PATIENTS WHO MAY HAVE CULTURE-NEGATIVE (PULMONARY) TUBERCULOSIS

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

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

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.

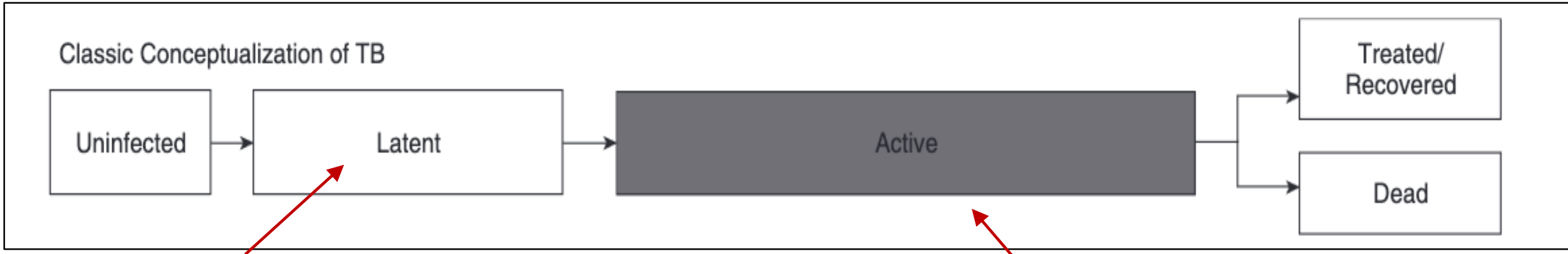
FOCUS OF TALK

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.
Esmail H (2022) eBioMedicine 78: 103928
Pai M (2016). *Nat Rev Dis Primers* **2**: 16076

HISTORICAL VIEW OF TUBERCULOSIS



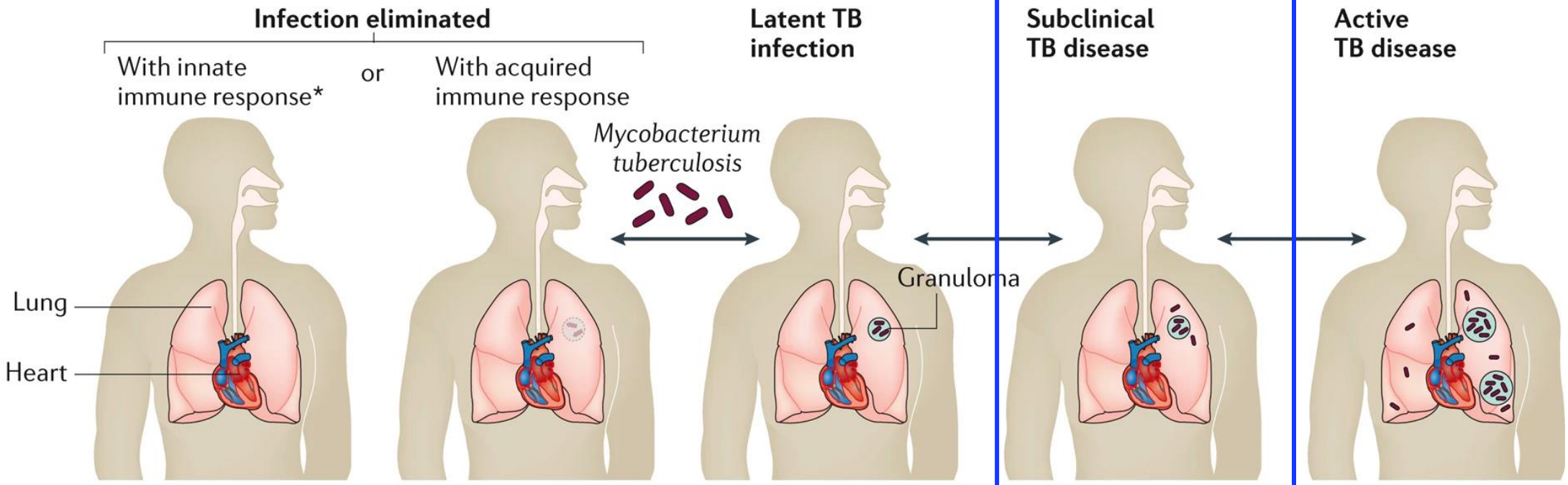
Persons with latent TB

- 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

Esmail H (2022) eBioMedicine 78: 103928; Kendall EA (2021) Am J Respir Crit Care Med. 203(2):168-174

