Diagnosis and Medical Management of TB Disease

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Has the following disclosures to make:

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

Diagnosis and Medical Management of TB Disease

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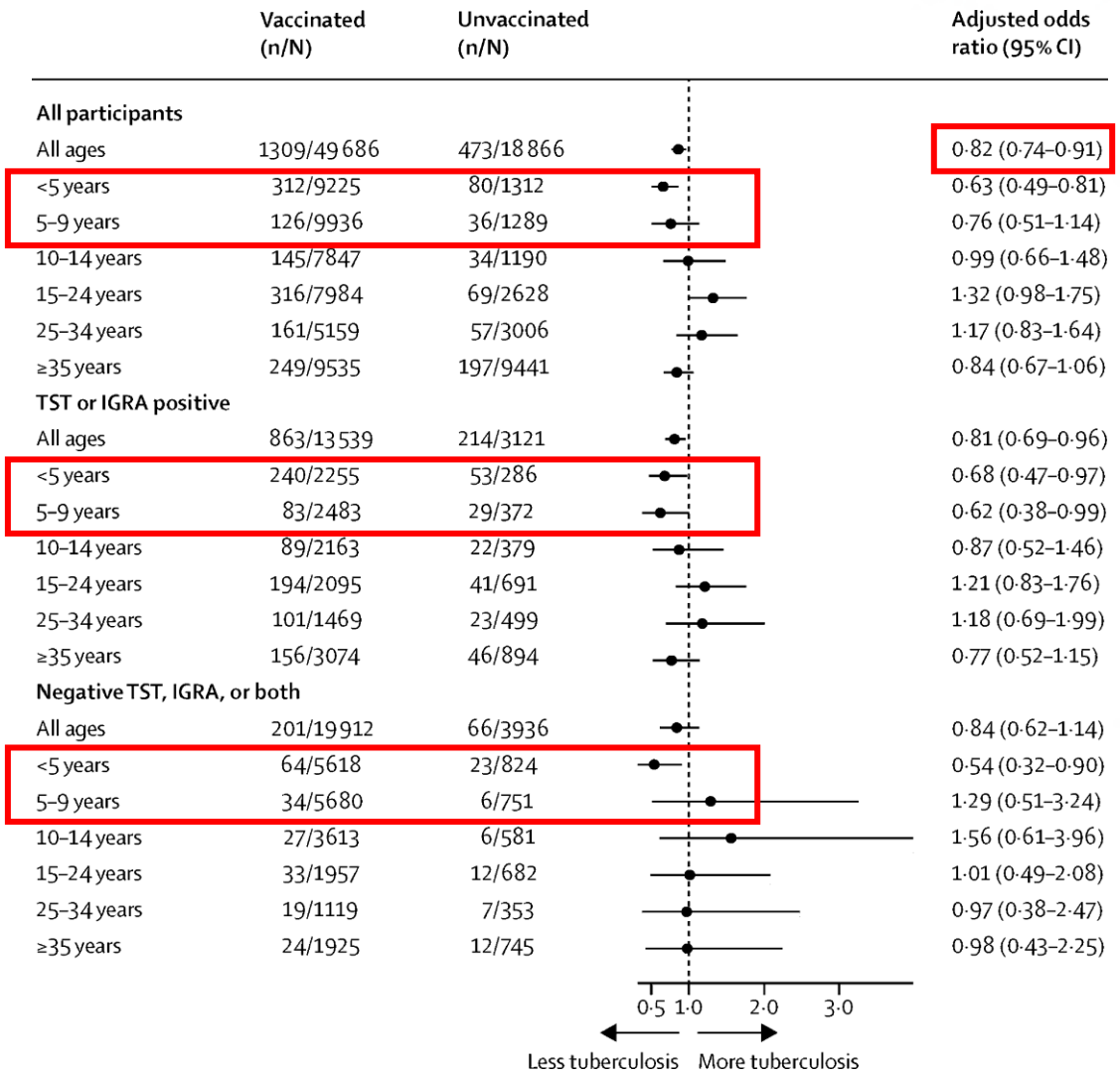
BCG

