What's Heartland Talking About?

World TB Day

March 24, 2021

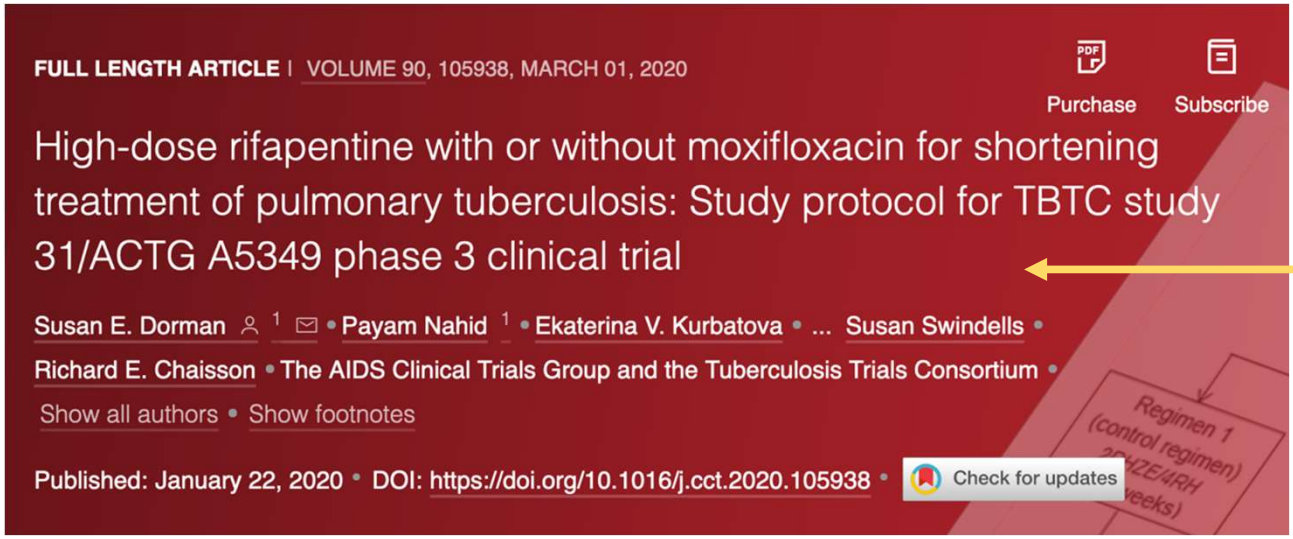
Barbara Seaworth, MD has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity

Lisa Armitige, MD, PhD has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity

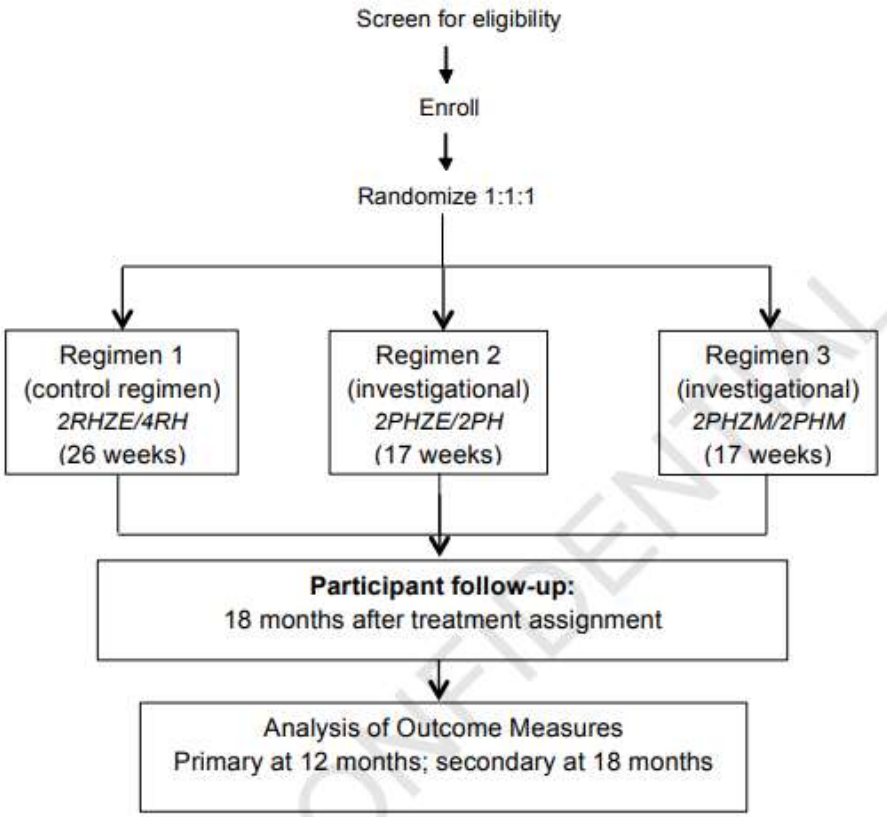
High-dose rifapentine *with or without* moxifloxacin for shortening treatment of pulmonary tuberculosis: TBTC Study 31/ACTG A5349 phase 3 clinical trial



