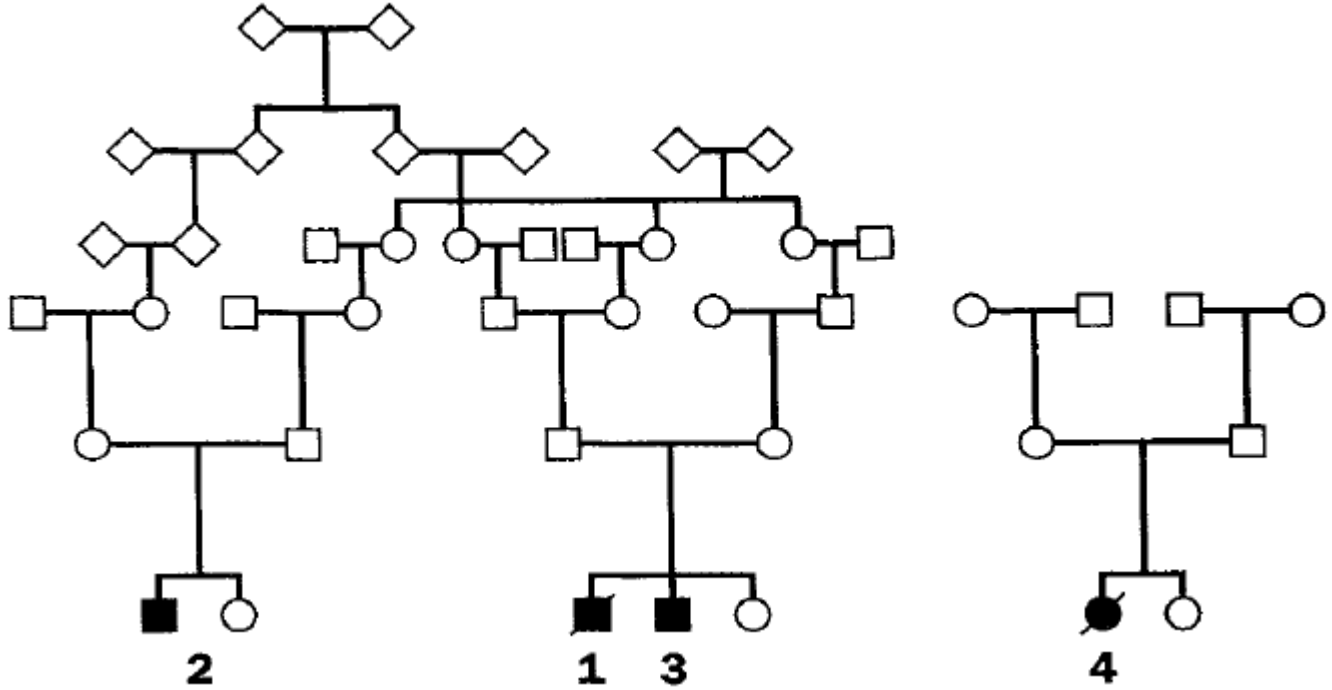
12 sputum AFB culture : *M.avium*

3years later
CNS mass open biopsy:
Chronic granulomatous inflammation, AFB stain positive, NTM PCR: positive

Familial disseminated atypical mycobacterial infection

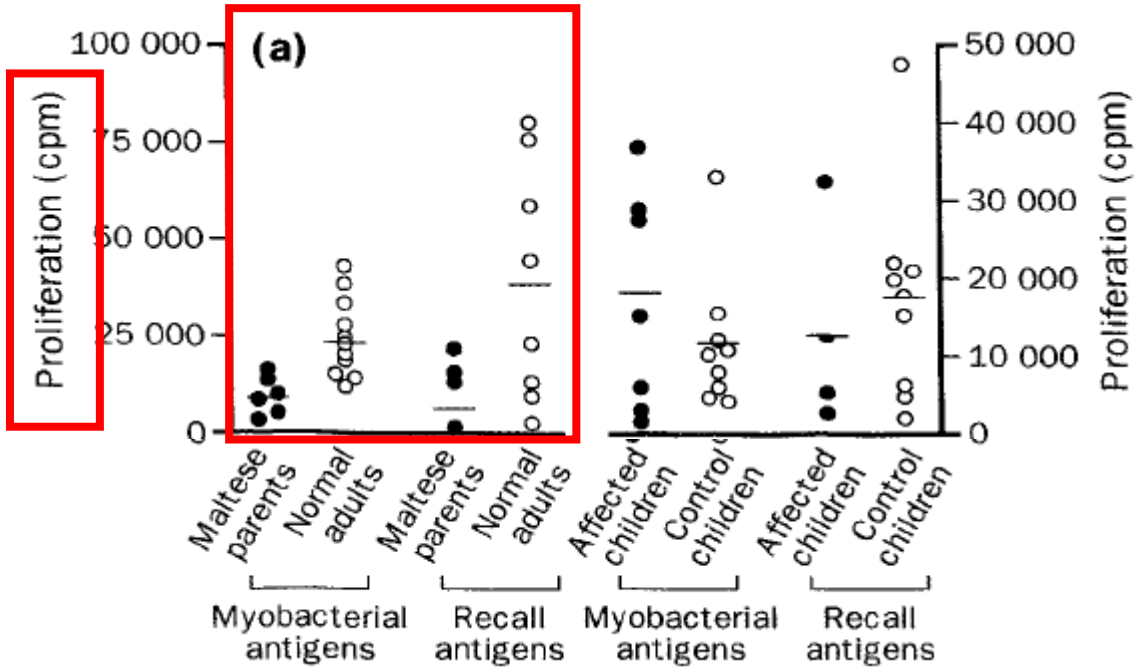
- 6 children with disseminated atypical mycobacterial infection
  - 4 children from same town, Malta
  - No recognized immunodeficiency

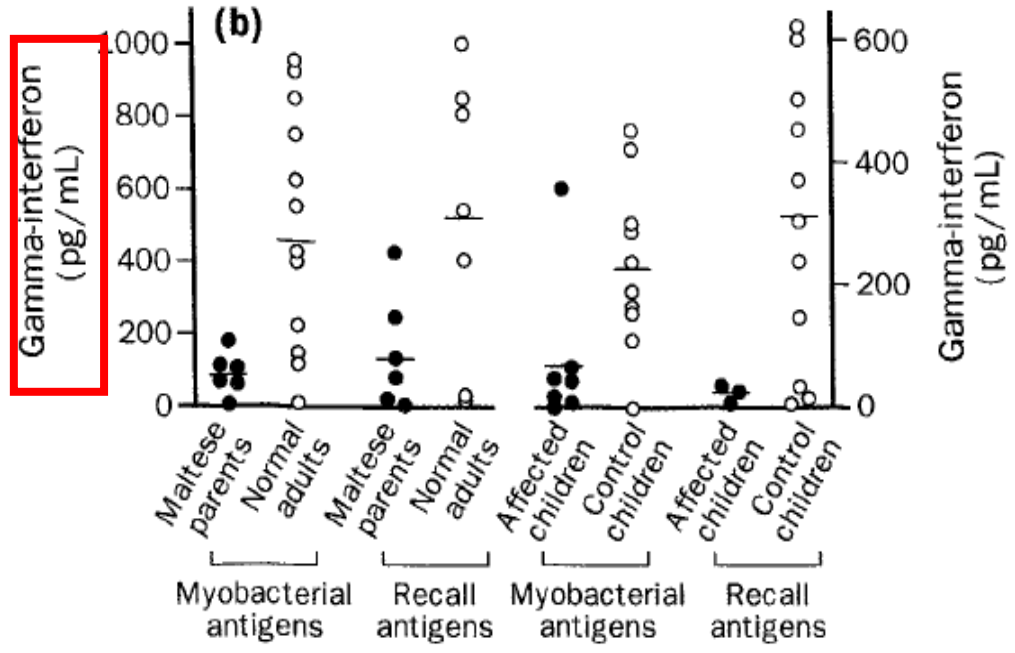
- Fever, weight loss, anemia
- lymphadenopathy
- splenomegaly



Lancet 1995;345:79

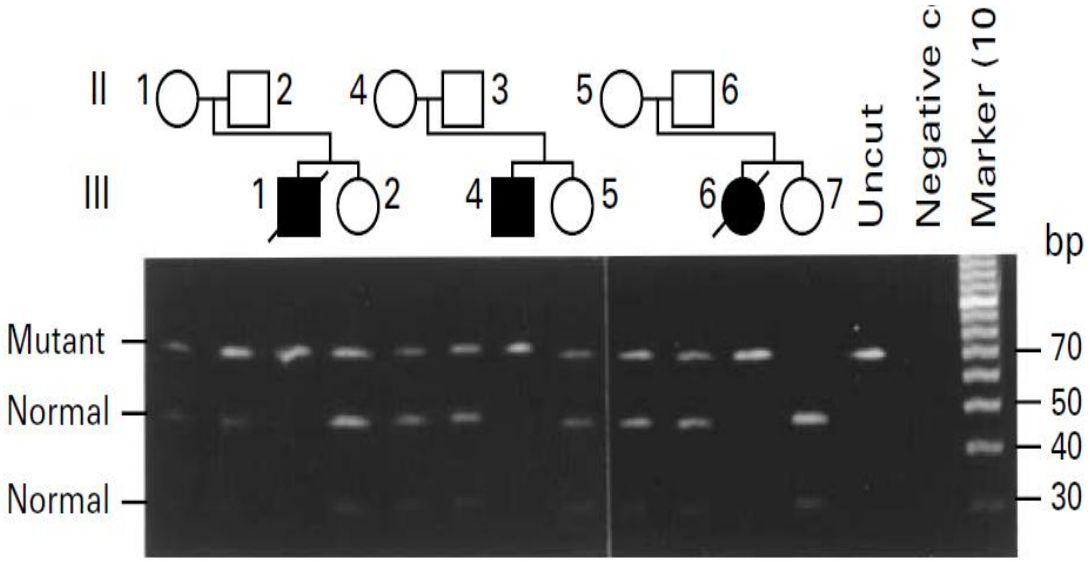
Familial disseminated atypical mycobacterial infection