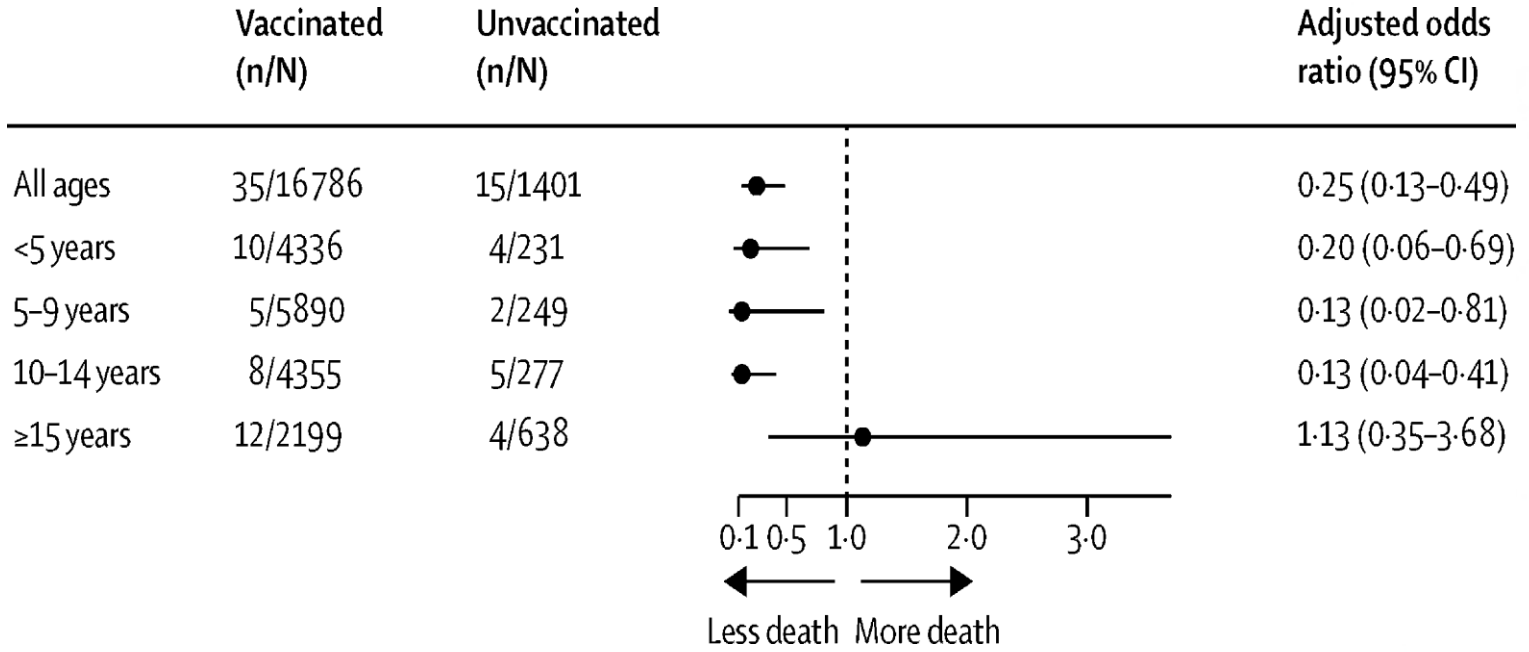
What does it do? Who does it protect?

Figure 2 BCG vaccination at birth and the risk of all tuberculosis, stratified by infection status and age



The Lancet Global Health
Volume 10 Issue 9: e1307-e1316
(September 2022)

Figure 3 BCG vaccination at birth and the risk of death, stratified by age



PLOS ONE

RESEARCH ARTICLE

Tuberculosis Infection in the United States: Prevalence Estimates from the National Health and Nutrition Examination Survey, 2011-2012

Roque Miramontes*, Andrew N. Hill, Rachel S. Yelk Woodruff, Lauren A. Lambert, Thomas R. Navin, Kenneth G. Castro, Philip A. LoBue

Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America

- 9756 total participants
- 7821 age 6+
- 5421 foreign born
- 6064 with both TST and IGRA results

Table 6. Agreement between the Tuberculin Skin Test and Interferon Gamma Release Assay Test Results for Tuberculosis Infection in the Civilian, Noninstitutionalized U.S. Population, Ages 6+, 2011–2012.