Detailed description of the study protocol published in *Contemporary Clinical Trials*, 2020

TBTC Study 31 Rifapentine-containing TB treatment shortening regimens

Schematic of Study Design:



What was studied?

H = isoniazid
P = rifapentine
M = moxifloxacin
R = rifampicin
E = ethambutol
Z = pyrazinamide

TBTC Study 31 was a three-arm trial of

1. 2H**P**ZE/2H**P** (4 months)
2. 2H**P**Z**M**/2H**PM** (4 months)
3. 2HRZE/4HR (6 months) – control arm

Notes:
- **High-dose P = 1200 mg daily**
- Moxifloxacin dose = 400 mg
- Treatment taken 7 days a week (7/7)
- Treatment directly observed at least 5/7 days/week (DOT implementation varied by site context)
- Food guidance: food with P, no food with R (taking rifapentine with a meal increases its bioavailability)

Primary Objectives 17 week regimens

- Evaluate efficacy of a rifapentine-containing regimen to determine whether the **single substitution of rifapentine for rifampin** makes it possible to reduce to 17 weeks the duration of treatment for drug-susceptible pulmonary TB

- To evaluate the efficacy of a rifapentine-containing regimen that **in addition substitutes moxifloxacin for ethambutol and continues moxifloxacin during the continuation phase,** to determine whether it is possible to reduce to 17 weeks the duration of treatment for drug-susceptible pulmonary TB

Secondary Objectives

- To evaluate the safety of the investigational regimens
- To evaluate the tolerability of the investigational regimen
- To collect and store biospecimens from consenting participants for the purpose of future research
- To determine the correlation of mycobacterial and clinical markers with time to culture conversion, treatment failure, and relapse.

34 trial sites in 13 countries on 4 continents

- USA
- Peru
- Brazil
- Haiti
- Uganda
- Kenya
- Zimbabwe
- Malawi
- South Africa
- India
- Thailand
- Hong Kong
- Vietnam

Noninferiority = “no worse than”

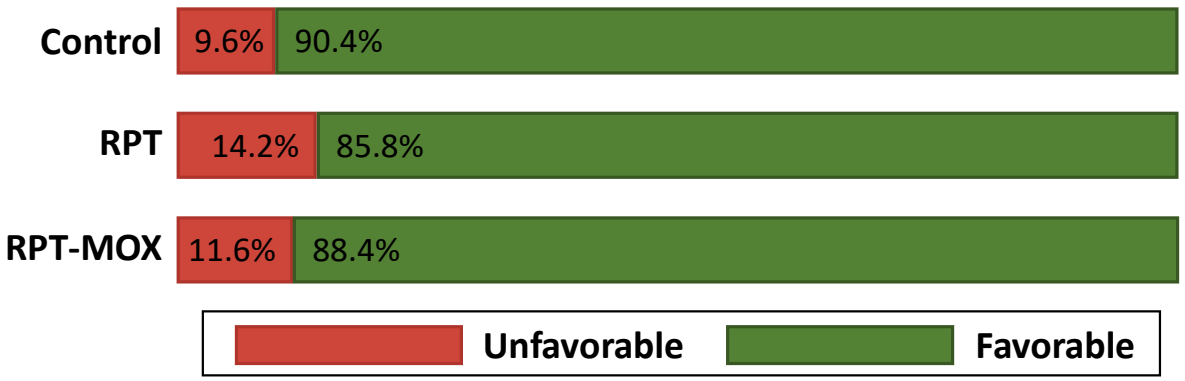
- TBTC Study 31 tested whether the two experimental regimens were no worse than the control regimen by a **prespecified amount**, called a **noninferiority margin**.
- For this trial, the noninferiority margin was set at 6.6%.
- This means that an experimental regimen would be deemed noninferior to (no worse than) the control if the upper bound of the 95% confidence interval for the risk difference between the experimental regimen and the control was less than 6.6%.
- So when you read the results of TBTC Study 31, remember to compare the upper bound of the 95% CIs in the efficacy analysis to 6.6%.

