Post-Tuberculosis Lung Disease

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Post -TB lung disease overview

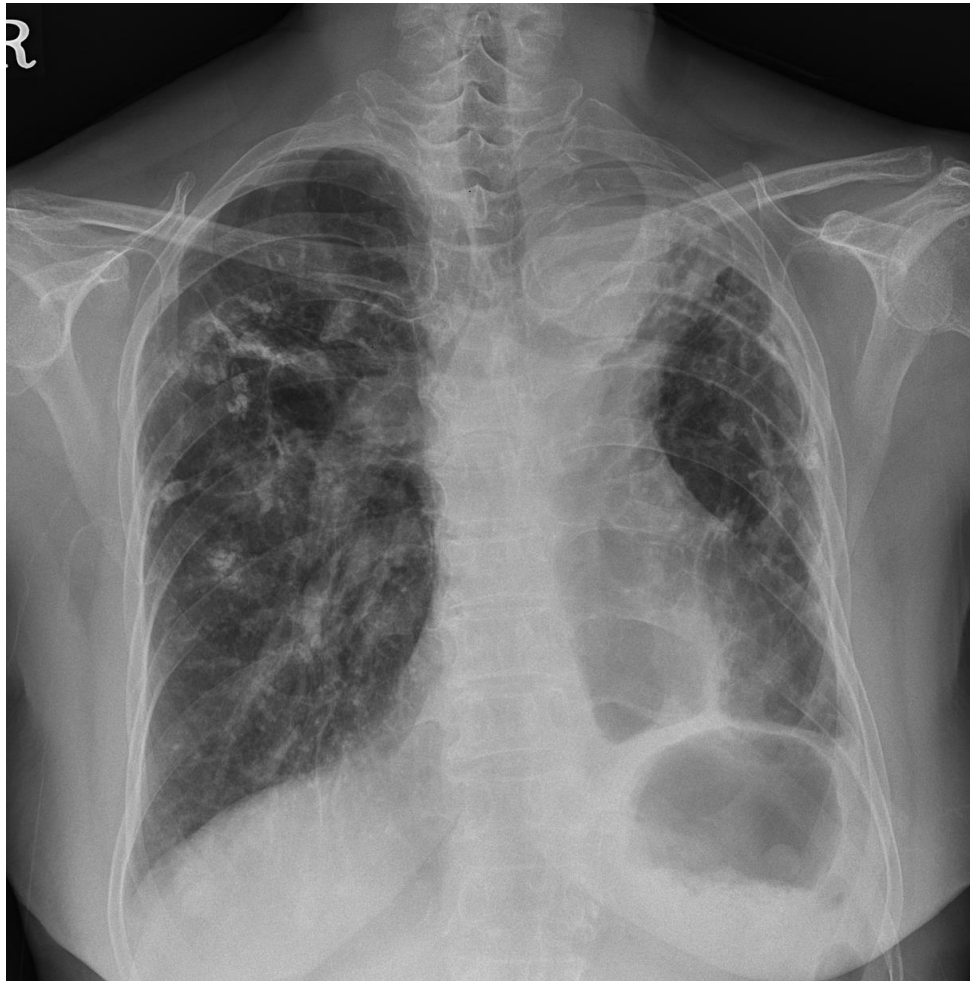
- Definition
- Epidemiology and disease burden
- Pathophysiology
- Screening and diagnosis
- Management and Prevention

F/65 , Post-TB lung disease

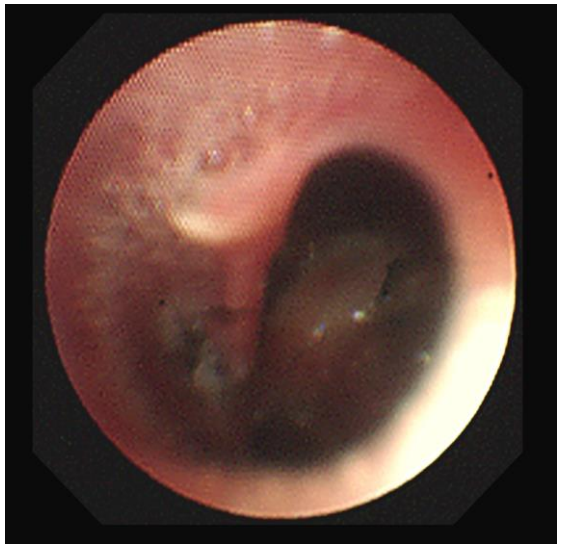
- I have sputum and cough for more than 10 years.
- I always have trouble breathing when I have a cold.

Date: 09/02/24

		Ref	Pre	% Ref	Post	% Ref	%Chg
Spirometry							
FVC	Liters	3.23	1.48	46	1.52	47	3
FEV1	Liters	2.43	0.89	37	0.92	38	3
FEV1/FVC	%	76	60		60		
FEV3	Liters		1.26		1.28		2
FEV6	Liters		1.45		1.45		0
FEF25-75%	L/sec	2.31	0.43	19	0.44	19	0
IsoFEF25-75	L/sec	2.31	0.43	19	0.58	25	34
FEF50%	L/sec	3.10	0.59	19	0.58	19	-2
PEF	L/sec	5.45	2.34	43	2.44	45	4
FET100%	Sec		7.22		8.98		24
FIF50%	L/sec		1.32		1.50		14



M/53, TB → NTM → BPF



2016.07, AFB smear +
DS-TB

2022.3 ~
Smear+
M. intracellulare

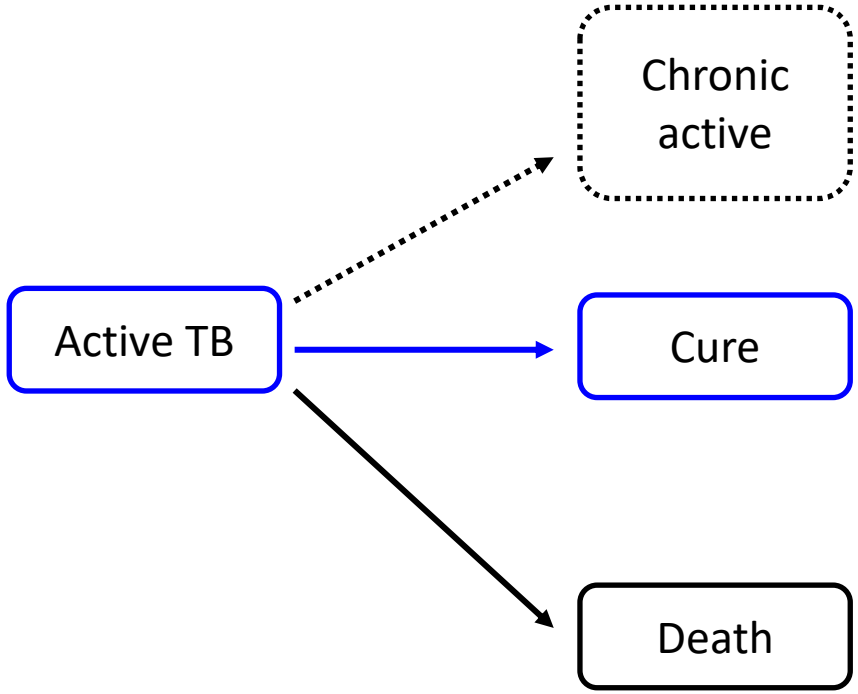
2024.02
M. Intracellulare infection
Bronchopleural fistula

Beyond the CURE

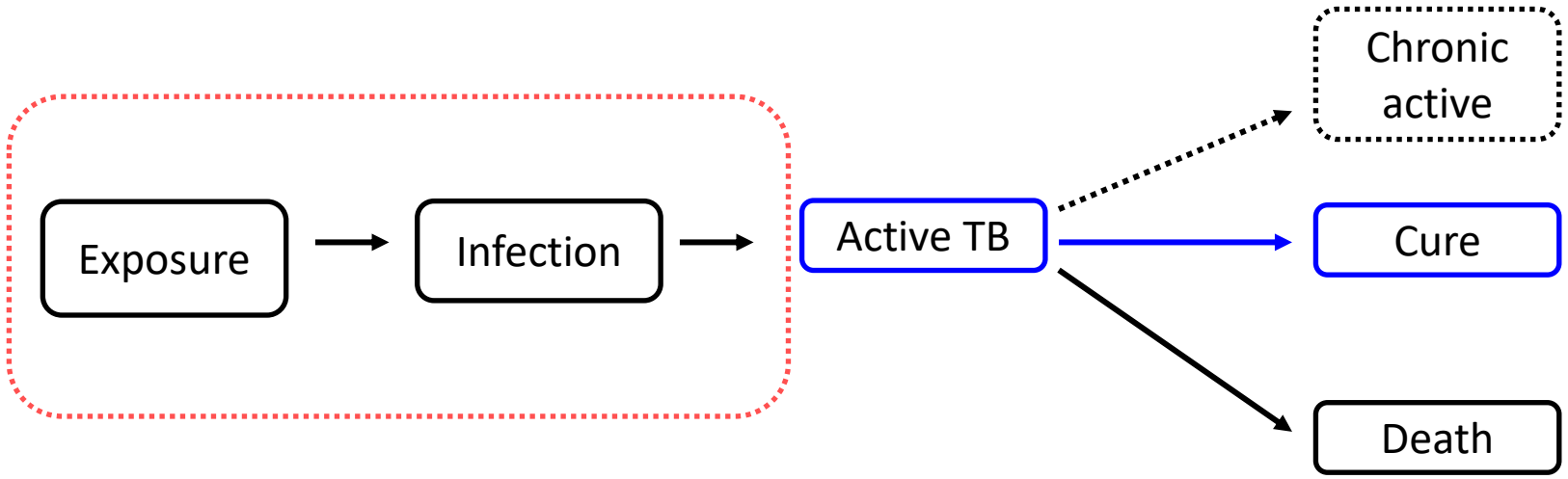
- Congratulation! you are graduated from TB.
- Bye~

- Re-visiting the clinic
  - Chronic respiratory symptoms
  - Chronic physical impairment
  - Recurrent respiratory infection
  - Death

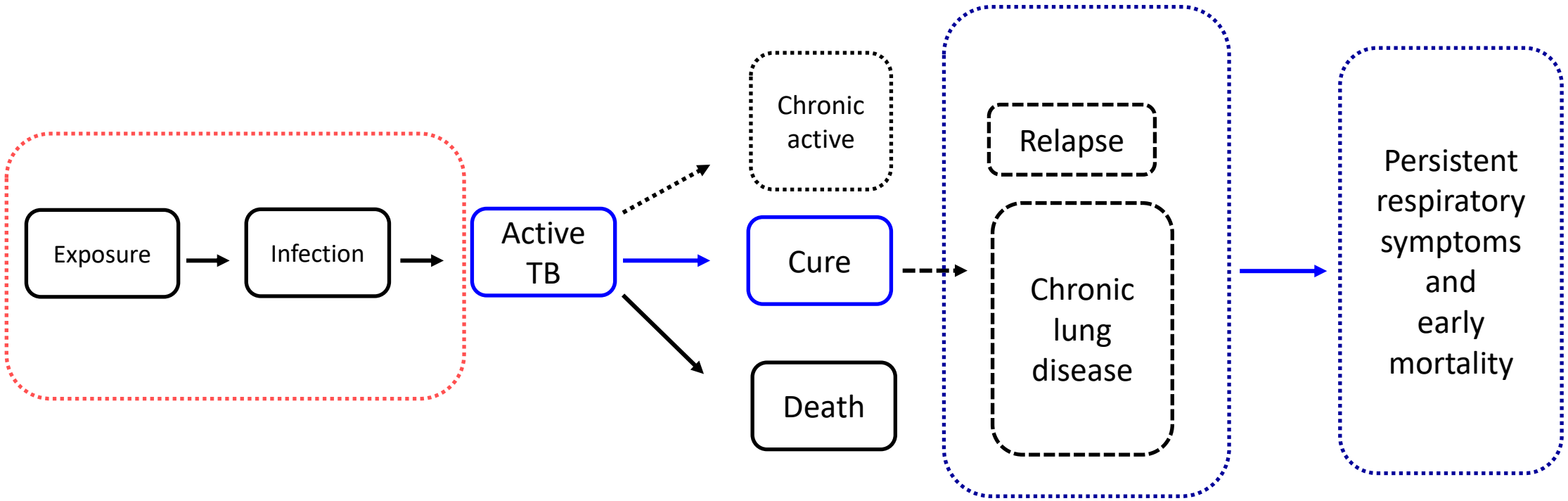
Tuberculosis as an acute illness



Tuberculosis as a sub-acute illness



Tuberculosis as a chronic illness



Post-TB : TB survivor

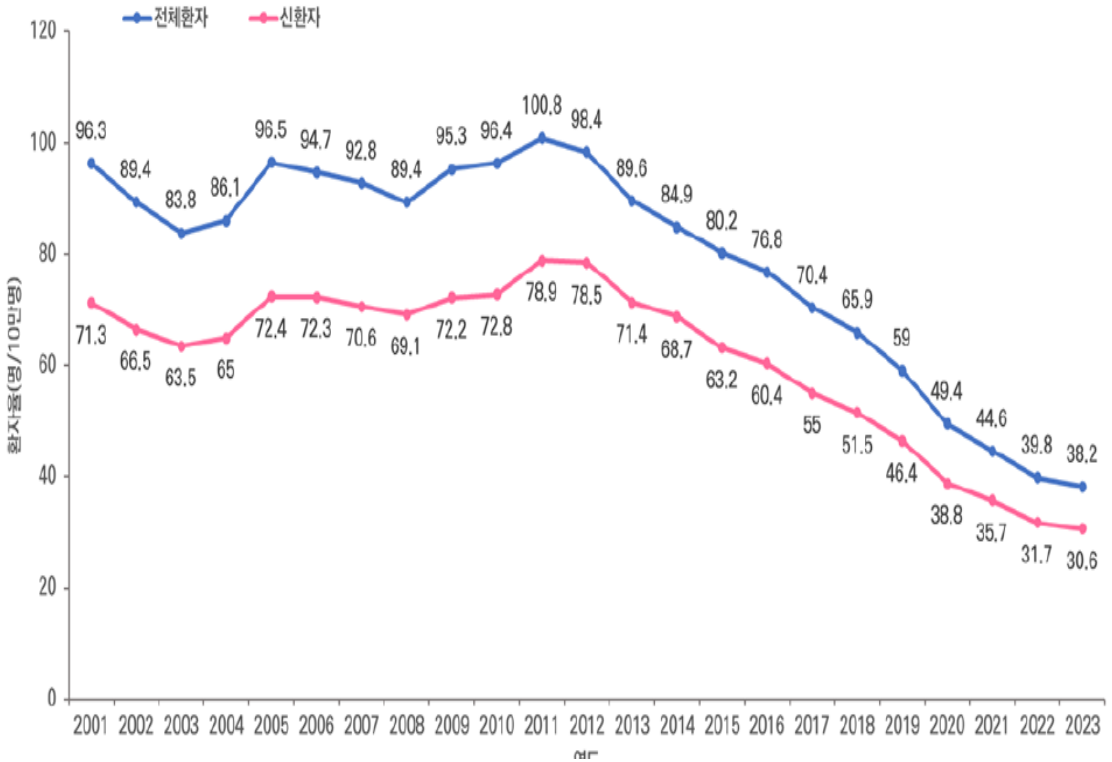
❖ Korea

- TB treated 338,371 (2011-2020)
- Death during Tx 31,661
- TB survivors 306,710 (2011-2020)