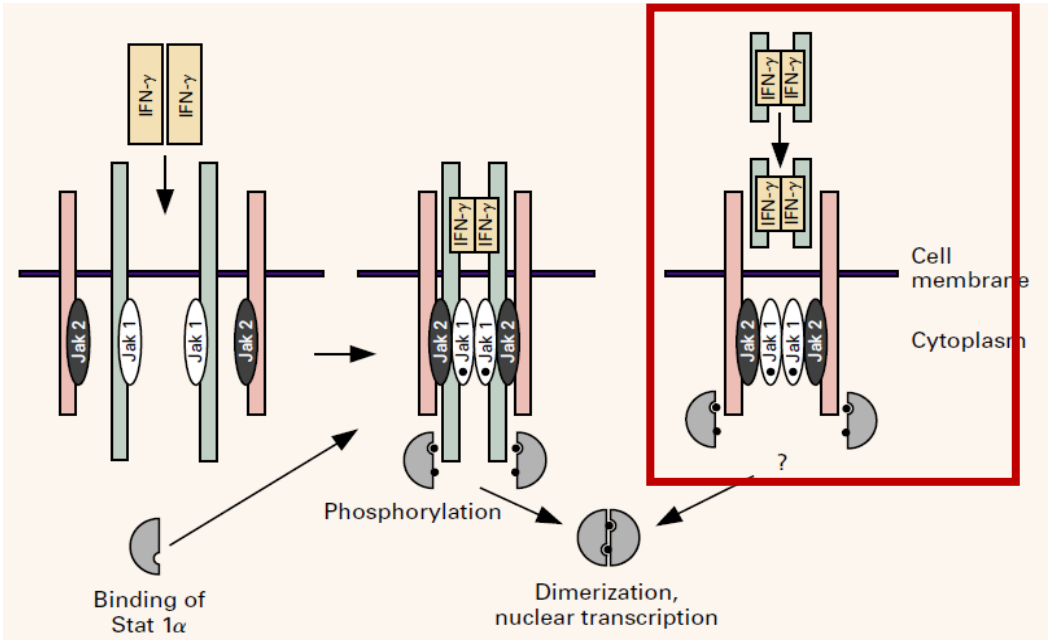


Lancet 1995;345:79

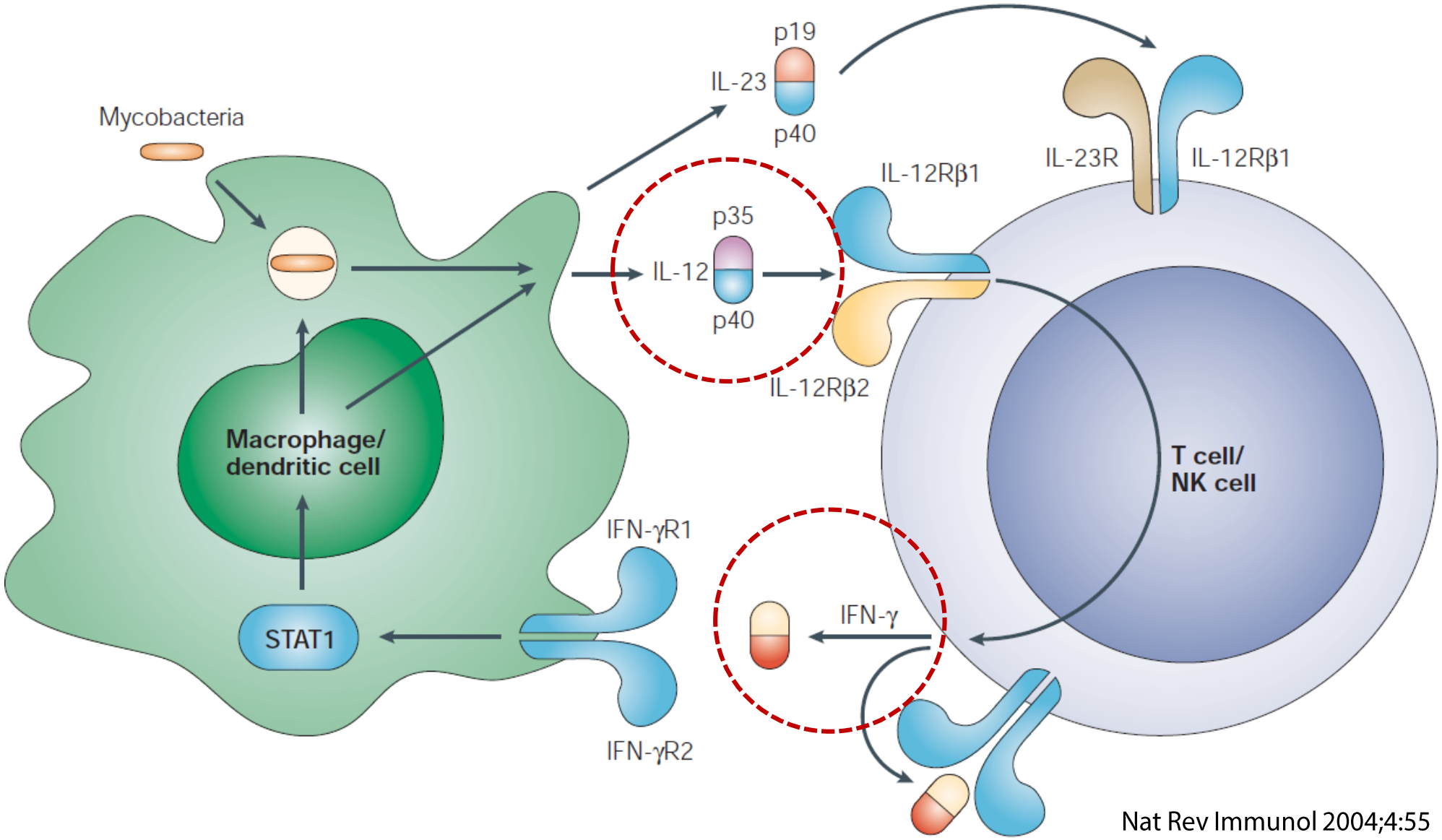
A mutation in the IFN-γ receptor gene in familial case



IFN-γ receptor 1gene



N Engl J Med 1996;335:1941



Nat Rev Immunol 2004;4:55

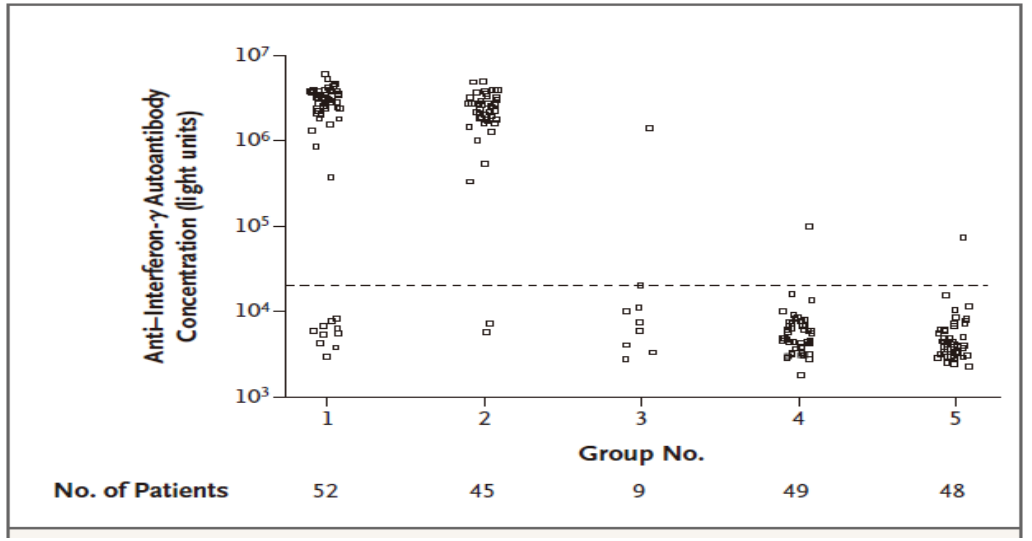
Genetic susceptibility to mycobacterial infection

Gene	Mode of inheritance	Underlying pathogenic disorder
IFN-γ Receptor 1	AD, AR	Impaired cellular response to IFN-γ
IFN-γ Receptor 2	AR	Impaired cellular response to IFN-γ
STAT1α	AD	Impaired cellular response to IFN-γ, IFNα/β
IL-12p40 subunit	AR	Lack of IL-12 production leading to defective activation and differentiation of TH1 cells
IL-12 receptor β1subunit	AR	Defective IL-12 signaling resulting in suboptimal activation and differentiation of TH1 cells
Tyrosine kinase 2	AR	Impaired response to IL-12, IFNα/β, and IL-10
NF-kB essential modulating factor (NEMO/IKBKG)	X-linked	Selective impairment of IL-12 production in monocytes and dendritic cells, partially attributed to impairment of CD40L- IL-12 pathway
MonoMAC syndrome	AD and sporadic	NK- and B-cell lymphocytopenia, Frequent CD4 / CD8 lymphocytopenia
Interferon stimulated gene 15 (ISG15)	AR	Decreased production of IFN-γ by T and NK cells
Interferon regulatory factor 8 (IRF8)	AD, AR	Inadequate priming of T cells to produce IFN-γ
Cytochrome b-245, β polypeptide (CYBB)	X-linked	Selective defect in monocyte-derived macrophage oxidative burst

Clin Chest Med 2015;36:1

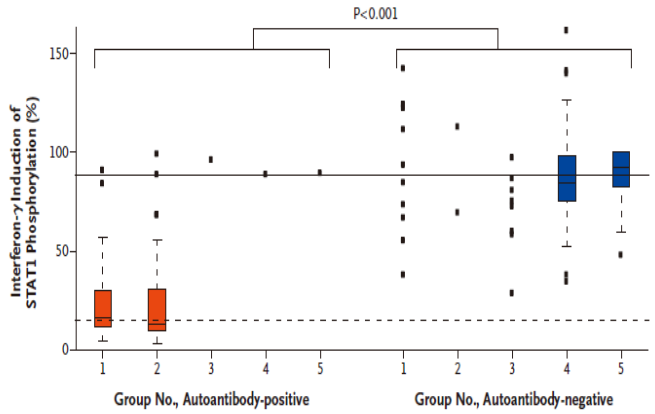
Adult-onset Immunodeficiency IFN-γ autoantibodies

- 204 patients in Thailand and Taiwan
  - G1 :disseminated NTM infection
  - G2 : opportunistic infection w/wo NTM infection
  - G3 : disseminated tuberculosis
  - G4 : pulmonary tuberculosis
  - G5 : health control



	Group1 (n=52)	Group2 (n=45)	Group3 (n=9)	Group4 (n=49)	Group5 (n=48)
Age, median	50	49	38	43	38
range	18-78	22-69	21-74	18-77	21-62
Male,n (%)	21 (40)	17 (38)	3 (33)	28 (57)	22 (46)

