

CULTURE-NEGATIVE ("PAUCIBACILLARY") PULMONARY TUBERCULOSIS

ALONG THE TB DISEASE SPECTRUM

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OBJECTIVES

1. identify the limitations in viewing tuberculosis as a binary disease process (latent vs active)
2. describe the TB disease spectrum
3. understand the definition and epidemiology of subclinical tuberculosis, including its role in TB transmission
4. Discriminate which patients meet the criteria for “culture-negative” tuberculosis
5. summarize treatment regimen(s) for “culture-negative tuberculosis”

OUTLINE

1. Introduction (case)
2. Conceptualizing TB infection states
 - Historic view of tuberculosis as a binary disease process (“latent” vs “active”)
 - TB as a disease spectrum
3. Epidemiology of culture-negative/subclinical tuberculosis
 - frequency
 - natural history
 - role in TB transmission
4. Adapting the concept of “culture-negative” tuberculosis to practice
 - who fits the definition, programmatically
 - treatment regimens



ARS QUESTION 1: WHICH OF THE FOLLOWING PATIENTS ARE LIKELY TO HAVE CULTURE-NEGATIVE (PULMONARY) TUBERCULOSIS?

- CHOOSE THE BEST ANSWER or ANSWERS FROM BELOW
 1. very young children (<5 yrs old)
 2. patients with extrapulmonary disease
 3. patients with subclinical disease
 4. patients who have been inadequately investigated