	Overall Prevalence,%	U.S.-born Prevalence,%	Foreign-born Prevalence,%
TST Positive/IGRA Positive	2.1	0.6	9.3
TST Positive/IGRA Negative	2.6	0.9	11.2
TST Negative/IGRA Positive	2.9	2.2	6.6
TST Negative/IGRA Negative	92.4	96.3	72.9

~20%

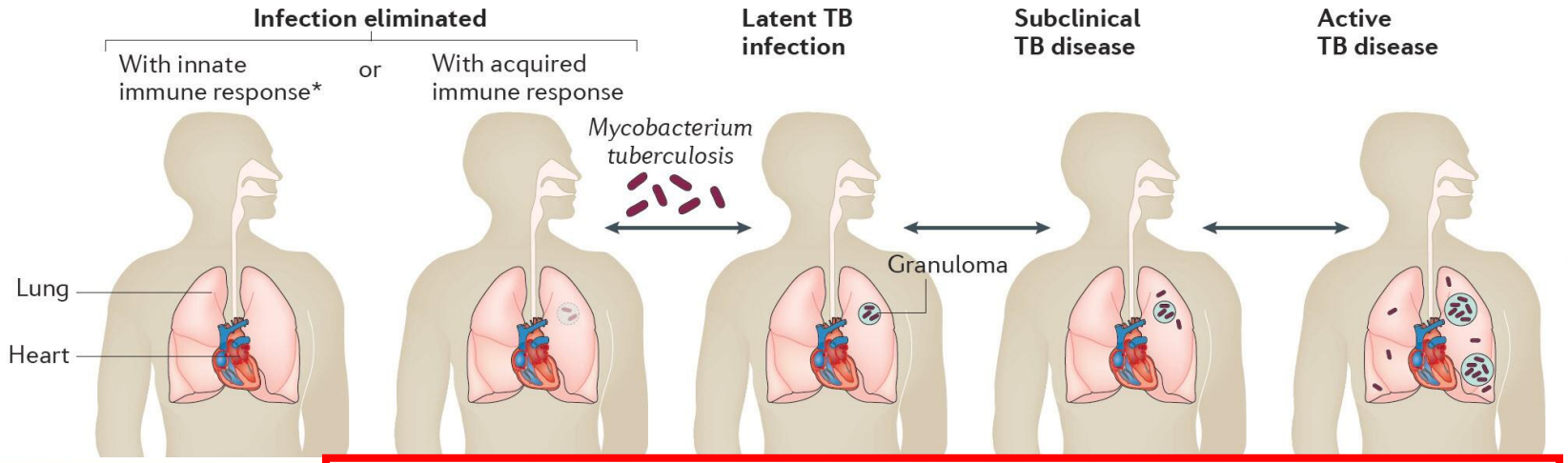
doi:10.1371/journal.pone.0140881.t006

Miramontes R, Hill AN, Yelk Woodruff RS, Lambert LA, Navin TR, et al. (2015) Tuberculosis Infection in the United States: Prevalence Estimates from the National Health and Nutrition Examination Survey, 2011-2012. PLOS ONE 10(11): e0140881. https://doi.org/10.1371/journal.pone.0140881
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0140881