Noninferiority is different than testing whether one thing is better than another (superiority) or equal to another (equivalence).

Unique and notable features of TBTC Study 31

- **Pivotal** treatment-shortening study and the largest drug-sensitive TB treatment trial in recent decades.
- **Inclusive** eligibility criteria (with respect to age, HIV status, severity of TB disease presentation).
- **Collaborative** implementation by two TB research networks: TBTC (CDC) and ACTG (NIH).
- **Rigorous** data management system custom built for this trial by CDC.
- **Harmonized and standardized** mycobacteriology lab procedures (microbiological testing using both solid and liquid media for outcome assessment).
- **Future-oriented** and designed to enable further research through a biorepository of sputum, urine, and blood specimens.
- **Multi-layered** with multiple sub-studies (transcriptomics, biomarkers, PK/PD, adolescents).

S31/A5349 Primary Efficacy Results Assessable Analysis Population



12 months after treatment

Finally, a Shorter Treatment for Active TB Disease

- **Regimen 3 (Rifapentine, Moxifloxacin, INH and PZA)**
  - **NON-INFERIOR to control** means:
    - **"it is as good"** as the control
    - Not identical
  - **Efficacy** –
    - Rifapentine/Moxifloxacin **88.4%** -
    - Control **90.4%**
    - Met for all primary analysis
    - Met for all secondary analysis
    - Robust across all subgroups: HIV-infection, adolescents, diabetes as well as composite measures of disease burden
  - Safety and Tolerability similar

Regimen Two Does Not Provide a Shorter Treatment for Active TB Disease

- **Regimen 2 (Rifapentine, INH, Ethambutol, and PZA) did not meet non-inferiority criteria for efficacy**
  - Means "**it is not as good as**" the control
  - **Efficacy** - Rifapentine/INH/EMB/PZA **85.8 %** Control **90.4 %**
    - **Not-Met in any analysis**, except in select participant sub-groups, specifically those with lower burden of disease. for all primary analysis
  - Safety and Tolerability similar

Results will be published in New England Journal Medicine soon

- Dr. Payam Nahid will discuss in more detail as part of Curry Center's World TB Day Event

Low-level rifampin-resistance associated *rpoB* mutations

- Also referred to as disputed, discordant, low-level, or mutations associated with borderline resistance
- Associated with a high degree of treatment failure/relapse* when RIPE used
- Examples:
  - Leu430Pro (Leu511Pro), Asp435Tyr (Asp516Tyr), His445Asn (His526Asn), His445leu (His526Leu), Leu452Pro (Leu533Pro), Ile491Phe (Ile572Phe)
- Often test susceptible by growth-based DST

Dilemma: Molecular test shows resistance, MGIT DST shows susceptible
Agar sometimes will be resistant, other times susceptible – WHY?

*Van Deun A, et al. 2009, Rigouts L et al. 2013, Van Deun A, et al, 2013, Shah NS, et al. 2016

Revised Critical Concentration For Rifamycin

- Released February 2021
- Based on systematic review of critical concentrations and consensus from WHO Technical Expert Group meeting 2/24/2020

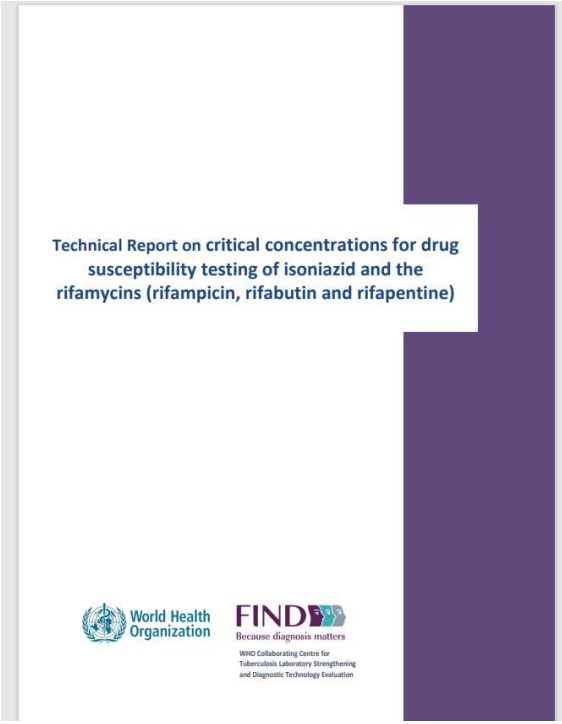


Table 1. Critical concentrations for INH and the rifamycins.