RATIONALE

ANSWERS 1-4 ARE EACH, IN A CERTAIN SENSE, CORRECT BECAUSE

1. tuberculosis in children is a paucibacillary disease
2. in patients with extrapulmonary tuberculosis, the compartment with the disease may not be **easy to sample** or simply **not have been sampled**
3. mycobacterial cultures from patients with incipient and subclinical tuberculosis are often only intermittently positive
4. a diagnosis of tuberculosis may not have been suspected or may not have been appropriately investigated

DiNardo (AR) (2016) Tuberculosis 101 (Suppl): S3105-S108

Jaganath D (2022). Infect Dis Clin North Am. 36(1):49-71.

Esmail H (2022) eBioMedicine 78: 103928

Pai M (2016). Nat Rev Dis Primers 2: 16076



FOCUS OF TALK

patients with subclinical tuberculosis

- frequently culture-negative
- epidemiologically significant
 - prevent appearance of clinical disease
 - impact TB transmission
- departure from the “one-size-fits-all” paradigm of care
- (opportunity to save costs / reduce adverse effects)

DiNardo (AR) (2016) Tuberculosis 101 (Suppl): S3105-S108

Jaganath D (2022). Infect Dis Clin North Am. 36(1):49-71.

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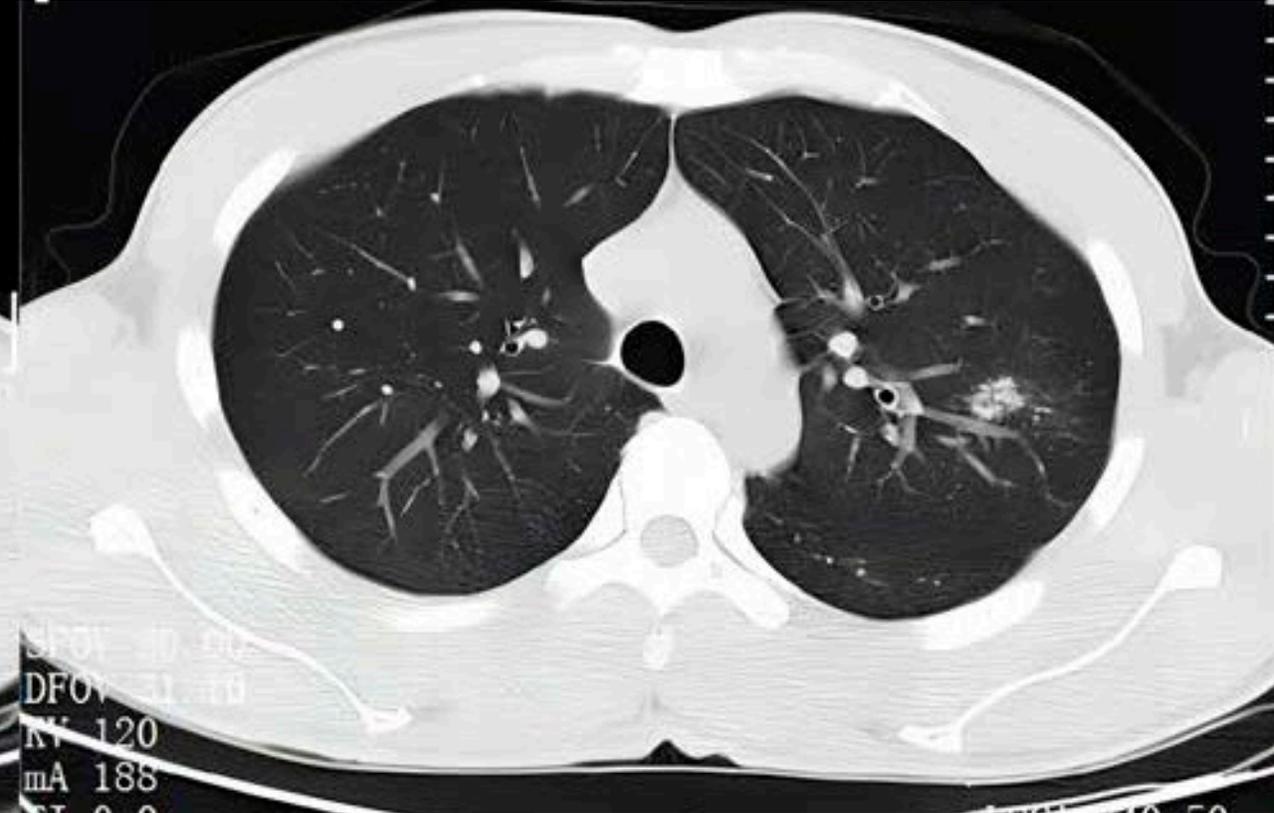
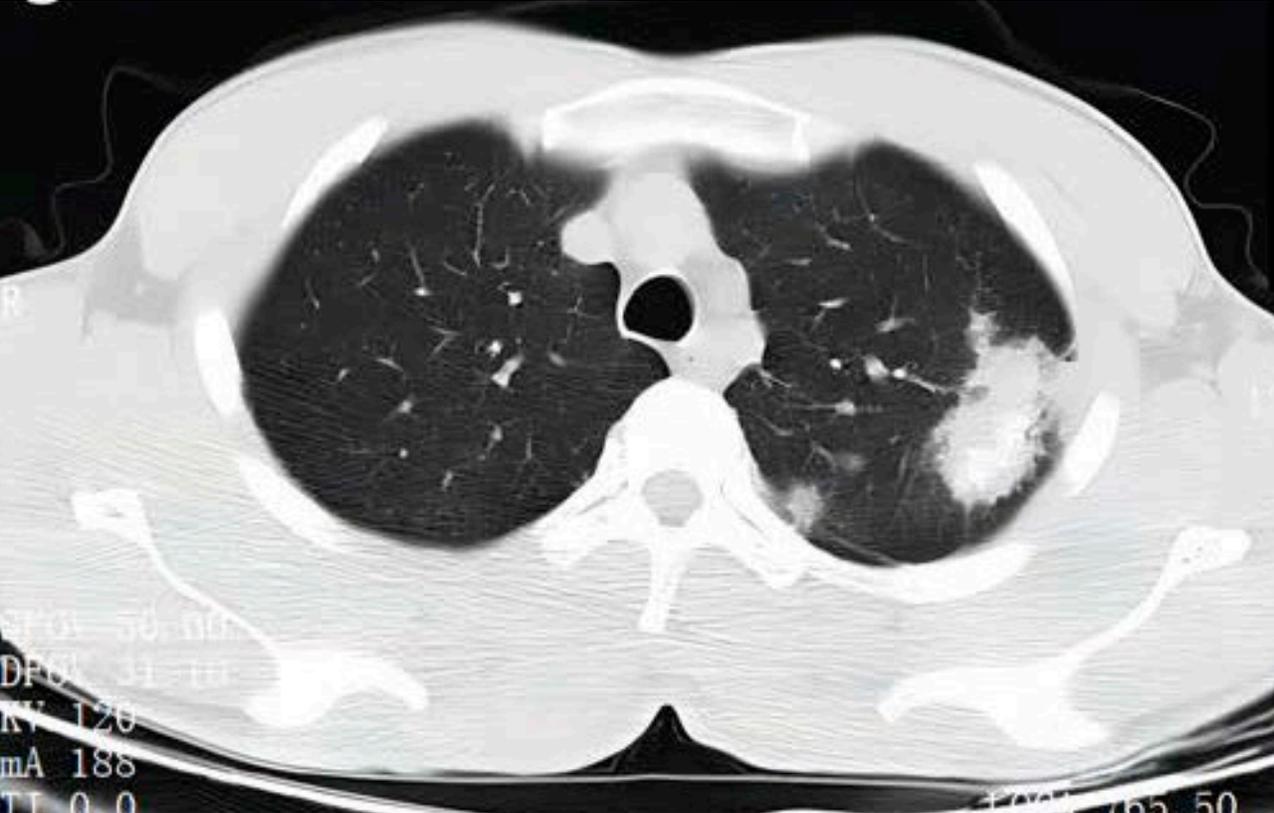
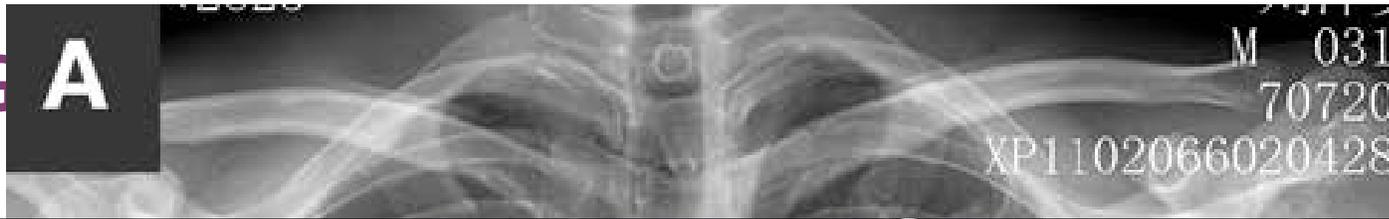
Pai M (2016). Nat Rev Dis Primers 2: 16076