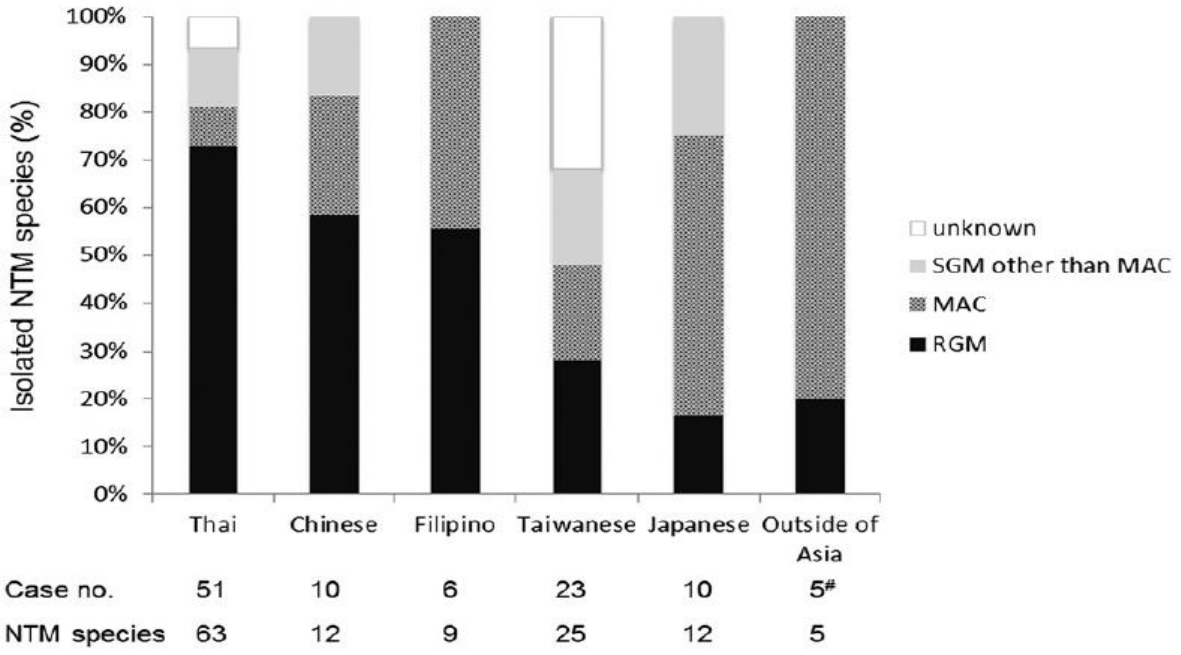
STAT1 phosphorylation

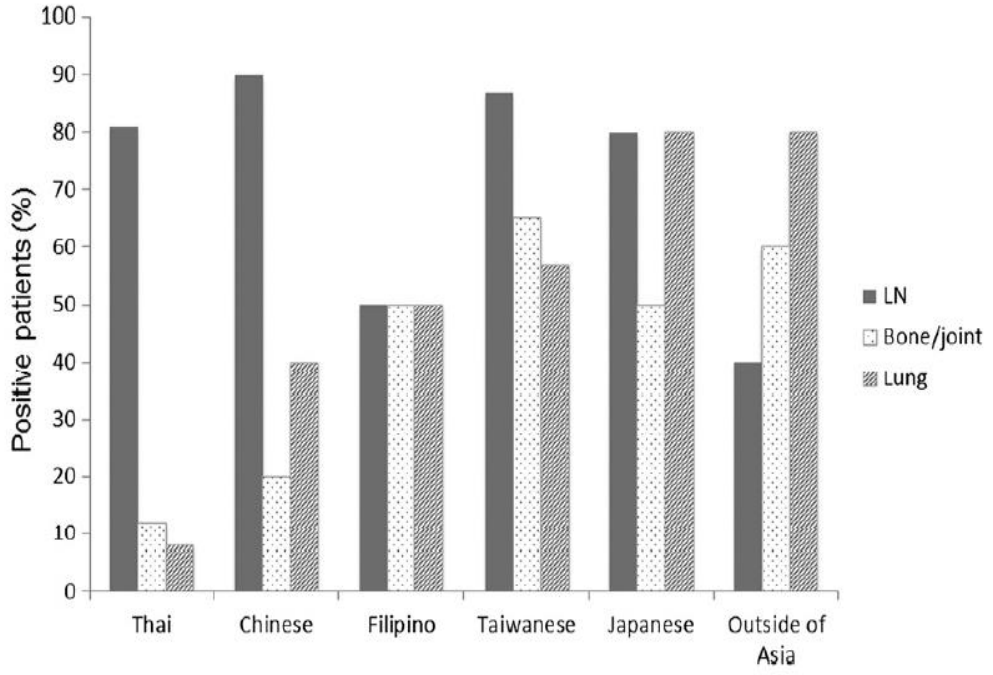


N Engl J Med 2012;367:725

Patient ethnicity and causative species – auto-IFN-γ Ab

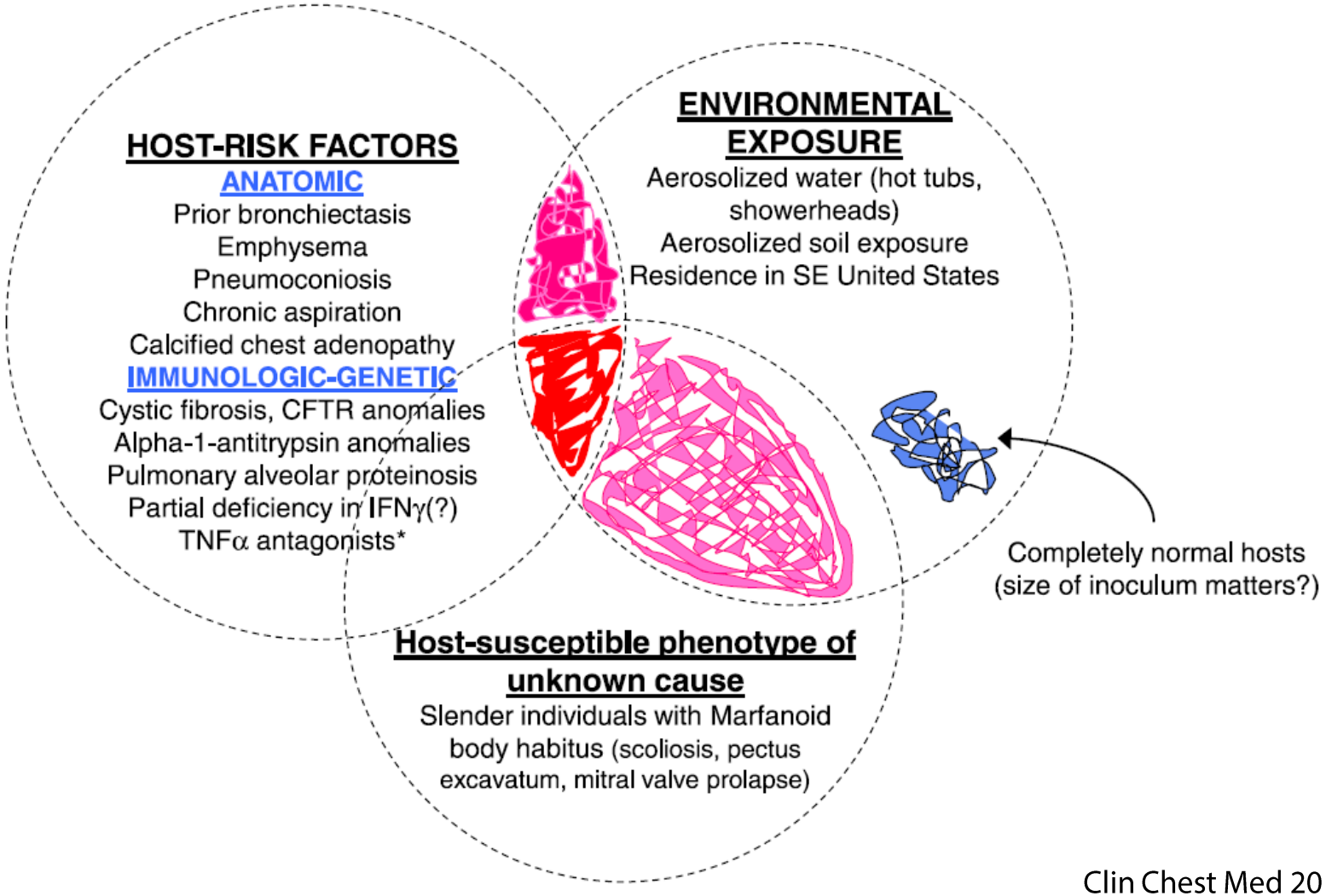
- 111 patients with IFN-γ autoAB with NTM infection, Jan 2004 – Nov 2016
  - 106 patients with disseminated NTM infection
  - 5 patients with localized NTM infection
  - 106 patients from Asia, 5 patients from outside Asia





Diag Microbiol Infec Dis 2017;88:308

Risk factors for NTM pulmonary disease



Clin Chest Med 2015;36:1

Risk factors for pulmonary NTM infection and disease - Host

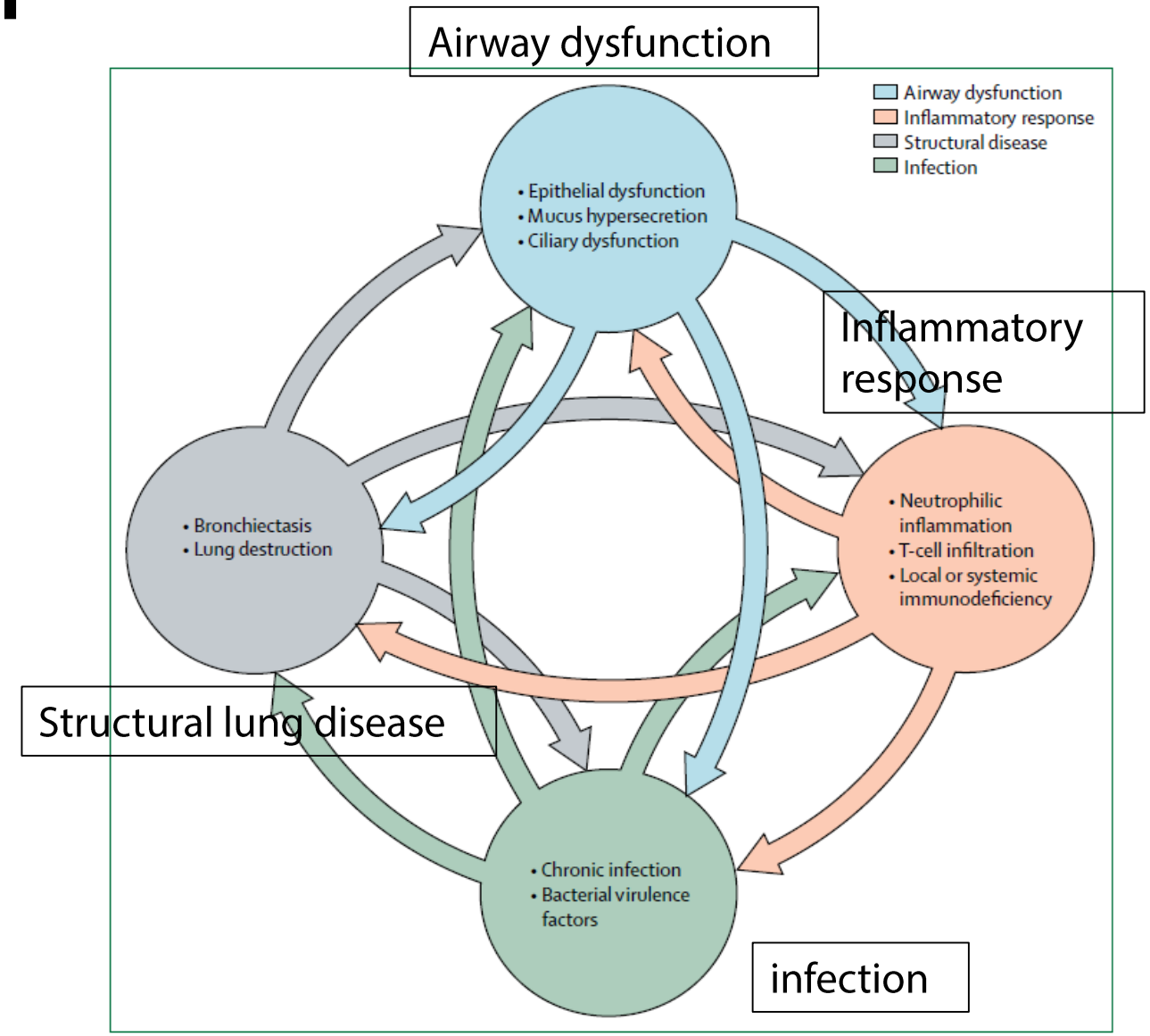
Risk factor	RR, OR or Relative prevalence
Lung Disease	
Bronchiectasis	44-187.5
COPD	2-10
Lung cancer	3.4
Immunosuppression	
Rheumatoid arthritis	1.5, 1.9
Immunomodulatory drugs Anti-TNF agents Others	1.3 2.2 1.6-2.9
Steroid use	1.6, 8
Others	
Thoracic skeletal abnormalities	5.4
Low body weight	9.1
Gastroesophageal reflux disease	1.5, 5.3

Clin Chest Med 2015;36:13

Bronchiectasis – ciliary dysfunction

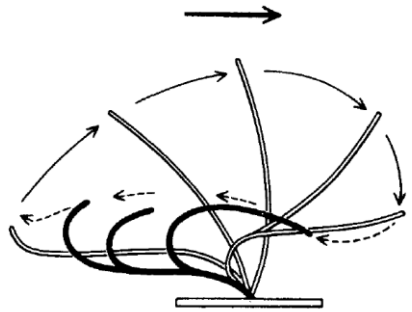
- Impaired muco-ciliary clearance and retention of airway secretion

- Disrupt host's defences and render the airways more susceptible to establishment of chronic infection