Drug	LJ	7H10	7H11	MGIT
Isoniazid	0.2	0.2	0.2	0.1
Rifampicin[a]	40	0.5	1.0	0.5
Rifabutin[b]	–	–	–	–
Rifapentine[c]	–	–	–	–

Changes indicated in red

Critical concentration: the lowest concentration of an anti-TB agent in vitro that will inhibit the growth of 99% of phenotypically wild type isolates of MTB

9789240017283-eng.pdf (who.int)

Treatment of Patients with Discordant Mutations

- **WHO Technical Expert Group 2020 recommended:**
  - Change in critical concentration for rifampin in 7H10 agar and MGIT broth media, decreasing critical concentration to 0.5
    - Eliminates most of those previously reported as “falsely susceptible”
  - Seven borderline resistance” rpoB mutations, which have been referred to as “discordant”, disputed”, ‘occult” or (sub-breakpoint) “low-level resistance” mutations in the literature need to be treated with an MDR-TB regimen according to the latest WHO guidelines.

Transitioning to Targeted Next Generation Sequencing Assay

- Panel expanded to 24 amplicons
- Isoniazid: expanded to sequence the entire katG gene
- Linezolid: rplC, rrl
- Bedaquiline: atpE, rv0678 (mmpR), pepQ
- tlyA dropped

	SANGER
1	*rpoB*-RRDR
2	*inhA*
3	*katG*
4	*gyrA*
5	*rrs*
6	*pncA*
7	*embB*
8	*eis*
9	*tlyA-1*
10	*tlyA-2*
11	*rpoB-170*
12	*gyrB*
13	*ahpC*
14	*fabG-609*

BEFORE

	tNGS
1	*rpoB*-RRDR
2	*rpoB-170*
3	*katG-1*
4	*katG-2*
5	*katG-3*
6	*katG-4*
7	*inhA*
8	*fabG-609*
9	*pncA*
10	*embB*
11	*gyrA*
12	*gyrB*
13	*rrs*
14	*eis*
15	*rv0678*
16	*atpE*
17	*pepQ-1*
18	*pepQ-2*
19	*pepQ-3*
20	*ahpC*
21	*rplC-1*
22	*rplC-2*
23	*rrl-1*
24	*rrl-2*

AFTER

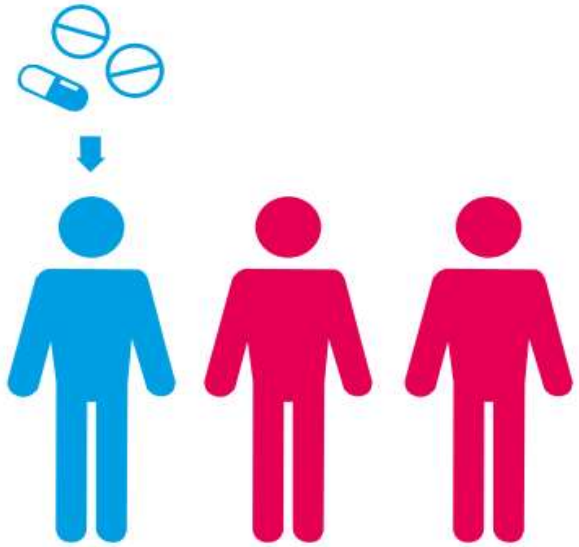
Added Discontinued

CDC Infectious Diseases Pathology Branch and MDDR

- Testing for possible Mycobacterial infections using formalin fixed samples (< 2wks or paraffin embedded)
- Requestor first contacts state health department and then IDPB for consult and approval
  - Pathology@cdc.gov
  - https://www.cdc.gov/ncezid/dhcpp/idpb/specimen-submission/mycobacterium.html
- Requestor ships fixed sample to IDPB for testing
- If MTBC detected and submitter requests MDDR, DNA transferred
- MDDR performed and results reported to requestor and IDPB

Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis,

27-29 October 2020



World Health Organization

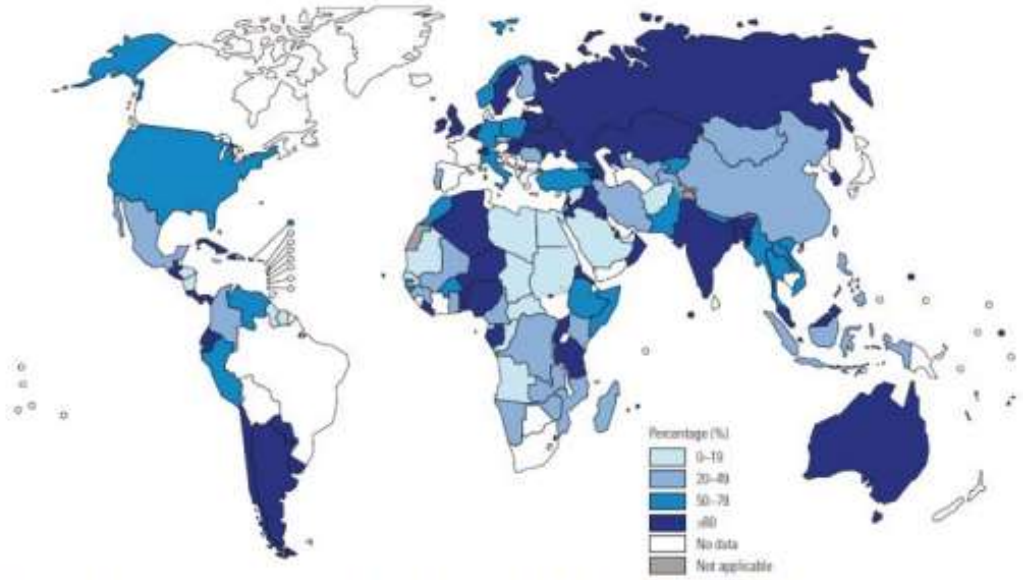
Box 1. Pre-2021 definition of XDR-TB, formulated in 2006 (13)

XDR-TB: TB that is resistant to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance

TB: tuberculosis; XDR-TB: extensively drug-resistant tuberculosis

Fig. 1. Percentage of MDR/RR-TB cases tested for susceptibility to fluoroquinolones, 2019

Source: WHO, 2020.



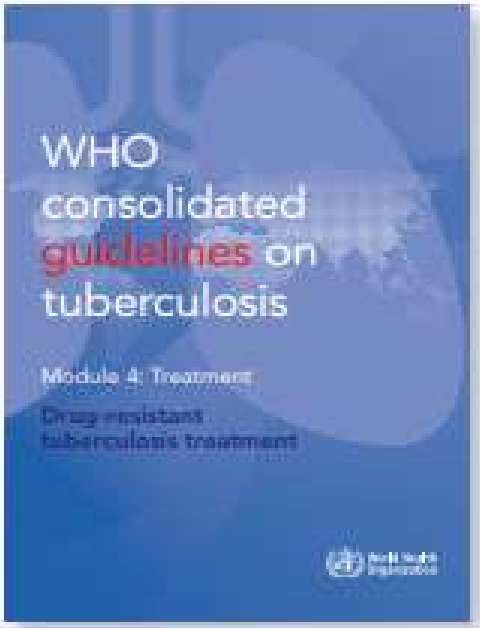
MDR/RR-TB: multidrug-resistant or rifampicin-resistant tuberculosis; WHO: World Health Organization.

WHO recommendations on the treatment of DR-TB and XDR-TB

All patients with MDR/RR-TB, including those with additional resistance to fluoroquinolones, may benefit from effective **all-oral treatment regimens**, shorter or longer.

1. For MDR/RR-TB patients without previous exposure to second-line treatment and bedaquiline, without fluoroquinolone resistance and no extensive TB disease or severe extrapulmonary TB, the preferred treatment option is a **shorter, all-oral, bedaquiline-containing regimen**. In this group of patients, national programmes can phase out use of the injectable-containing shorter regimen.

2. For MDR/RR-TB patients with extensive TB disease, severe forms of extrapulmonary TB, those with resistance to fluoroquinolones or who have been exposed to treatment with second-line drugs will benefit from an **individualized longer regimen** designed using the priority grouping of medicines.