CASE 1

November 2020

- 32-year-old male presented to the ER with chest pain and shortness . CXR showed a left sided pneumothorax
- admitted to hospital and treated with inhaled oxygen therapy
- chest CT showed scattered nodules in the left upper lobe, with calcification in the lesion.

LUNG A



CASE 1, continued

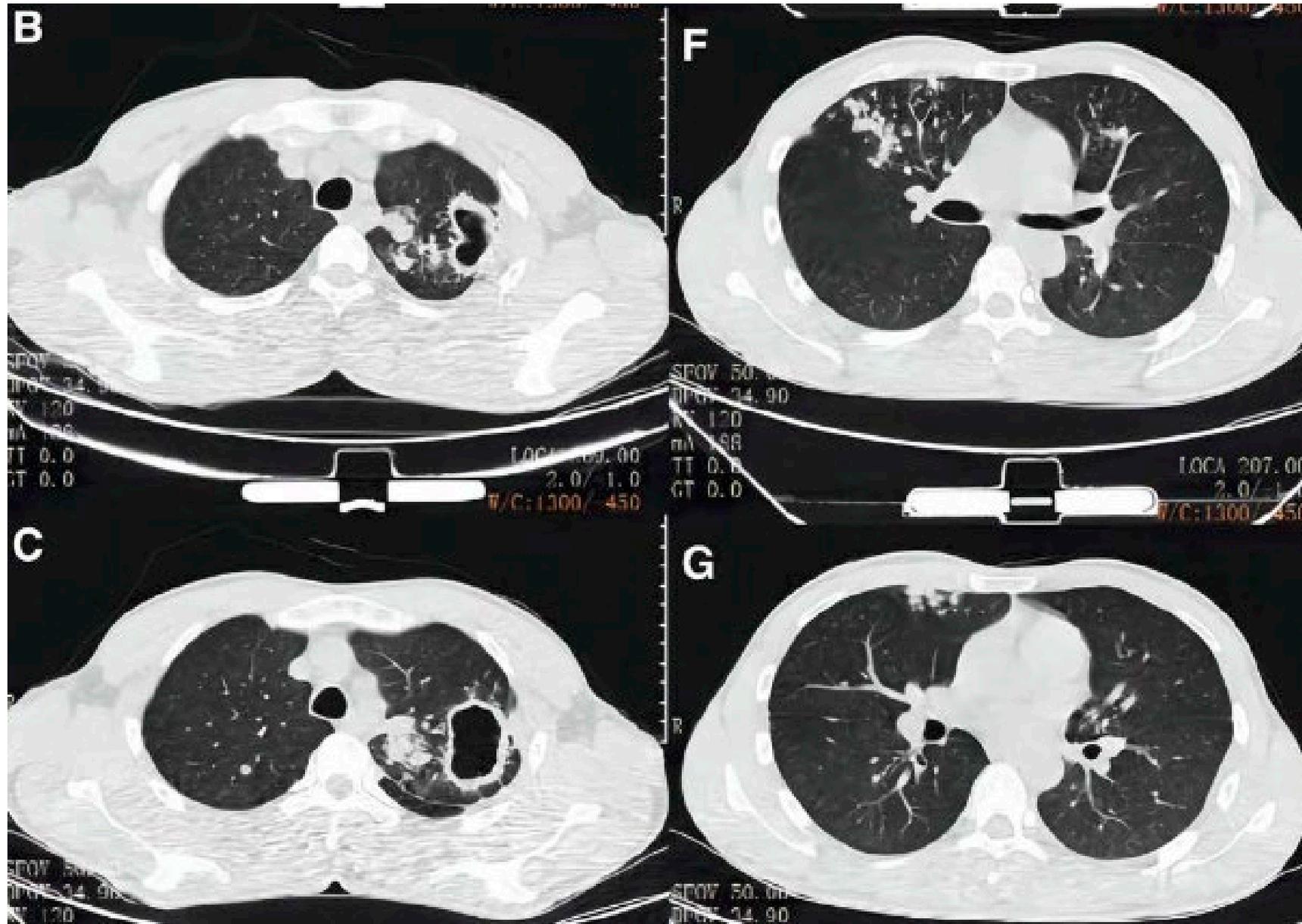
November 2020

- TST placed, positive
- bronchoscopy performed, targeting left upper lobe lesions
 - After six weeks, AFB cultures resulted as negative
- No TB therapy given

April 2022 (~18 months later)

- represented to care with persistent cough and expectoration lasting for 3 months. Sputum “purulent, yellow.”
- repeat chest imaging performed –nodules, consolidations and patchy opacities seen in **RUL and LUL** apical segments, **lingula and left lower lobe**. **Multiple thin-walled cavities** in LUL.

IMAGING in 2022



CASE 1, outcome

- 3 consecutive sputum smear tests performed and sent for culture
 - AFB 2+, 2+, and 3+.
 - Sputum Gene Xpert MTB/ positive for TB DNA, negative for rifampicin-R
 - AFB culture was positive for MTB
- Initiated treatment with 2HRZE/4HR
- clinical symptoms improved over 3 months, with marked improvement in chest imaging at 3 months. Completed therapy at 6 months

-
- in September 2022, patient's 11-year-old daughter diagnosed with pulmonary TB *[NOTE, this case was reported from China; unclear if contact investigation undertaken]*



CONCEPTUALIZING TB INFECTION STATES

HISTORICAL VIEW OF TUBERCULOSIS

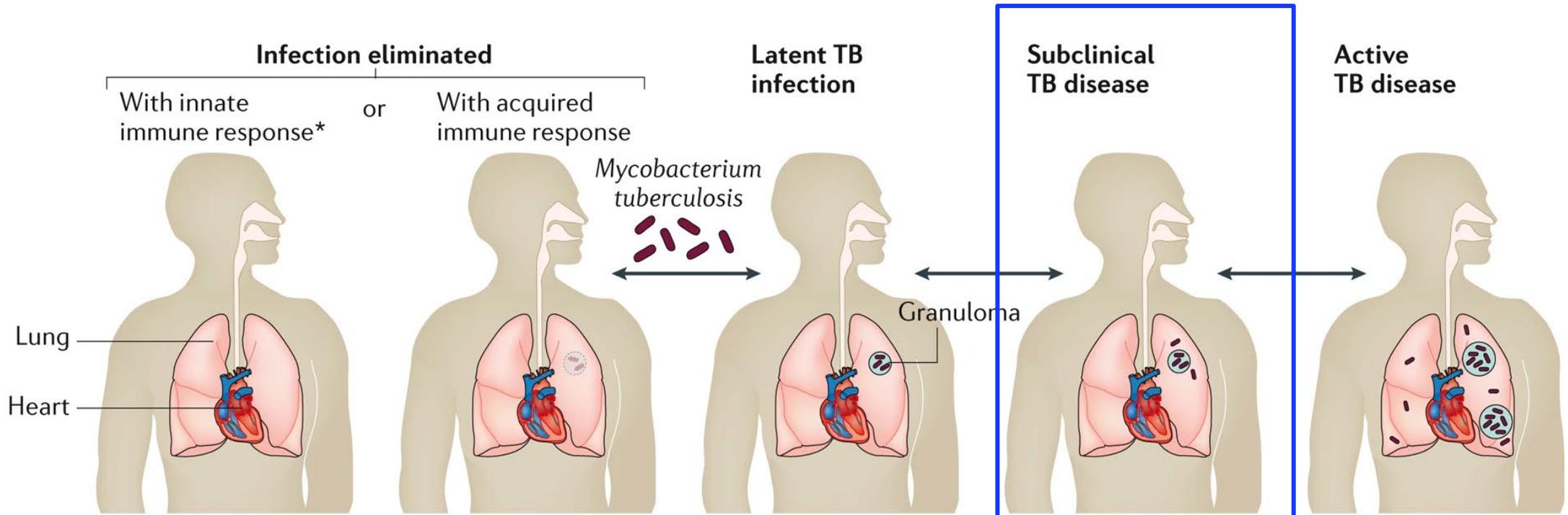


Persons with latent TB

- identified by demonstrating immune sensitization to MTB (positive TST or IGRA)
- assumed to be infected with low numbers of organisms contained within granuloma and causing minimal pathology
- have no symptoms or evidence of disease
- MTb not recovered from culture of routine samples
- 90% of time, disease doesn't progress
- no transmission

Persons with active TB

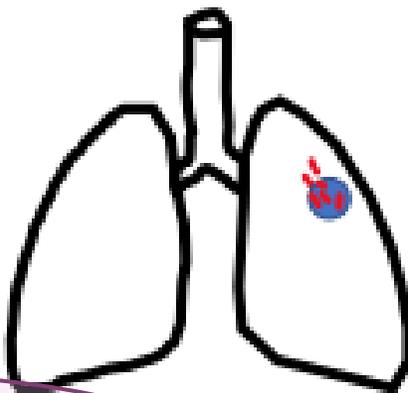
- assumed to have large numbers of organisms (not contained by the immune response)
- have manifest pathology and symptoms
- MTb typically recovered on culture
- disease progresses relentlessly
- lots of transmission



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

SUBCLINICAL TB: a closer look

operationally,
subclinical TB is
often culture-
negative TB

TB Spectrum		
Clinical	Asymptomatic <i>"Subclinical, bacteriologically negative" or "incipient disease"</i>	Asymptomatic <i>"Subclinical, bacteriologically positive disease"</i>
Smear	-	-/+
Culture	-	+
Molecular (Xpert)	-	-/+
CXR (Pulmonary TB)	Minimal abnormalities	
Identification	Active Case Finding	

INCIPIENT TUBERCULOSIS

TABLE 1 Defining criteria for the five categorical states of tuberculosis

Categorical state of TB	Presence of criterion				
	<i>M. tuberculosis</i> exposure	Person has viable <i>M. tuberculosis</i> pathogen	<i>M. tuberculosis</i> has metabolic activity to indicate ongoing or impending progression of infection	Radiographic abnormalities or microbiological evidence of active, viable <i>M. tuberculosis</i>	Person has symptoms suggestive of active <i>M. tuberculosis</i> disease
Eliminated TB infection	X				
Latent TB infection	X	X			
Incipient TB infection	X	X	X		
Subclinical TB disease	X	X	X	X	
Active TB disease	X	X	X	X	X

ARS QUESTION 2: HOW COMMON IS CULTURE-NEGATIVE TUBERCULOSIS IN HIGH-INCOME SETTINGS?