90% of treated patients

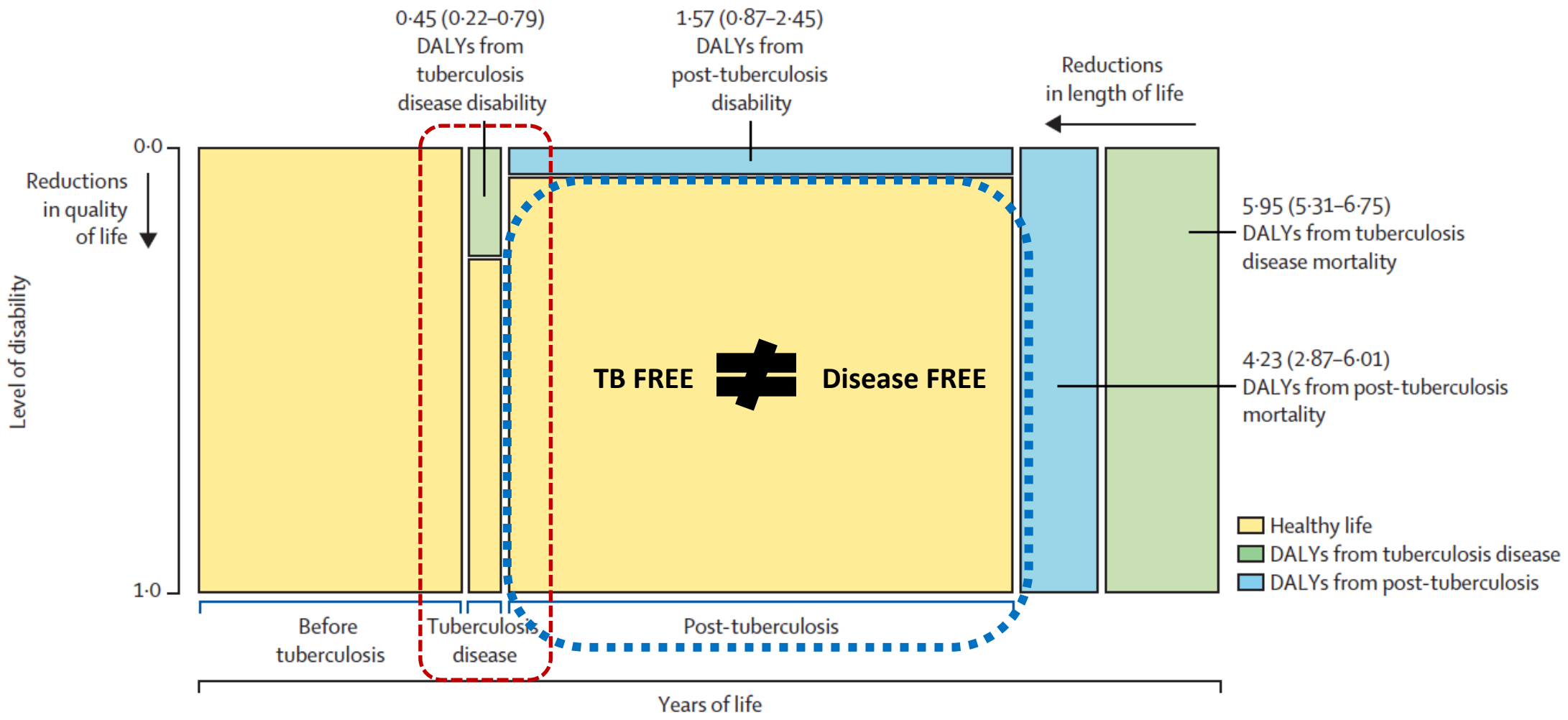
❖ Global

- TB developed 3억6천3백만 (1980-2019)
- TB treated 1억7천2백만
- TB survivors 1억5천5백만 (2020)



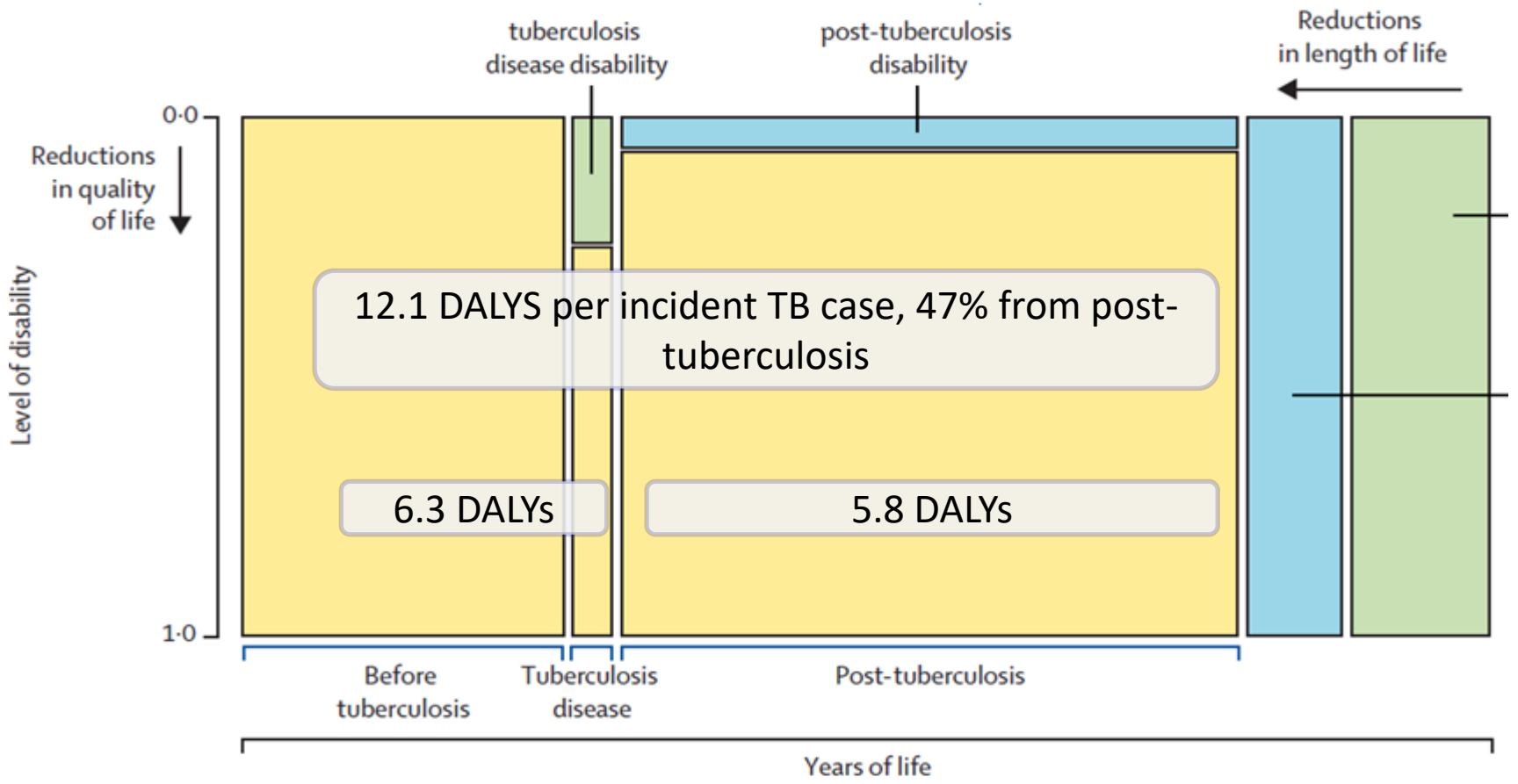
Lancet Infect Dis 2021

Post-tuberculosis mortality and morbidity



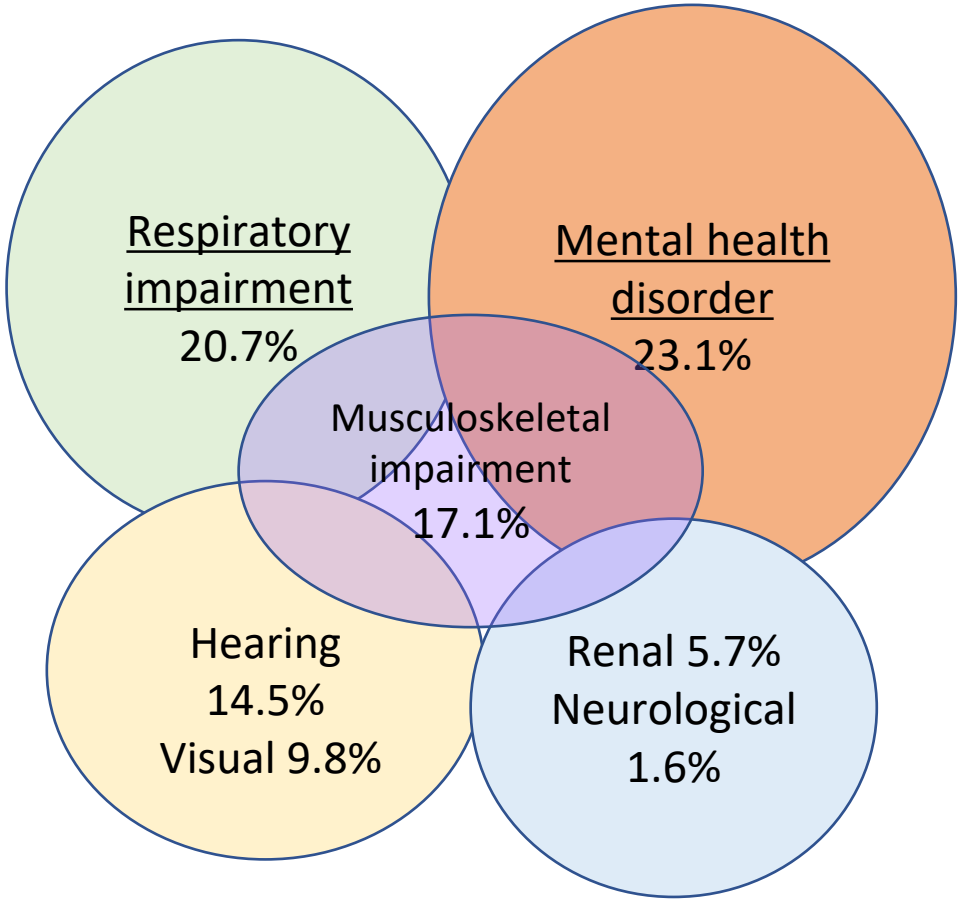
Lancet Glob Health 2021;9: e1679–87

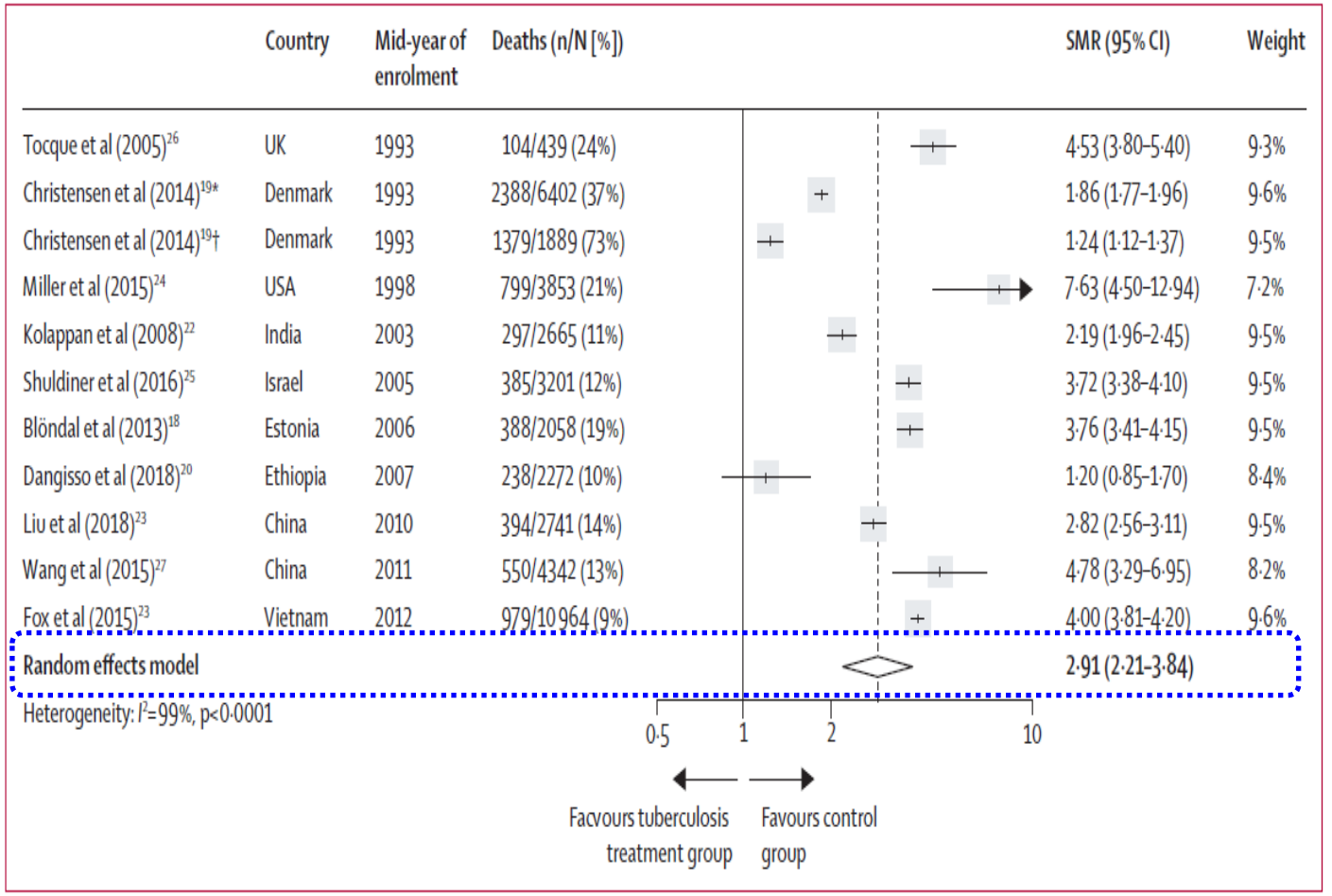
Lifetime burden of disease due to tuberculosis