Tests for Tuberculosis

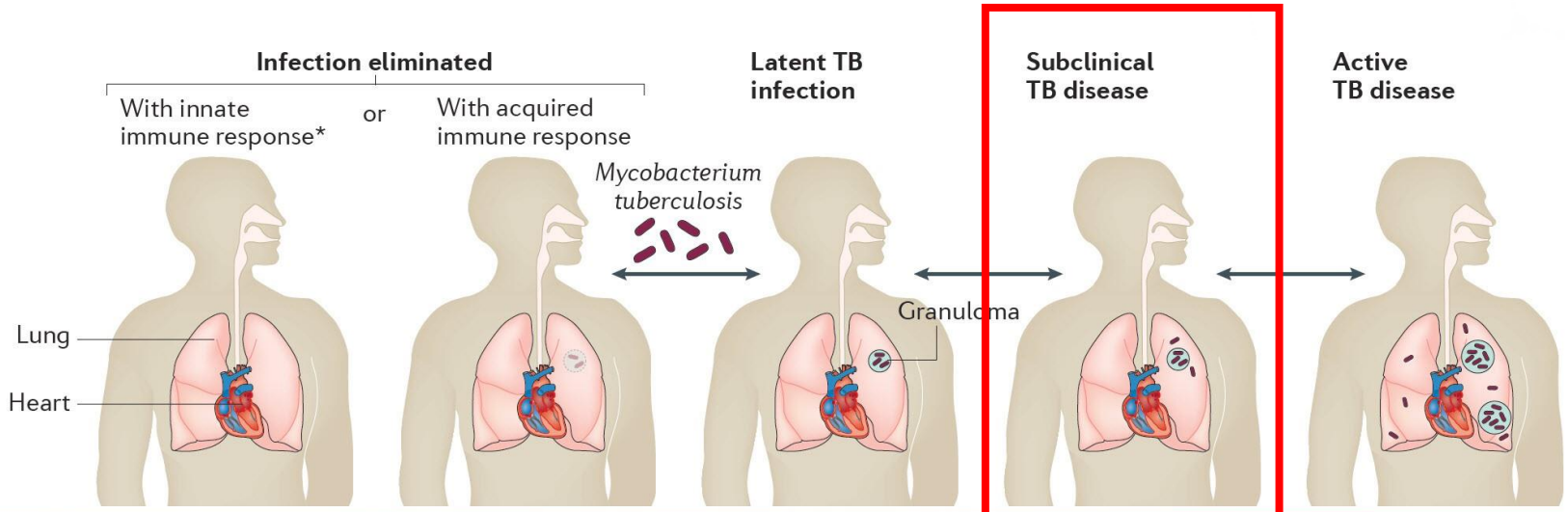
……are still not awesome

Tuberculosis Spectrum of Disease



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

Tuberculosis Spectrum of Disease



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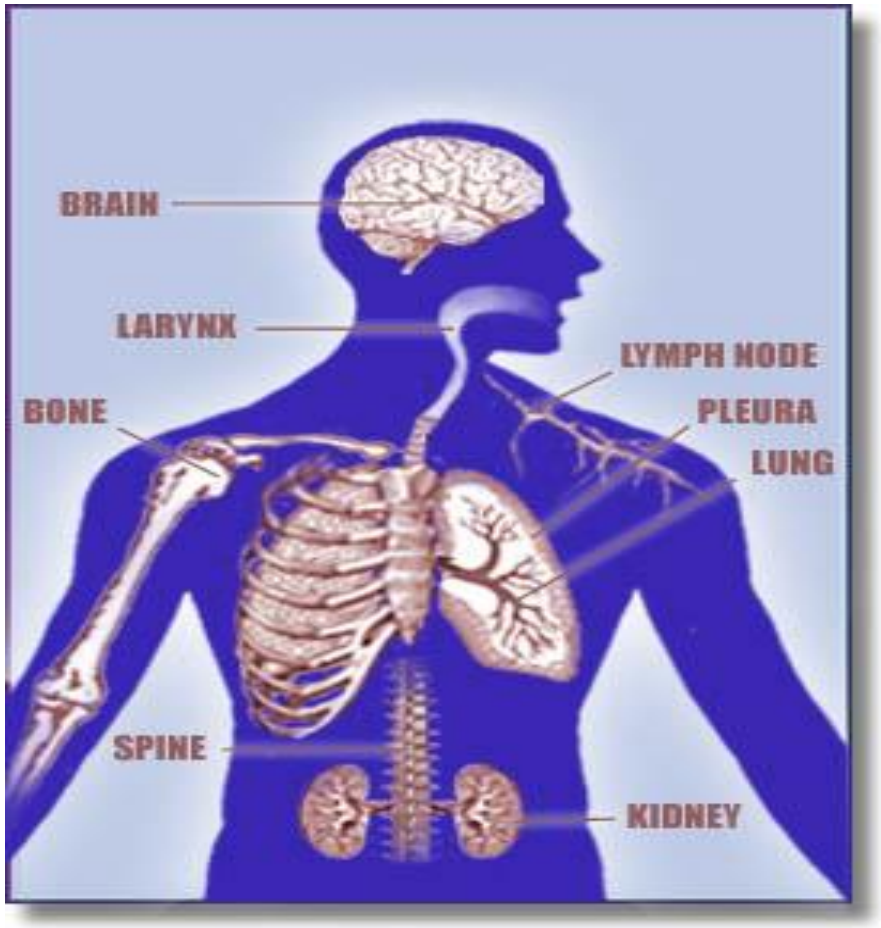
Diagnosing Active Tuberculosis