1. <10% of cases
2. 15-20% of all cases
3. 20-40% of cases
4. 60-80% of cases

HOW COMMON IS CULTURE-NEGATIVE TUBERCULOSIS?

- adult surveillance data, HIV-negative adults, New York, 2011-2013:
 - culture-negative PTB defined as: clinical and radiographic presentation consistent with TB, 3 negative results on sputum culture, and improvement with anti-tuberculous treatment
 - sputum induction with hypertonic saline to collect adequate samples, particularly for those with nonproductive cough, was NYC standard of care
 - **15% with culture-negative PTB**
- other high-income countries: **15-20%**
- Korle-Bu Teaching Hospital (KBTH), Accra, Ghana: **69%**
- globally (WHO data): **37%**

Nguyen MH (2019) ,JAMA Netw Open. 2019;2(2):e187617.; Tuberculosis Unit, National Infection Service, Public Health England. *Tuberculosis in England: 2018*. London, England: Public Health England; Afriyie-Mensah JS (2023). Tuberc Res Treat: 6648137; Global tuberculosis report 2023. Geneva: World Health Organization; 2023.



CHEST IMAGING IN CULTURE-NEGATIVE TB

CT Findings Associated with TB

“Active” TB

Centrilobular nodules

“Tree in bud”

Miliary nodules

Cavitation

“Ground glass” opacities

“Prior” TB

Fibrosis

Calcifications

Bronchiectasis

Isolated pleural thickening

It should be noted that lesions with radiographic appearance of “prior” disease may still be associated with the presence of live mycobacteria in respiratory samples.



CHEST IMAGING IN CULTURE-NEGATIVE TB, 2

MINIMAL DISEASE?

Table 2. Clinical and Radiographic Presentation of Patients With Active PTB Stratified by Sputum Culture Results

Symptom or Finding	PTB Culture Result, No. (%) ^a		P Value ^{a,b}
	Negative (n = 116)	Positive (n = 680)	
Cough	57 (68)	543 (89)	<.001
Sputum production	36 (64)	366 (68)	.58
Fever	41 (49)	313 (51)	.66
Night sweats	25 (30)	230 (38)	.16
Weight loss	40 (39)	317 (51)	.03
Hemoptysis	15 (18)	155 (25)	.12
Swollen glands	7 (8)	22 (4)	.07
Chest pain	28 (33)	190 (31)	.71
No symptoms	30 (26)	68 (10)	<.001
AFB smear positive	0	376 (63)	<.001
Cavitation on CXR	10 (7)	186 (28) ^c	<.001
Cavitation on chest CT	22 (26) ^d	243 (59) ^d	<.001



**WHAT IS THE FREQUENCY OF DISEASE
PROGRESSION IN PATIENTS WITH
CULTURE-NEGATIVE TB?**

Diagnosis of sputum smear- and sputum culture-negative pulmonary tuberculosis

R. L. COWIE, M. E. LANGTON, B. C. ESCREET

Summary

A group of patients with new or enlarging apical lung lesions thought to be tuberculous was randomly selected for observation without treatment. All were tuberculin-positive and all had sputum negative for *Mycobacterium tuberculosis* on direct examination and on culture.

STUDY DESIGN

- South African black male **gold miner workers**
- **new or enlarging apical lung lesions** found on routine 6-monthly chest radiography.
- admitted to hospital for
 - a Mantoux test (5 TU) read at 72 hours
 - at least 3 early-morning sputum collections
- Those with TST reactions > 9 mm with smear -negative sputum on smear examination were reviewed after an interval of 2 months.
 - chest radiography was repeated
 - results of previously obtained sputum cultures for MTB reviewed
- if sputum cultures (obtained previously) were negative and the apical lesion still present, enrolled in one of two study arms:

A. antituberculosis
therapy -3RHZE (3mth)

vs

B. observation without
treatment

STUDY DESIGN, continued

- Subjects in the observation only group were followed by chest radiography every 3 months for 3 years, then every 6 months until 5 years after their inclusion in the study.
- Further sputum specimens were submitted for smear and culture if there was any progression of the radiographic lesion or if the original lesion was thought to suggest bacteriologically positive disease
- *“It was our policy to seek a histological diagnosis [by transbronchial biopsy] whenever the features of the lesion suggested non-tuberculous **disease** or where **active TB was suspected because of radiological progression but could not be confirmed bacteriologically.**”*

RESULTS

- 152 enrolled in “observation without treatment” group
- **radiographic progression** of initial lesions occurred in 88 of the 152 subjects (58%)
 - all 88 individuals with radiographic progression were culture-positive (100% with radiographic progression; 58% of total)
- TB diagnosis occurred at a mean of 19.8 months (SD± 14 months) after study entry
- by comparison, only 14% of those given AT therapy developed TB
- “We closed this study once it became apparent that the majority of our subjects were developing PTB. ***We were appalled by the rapidity with which the disease could progress and we have seen extensive destructive infectious disease develop during the 3 months between follow-up visits.***”