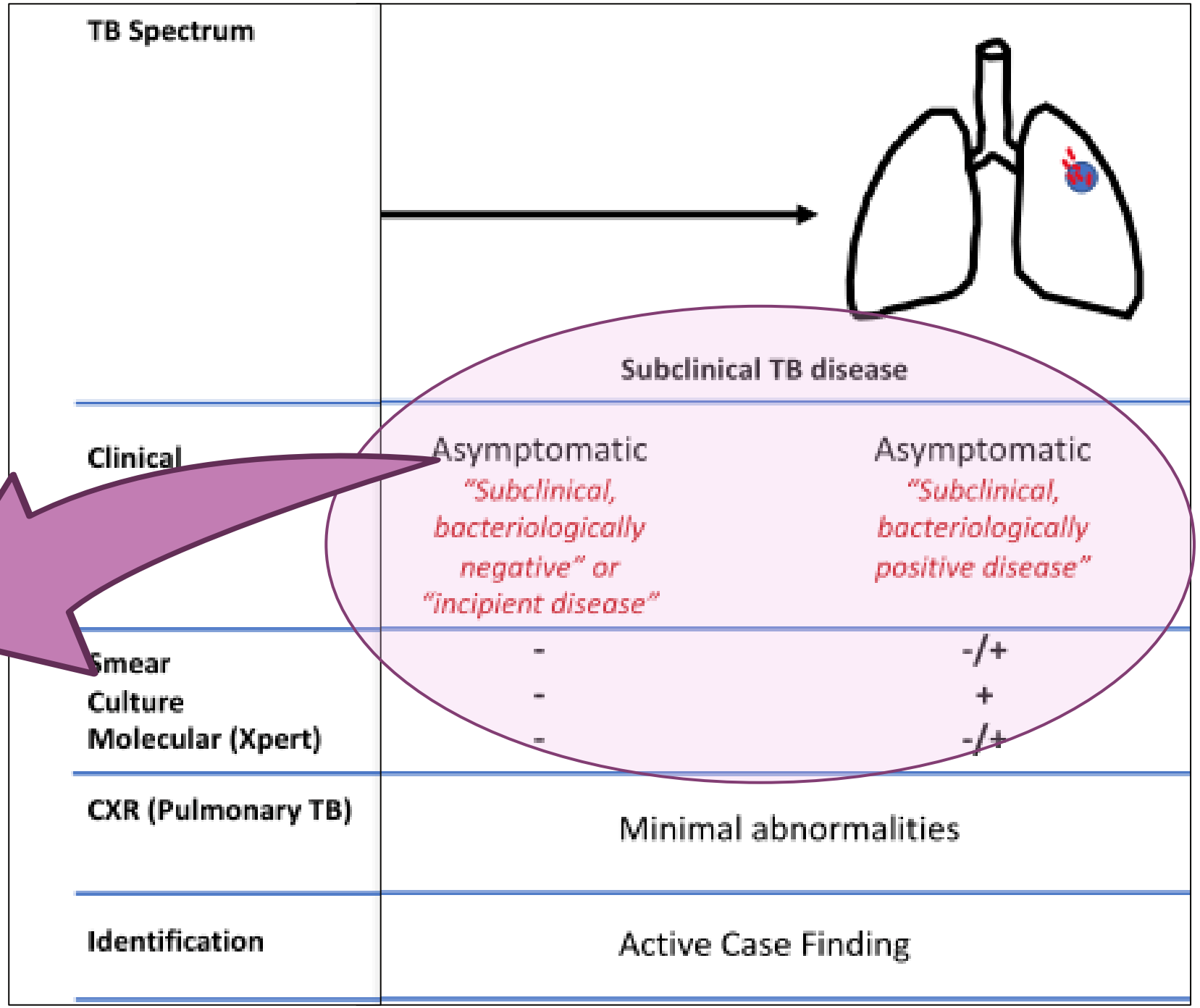


TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms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