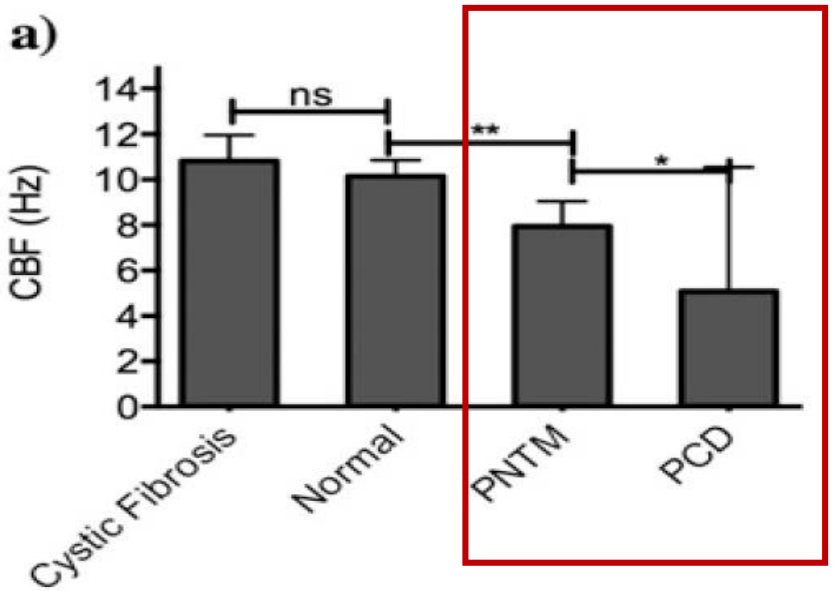


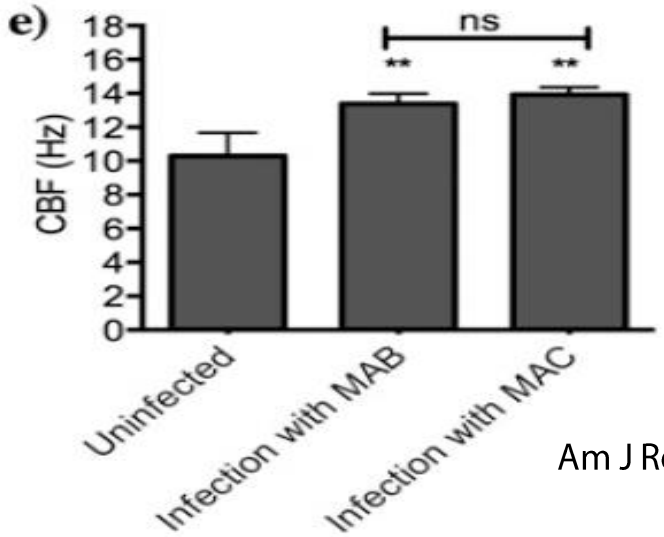
Lancet 2018;392:880

Abnormal ciliary beat frequency in pNTM epithelium



- National Institute of Health (NIH), USA
- 58 pNTM, 8PCD, 5CF, 41 HC
- Primary human respiratory epithelial cells from inferior nasal turbinate
- Ciliary beat frequency (CBF) – mucociliary clearance using video-microscopy
- Mycobacterial infection does not reduce CBF in pNTM patients

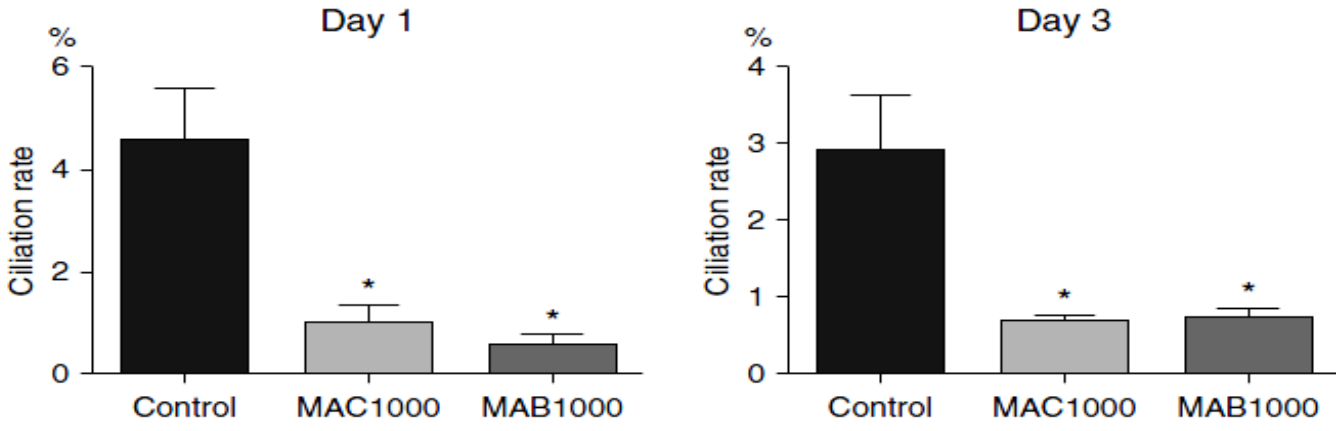




Am J Respir Crit Care Med 2013;187:1374

Transcriptional Response of Respiratory Epithelium to NTM

- National Institute of Health (NIH), USA
- Normal human bronchial epithelial cells, commercially available
- Infection M.avium and M.abscessus in air-liquid interface (ALI)
- RNA sequencing at Days 1 and 3 after infection
  - Down regulation at D3 : cilia- related genes
  - Upregulation at D3 : cytokine/chemokine (IL-32)



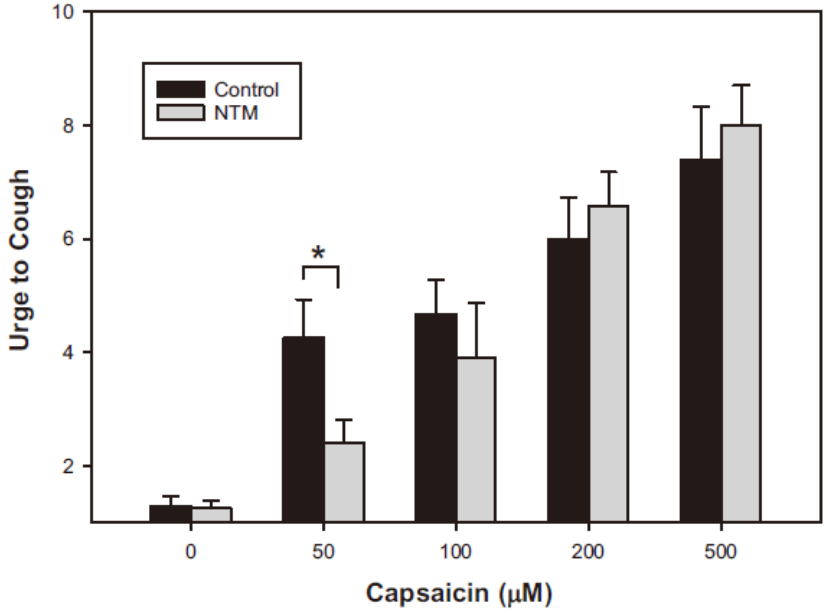
Am J Respir Cell Mol Biol 2018;58:241

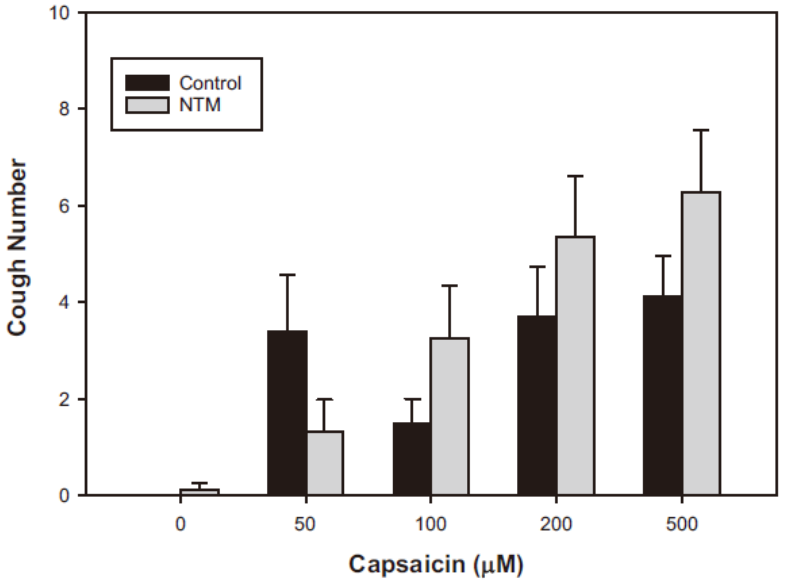
Lady windermere's syndrome

- Syndrome of nodular bronchiectasis in older woman without preexisting lung disease
- Associated pulmonary MAC infection
- From an Oscar Wilde play about a fastidious female character who never coughs
- Can affect the RML and lingular areas that may be more dependent on voluntary expectoration

Cough physiology in elderly women with NTM pulmonary infections

- Airway clearance – an accurate urge to cough (UTC) sensation and functional cough motor pattern necessary
- Capsicin-induced reflex cough to assess the UTC(1-10) and cough motor pattern
- University of Florida
  - 8 female subjects > 65 years with pNTM infections
  - 6 age-matched control subjects without respiratory symptoms

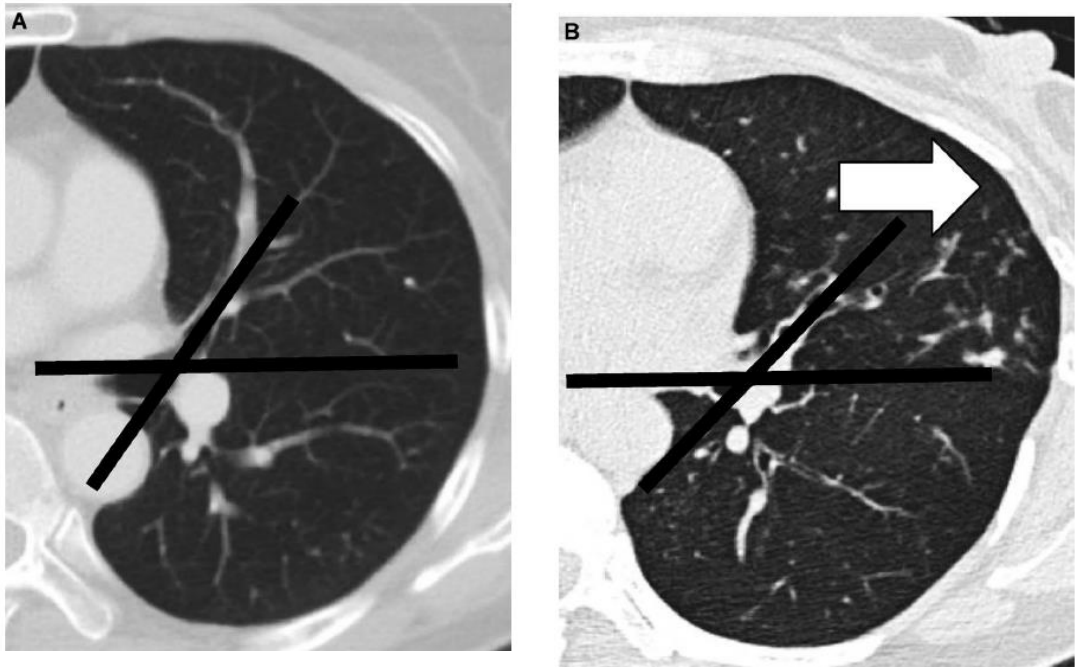




J Appl Physiol 2016;122:1262

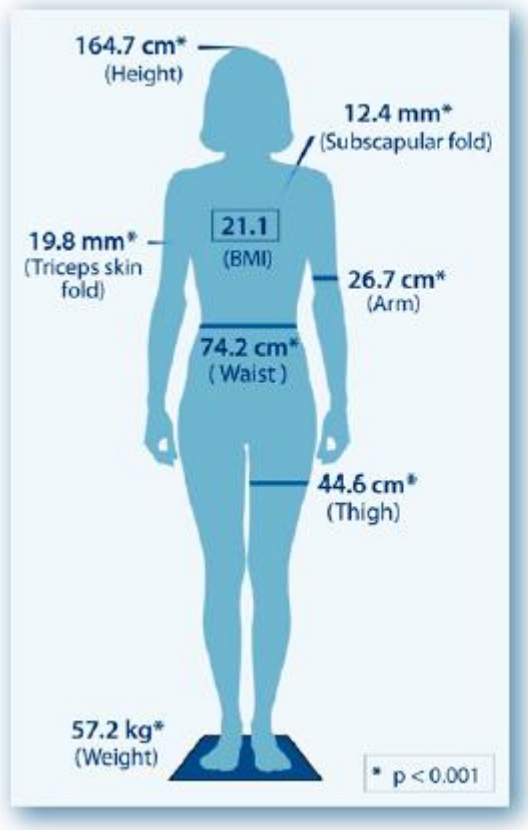
Bronchial angles are associated with NTM lung disease