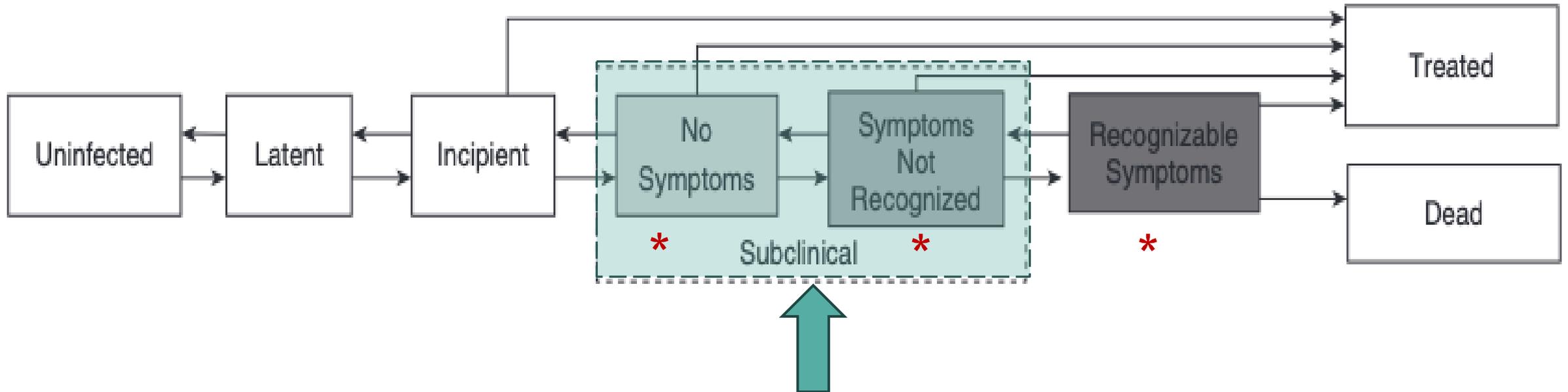
APPLICABILITY?

rates of progression of culture-negative or subclinical tuberculosis in other studies

- Hong Kong Chest Service (1984): **57%**
- Okada K (2012): **17%** bacteriologically confirmed
- rifampin-resistant household contacts, South Africa: **34.5%**
- Richards AS (2023), Bayesian framework model: among patients with **prevalent subclinical disease*** at baseline, after 5 years:
 - 40% recovered and 50% never developed symptoms
 - **18% died from tuberculosis**
 - **14% still with infectious TB**
 - **28% with minimal disease, at risk of re-progression**

** subclinical disease defined as "asymptomatic but infectious"*

HOW IMPORTANT IS SUBCLINICAL DISEASE TO TB TRANSMISSION (SPREAD OF DISEASE IN POPULATIONS)?



TRANSMISSION from subclinical TB DEPENDS ON

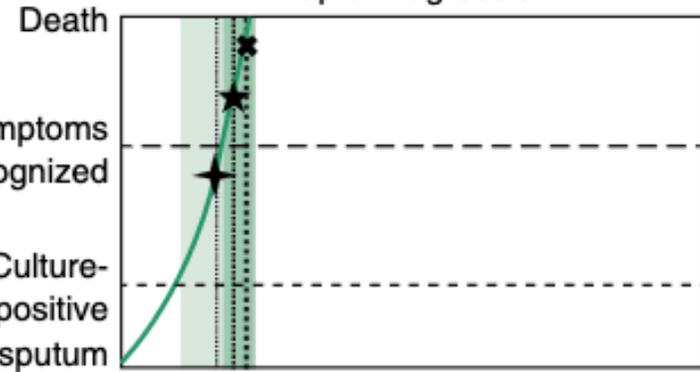
1. proportion of TB that is subclinical
2. Pace of progression/ phase of TB spectrum for patients with SC TB
3. fluctuations in infectiousness in different phases of TB spectrum

IMPACT OF SUBCLINICAL (CULTURE-POSITIVE) TB ON POPULATION TRANSMISSION

NATURAL HISTORY

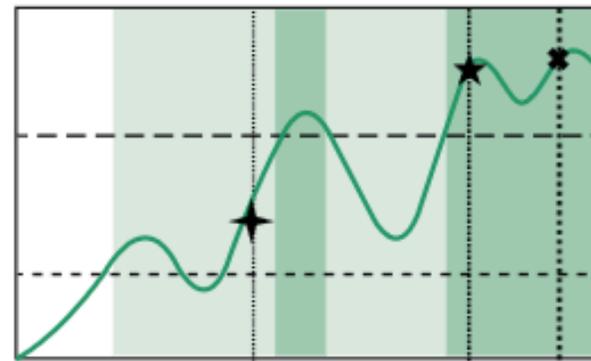
A

Rapid Progression



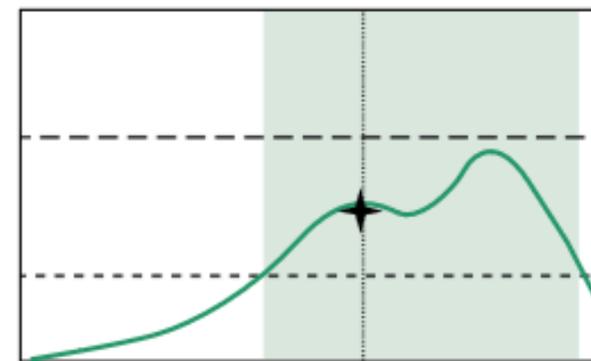
B

Slow Progression, Intermittent Containment



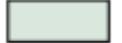
C

Spontaneous Resolution



Culture-positive TB person-time:

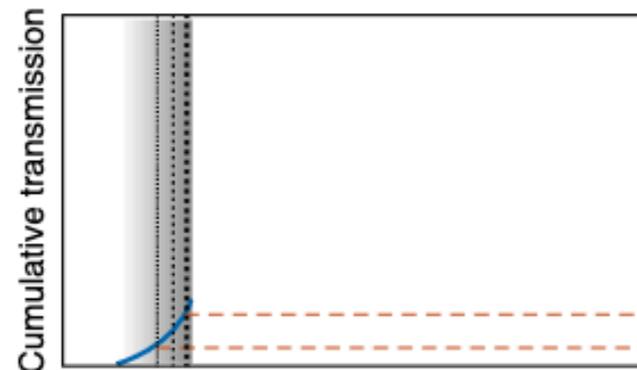
Asymptomatic



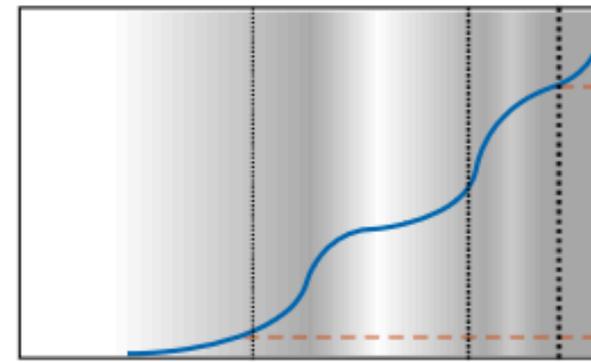
Symptomatic



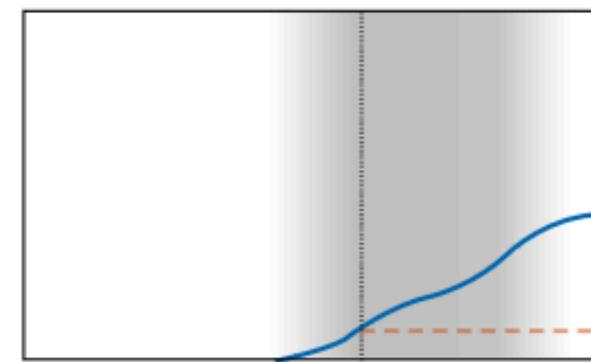
TRANSMISSION



Time since start of TB disease



Time since start of TB disease



Time since start of TB disease

Infectiousness:



Low High

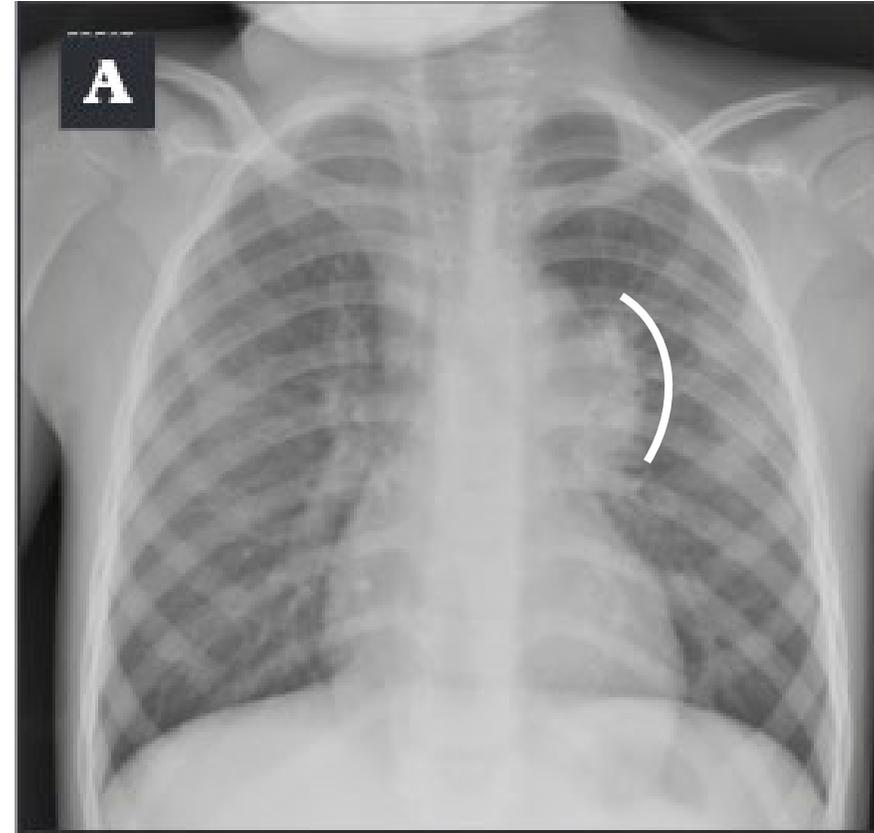
Transmission averted through symptom-independent active TB case finding

CASE 2

- 9-year-old from Egypt who presents for TB screening and testing for immigration/refugee health. Asymptomatic for TB disease; no underlying health conditions.
- QFT positive [nil: 0.19, TB1 – nil: 10, TB2 – nil: 10, mitogen: 10]
- **Sputum samples:**
 - AFB smear negative, culture negative X 3
 - PCR negative x1 (1 tested)
- CXR: Left hilar adenopathy. Lungs clear.
- Chest CT: region of linear opacity within the posterior left upper lobe, with an associated 5-6mm noncavitary nodule. Enlarged left paratracheal lymph node. Additional noncavitary 7-mm nodule within the anterior right middle lobe. No airspace consolidation or pleural effusion elsewhere

CASE 2, continued

- Initiated on RIPE
- weight increased: 87.5 lbs to 94.5 lbs
- repeat chest imaging was not done
- completed **six months of therapy**





ARS QUESTION 3: COULD THIS CHILD HAVE BEEN TREATED WITH FOUR RATHER THAN SIX MONTHS OF THERAPY?

1. No
2. yes
3. Maybe
4. help



CLINICAL CRITERIA FOR “CULTURE-NEGATIVE” TUBERCULOSIS

clinical inclusion factors

- IGRA or TST positive
- radiographic evidence of possible or definite TB
- with or without symptoms – “minimal disease” as judged by clinician

clinical exclusion factors

- extrapulmonary tuberculosis (detailed ROS, other imaging or sampling as called for) (per GL)
- HIV-positive (per GL)
- anticipated risk of MDR TB
- children? (per GL)
- other?



MINIMUM LABORATORY INVESTIGATION OF "CULTURE-NEGATIVE" TUBERCULOSIS

- collection of at least 2 sputum samples (utilizing sputum induction with hypertonic saline, if necessary) for
 - AFB smear and culture
 - rapid molecular testing for *M. tuberculosis*
 - Other diagnostic procedures, such as bronchoscopy with bronchoalveolar lavage and biopsy of larger nodules or masses
-



TREATMENT FOR CULTURE-NEGATIVE TB

once 3 respiratory samples have been collected

- initiate intensive phase of daily RIPE (INH, RIF, PZA, EMB)
- continue all four drugs, *even when the initial bacteriologic studies are negative.*
- If all cultures **on adequate samples** are negative, patient meets definition of culture-negative tuberculosis

reassess clinical signs and symptoms and imaging after 2 months.

- if there is a clinical or radiographic response, the continuation phase consisting of INH and RIF alone may be shortened to 2 months.
- *"Alternatively, if there is concern about the adequacy of workup or the accuracy of the microbiologic evaluations, a standard 6-month regimen remains preferred"*



CAUSES OF FAILURE TO RECOVER MTB FROM RESPIRATORY SAMPLES

- low bacillary load (subclinical TB, child)
- temporal variations in the number of expelled bacilli (subclinical TB)
- recent use of antibiotics with bactericidal activity against MTb—i.e., fluoroquinolones (technical/clinical issue)
- inadequate sputum specimens (technical issue)
- overgrowth of cultures with other microorganisms (technical issue)
- errors in specimen processing (technical issue)
- wrong compartment sampled (imperfect investigation/patient has EPTB)