Lancet Glob Health 2021;9: e1679–87

Tuberculosis related disability and post-TB long term mortality

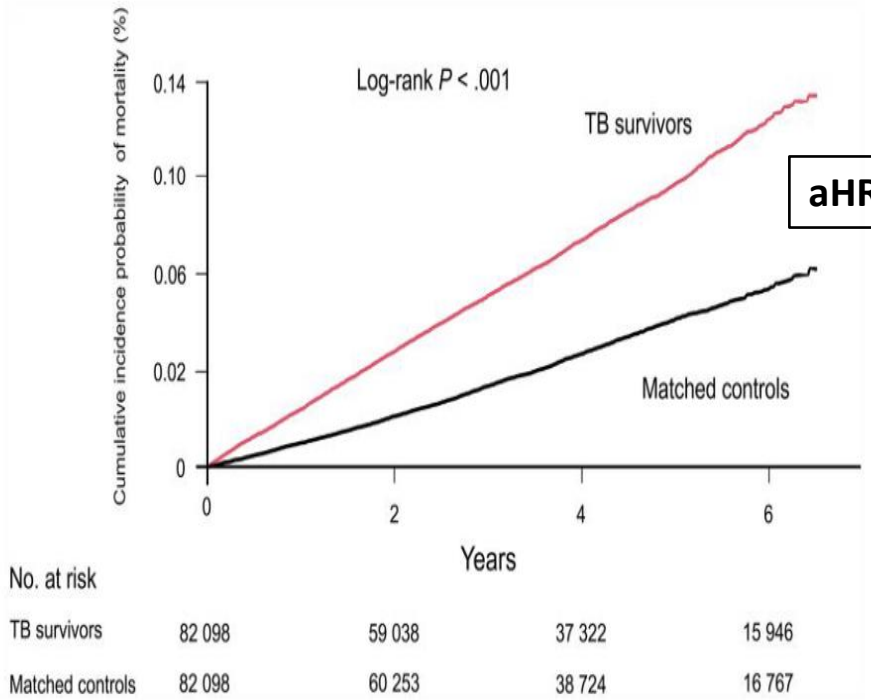




BMC Med 2021;16:203, Lancet Infect Dis 2019;19:1129

Post-tuberculosis mortality in Korea

TB survivors 2010-2017 and matched control



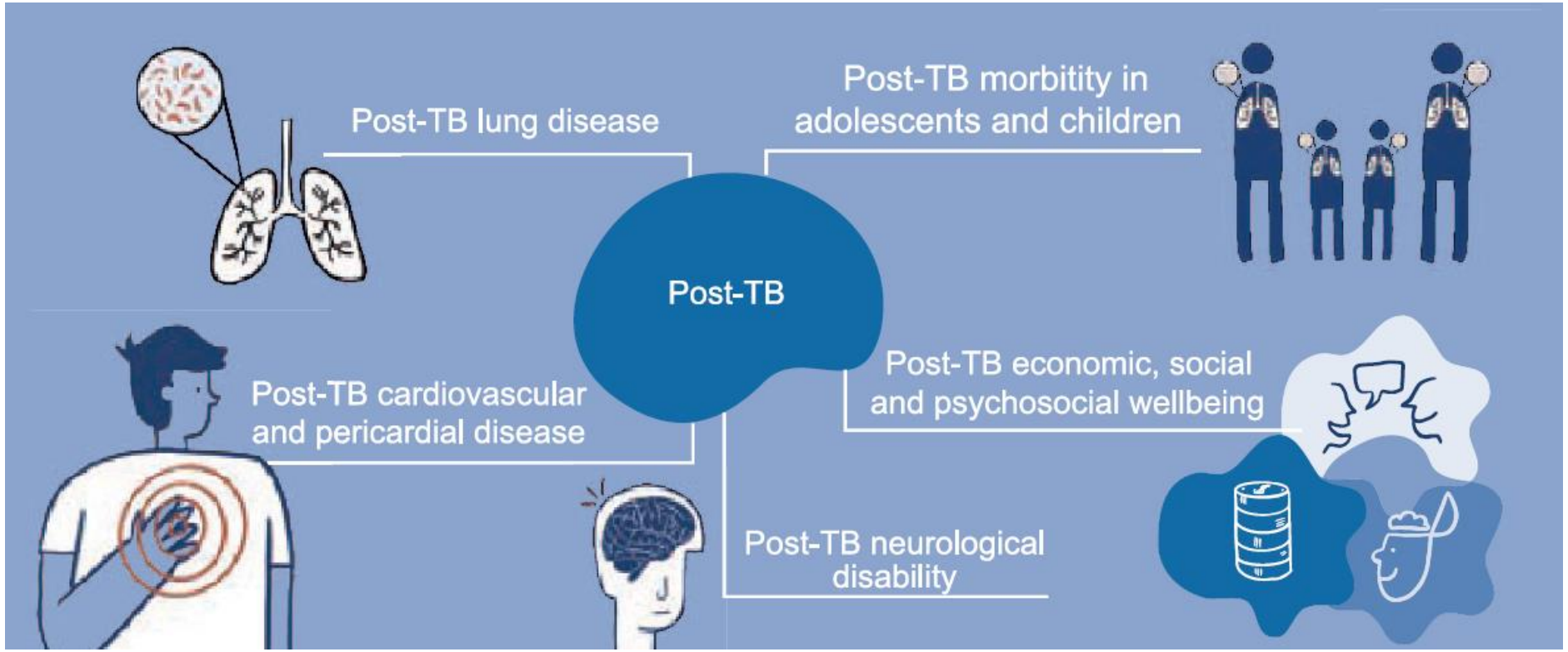
aHR 1.86

Cause of death following TB diagnosis

Causes of death	Total period *n* (%)	Within 1 year *n* (%)	1–5 years *n* (%)	After 5 years *n* (%)
Tuberculosis	21 070 (20.3)	15 278 (37.7)	3 884 (10.7)	1 908 (7.1)
Pneumonia	4 802 (4.6)	1 389 (3.4)	1 690 (4.6)	1 723 (6.4)
CLRD	5 307 (5.1)	1 107 (2.7)	2 108 (5.8)	2 092 (7.8)
Lung cancer	9 897 (9.5)	4 287 (10.6)	3 869 (10.6)	1 741 (6.5)
Other cancers	14 980 (14.4)	5 226 (12.9)	5 955 (16.3)	3 799 (14.2)
CDVD	6 250 (6.0)	1 799 (4.4)	2 247 (6.2)	2 204 (8.2)
CBVD	6 152 (5.9)	1 924 (4.7)	2 408 (6.6)	1 820 (6.8)
DM	4 548 (4.4)	1 302 (3.2)	1 918 (5.3)	1 328 (5.0)
Hypertension	1 319 (1.3)	368 (0.9)	510 (1.4)	441 (1.6)
Others	28 307 (27.3)	7 368 (18.2)	11 487 (31.5)	9 452 (35.4)
Unknown	1 050 (1.0)	467 (1.2)	361 (1.0)	222 (0.8)
Total	103 682 (100.0)	40 515 (100.0)	36 437 (100.0)	26 730 (100.0)

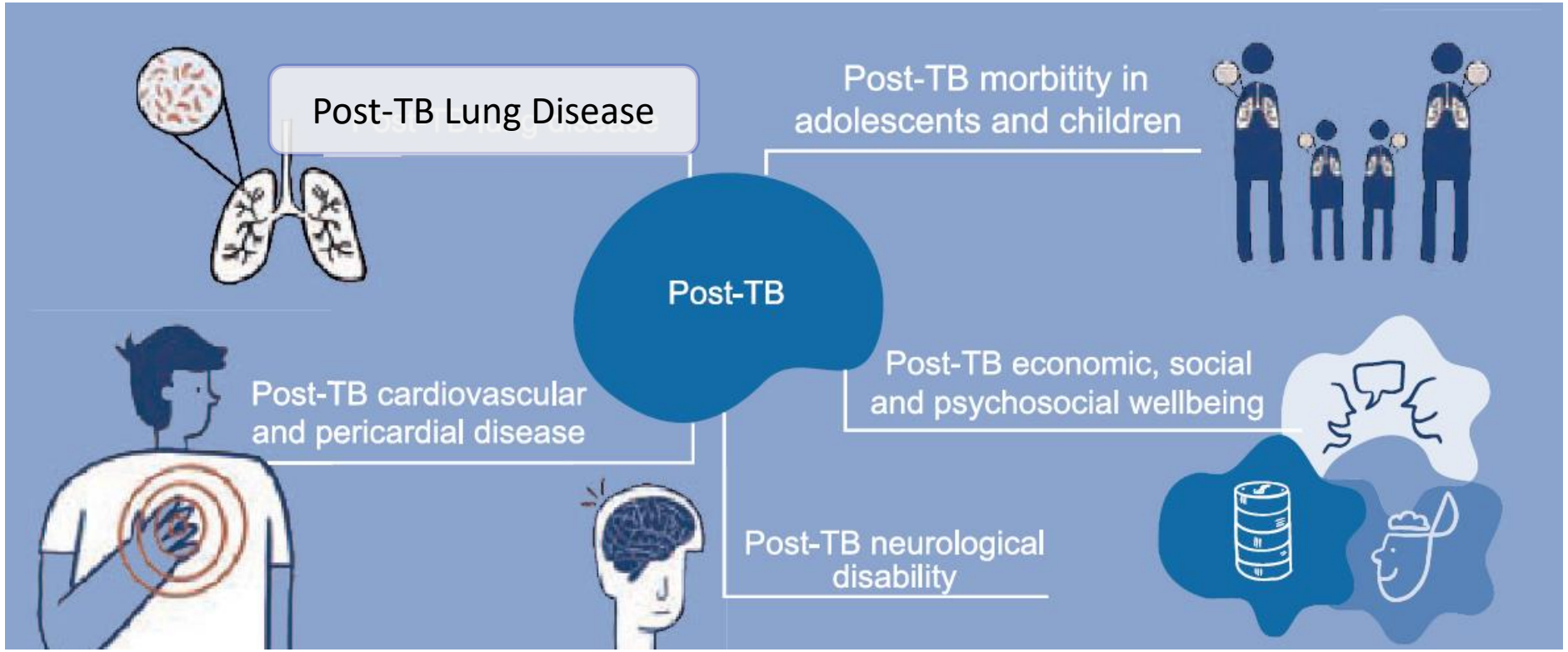
CID 2023;76:e973, IJTLD 2020;24:492

Post-TB health and wellbeing



International Post-Tuberculosis symposium and working group

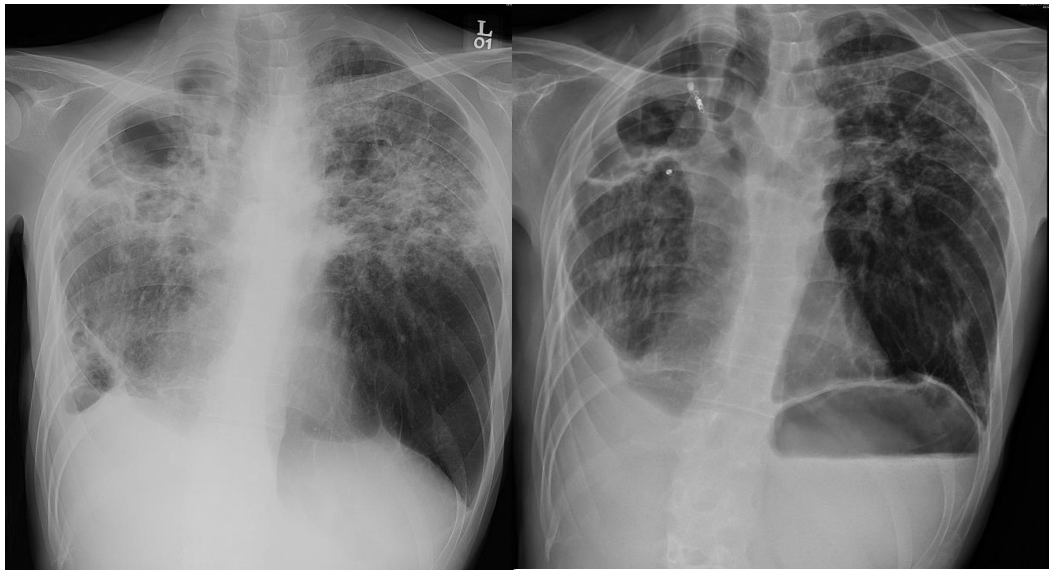
Post-TB health and wellbeing

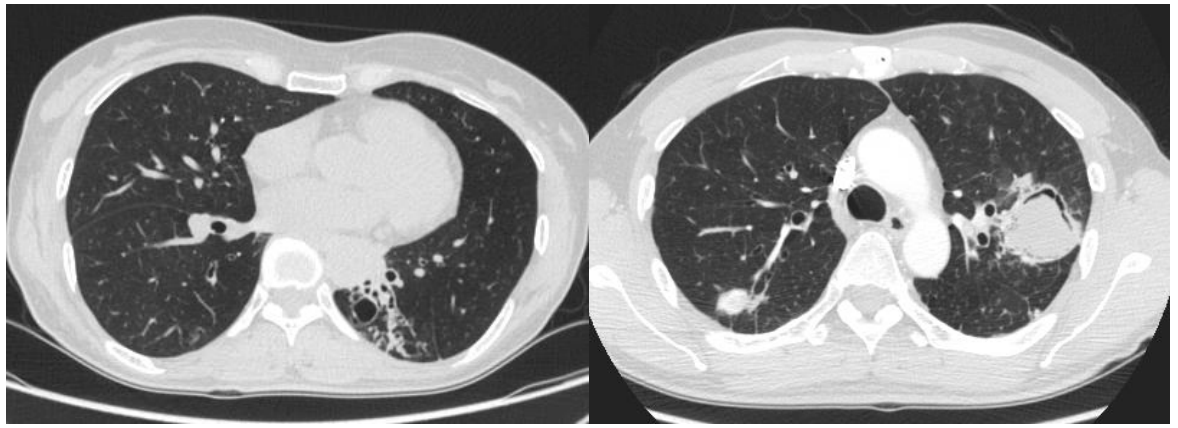


International Post-Tuberculosis symposium and working group

What is 'Post-TB lung disease' ?