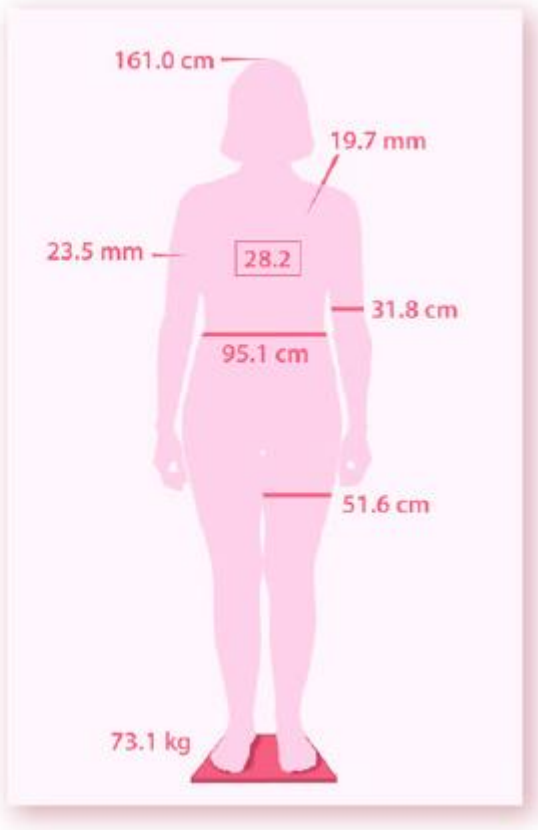
- Case-control study to investigate the relationship between NB NTM lung disease and anatomical risk factors
- 50 patients with NB NTM-LD and 100 healthy controls, SNUBH
- Measurement of angle ; RML and lingular segment
- RML : 51.7° (cont) vs 46.8 ° (pt)
- Lingular : 34.1° (cont) vs 26.9 ° (pt)
- Acute angles → Ineffective drainage



Int J Tuberc Lung Dis 2017;21:1169

Phenotype of unknown cause





- Cases 63 pNTM infection

  Middle aged white women

  Slender, tall

  Scoliosis (51%)

  Pectus excavatum (11%)

  Mitral valve prolapse (9%)

  Higher % of CFTR genes (36.5%)

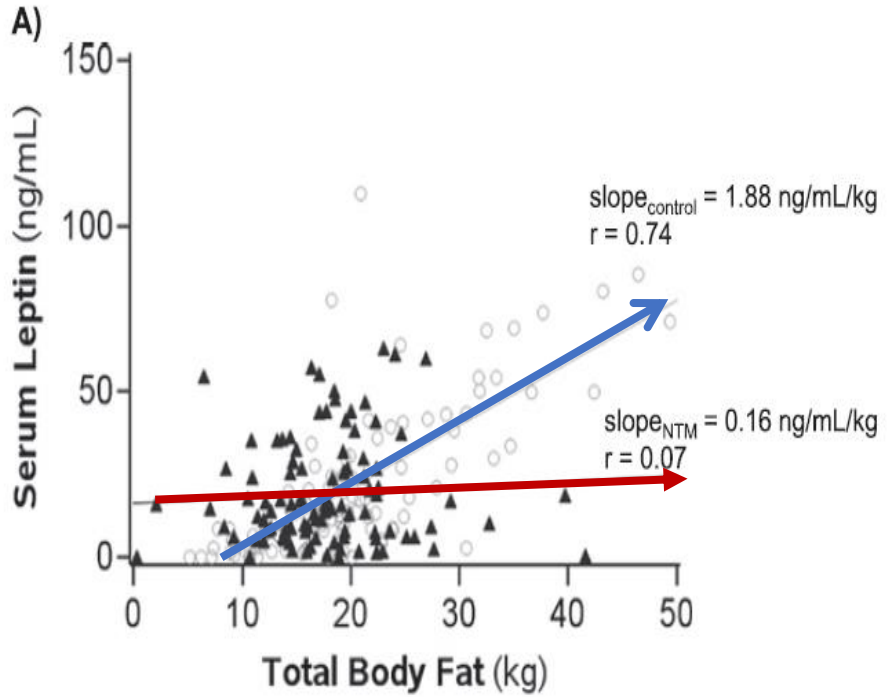
  No cellular immune defects

Am J Respir Crit Care Med 2008;178:1066

Unique body and immune phenotype in patients with NTM LD

- National Jewish Health, USA, 103 NTM LD, 101 Controls

	NTM lung LD (n=103)	Controls (n=101)	p
Height	166.94 (7.62)	161.83 (84.0)	<0.0001
Weight	61.77 (1.23)	63.12 (1.49)	0.48
BMI	22.06 (3.81)	23.98 (5.07)	0.003
Body fat %	28.46 (7.42)	31.28 (7.60)	0.008
Total body fat, kg	17.84 (6.61)	20.43 (8.82)	0.02
Leptin, ng/ml/kg	1.25	0.92	0.03
Adiponectin, ug/ml/kg	1.56	1.04	0.25



Am J Respir Crit Care Med 2013;187:197

Phenotypic, immunologic and clinical characteristics, NTM and BE

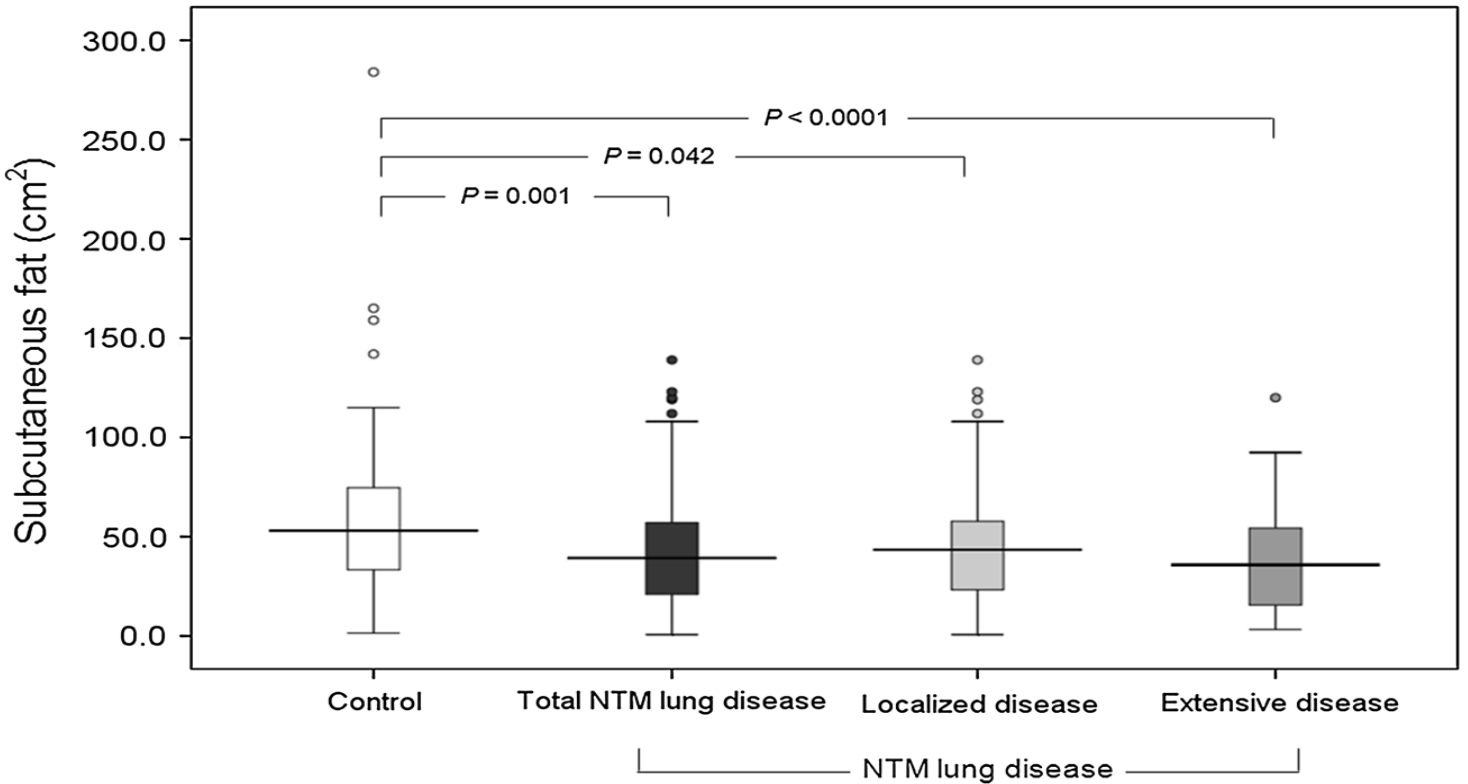
- 84 patients with NTM LD, NB form, 47 patients with non-NTM BE, SNUH, Korea

	NTM lung disease (n=84)	Non-NTM BE (n=47)	p
Height(cm, median)	160 (156,168)	159 (153,167)	0.23
Weight (kg, median)	54.0 (48.3, 60.0)	55.5 (51.0, 63.0)	0.04
BMI (kg/m2, median)	20.8 (19.3, 22.1)	22.2 (20.5, 24.2)	<0.01
Scoliosis, n (%)	20 (23.8)	4 (8.5)	0.04
Pectus excavatum, n (%)	6 (7.1)	0 (0)	0.09

BMC Infec Dis 2013;13:558

The impact of low subcutaneous fat in pNTM patients

- 148 patients with NTM LD, 142 age- and sex-matched control, Ewha Womans University, Korea, 43 FC form, 105 NB form
- Chest CT prior to diagnosis of NTM lung disease, NTM was identified < 3mo
- Asses abdominal subcutaneous fat on chest CT at the mid-pole level of left kidney

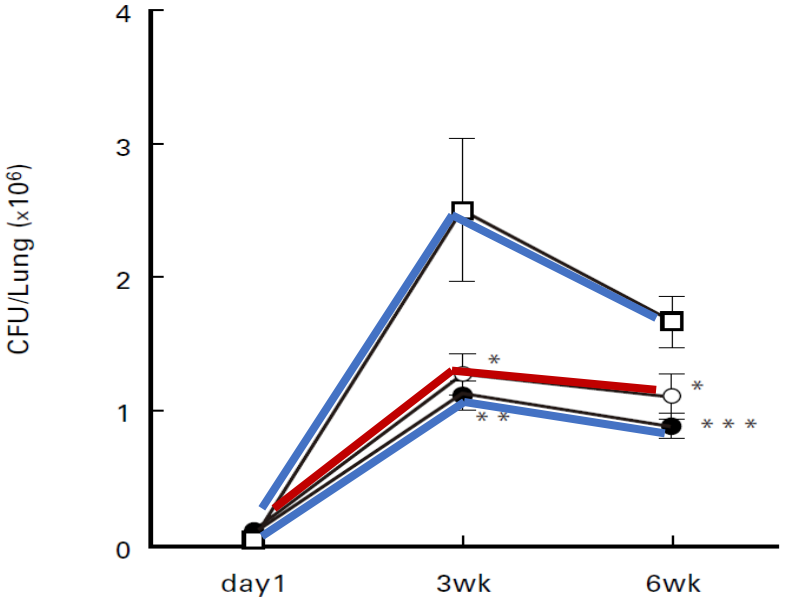


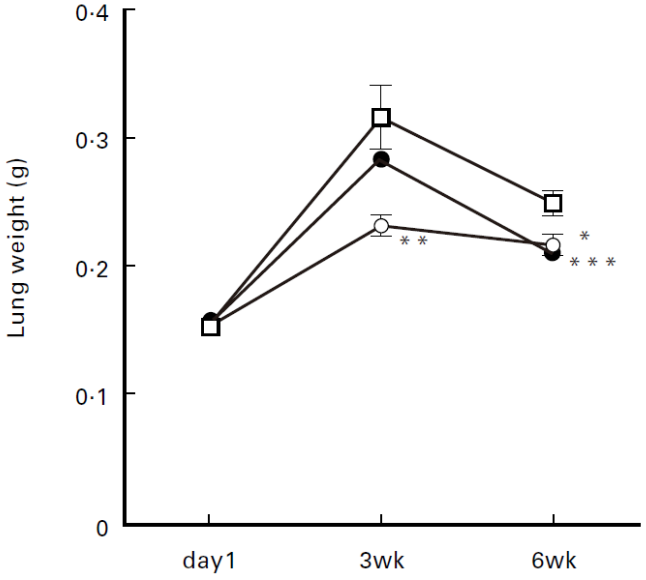
Lung 2014;192:395

Effect of oestrogen on MAC pulmonary infection in mice

- National Minami-Kyoto Hospital, Kyoto University, Japan
- Specific-pathogen free DBA/2 female mice, 6wks
- MAC intra-tracheal infection