3. Novel **BPaL regimen** for MDR-TB with additional quinolone resistance under operational research conditions.

BPaL: bedaquiline, pretomanid and linezolid; DR-TB: drug-resistant tuberculosis; MDR/RR-TB: multidrug-resistant or rifampicin-resistant tuberculosis; TB: tuberculosis; WHO: World Health Organization; XDR-TB: extensively drug-resistant tuberculosis.

Revised XDR-B definition will need to:

- Consider the key role of FQNs in the treatment of MDR/RR-TB
- Disregard the 2nd line injectable agents
- Consider the important role of the new or repurposed drugs in Group A especially bedaquiline and linezolid as part of the longer regimens, and the BPaL regimen
- Be feasible for implementation by NTPs
- Be practical and useful for making clinical decisions and when deciding on eligibility while designing treatment regimens
- Identify a resistance pattern that signals the need for an important change in the treatment options

Definition of pre-XDR-TB and updated definition of XDR-TB[a]

Pre-XDR-TB: TB caused by MTB *(M. tuberculosis)* strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone.

XDR-TB: TB caused by MTB *(M. tuberculosis)* strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone and at least one additional Group A drug[b]

MDR/RR-TB: multidrug-resistant or rifampicin-resistant tuberculosis; TB: tuberculosis; XDR-TB: extensively drug-resistant tuberculosis

[a]The fluoroquinolones include levofloxacin and moxifloxacin, because these are the fluoroquinolones currently recommended by WHO for inclusion in shorter and longer regimens.

Group A drugs are currently levofloxacin or moxifloxacin, bedaquiline and linezolid; therefore, XDR-TB is MDR/RR-TB that is resistant to a fluoroquinolone and either bedaquiline or linezolid (or both). The Group A drugs may change in the future; therefore, the terminology "Group A will apply to any Group A drugs in the future.

Annex 1: Grouping of medicines recommended for use in longer MDR-TB regimens[a]

Groups & steps	Medicine	
Group A: Include all three medicines	levofloxacin *OR*	Lfx
	moxifloxacin	Mfx
	bedaquiline[b,c]	Bdq
	linezolid[d]	Lzd
Group B: Add one or both medicines	clofazimine	Cfz
	cycloserine *OR*	Cs
	terizidone	Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	ethambutol	E
	delamanid[c,e]	Dlm
	pyrazinamide[f]	Z
	imipenem–cilastatin *OR*	Ipm–Cln
	meropenem[g]	Mpm
	amikacin *OR*	Am
	streptomycin[h]	(S)
	ethionamide *OR*	Eto
	prothionamide[i]	Pto
	p-aminosalicylic acid[i]	PAS

Subclinical TB

TB disease due to viable MTB that does not cause clinical TB related symptoms but causes other abnormalities that can be detected using existing radiologic or microbiologic assays

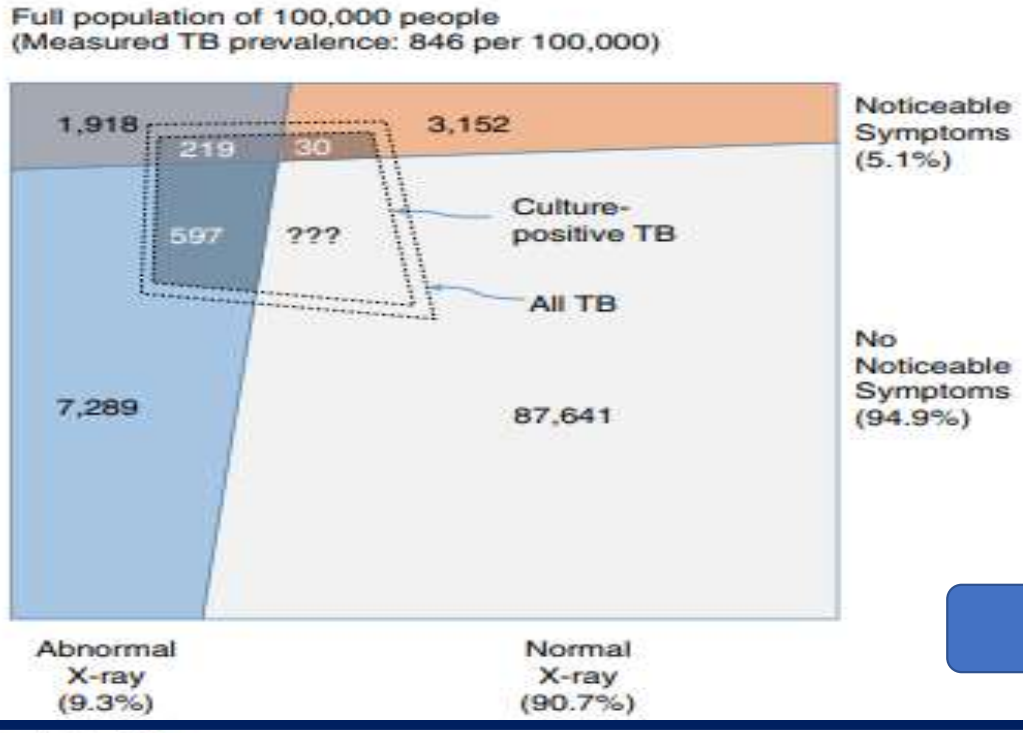
Microbiologic positivity in the absence of symptoms