- Chronic respiratory abnormality with or without symptoms, partially attributed to previous tuberculosis





Tracheobronchial stenosis | Bronchiectasis | Chronic pulmonary aspergillosis | Small airway disease | Restrictive lung disease

Chronic cough and sputum | Hemoptysis | Dyspnea

IJTLD 2020;8:820, KJIM 2024;39:7

Residual respiratory disability after successful treatment of TB

61 studies with 41,014 people with PTB

Post-TB respiratory impairment : lung function

- 59.1% of patients with pTB (vs 5.4% of controls)
- 17.8% obstruction
- 21.3% restriction
- 12.7% mixed pattern

Post-TB disability

- MRC dyspnea score (score 3-5 in 24.7%)
- 6MW 440.5m (78.9% of predicted), 403m among MDR-TB (70.5% of predicted)
- HR-QOL (SGRQ)

Post-TB respiratory complications

- incidence of lung cancer IRR 4.0 compared to controls
- persistent cavity 31.4%
- fibrosis 37.4%
- bronchiectasis 16.8%
- chronic pulmonary aspergillosis 1.9%

eClinicalMedicine 2023;59:101979

Heterogeneity of PTLD

Box 1. Consensus definition and proposed clinical patterns of post-TB lung disease (PTLD) from the First International Post-Tuberculosis Symposium(156)

Minimum case definition of PTLD: Evidence of chronic respiratory abnormality, with or without symptoms, attributable at least in part to previous tuberculosis.

Proposed clinical patterns of PTLD:

(1) Airways: TB-associated **obstructive lung disease** with airway obstruction on spirometry OR **bronchiectasis** on chest radiography

(2) Parenchyma: **Cavitation, parenchymal destruction**, or fibrotic change on chest radiography OR **aspergillus-related lung disease** on imaging and/or blood testing

(3) Pleural: **Pleural thickening** on chest imaging

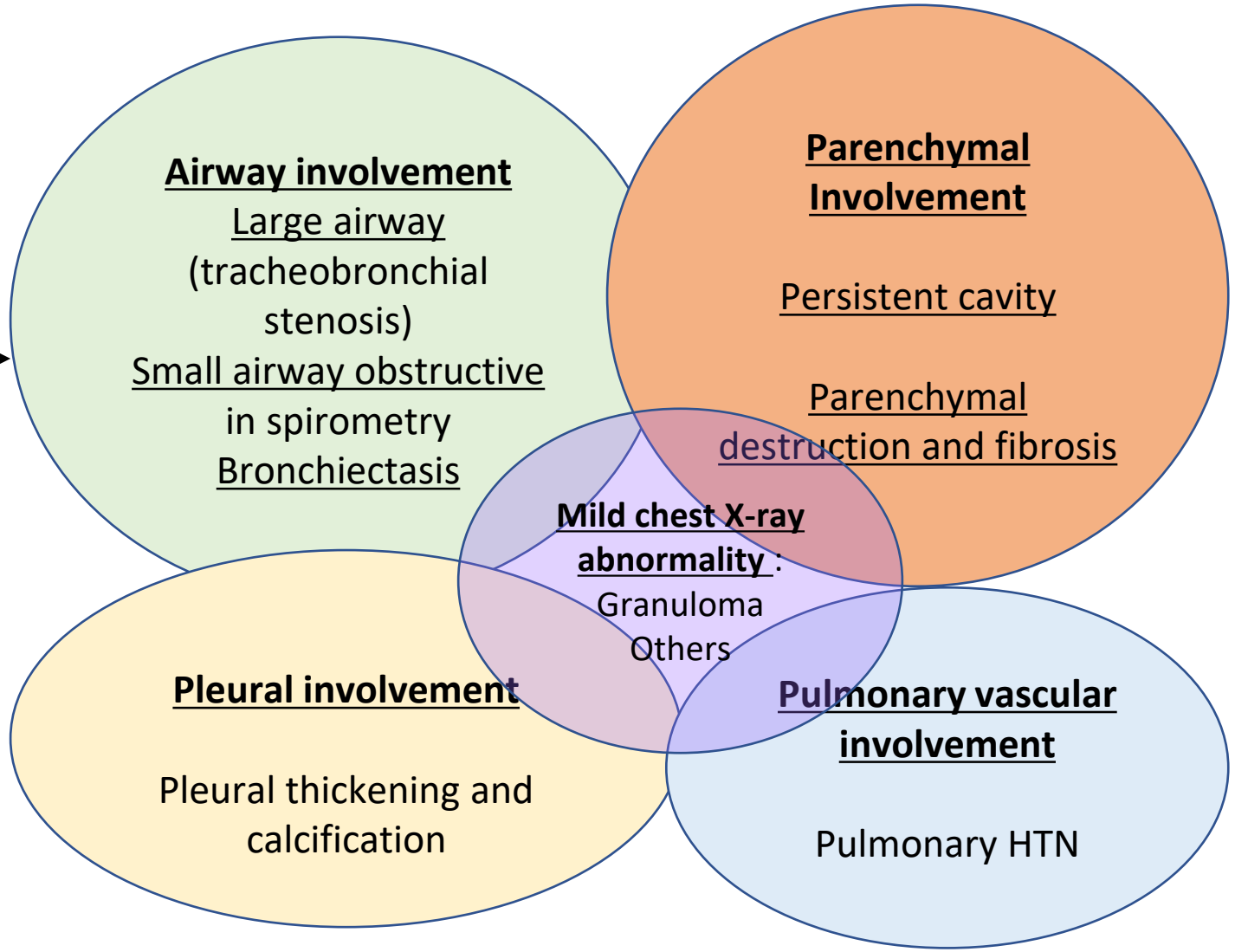
(4) Pulmonary vascular: **Pulmonary hypertension** with elevated pulmonary artery pressures on echocardiography and/or right heart catheterization

(5) Other: Other pathology not meeting the above criteria.

AJRCCM 202402-0374SO

Heterogeneity of PTLD

- Host : local lung and systemic immunity environment
- Pathogen
- Interaction

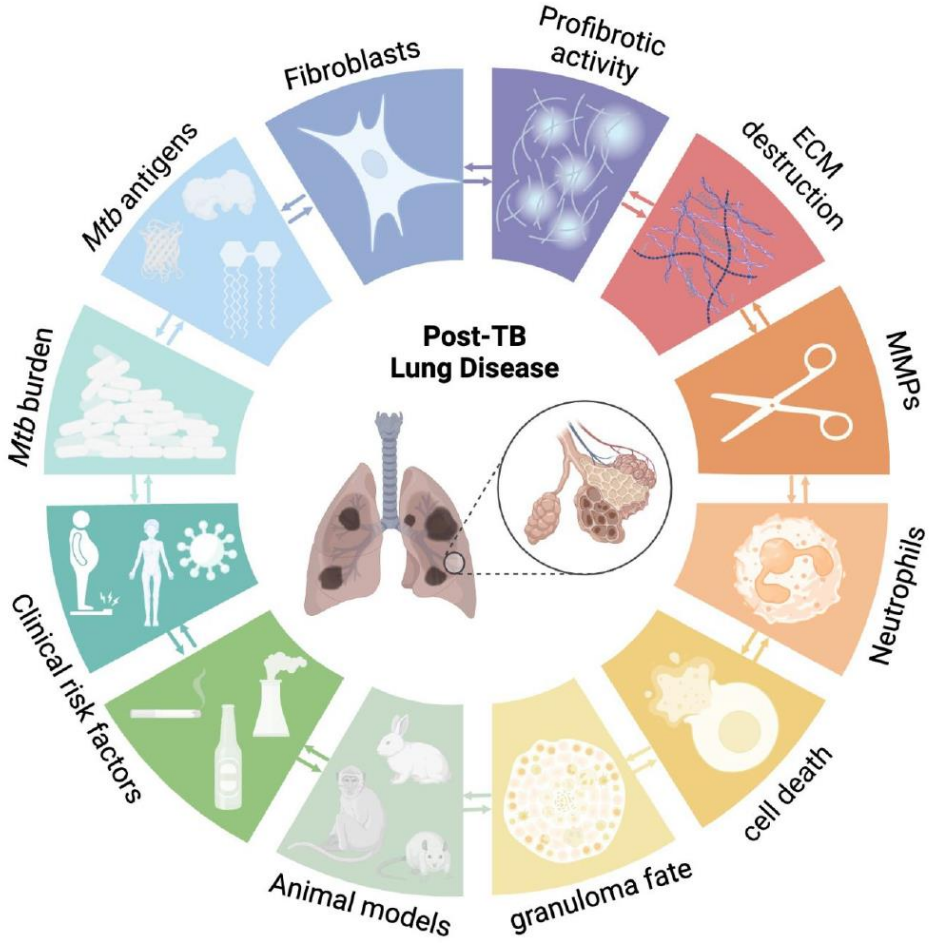


- Persistent symptom and disability
- Early mortality

Pathogenesis of post-TB lung disease

Pathogenesis of Post-Tuberculosis Lung Disease: Defining Knowledge Gaps and Research Priorities at the 2nd International Post-Tuberculosis Symposium

- Matrix destruction, MMPs and Neutrophils
- Fibroblasts and profibrotic activity
- Granuloma fate and cell death pathways
- Mycobacterial factors and pathogen burden
- Interactions between clinical risk factors and pathogenesis of PTLD
  - HIV /Diabetes /undernutrition



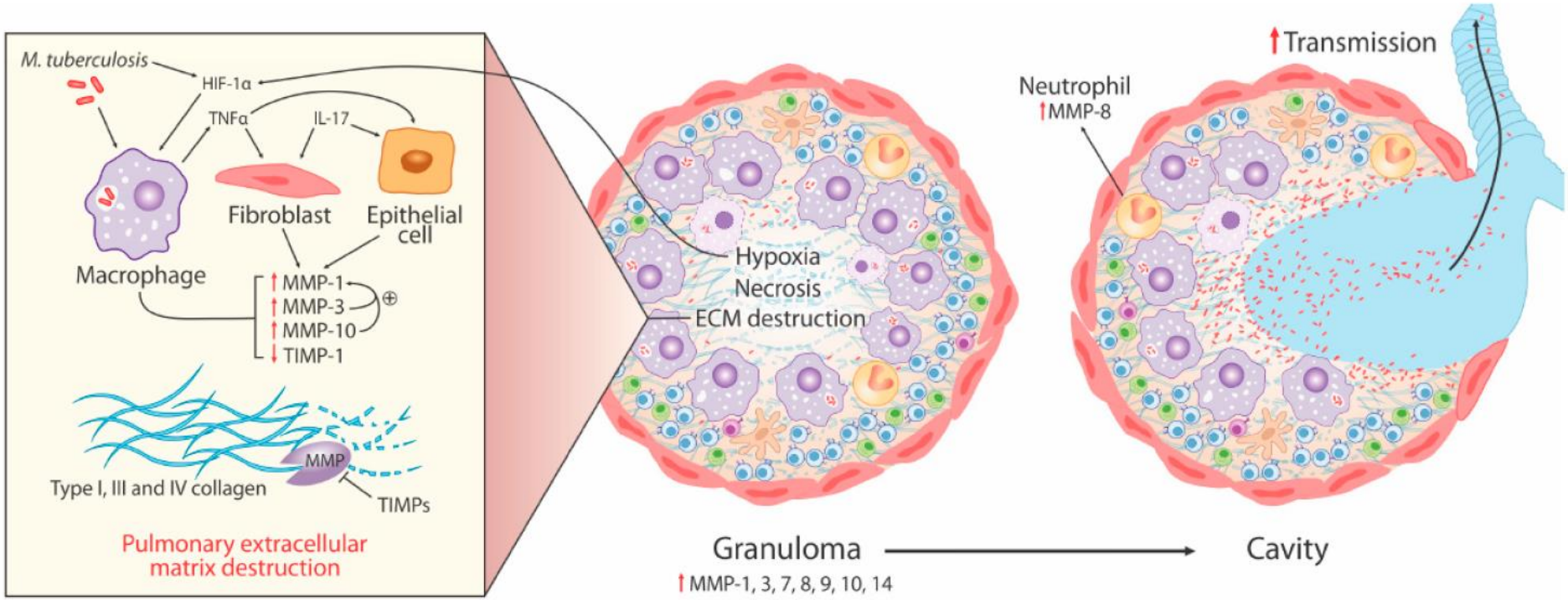
AJRCCM 202402-0374SO

MMPs and lung destruction

- Matrix Metalloproteinase : a family of host enzyme that collectively degrade the extracellular matrix (collagenases, gelatinases and stromelysins)
  - Essential to degrade the structural fibrils of the lung

- MMPs are physiologically tightly regulated but are upregulated in monocytes, macrophages, and neutrophils directly in response to Mtb infection and via cellular networks, including uninfected stromal cells, without compensatory upregulation of specific inhibitors TIMPS