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

SUBCLINICAL TB: a closer look

operationally, subclinical TB is often culture-negative TB



Esmail H (2022) eBioMedicine 78: 103928

INCIPIENT TUBERCULOSIS

TABLE 1 Defining criteria for the five categorical states of tuberculosis

Categorical state of TB	Presence of criterion				
	M. tuberculosis exposure	Person has viable *M. tuberculosis* pathogen	*M. tuberculosis* has metabolic activity to indicate ongoing or impending progression of infection	Radiographic abnormalities or microbiological evidence of active, viable *M. tuberculosis*	Person has symptoms suggestive of active *M. tuberculosis* 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

Drain PK (2018). Clin Microbiol Rev. 31(4):e00021-18.

CHEST IMAGING IN CULTURE-NEGATIVE TB

CT Findings Associated with TB	
"Active" TB	**"Prior" TB**
Centrilobular nodules	Fibrosis
"Tree in bud"	Calcifications
Miliary nodules	Bronchiectasis
Cavitation	Isolated pleural thickening
"Ground glass" opacities	

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.

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

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

Nguyen MH (2019) JAMA Netw Open. 2(2):e187617

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

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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

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

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

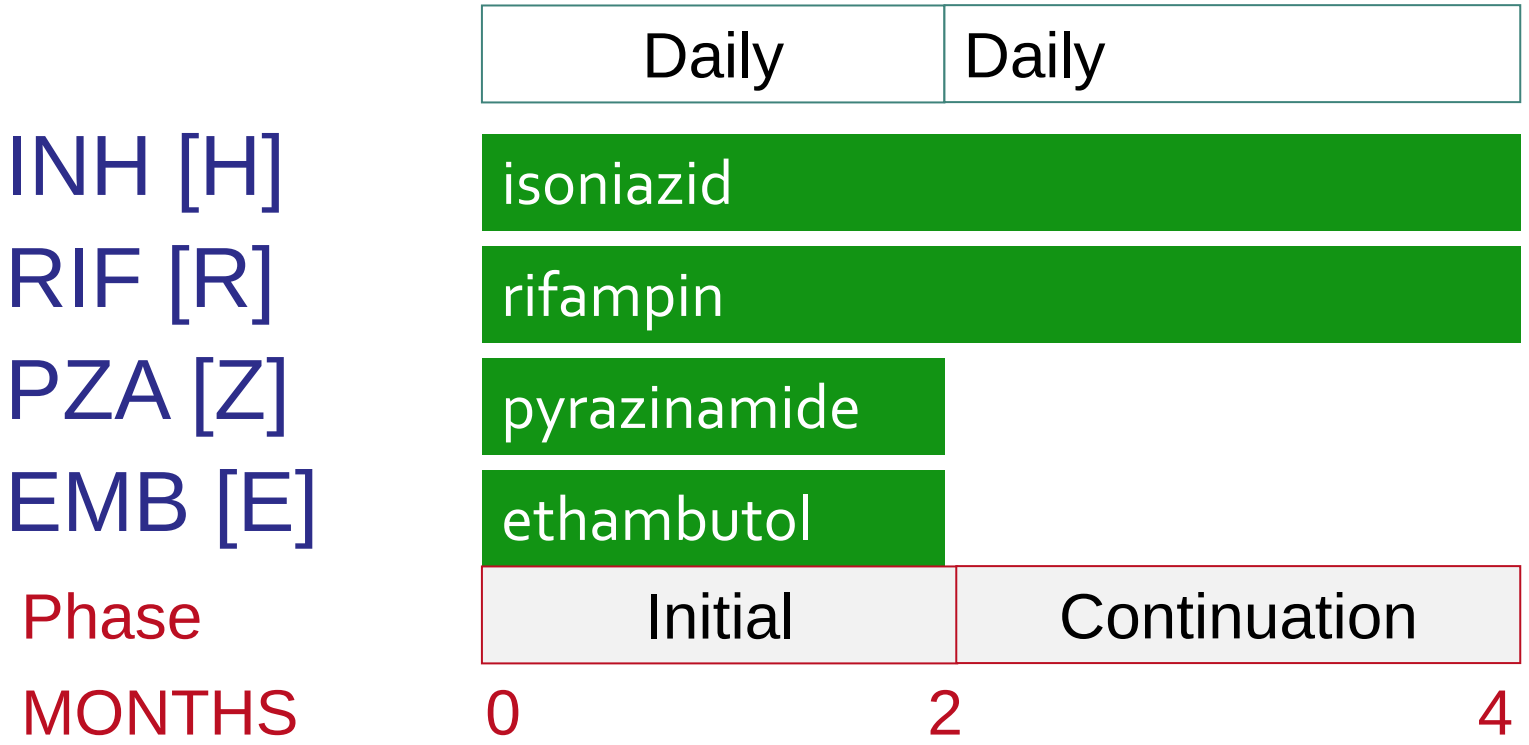
reassess clinical signs and symptoms and imaging after 2 months.