Sites of TB Disease

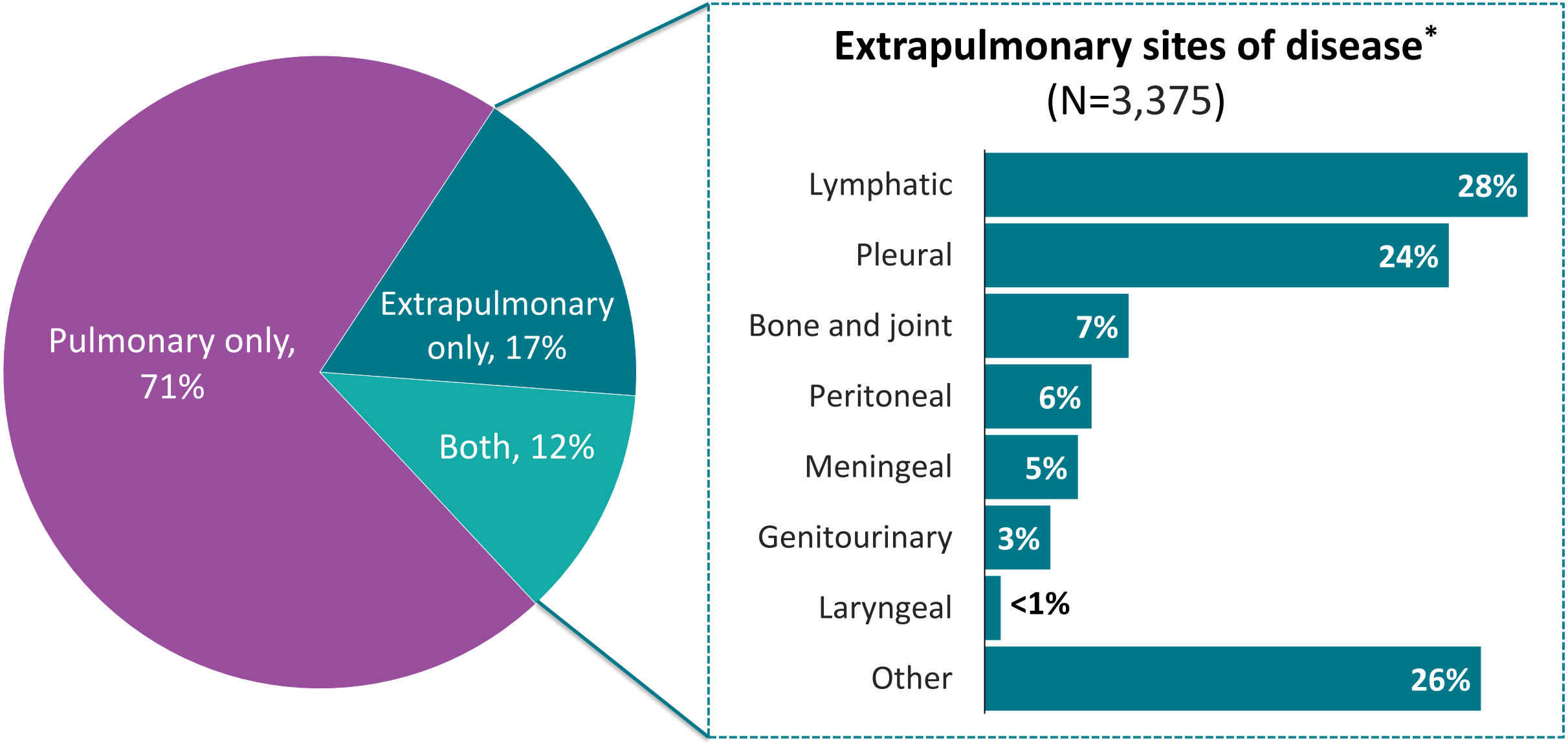
- Lungs

Extrapulmonary:

- Larynx
- Pleural effusion
- Kidneys
- Lymphatics
- Bones & joints
- Miliary (disseminated)



Percentage of TB Cases by Site of Disease, United States, 2024



* Persons might have more than one extrapulmonary site of disease.