MMPs contribute to extracellular matrix (ECM) destruction in pulmonary TB

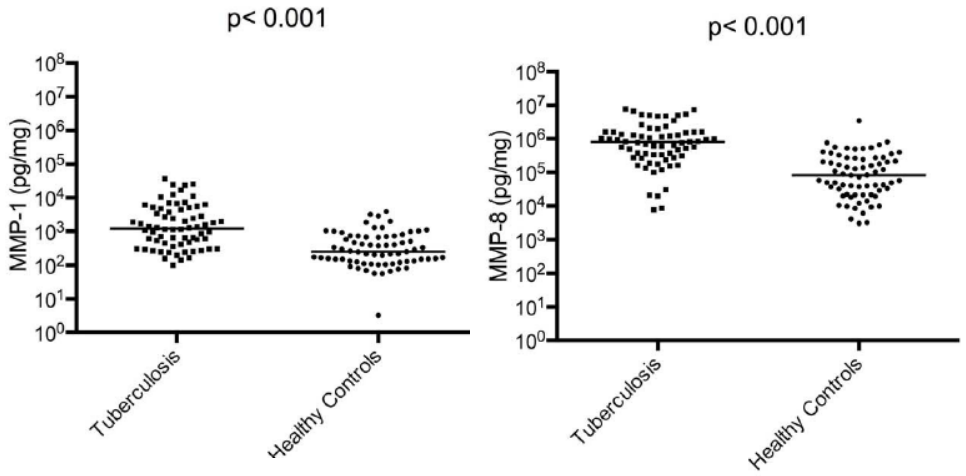


Macrophages, lymphocytes, neuturophiles secreted MMPs and contributed to lung ECM (type I, II, and IV collagens) destruction, cavity formation and Tb dissemination

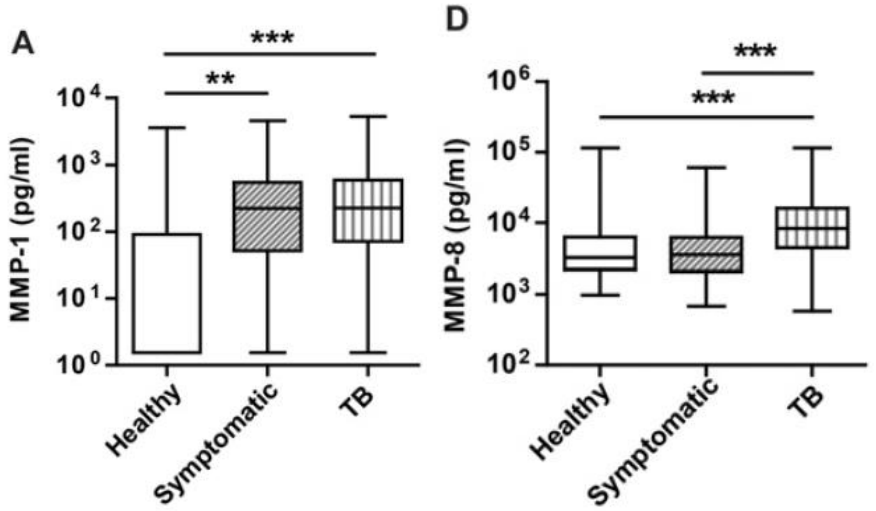
Int. J. Mol. Sci. 2019, 20, 1350

MMPs in serum and lung tissue of patients with pTB

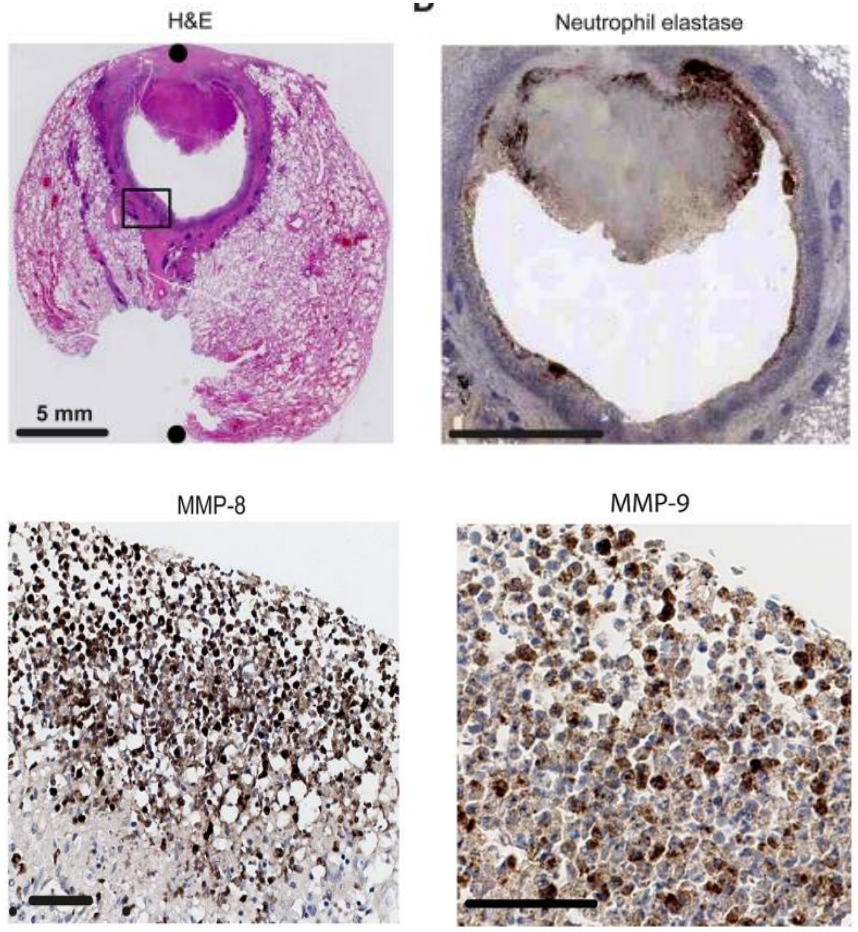
Induced sputum MMP concentration



Blood MMP concentration



Human lung tissue, pTB cavity



PLOS ONE 2013;8:e61333, PLOS ONE 2015;0117605/1004917

Association of poor treatment outcome with MMPs and TIMS

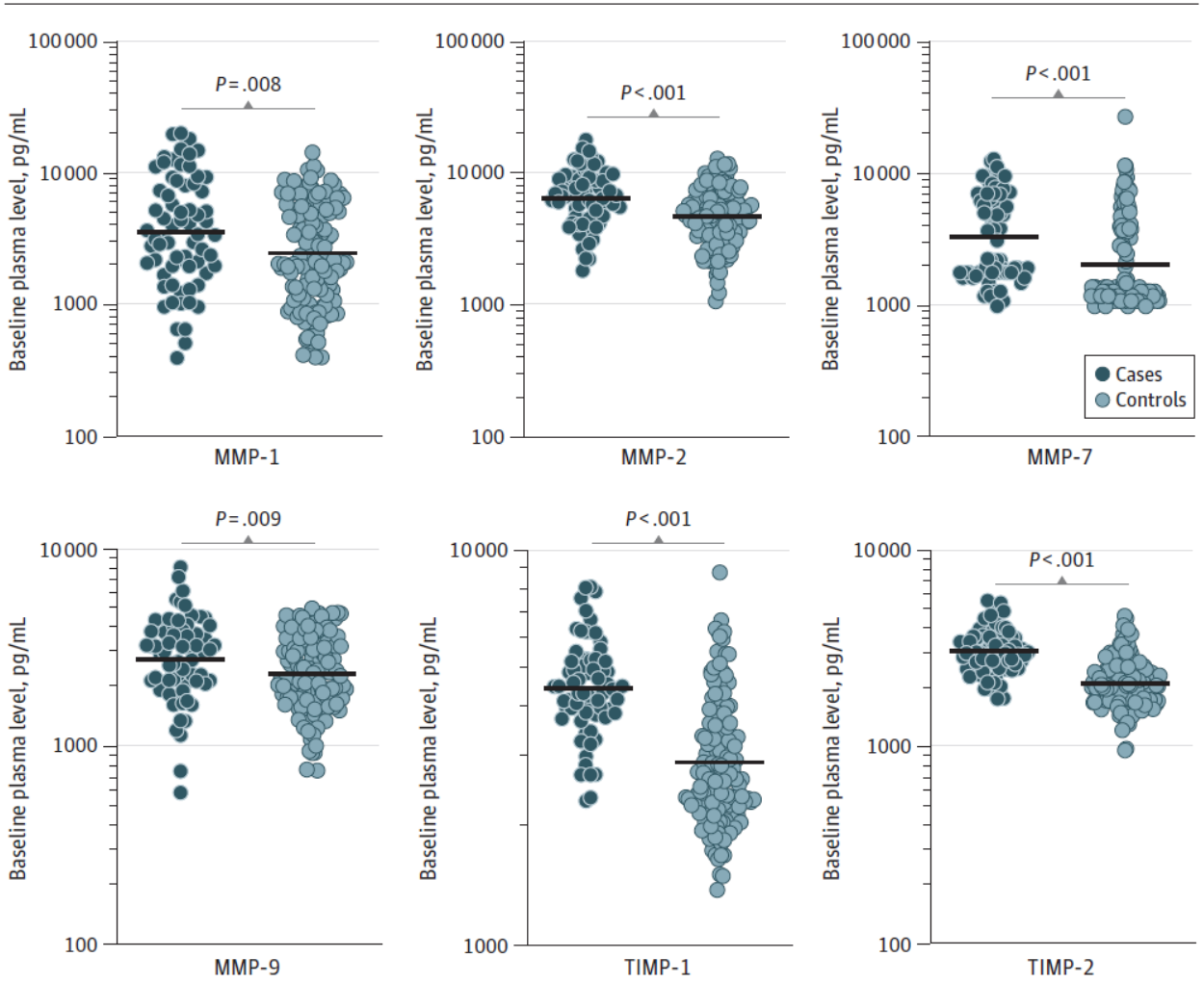


Table 2. Association of the Baseline MMP and TIMP Levels With Treatment Outcomes

	Univariate model		Multivariable model	
Marker	OR (95% CI)	*P* value	aOR (95% CI)[a]	*P* value
MMP-1	1.36 (1.01-1.85)	.04	1.32 (0.95-1.84)	.10
MMP-2	2.76 (1.40-5.48)	.004	3.26 (1.51-7.03)	.003
MMP-3	0.48 (0.27-0.88)	.02	0.45 (0.22-0.92)	.03
MMP-7	1.75 (1.18-2.61)	.006	1.71 (1.09-2.68)	.02
MMP-8	2.04 (1.33-3.14)	.001	2.16 (1.34-3.47)	.001
MMP-9	1.80 (0.89-3.64)	.10	2.16 (0.99-4.67)	.051
MMP-12	1.15 (0.30-4.41)	.84	1.29 (0.30-5.50)	.73
MMP-13	0.20 (0.02-2.39)	.20	0.18 (0.01-2.77)	.22
TIMP-1	7.55 (2.85-19.9)	<.001	8.23 (2.92-23.22)	<.001
TIMP-2	12.50 (3.98-41.82)	<.001	14.31 (3.83-53.39)	<.001
TIMP-3	0.94 (0.29-3.02)	.92	0.75 (0.23-2.47)	.64
TIMP-4	1.01 (0.62-1.63)	.98	1.00 (0.59-1.70)	>.99

JAMA Network Open. 2020;3(12):e2027754

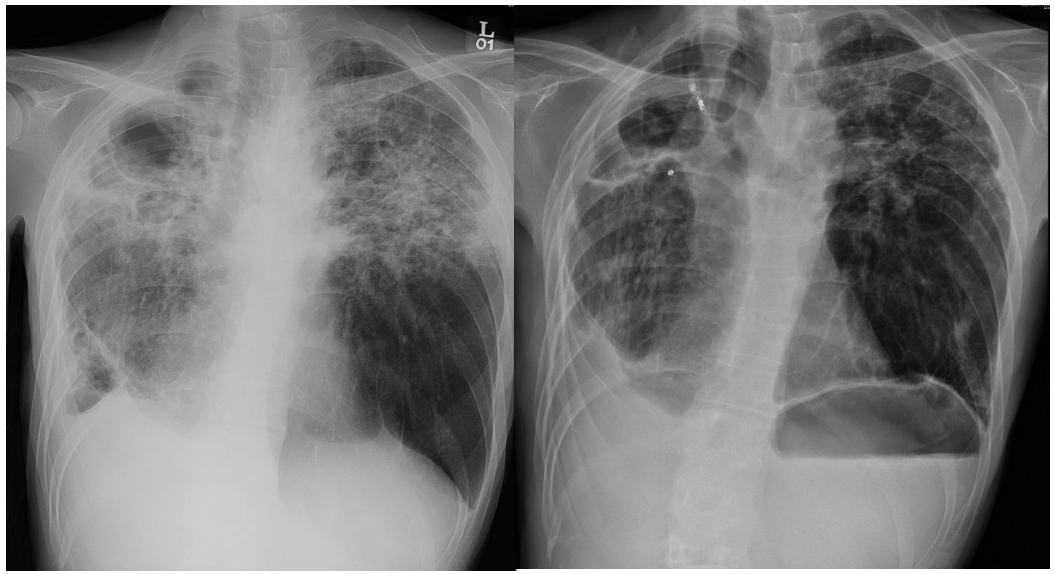
Diagnosis or Screening of PTLD

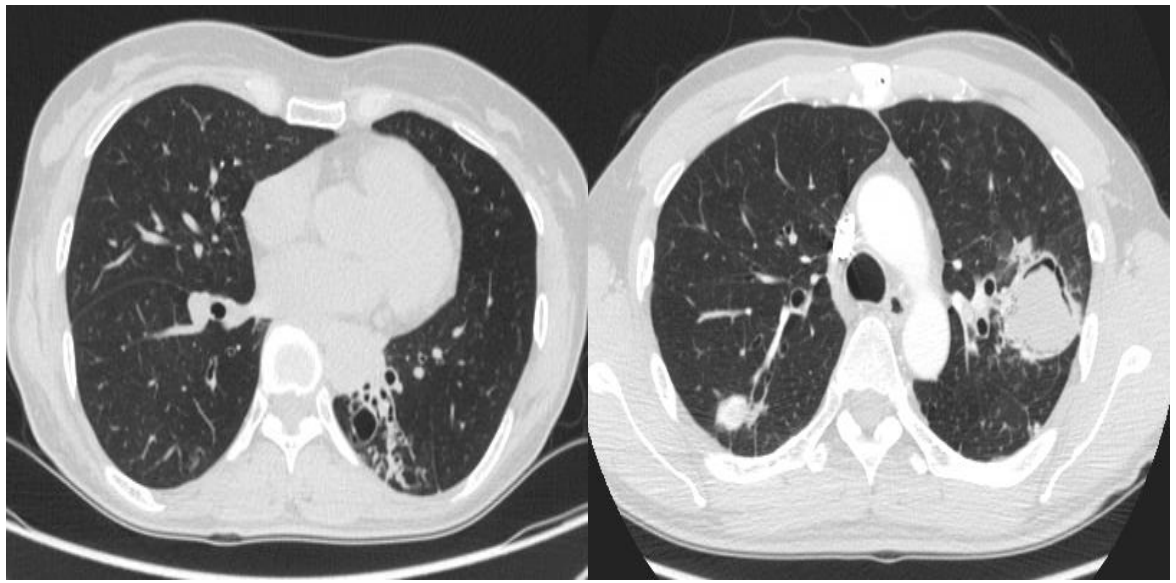
1. Screening for PTLD within health systems
   - All people with pulmonary TB ?
   - Which population? Symptomatic? Advanced lung involvement? With co-morbidities?
2. Clinical evaluation of TB survivors with residual or recurrent respiratory symptoms:
   - Recurrence
   - Non-TB respiratory infection screening : NTM ? Fungus?
   - Chronic respiratory disease : COPD, bronchiectasis
   - Cardiovascular morbidity ?
   - Lung cancer ?