- 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"*

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

SHORTENED REGIMEN FOR CULTURE-NEGATIVE TB

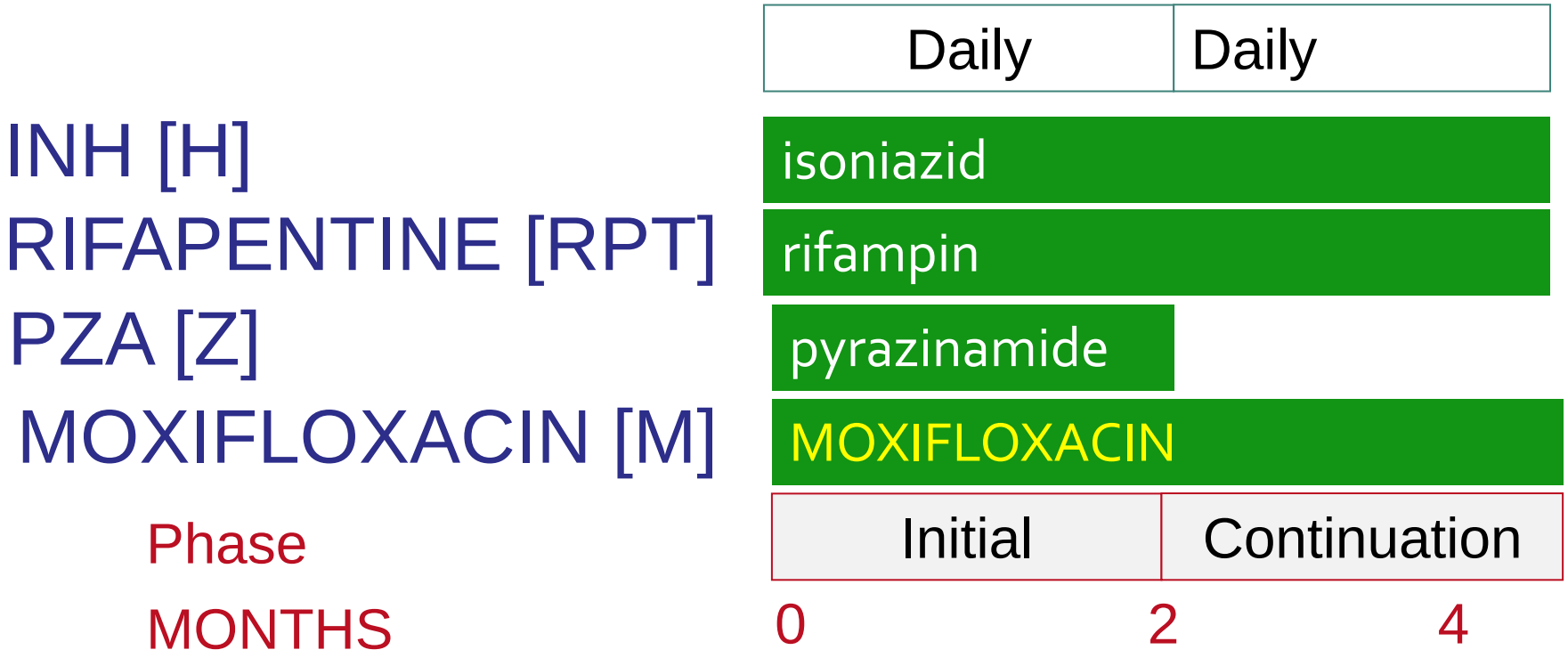
***HIV-negative adults and children ≥ 16 yrs**