  □Ovariectomy / ○Ovariectomy with E2 (Estradiol, subcutaneous) /● sham control





Clin Exp Immunol 2001;123:428

Normal estrogen, but low dehydroepiandrosterone levels in women with pMAC

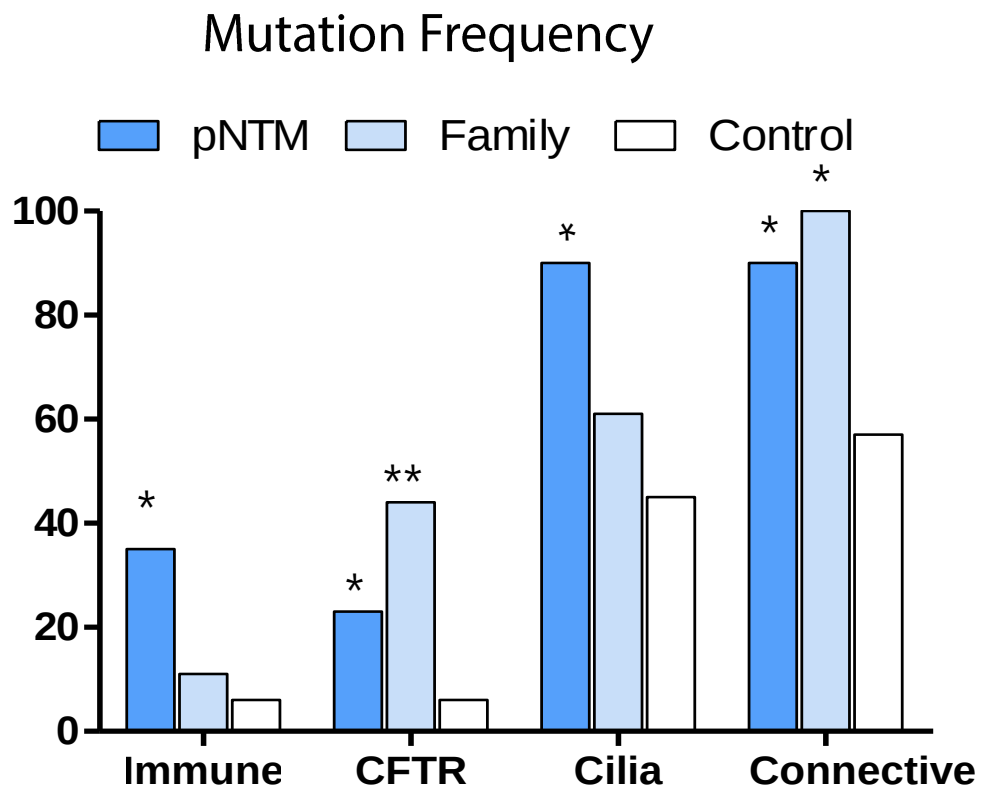
- Lankenau Medical Center, USA
- Post-menopausal status women
  - Patients with pulmonary MAC infection (n=35)
  - Age-matched control (n=27)

	Control (n=27)		Patients with MAC (n=35)		p
	N	Mean (SD)	N	Mean (SD)	
Ultrasensitive estradiol, pg/ml	26	9 (8)	30	9 (9)	0.364
Estrone, pg/ml	26	28 (17)	32	27 (13)	0.665
DHEA-S, ug/dl	15	59 (22)	15	33 (20)	0.001

Ann Am Thorac Soc 2014;11:908

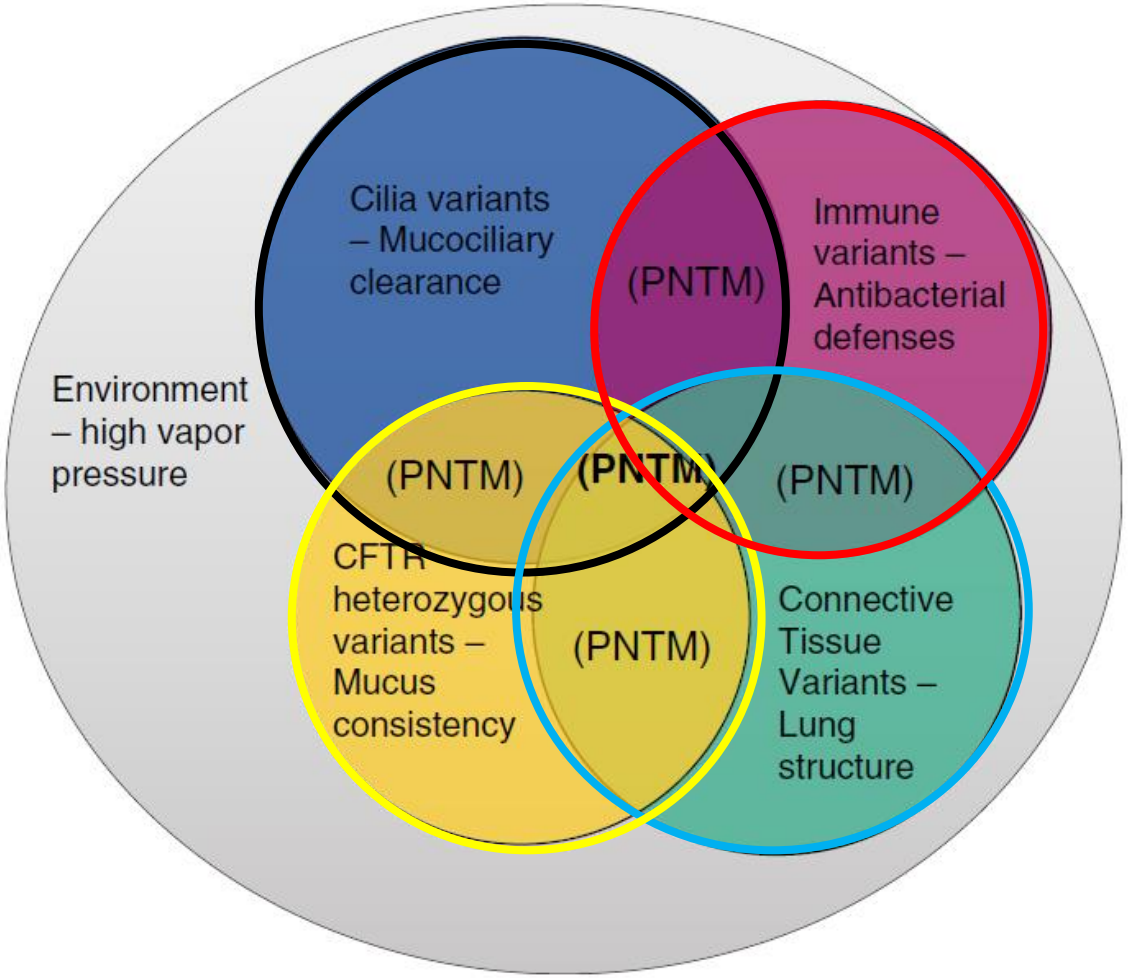
Whole-exome sequencing in pNTM infection

- National Institute of Health (NIH), USA
- 69 white pNTM patients, 18 of their unaffected family members, 1000G control
- Candidate gene analysis : immune, CFTR, cilia and connective tissue gene sets
- Average number of variants across all categories
  - 5.26 in pNTM patients vs 1.98 in control subjects



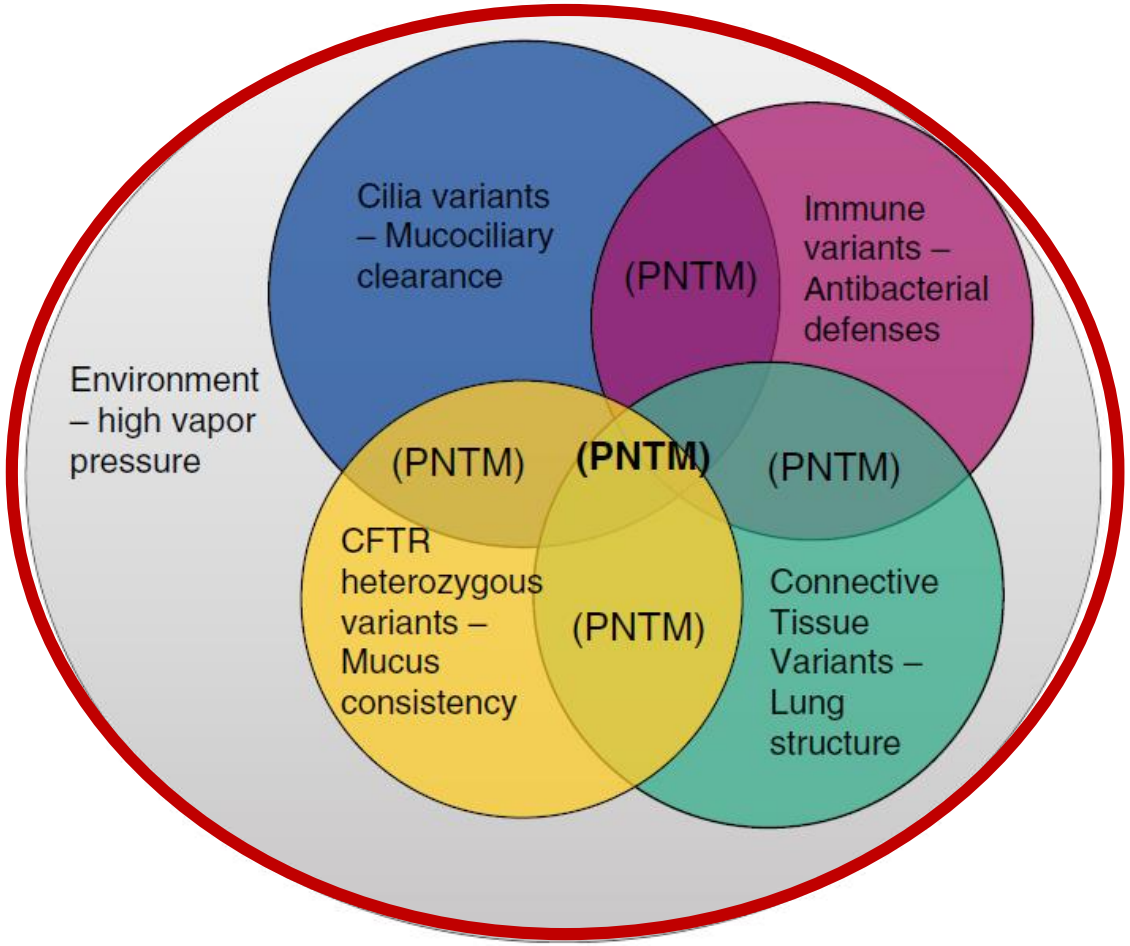
Am J Respir Crit Care Med 2015;192:618

Multiple category "hits" leading to infection



Am J Respir Crit Care Med 2015;192:618

Multisystem, Multigenic Disease with Environmental exposure



Am J Respir Crit Care Med 2015;192:618

Risk factors for pulmonary NTM infection and disease - Environment

Risk factor	RR, OR or Relative prevalence
Environmental : Individual exposures	
Water :Indoor swimming pool use (in past 4mo)	5.9 (1.3, 26.1)
Swimming pool use at least once/mo (in/outdoor in 5yrs)	0.15 (0.04-0.67)
Soil exposure	5.9
Environmental : climate and population factors	
Water : Proportion of areas as surface water	4.6
Mean daily potential evapotranpiration	4.0
Soil : Copper soil levels, per 1ppm increase	1.2 (1.0, 1.2)
Sodium soil levels, per 0.1 ppm increase	1.9 (1.2, 2.9)
Manganese soil levels, per 100ppm increase	0.7 (0.4, 1.0)
Increased average topsoil depth	0.87 (M.intracellulare)
Soil bulk density	1.8 (M.kansasii)