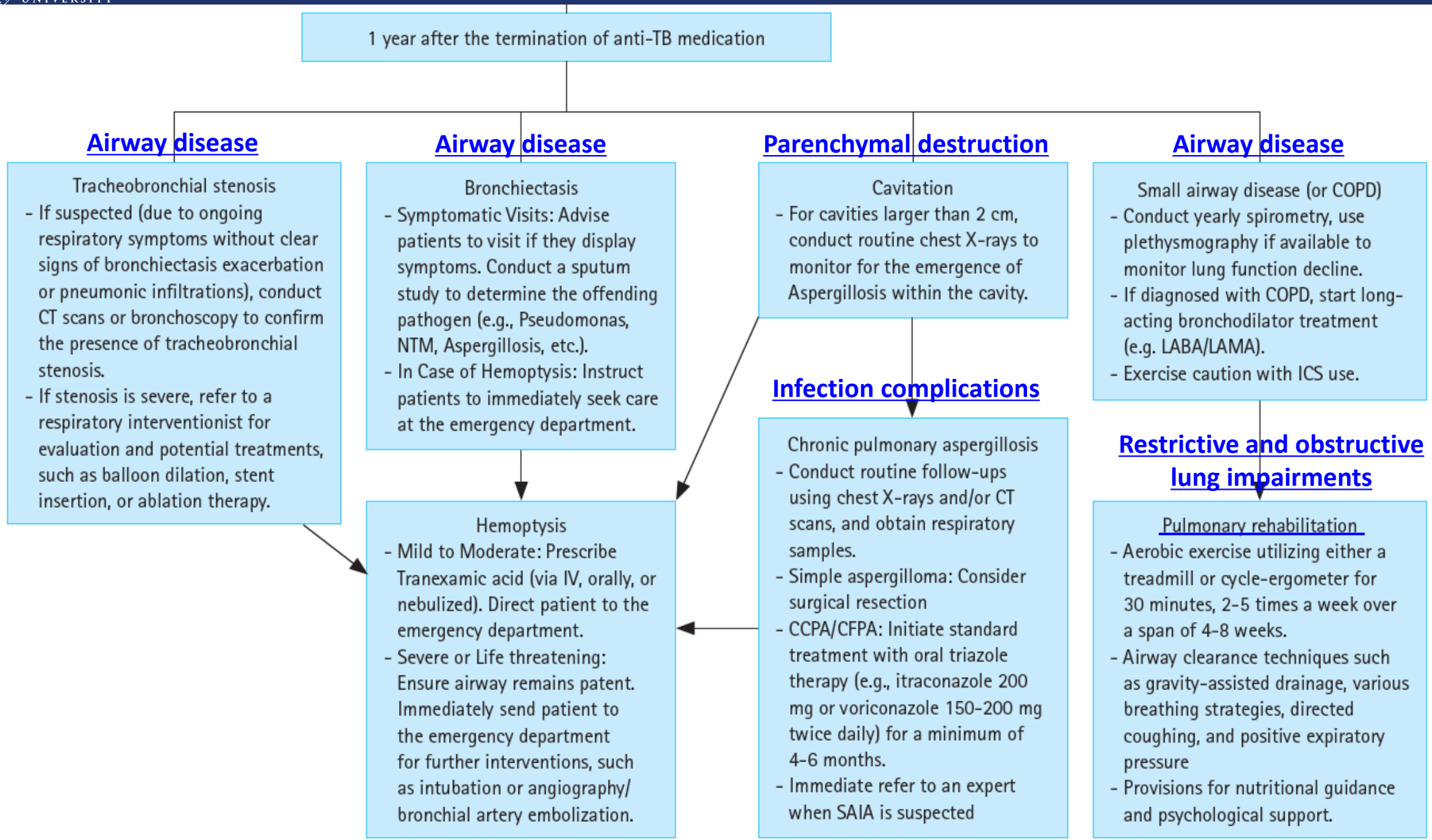
IJTLD OPEN 20241(3):111–123

Management of PTLD

❖ Management focused on the characteristics of PTLD





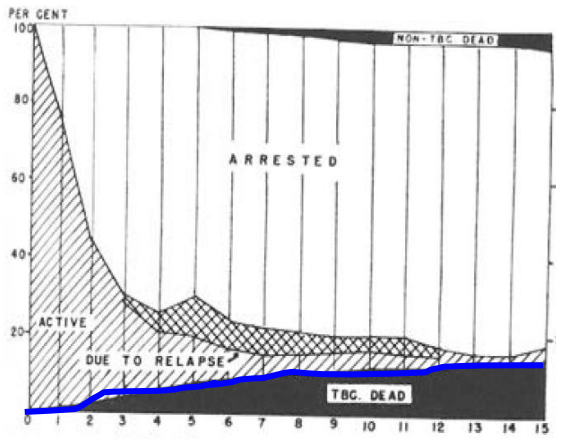


Korean J Intern Med 2024;39:7

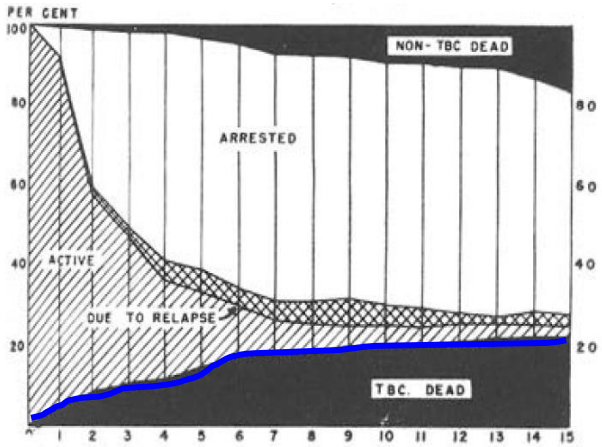
Prevention of PTLD

- The key to prevention and reducing the incidence of PTLD is early diagnosis and adequate treatment of TB in order to minimize residual lung damage.

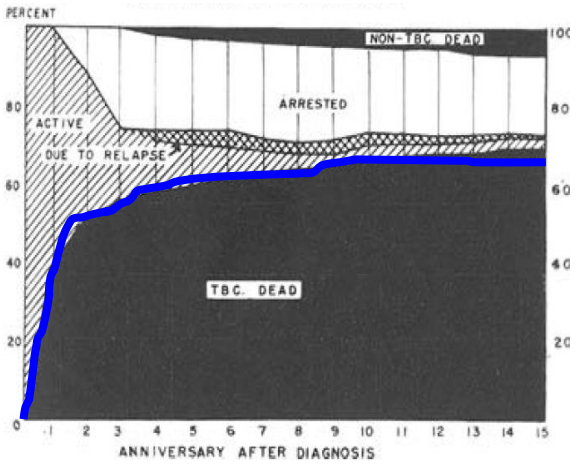
Minimal TB



Moderate TB



Advanced TB



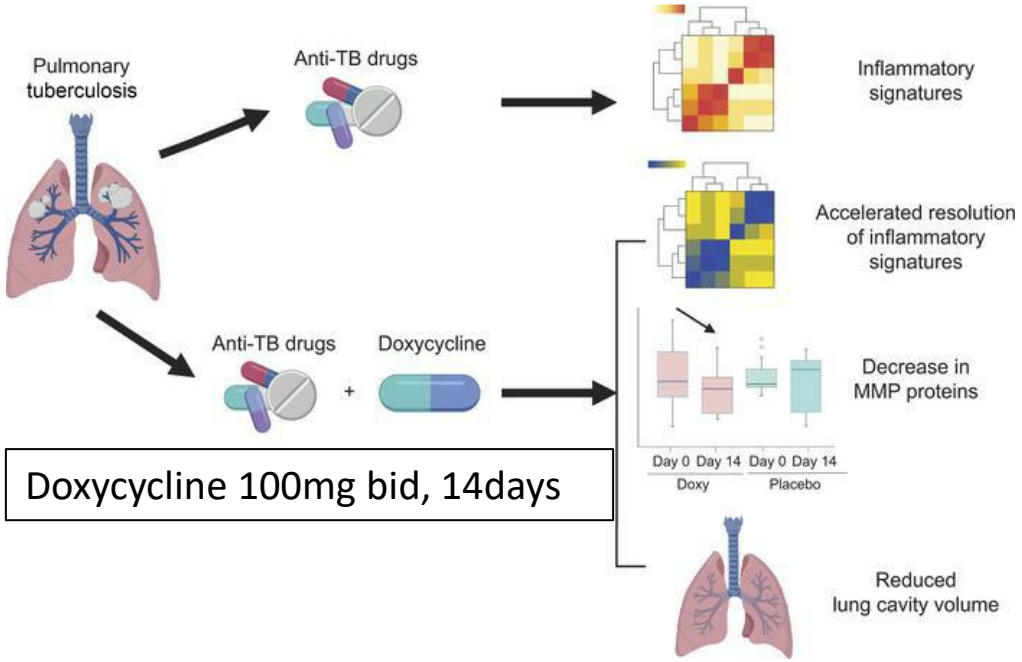
Am Rev Respir Dis 1960;81:839

Doxycycline host-directed therapy in human pulmonary tuberculosis

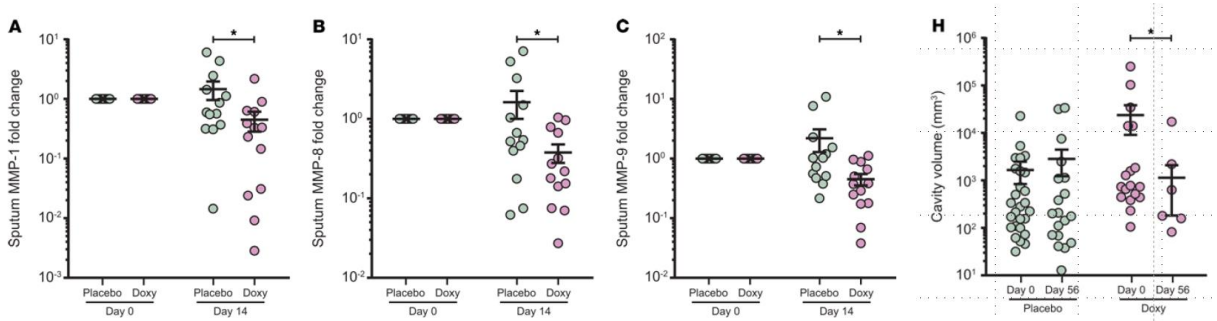
- Only licensed MMP inhibitor with broad spectrum MMP inhibitory activity
- Mtb-induced MMP secretion in cellular models
- MMP inhibition improved drug efficacy in the mouse model
- Inhibits MMP activity in periodontal disease at 20 mg twice daily
- A first-in-human pilot phase II randomized, double-blind, placebo-controlled trial
  - 2015-2017, National University Hospital and Tuberculosis Control Unit in Singapore
  - Primary outcome : Procollagen III N-terminal propeptide (matrix degradation product) change

J Clin Invest. 2021;131(15):e141895

Doxycycline host-directed therapy in human pulmonary tuberculosis



Doxycycline 100mg bid, 14days



- 15 doxycycline, 15 placebo
- Rapidly down-regulating type I and II interferon and innate immune response genes
- Reduced sputum MMP-1, -8, -9, -12 and -13, suppressed type I collagen and elastin destruction
- Reduced pulmonary cavity volume without altering sputum mycobacterial loads
- Procollagen III N-terminal propeptide change (nonsignificant)