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

NEW REGIMEN FOR DRUG-SUSCEPTIBLE PULMONARY TB

***Adults and children ≥ 12 yrs of age**



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

Hamada Y (2016). Ann Am Thorac Soc. 13(9):1657-8

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

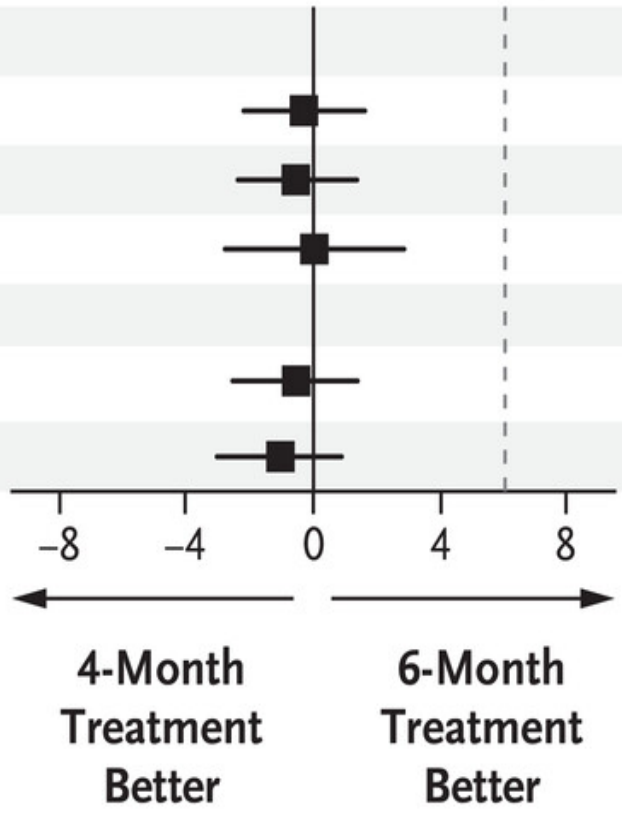
Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

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. Hesseling, 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

	No. of Patients	4-Month Treatment	6-Month Treatment	Risk Difference (95% CI)
		no. of participants with event/total no. (%)		*percentage points*
Primary outcome				
Modified intention-to-treat population	1145	16/572 (3)	18/573 (3)	–0.3 (–2.3 to 1.6)
Per-protocol population	1121	14/563 (2)	17/558 (3)	–0.6 (–2.5 to 1.4)
Intention-to-treat population	1204	44/602 (7)	44/602 (7)	0 (–2.9 to 2.9)
Key secondary outcome				
Modified intention-to-treat population	910	10/450 (2)	13/460 (3)	–0.6 (–2.6 to 1.4)
Per-protocol population	895	8/445 (2)	13/450 (3)	–1.1 (–3.1 to 0.9)



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
			percentage points	
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)		

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

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.