Clin Chest Med 2015;36:13

NTM Everywhere





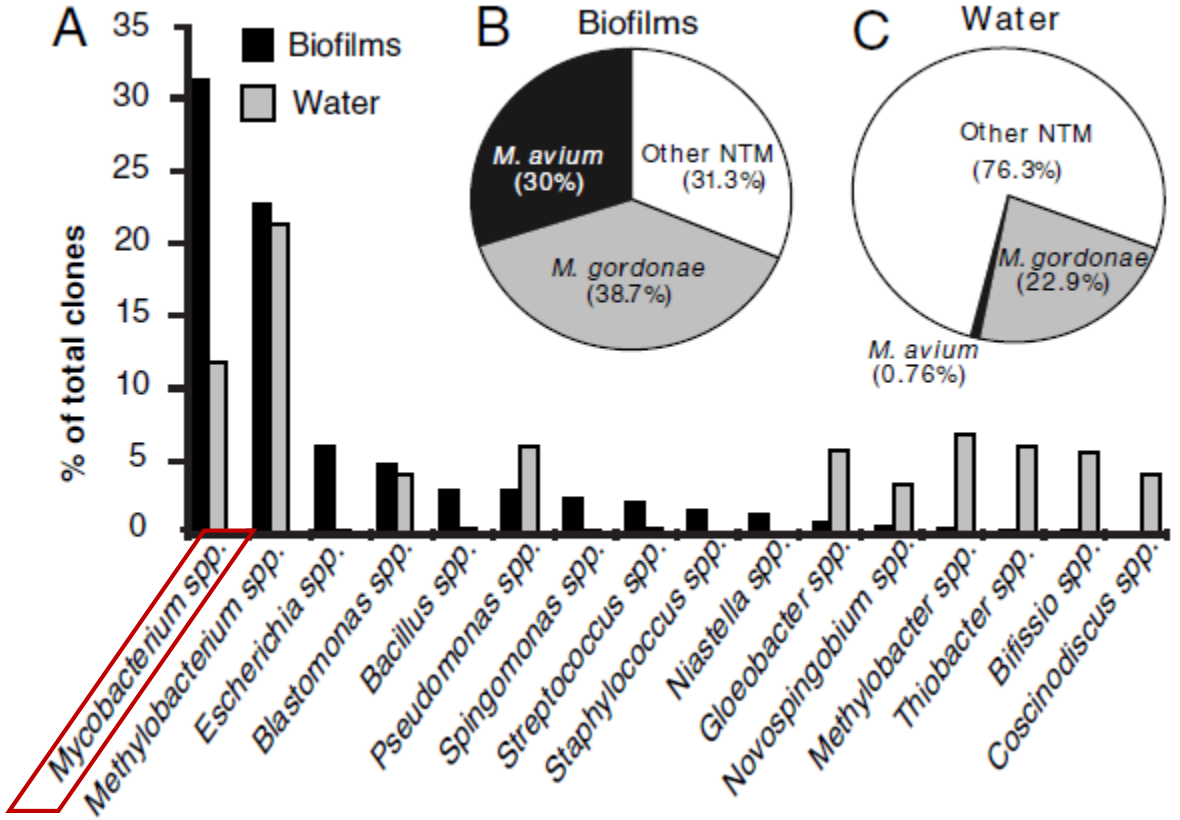




Courtesy of Pf.Jeon Doo Soo

Opportunistic pathogens enriched in showerhead biofilms

- University Colorado, Denver, USA
- Showerhead biofilm swab samples
- Home, public buildings, apartment buildings
- 52 samples
- Ribosomal RNA gene sequencing



PNAS 2009;106:16393

Home sampling studies

- **Isolation of nontuberculous mycobacteria (NTM) from household water and shower aerosols in patients with pulmonary disease caused by NTM.** J Clin Microbiol 2013, Queensland, Austrailia

- **The recovery of Mycobacterium avium-intracellulare complex (MAC) from the residential bathrooms of patients with pulmonary MAC.** Clin Infec Dis 2007, Osaka, Japan

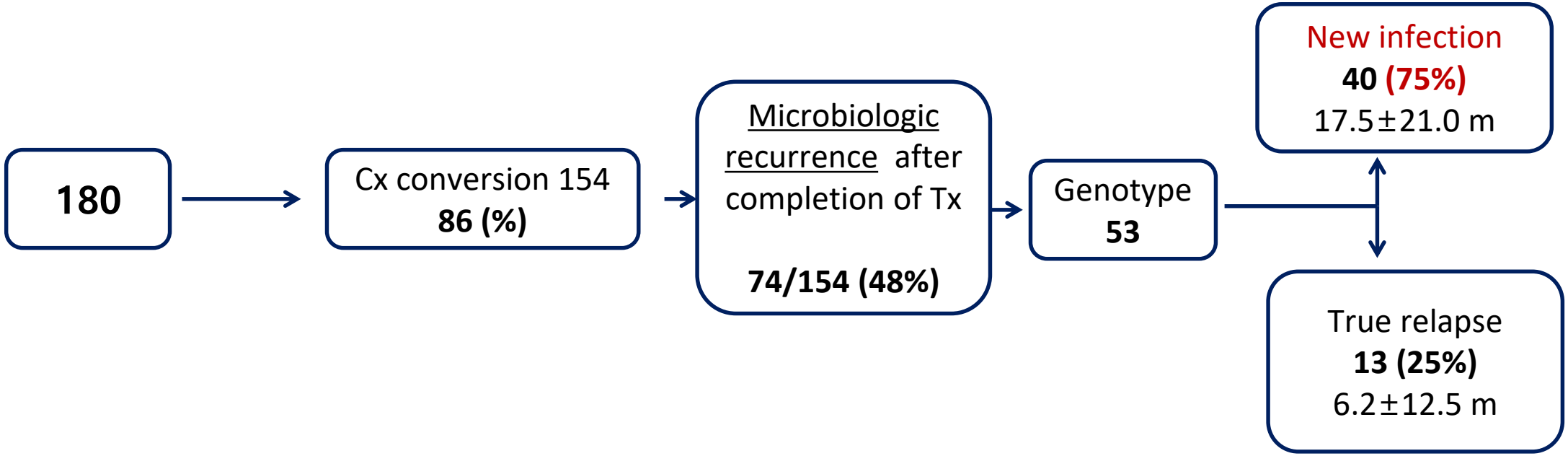
- **Distribution and Respiratory Activity of Mycobacteria in Household Water System of Healthy Volunteers in Japan**. Plos One, 2014, Osaka, Japan

- **Nontuberculous Mycobacteria from Household Plumbing of Patients with Nontuberculous Mycobacteria Disease**. Emerging infec Dis 2011, Verginia, USA

- **Mycobacaterium avium in a shower linked to pulmonary disease**. Journal of water and health, 2006, Denver, USA

Exposure – frequent reinfection

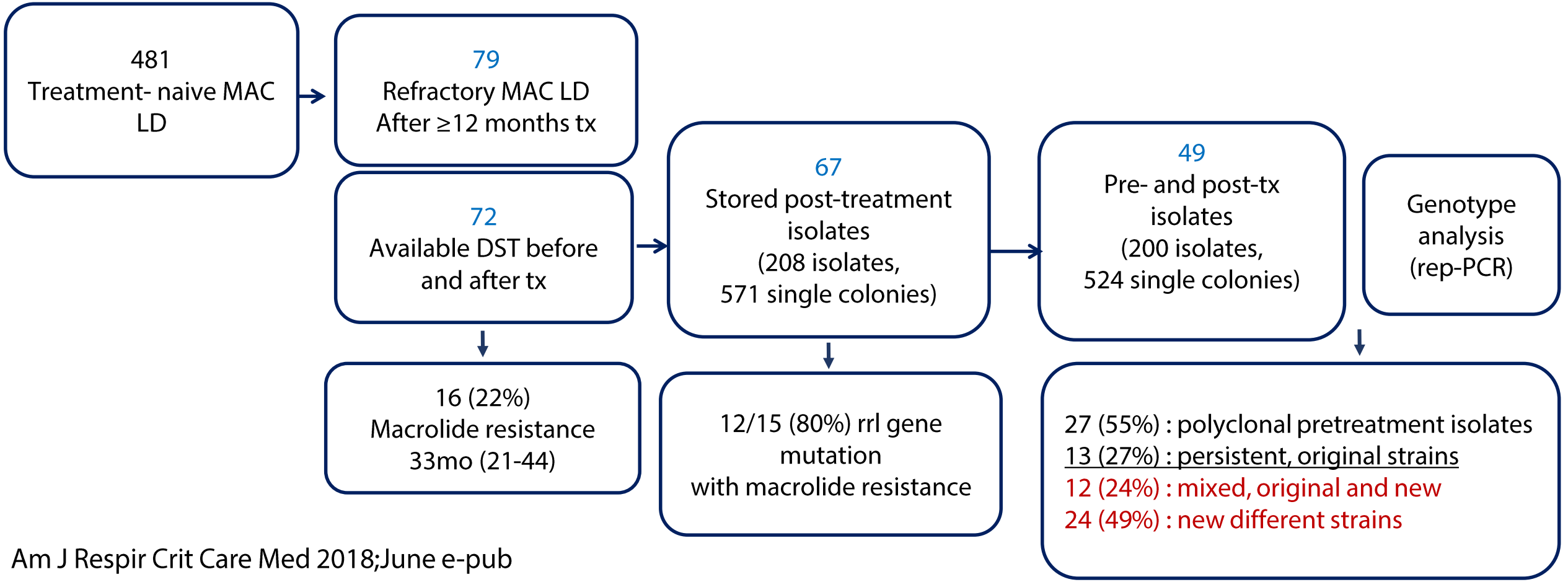
- Retrospective observational cohort study, University of Texas Health center, USA, at least 12mo treatment, 3.5 Y FU
- MAC lung disease patients



Chest 2014 ;146:276-82

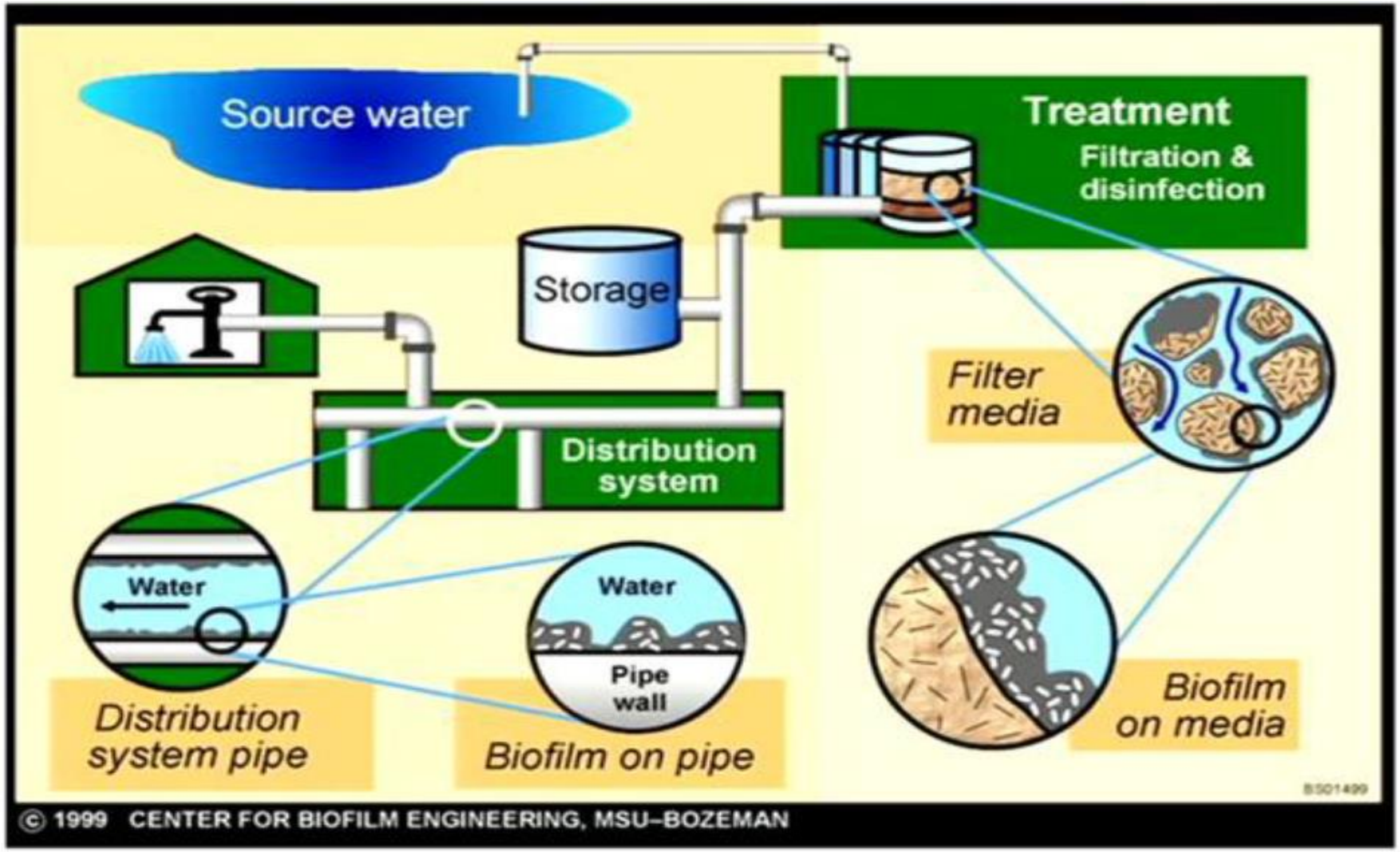
Development of macrolide resistance and reinfection in refractory MAC LD