TABLE 1 Defining criteria for the five categorical states of tuberculosis

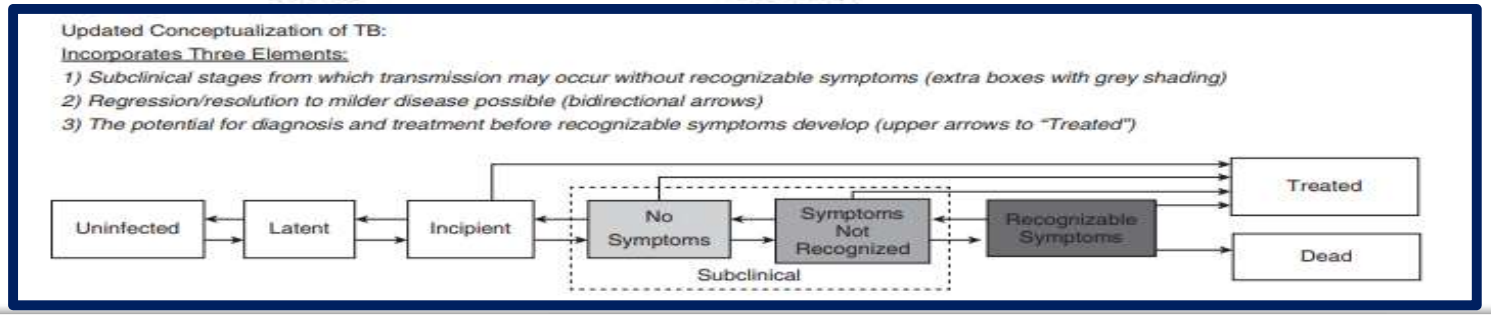
Categorical state of TB	Presence of criterion				
	M. tuberculosis exposure	Person has viable *M. tuberculosis* pathogen	*M. tuberculosis* has metabolic activity to indicate ongoing or impending progression of infection	Radiographic abnormalities or microbiological evidence of active, viable *M. tuberculosis*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