Signs & Symptoms Pulmonary TB

Pulmonary Symptoms:

- Productive prolonged cough of over 3 weeks duration
- Chest pain
- Hemoptysis

Systemic Symptoms:

- Fever
- Chills
- Night sweats
- Appetite loss
- Weight loss
- Easy fatigability

Evaluation for TB

- Medical (and social) history
- Physical examination
- Testing for TB infection
- Chest radiograph
- Bacteriologic or histologic exam

No CXR study shows findings specific for TB

Cavitary process are more likely to be TB

Common mimics of TB =

- Non-tuberculous mycobacteria (NTM)
- fungal infection
- bacterial abscesses
- necrotic neoplasm (especially lung neoplasm)

CXR - special situations

- Pregnant women who are highly suspected of having TB and are being evaluated for active disease should undergo a CXR without delay, even during the first trimester

- Patients suspected of extrapulmonary TB should have a CXR to R/O pulmonary TB

Yes! You can X-ray a pregnant patient!

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG COMMITTEE OPINION

Number 723 • October 2017 *(Replaces Committee Opinion Number 656, February 2016)*

Committee on Obstetric Practice

This document is endorsed by the American College of Radiology and the American Institute of Ultrasound in Medicine. This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. Member contributors included Joshua Copel, MD; Yasser El-Sayed, MD; R. Phillips Heine, MD; and Kurt R. Wharton, MD. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Table 2. Effects of Gestational Age and Radiation Dose on Radiation-Induced Teratogenesis ⇦

Gestational Period	Effects	Estimated Threshold Dose*
Before implantation (0–2 weeks after fertilization)	Death of embryo or no consequence (all or none)	50–100 mGy
Organogenesis (2–8 weeks after fertilization)	Congenital anomalies (skeleton, eyes, genitals)	200 mGy
	Growth restriction	200–250 mGy
Fetal period	**Effects**	**Estimated Threshold Dose***
8–15 weeks	Severe intellectual disability (high risk)†	60–310 mGy
	Intellectual deficit	25 IQ-point loss per 1,000 mGy
	Microcephaly	200 mGy
16–25 weeks	Severe intellectual disability (low risk)	250–280 mGy*

*Data based on results of animal studies, epidemiologic studies of survivors of the atomic bombings in Japan, and studies of groups exposed to radiation for medical reasons (eg, radiation therapy for carcinoma of the uterus).

†Because this is a period of rapid neuronal development and migration.

Modified from Patel SJ, Reede DL, Katz DS, Subramaniam R, Amorosa JK. Imaging the pregnant patient for nonobstetric conditions: algorithms and radiation dose considerations. Radiographics 2007;27:1705–22.

Table 3. Fetal Radiation Doses Associated With Common Radiologic Examinations ⇦

Type of Examination	Fetal Dose* (mGy)
Very low-dose examinations (<0.1 mGy)	
Cervical spine radiography (anteroposterior and lateral views)	<0.001
Head or neck CT	0.001–0.01
Radiography of any extremity	<0.001
Mammography (two views)	0.001–0.01
Chest radiography (two views)	0.0005–0.01
Low- to moderate-dose examinations (0.1–10 mGy)	
Radiography	
Abdominal radiography	0.1–3.0
Lumbar spine radiography	1.0–10
Intravenous pyelography	5–10
Double-contrast barium enema	1.0–20
CT	
Chest CT or CT pulmonary angiography	0.01–0.66
Limited CT pelvimetry (single axial section through the femoral heads)	<1
Nuclear medicine	
Low-dose perfusion scintigraphy	0.1–0.5
Technetium-99m bone scintigraphy	4–5
Pulmonary digital subtraction angiography	0.5
Higher-dose examinations (10–50 mGy)	
Abdominal CT	1.3–35
Pelvic CT	10–50
^{18}F PET/CT whole-body scintigraphy	10–50

Bacteriologic and Histologic Examinations

When lung or larynx is site of disease:

- 3 sputum specimens for

  AFB smear and culture (and 1 NAAT)