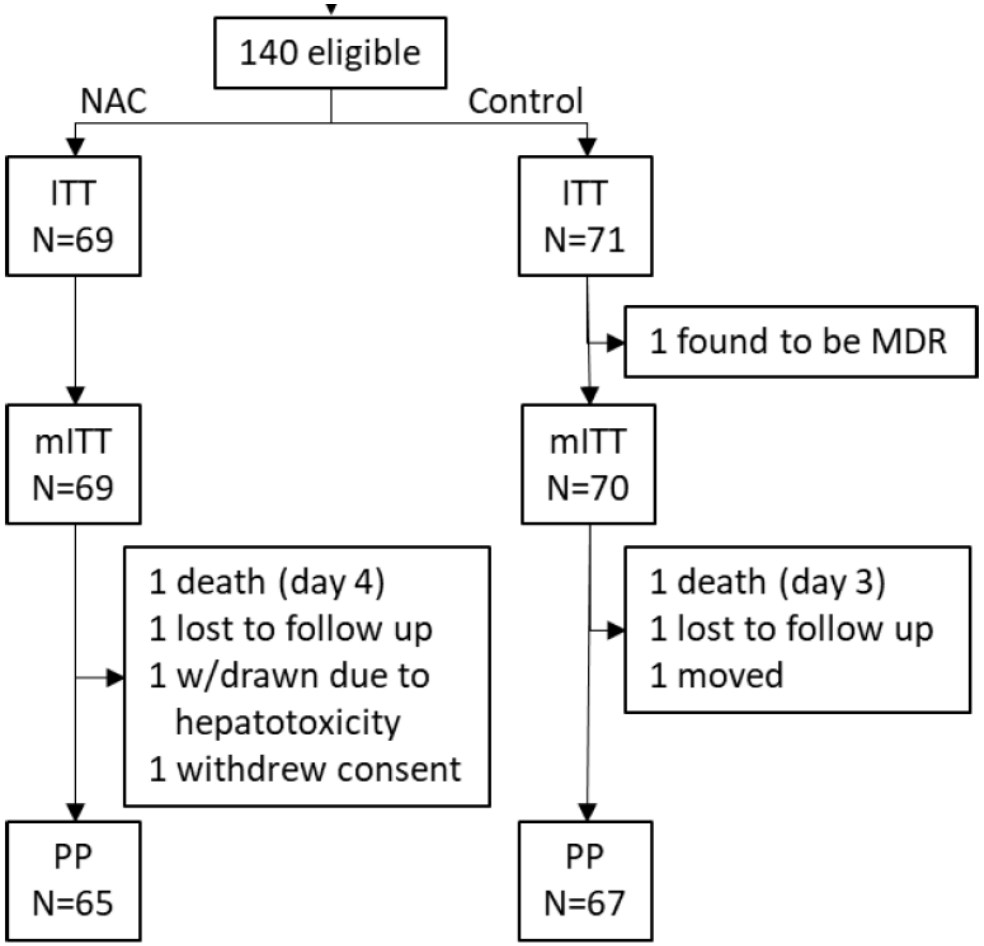
J Clin Invest. 2021;131(15):e141895

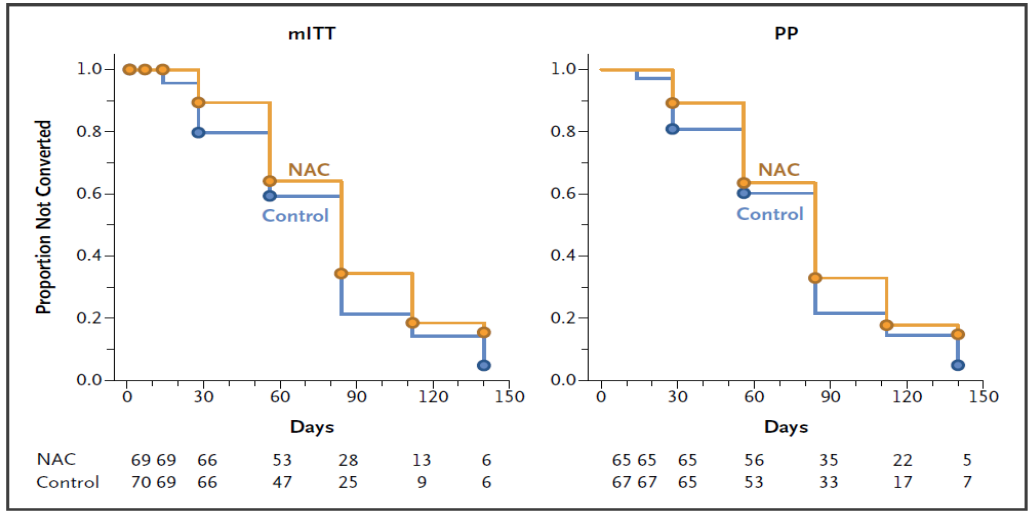
Adjunctive NAC and lung function in pulmonary TB

- N-acetylcysteine (NAC) : antimicrobial, antioxidant and immunomodulatory
- Phase 2, open-label, prospective, parallel-arm, randomized controlled trial
- March 2019 –May 2021
- Nested RCT in TB SEQUEL cohort study, Tanzania
  - 18 to 65 years of age, RIF susceptible TB, moderately or far-advanced pulmonary tuberculosis in CXR
  - 1200mg of oral NAC twice a day from days 1 to 112, 1:1 allocation
- The primary outcome was culture conversion
- Secondary outcomes included whole-blood glutathione levels and lung function

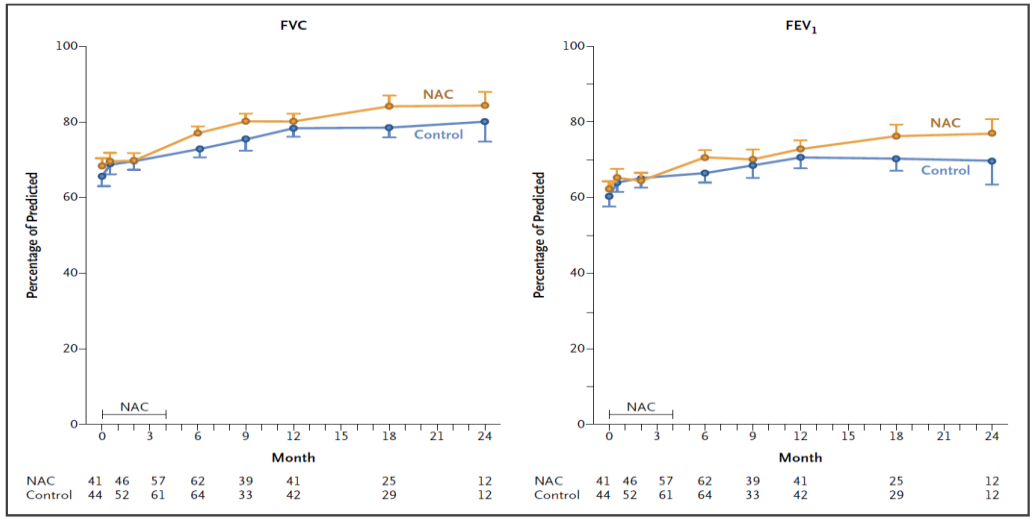
NEJM Evid 2024; 3 (9)

Adjunctive NAC and lung function in pulmonary TB





No difference in culture conversion



Improved lung function

NEJM Evid 2024; 3 (9)

Adjunctive host-directed therapies for pulmonary TB

- Host immune modulators
  - Protect the lung destruction
  - Shortened treatment duration (reducing lung inflammation, improving lesional drug penetration, inducing antimycobacterial activity)
  - Improving survival
- Host-directed therapies candidates
  - CC-11050 : a type 4 phosphodiesterase inhibitor with anti-inflammatory properties
  - Everolimus : mTOR inhibitors –induced autophagy
  - Auranofin :an orally bioavailable anti-inflammatory gold salt – in vitro antimycobacterial activity
  - Vitamin D : essential for host defenses against M.TB

Lancet Respir Med 2021;9: 897–908

Adjunctive host-directed therapies for pTB

- Prospective, open-label, phase 2, randomized controlled trial, South Africa
  - 18 to 65 years of age, RIF susceptible TB, moderately or far-advanced pulmonary tuberculosis in CXR
- CC-11050, everolimus, auranofin, or ergocalciferol in addition to standard tuberculosis therapy, or standard tuberculosis therapy alone (control) 1:1:1:1:1
- n=40 per group, apart from n=39 in the everolimus group after one patient withdrew consent), 1 to day 112 days
- The primary outcome : the safety and tolerability of the study treatments
- Secondary preliminary efficacy outcomes : sputum culture status and lung function

Lancet Respir Med 2021;9: 897–908

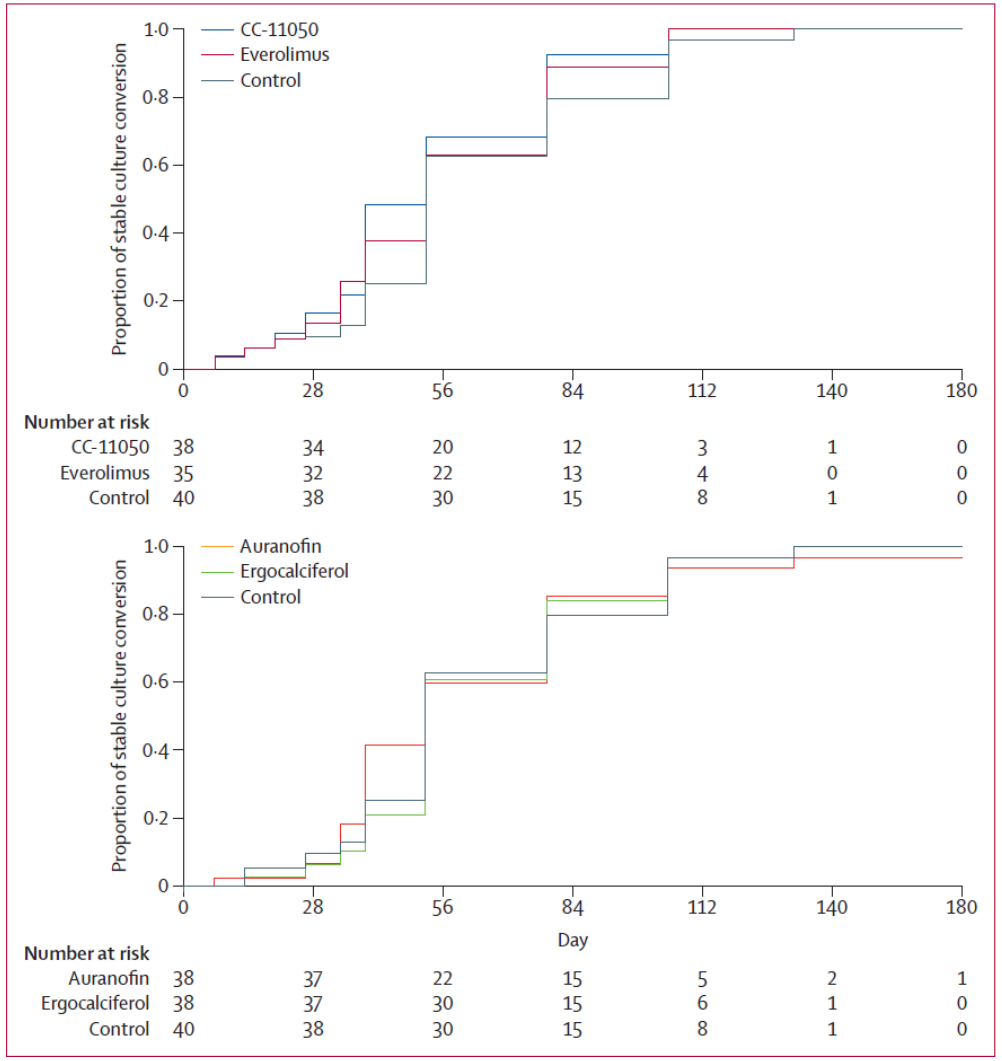
11 treatment-emergent serous adverse events

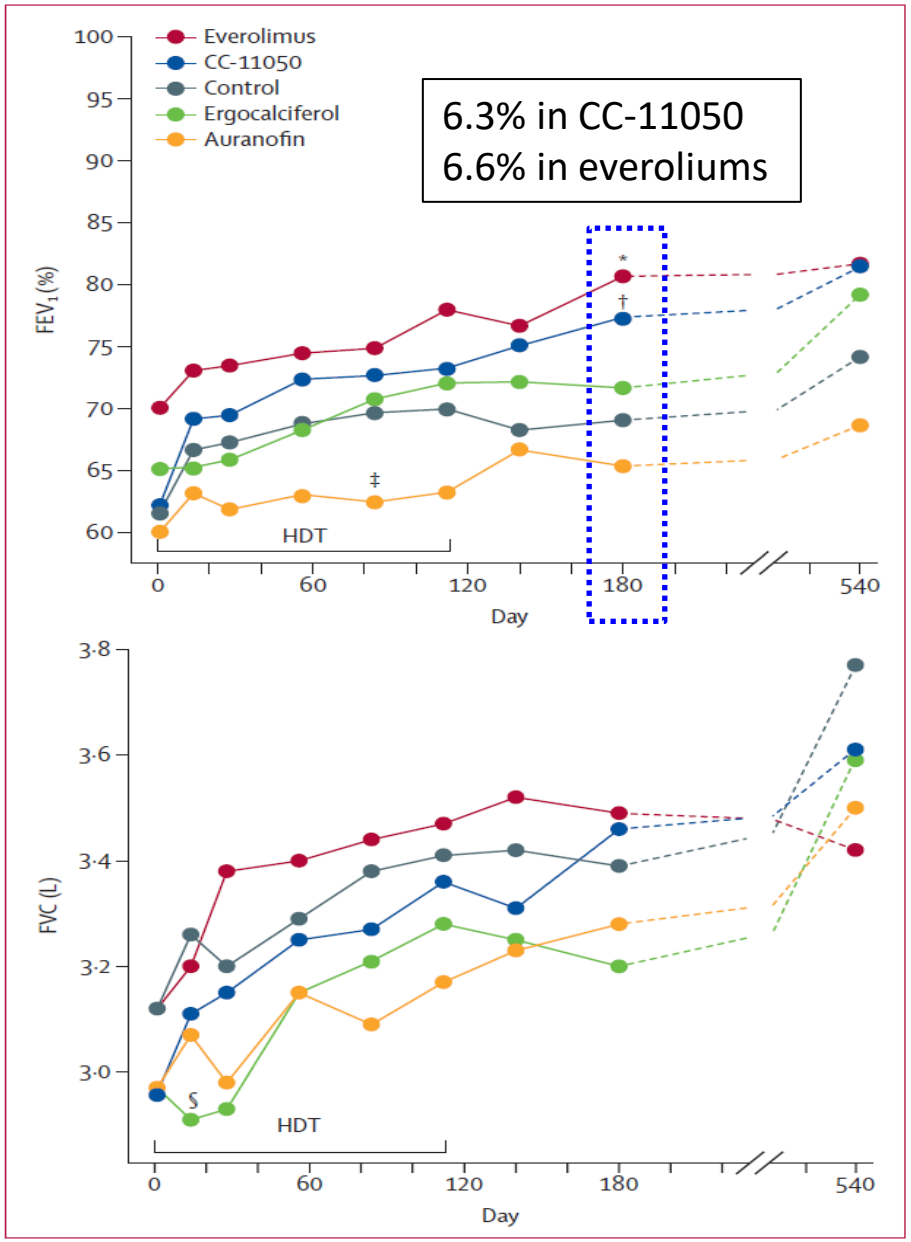
	Seriousness	Days from study entry to onset	Treatment relatedness		Action on study medications	Adverse event outcome
			To standard therapy	To host-directed therapy		
Control						
Ischiorectal abscess	Required hospital admission	107	Unrelated	NA	Maintained	Resolved
Drug-induced liver injury	Life-threatening	28	Probable	NA	Discontinued	Resolved
Drug-induced liver injury	Life-threatening	37	Probable	NA	Interrupted	Resolved
CC-11050	..	..	..	..	..	..
Everolimus						
Psychosis	Required hospital admission	124	Unrelated	Unrelated	Maintained	Resolved
Auranofin						
Syncope	Required hospital admission	12	Unrelated	Unrelated	Maintained	Resolved
Acute hepatitis B virus infection	Life-threatening	148	Unrelated	Unrelated	Interrupted	Resolved
Thrombocytopenia	Life-threatening	53	Unrelated	Probable	Discontinued	Resolved
Sepsis, disseminated intravascular coagulation, respiratory failure	Required hospital admission; resulted in death	14	Unrelated	Suspected unexpected serious adverse reaction	Host-directed therapy discontinued	Unresolved
Ergocalciferol						
Dysfunctional uterine bleeding	Required hospital admission	110	Unrelated	Unrelated	Maintained	Resolved
Tuberculous spondylitis	Medically significant	49	Unrelated	Possible	Maintained	Resolved
Acute pancreatitis	Required hospital admission	195	Unrelated	Unrelated	Occurred post-treatment	Resolved

NA=not applicable.