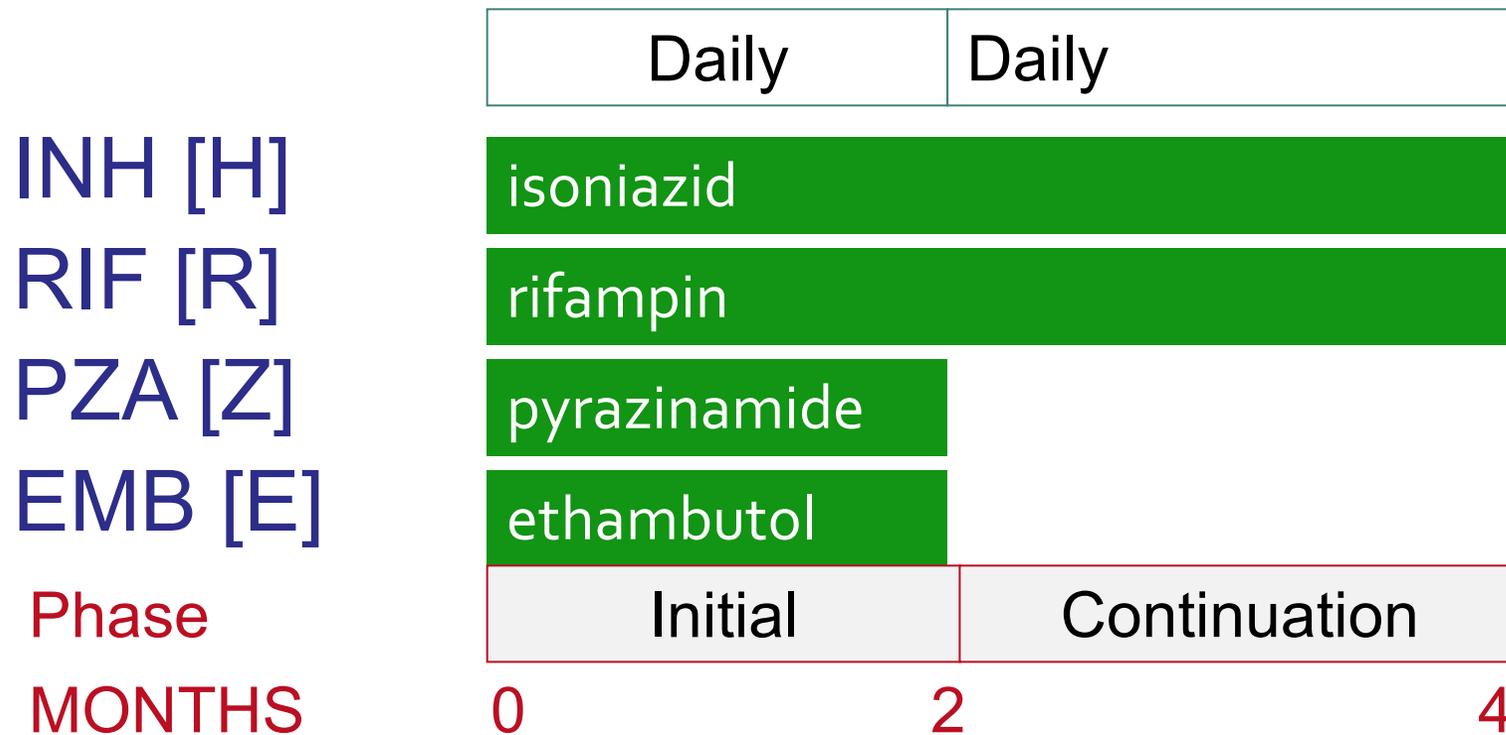
Lewinsohn DM (2017) Clin Infect Dis. 64(2):e1-e33.

Nahid P (2016). Clin Infect Dis. 63(7):e147-e195

Ho J (2015) Int J Tuberc Lung Dis 2015; 19:537–44.

SHORTENED REGIMEN FOR CULTURE-NEGATIVE TB

*HIV-negative adults and children ≥ 16 yrs



NEW REGIMEN FOR DRUG-SUSCEPTIBLE PULMONARY TB

*Adults and children ≥ 12 yrs of age

INH [H]

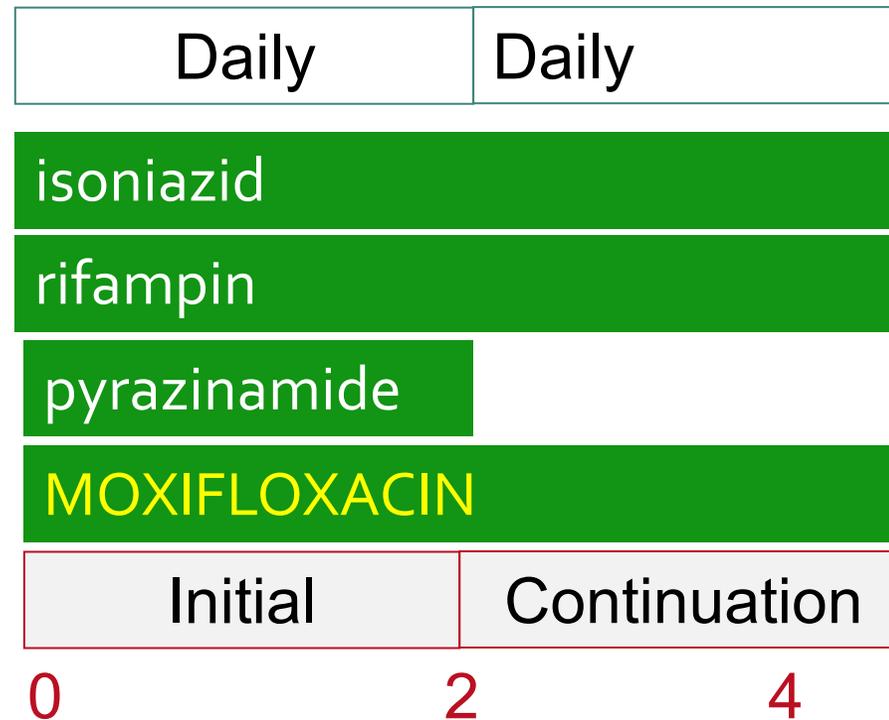
RIFAPENTINE [RPT]

PZA [Z]

MOXIFLOXACIN [M]

Phase

MONTHS



MMWR Morb Mortal Wkly Rep 2022;71:285–289.

DOI: <http://dx.doi.org/10.15585/mmwr.mm7108a1>.