- Collected 8-24 hours apart

  with at least 1 early morning specimen

Culture Yield

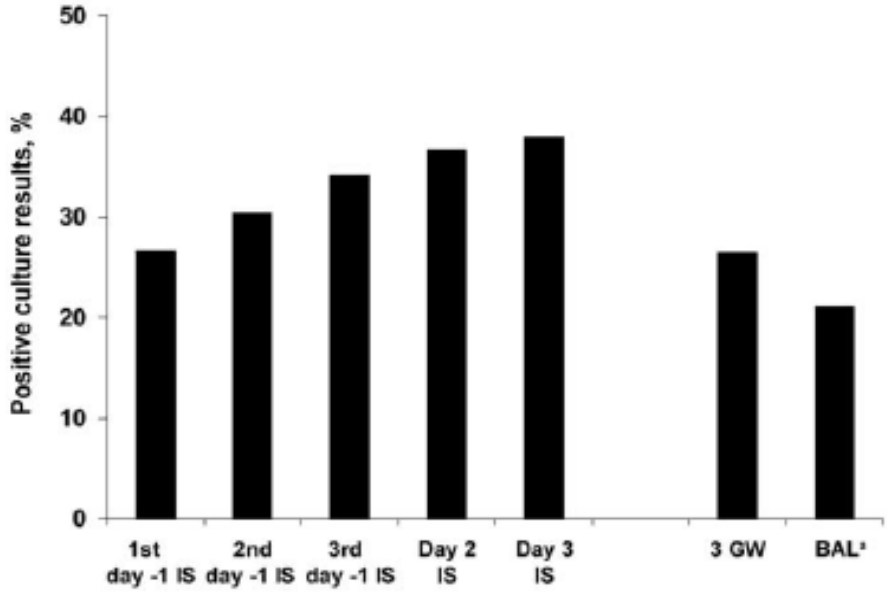


Figure 2. Proportion of subjects with cultures positive for *Mycobacterium tuberculosis*, by diagnostic technique, for 79 subjects with results for all 5 sputum samples obtained by induction with nebulized hypertonic saline (IS) and all 3 gastric washing (GW) specimens. Cumulative proportions are shown for the 5 IS samples. $P = .25$, by paired binomial probability test comparing diagnostic yield of all 5 IS samples versus 3 day 1 IS samples. *Bronchoalveolar lavage (BAL) culture results were available for 19 subjects.

Brown et al Clin Iinfect Dis 2007(44):1415

Bacteriologic and Histologic Examinations

Extrapulmonary Specimens

- Urine
- Cerebrospinal fluid *
- Pleural fluid *
- Pus
- Biopsy specimens

Do NOT collect specimens in Formalin or bacteriostatic saline!

*recovery poor

Laboratory Examination

- AFB smear
- AFB culture

- Nucleic acid amplification test (NAAT)
  - GeneXpert
  - Molecular Detection of Drug Resistance (MDDR)

- 3:3:1…..3 sputum specimens for AFB smear/AFB culture and 1 NAAT on the best one

Treatment of Tuberculosis Disease

From Guidelines on Treatment of Drug Susceptible TB Disease

- More is better. Daily dosing over intermittent dosing (especially emphasized in new guidelines)
  - Daily dosing is recommended during the initial phase
  - Daily or TIW dosing is recommended during the continuation phase
- Emphasis on case management
- Steroids empirically for TB meningitis (all cases) but not TB pericarditis
- Consider leaving PZA out in patients who are 75 years or older if likelihood of resistance is low
- TB/HIV: possibly treat for 6 months if on ARVs, 9 months if not on ARVs

Treatment of Patients with *Drug Susceptible* TB Disease

- Standard therapy
  - Initiation phase of therapy
    - 2 months INH, Rifampin, EMB and PZA
  - Continuation phase of therapy
    - 4-7 months INH and Rifampin
  - No PZA = 9 months of minimal treatment

- 4-month regimen (optimally dosed 7 days/week)
  - Initial phase
    - 2 months INH, rifapentine, moxifloxacin, PZA
  - Continuation phase
    - 2 months INH, rifapentine, moxifloxacin

Treatment of Culture-Positive Drug Susceptible Pulmonary TB

- General conclusions from the literature
  - 6 mo (26 wk) is the MINIMUM duration of Rx
  - 6 mo regimens require rifampin throughout and PZA for the first 2 months
  - 6 mo regimens are effective without INH (replace INH with a fluoroquinolone, continue EMB and PZA)
  - Intermittent regimens (2-3x/wk) are rarely warranted. If used:
    - GIVEN by DOT ONLY
    - Drug susceptible isolate
    - Regimen contains INH and rifampin