Lancet Respir Med 2021;9: 897–908

No difference in culture conversion



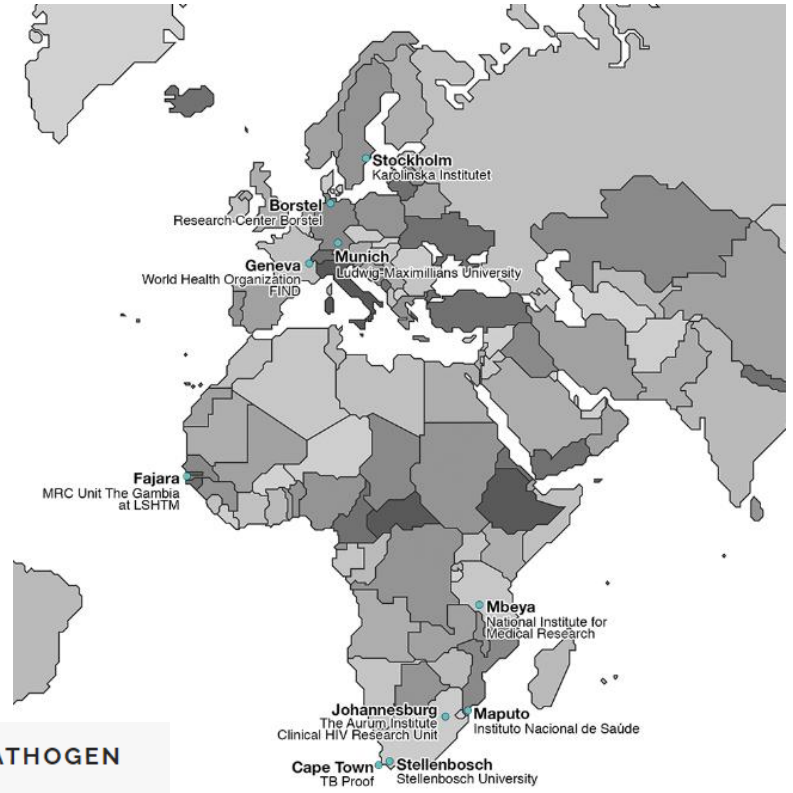


Lancet Respir Med 2021;9: 897–908

PTLD cohort

TB Sequel
RESEARCH CAPACITY DEVELOPMENT NETWORKING

- TB Sequel consortium in Africa and Europe
- TB Sequel cohort
  - Prospective, multi-country, multicenter, observational cohort study
  - 1.600 pTB patients at the time of TB diagnosis
  - Sep 2017 ~ Sep 2019
  - Follow up period of at least 24 months
  - Primary outcome : a proportion of Pt with severe pulmonary function impairment

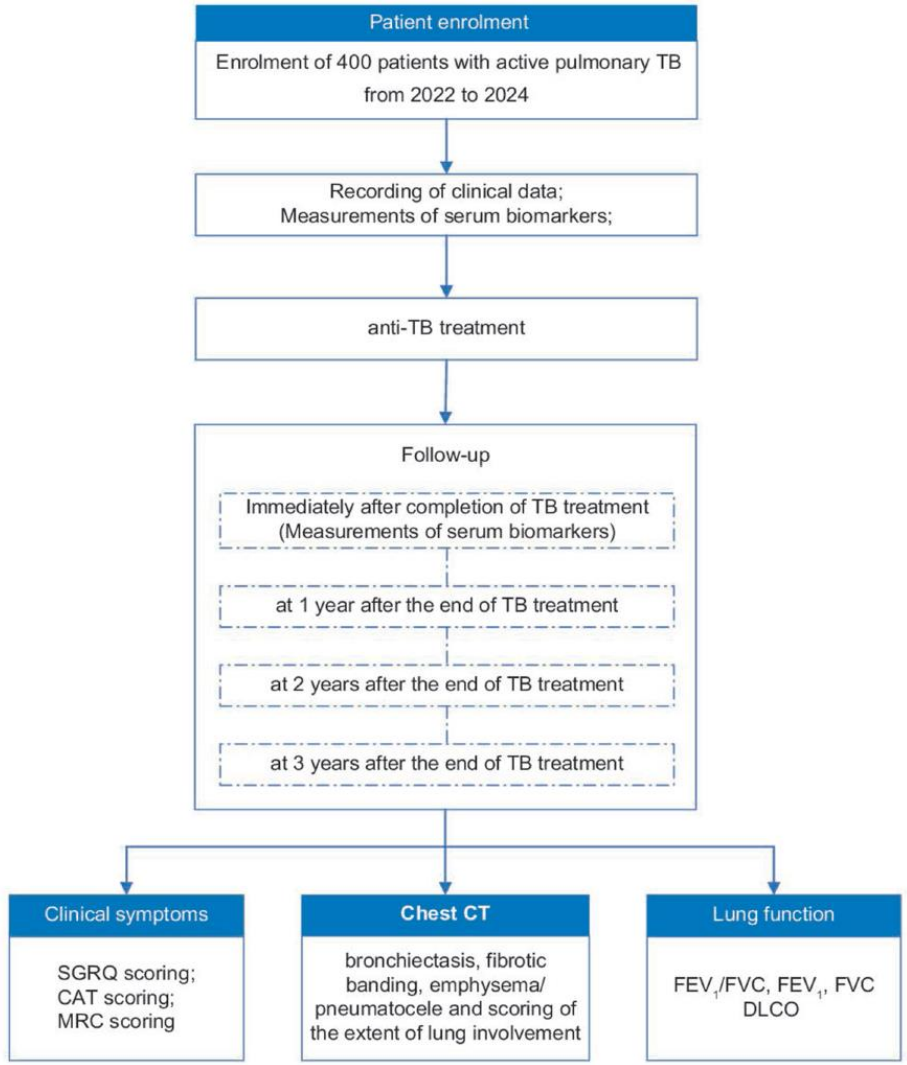


RESEARCH TASK 1: THE TB SEQUEL COHORT
RESEARCH TASK 2: THE NAC TRIAL
RESEARCH TASK 3: HOST AND PATHOGEN
RESEARCH TASK 4: SOCIO-ECONOMICS
RESEARCH TASK 5: POST-TB IMPLEMENTATION RESEARCH

https://www.tbsequel.org/research/

PTLD cohort in a Chines male smokers and non-smokers

- The prospective observational cohort
- To evaluate the effect of cigarette smoking on PTLD
- Peking University Third Hospital and Beijing Geriatric Hospital in China, 2022 ~2024
- 25–65 years newly diagnosed with pTB, male
- Primary outcome : longitudinal changes in lung function measurements



BMJ Open 2023;13:e065990

Post-TB lung disease registry
프로토콜 개발 및 다기관 연구 체계 구축

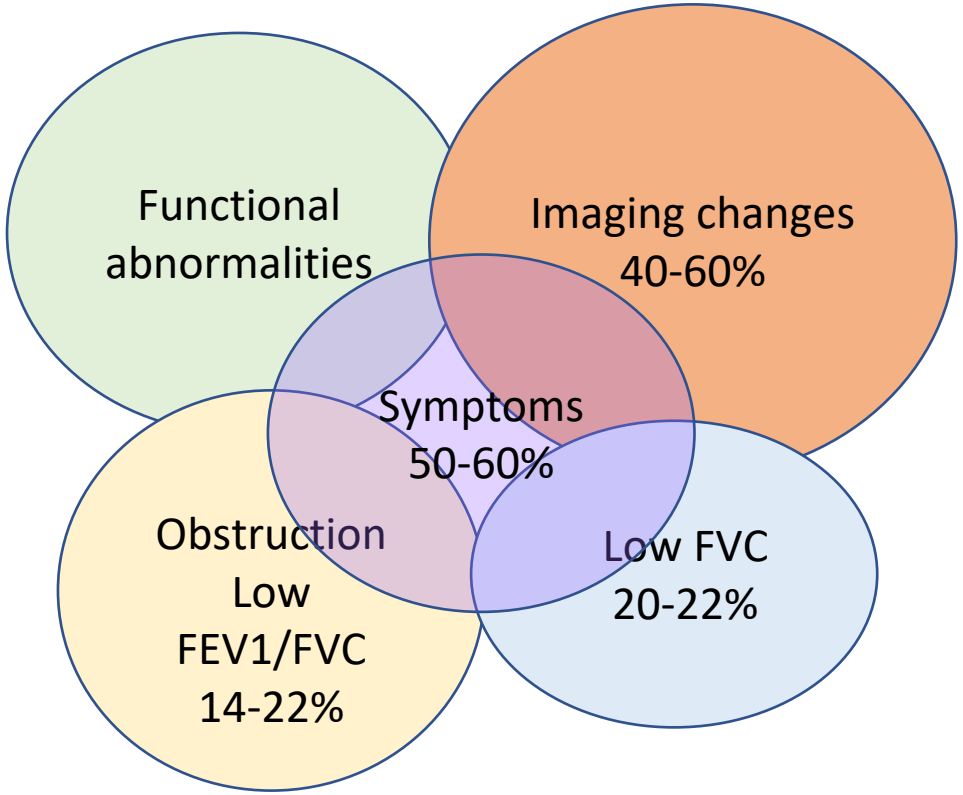
대한 결핵 및 호흡기 학회

결핵 및 NTM 연구회 2024

Summary

Post-TB lung disease, Why ?

- Monitoring impairment/disability as program outcome
- Patients : Understanding symptoms
- HCWs : Prevent decline, promote recovery and ensure linkage to care
- Policy maker : To guide resource allocation and intervention usage



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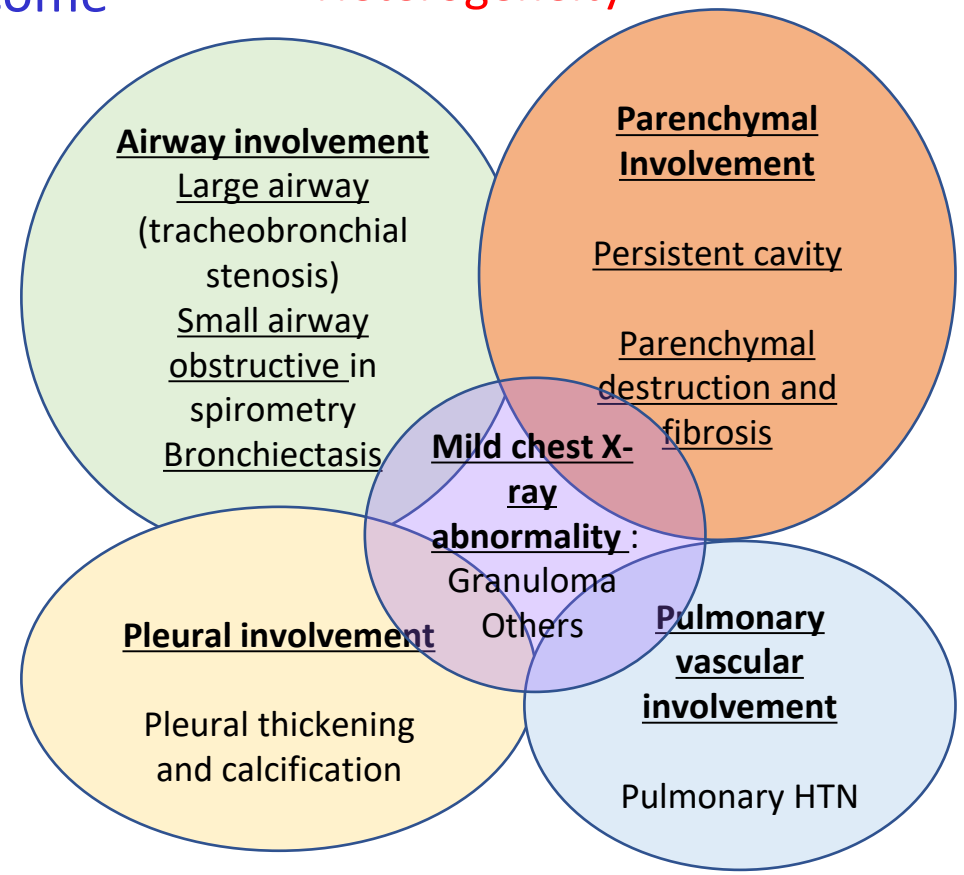
What to do ?

- Must include lung outcome not only microbiologic outcome
- Understand the pathophysiology of lung outcome
- Lung outcome modifying intervention

- New baseline assessment
- More specific definition of PTLD including severity
- Determine patient-centered outcomes
- Validate measurement of outcomes

- Research on poor outcomes

Heterogeneity



From Union 2023 Conference

Thank you for your attention!