Drain et al 2018

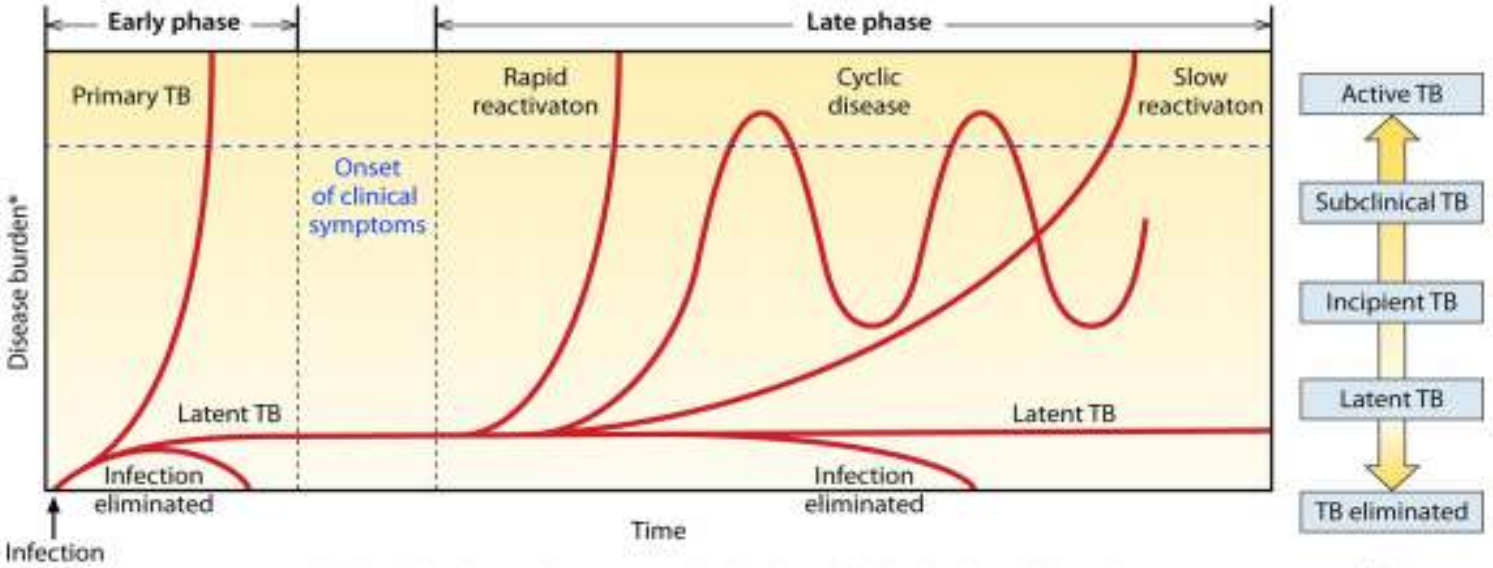
How Big of a Problem is Subclinical TB?



Kendall AJRCCM Jan 2021



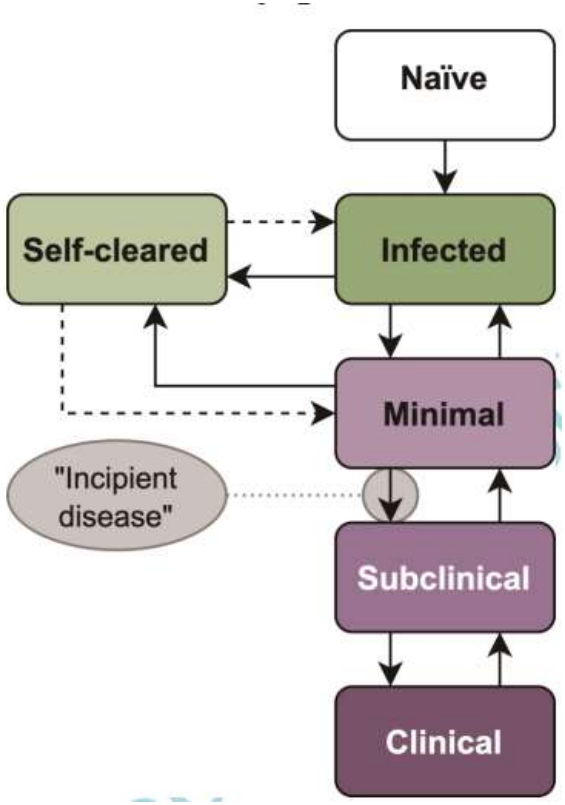
Pathways of TB Disease Progression



*Rising TB burden implies an increase in abundance of TB and pathogen biomarkers, compartment-specific changes in immunological responses, and a decrease in the probability of disease resolution in the absence of treatment.

FIG 1 Pathways of tuberculosis disease progression. After initial exposure, *M. tuberculosis* may be eliminated by the host immune response, persist as a latent infection, or progress to primary active disease. Following the establishment of latent infection, disease may persist in a latent form, naturally progress in a slow or rapid fashion to active tuberculosis, or cycle through incipient and subclinical states before developing into symptomatic disease or eventual disease resolution. Although not all possibilities for regression of disease burden are depicted, spontaneous recovery may occur in any of these clinical trajectories.

TB is a continuous spectrum from LTBI to Disease



"Active TB to one clinician may be subclinical TB to another"

Pierce, Subclinical TB: Some Flies in the Ointment. AJRCCM March9, 2021

Subclinical tuberculosis disease - a review and analysis of prevalence surveys to inform definitions, burden, associations and screening methodology.

Frascella et al, CID Sept 16, 2020