- Retrospective/ prospective observational cohort study, Jan 2002- Dec 2013, SMC, Korea



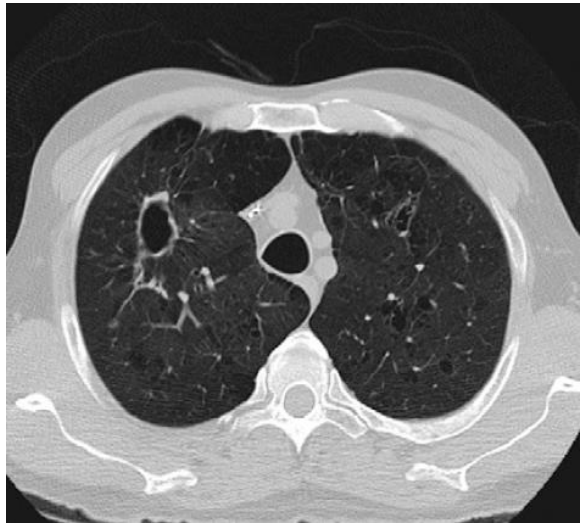
Am J Respir Crit Care Med 2018;June e-pub

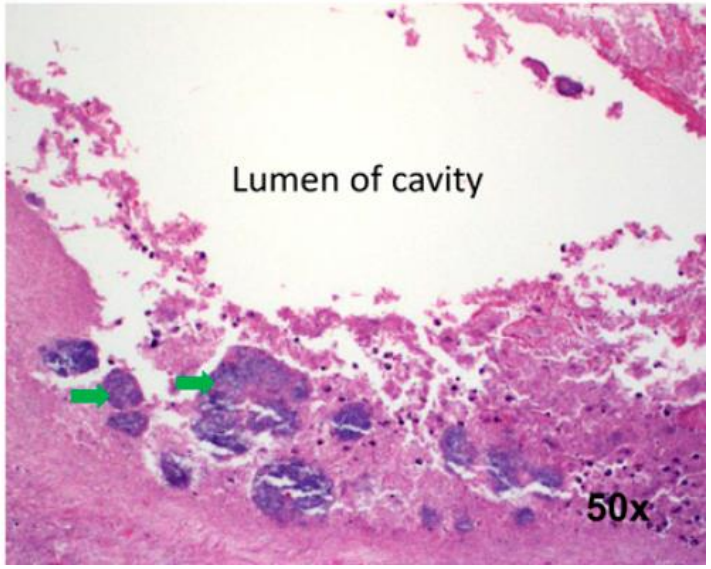
Mycobacteria biofilm – environment



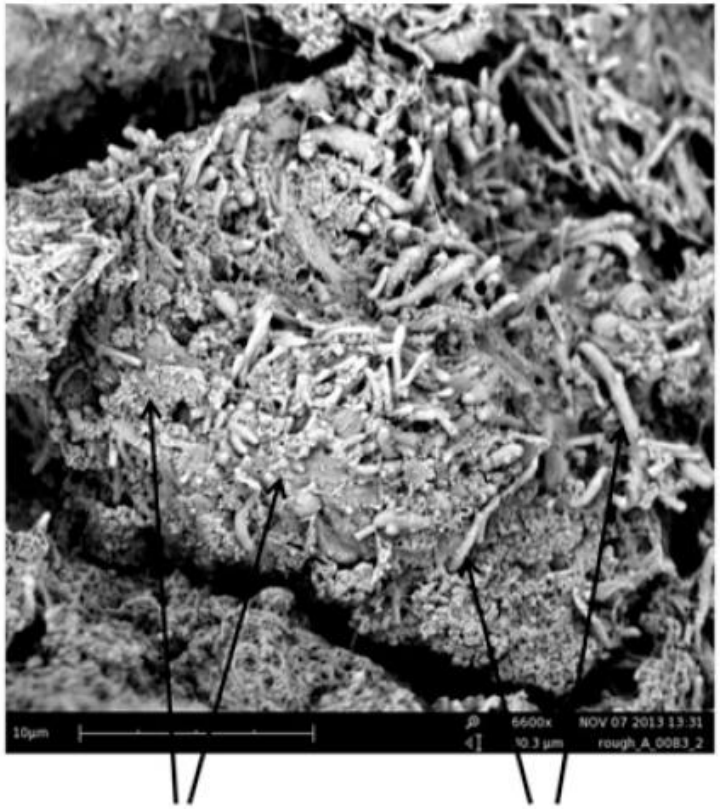
Mycobacteria biofilm – lung tissue

Am J Respir Crit Care Med 2016;193:2016

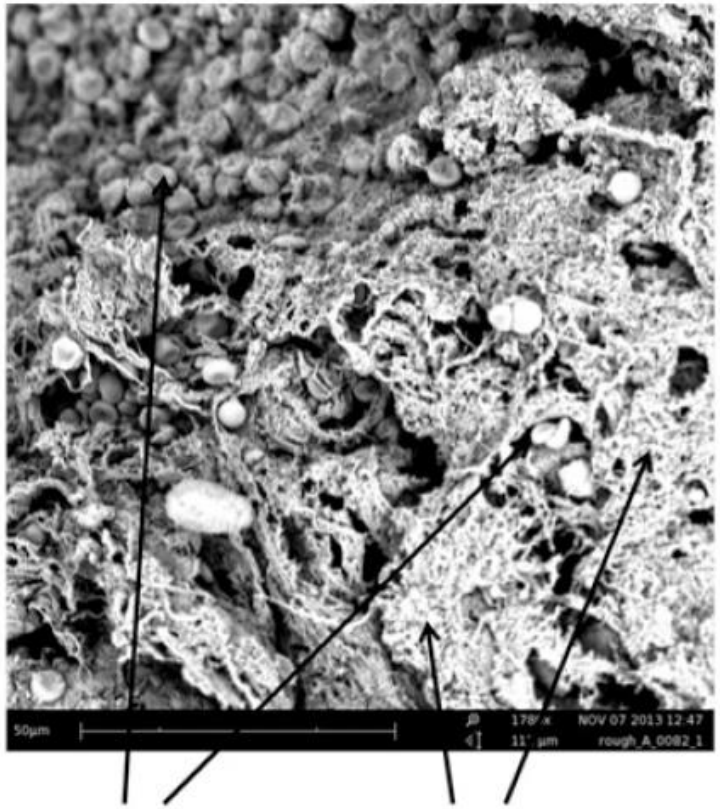




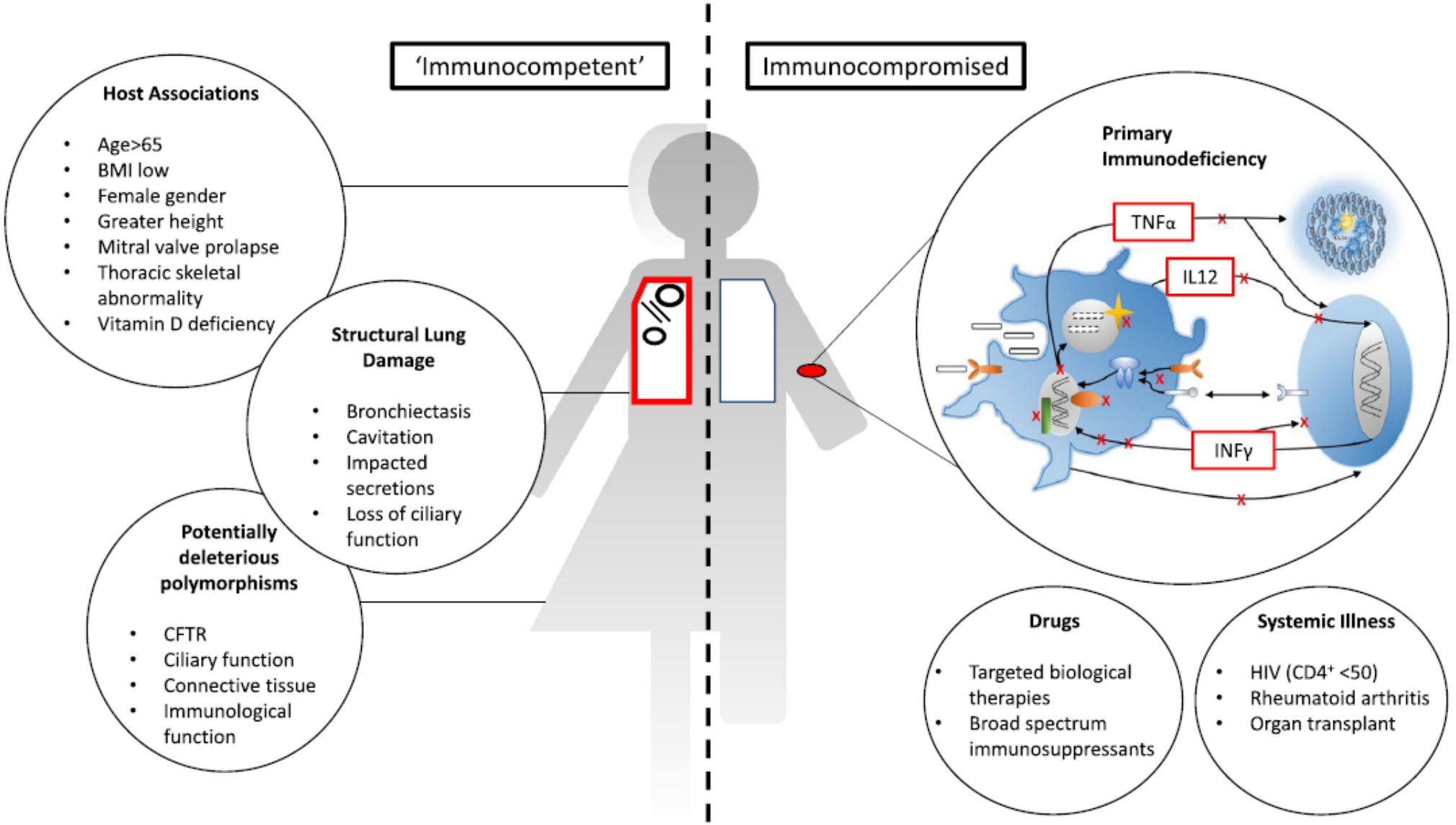
Cavity inner wall



Lung tissue remote from the cavity



55 YO man, M.abscessus infection, RUL cavity, surgical resection



BMC Medicine 2016;14:54

Measures to reduce NTM exposure

- Raise hot water heater temperature to 55 °C (130 ° F).
- Use bacteriologic filters (pore size ≤0.45 um or 0.2um) on taps and showerheads and change it periodically.
- Disinfect showerhead by submerging in household bleach for 30 minutes.
- Use showerhead with large holes to reduce mist formation (greater than 1mm diameter).
- Increase bathroom exhaust rate.
- For drinking and cooking, boiling (100 ° C) for 10 minutes kills NTM.
- Don’t drink from built in refrigerator tap or use ice.
- Get rid of any and all humidifiers.
- Avoid dust inhalation when gardening; moisten garden and potting soils.

All of these interventions are experiments.

Clin Chest Med 2015;36:35, National Jewish Mycobacterial Consultation 2015

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