PROPOSED EXCLUSION CRITERIA FOR 2HRZE/2HR TREATMENT OF CULTURE- NEGATIVE PULMONARY TUBERCULOSIS

Shortening the continuous phase with HR to 2 mo (total 4 mo, including 2- mo initial phase with HRZE and 2-mo continuation phase with HR) may be considered for patients with culture-negative pulmonary TB who do not meet any of the following criteria:

- A. Criteria already defined in the 2003 ATS/CDC/IDSA guidelines:
 - 1. HIV infection
 - 2. ~~Children <15 yr of age~~
 - 3. Extrapulmonary TB, including pleural disease
- B. Criteria not defined in the ATS/CDC/IDSA guidelines:
 - 1. Diabetes mellitus
 - 2. Chronic renal failure requiring dialysis
 - 3. Malignancy
 - 4. Receiving immunosuppressive therapy
 - 5. Lung cavitation
 - 6. Extensive pulmonary lesions
 - 7. Any exposure to anti-TB treatment initiated before culture specimen collection
 - 8. Known exposure to fluoroquinolones or other antibiotics active against TB for 7 d or more within 1 mo, or any exposure within 1 wk, before specimen collection for culture
 - 9. <100% direct observed therapy

SHORTER TREATMENT REGIMEN FOR CHILDREN (NOT YET ENDORSED BY ATS/IDSA/CDC)

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

MARCH 10, 2022

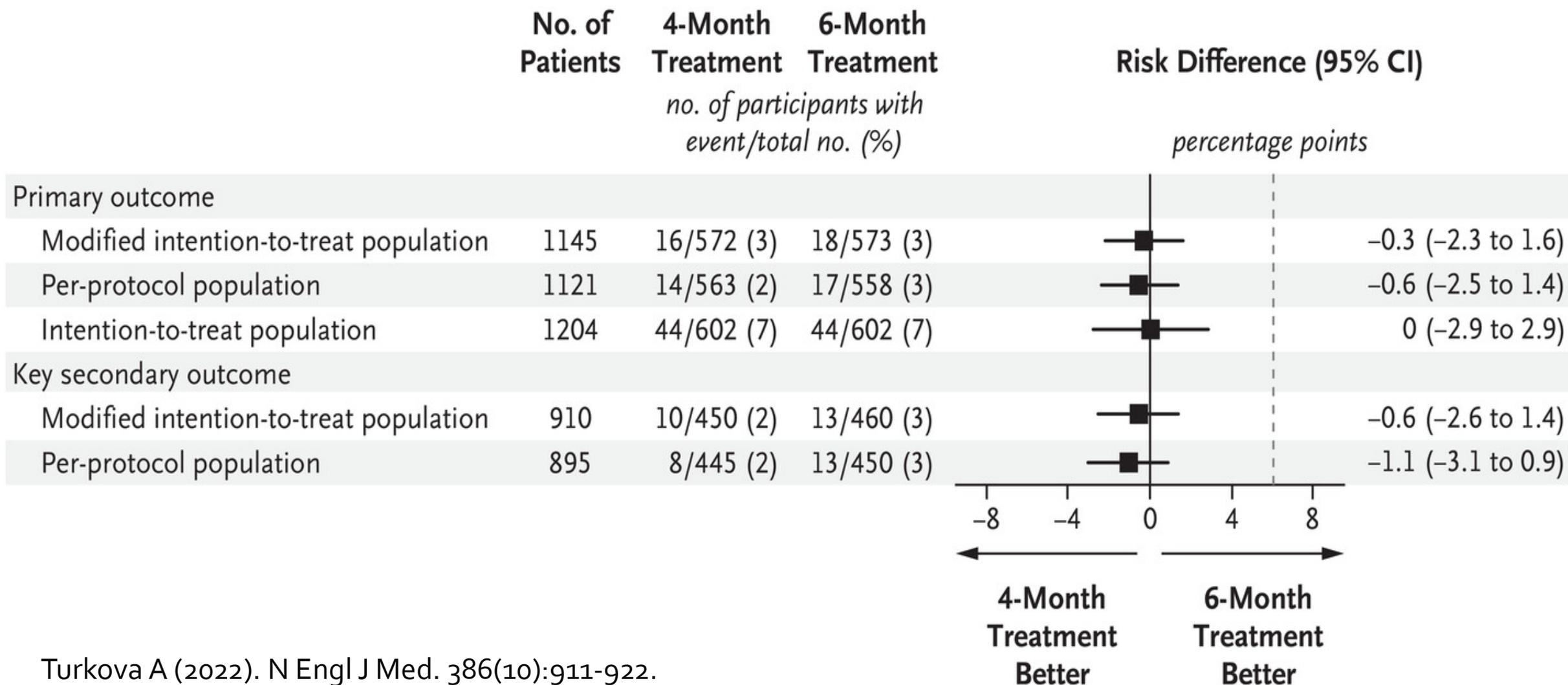
VOL. 386 NO. 10

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

A. Turkova, G.H. Wills, E. Wobudeya, C. Chabala, M. Palmer, A. Kinikar, S. Hissar, L. Choo, P. Musoke, V. Mulenga, V. Mave, B. Joseph, K. LeBeau, M.J. Thomason, R.B. Mboizi, M. Kapasa, M.M. van der Zalm, P. Raichur, P.K. Bhavani, H. McIlleron, A.-M. Demers, R. Aarnoutse, J. Love-Koh, J.A. Seddon, S.B. Welch, S.M. Graham, A.C. Hesselning, D.M. Gibb, and A.M. Crook, for the SHINE Trial Team*

- children <16 yrs of age
- median age 3.5 yrs
- lung or lymph node TB
- 11% HIV positive
- mild disease: smear negative, minimal disease on chest imaging
- culture or Gene Xpert positivity rate: 14% (7% culture-positive)

SHINE OUTCOMES



Turkova A (2022). N Engl J Med. 386(10):911-922.

SHINE OUTCOME, stratified by cause

Table 2. Primary Efficacy Analysis (Modified Intention-to-Treat Population).*

Outcome	4-Month Treatment (N= 572)	6-Month Treatment (N= 573)	Difference (95% CI)	
			Adjusted Analysis†	Unadjusted Analysis
			<i>percentage points</i>	
Unfavorable status — no. (%)	16 (3)	18 (3)	-0.4 (-2.2 to 1.5)	-0.3 (-2.3 to 1.6)
Death from any cause after 4 mo	7 (1)	12 (2)		
Loss to follow-up after 4 mo but during treatment period	0‡	1 (<1)		
Treatment failure				
Tuberculosis recurrence	6 (1)	4 (1)		
Extension of treatment	2 (<1)	0		
Restart of treatment§	1 (<1)	1 (<1)		
Favorable status — no. (%)	556 (97)	555 (97)		



SUMMARY

- Tuberculosis is more currently viewed as a spectrum of infection states, which may progress, stabilize, or even regress
- subclinical tuberculosis is an asymptomatic or nearly asymptomatic form of tuberculosis that is
 - often culture negative
 - may require active case finding to detect, thus likely underestimated
 - may make a significant contribution to TB transmission at the population level
- culture-negative tuberculosis may be treated with 4 months of TB therapy in adult patients who are HIV-negative, do not have extensive disease radiographically, and who are at low risk of drug resistance
 - caution in patients at risk of relapse (DM, renal failure, immune suppression, etc)
- a 4-month regimen for children <16 (2HRZ/2HR) has been demonstrated to be noninferior to six month standard RIPE, but is not yet officially endorsed in U.S.

THANK YOU



**APRIL 23, 2024
SESSION
EVALUATION**

Please complete the session evaluation using the QR Code or link below. We appreciate your feedback!

<http://tinyurl.com/WITBApril23>