ATS recommendations for treatment of tuberculosis

Table 2. Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

	Intensive Phase		Continuation Phase				
Regimen	Drug[a]	Interval and Dose[b] (Minimum Duration)	Drugs	Interval and Dose[b,c] (Minimum Duration)	Range of Total Doses	Comments[c,d]	Regimen Effectiveness
1	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	7 d/wk for 126 doses (18 wk), or 5 d/wk for 90 doses (18 wk)	182–130	This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.	Greater
2	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	110–94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.	*
4	INH RIF PZA EMB	7 d/wk for 14 doses then twice weekly for 12 doses[e]	INH RIF	Twice weekly for 36 doses (18 wk)	62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear-positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior.	*
							Lesser

Treatment of Culture-Positive Drug Susceptible Pulmonary TB

- General conclusions from the literature:
  - Without PZA - minimum duration is 9 months
  - Without rifampin – basically, treat like MDR
  - Streptomycin and ethambutol (EMB) are approximately equivalent in effect (BUT concern about increasing Streptomycin resistance among foreign born leads to preference of EMB for initial therapy)

TB Drugs Cleared by the Kidneys

- Ethambutol (EMB)
- Pyrazinamide (PZA)

- Levofloxacin
- Cycloserine
- Anything that is injected
  - Streptomycin
  - Amikacin
  - Capreomycin
  - Kanamycin

Treatment Regimen:
Active TB with renal insufficiency

- Renal insufficiency counted at CrCl <30

- Initial Phase (first two months):
  - INH 300mg po daily
  - Rifampin 600mg po daily
  - Ethambutol 15-25mg/kg po *thrice weekly*
  - PZA 25-35mg/kg po *thrice weekly*
  - Vitamin B6 50mg daily

- Continuation
  - INH and Rifampin x 4 – 7 months

TB Meningitis – Drug Penetration of CSF

Table 2. Anti-tuberculosis drugs used in TBM treatment [31–34,164].

Drug	Forms	Oral bio-availability (%)	Food effect	Plasma protein binding (%)	CNS penetration (%)
First-line					
Rifampicin	PO; IV	70	–30%	89	10–20
Isoniazid	PO; IV; IM	~100	–50% C_{max}	0–10	80–90
Pyrazinamide	PO	>90	None	~10	90–100
Ethambutol	PO	75–80	None	20–30	20–30
Rifabutin	PO	50	Decreased rate of absorption	85	50
Rifapentine	PO	70	None	98	-

Expert Review of Clinical Pharmacology, 12:3, 267-288

Drug Penetration of CSF

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Rifapentine	PO	70	None	98	-

Expert Review of Clinical Pharmacology, 12:3, 267-288

Drug Penetration of CSF

Table 2. (Continued).

Drug	Forms	Oral bio-availability (%)	Food effect	Plasma protein binding (%)	CNS penetration (%)
Levofloxacin	PO; IV	~100	None	24–38	70–80
Moxifloxacin	PO; IV	90	None	50	70–80
Ethionamide	PO	~100	None	~30	80–90
Cycloserine	PO	65–90	Slight decrease	~0	80–90

Table 2. (Continued).

Drug	Forms	Oral bio-availability (%)	Food effect	Plasma protein binding (%)	CNS penetration (%)
Linezolid	PO; IV	~100	–23% with high-fat meals	31	70
Bedaquiline	PO	Unknown	Increase	>99	Likely poor (limited data)
Delamanid	PO	25–47	Increase	>99	No human data
Pretomanid	PO	Unknown	Increase	93	No human data

Expert Review of Clinical Pharmacology, 12:3, 267-288

Smear Negative Pulmonary TB

- Sputum has been collected and has resulted smear and culture negative
- Treatment recommendations are for RIPE x 2 months, then rifampin/INH for 2 more months
- Consider leaving all 4 drugs or at least INH/rifampin/EMB

Management of Treatment Interruptions

- Initial phase of therapy
  - <14 days –complete standard # of doses
  - >14 days – restart from the beginning

- Continuation phase
  - >80% doses by DOT – if initial smear negative, may stop
  - Repeat culture
    - >3 month interruption restart from beginning
    - <3 month interruption, culture positive, restart
    - <3 month interruption, culture negative, give an additional 4 months

Relapsed Tuberculosis

- Most relapses occur within the first 6 – 12 months after stopping therapy but some occur 5 or more years later
- Nearly all drug susceptible patients who were treated with a rifamycin and received DOT will relapse with drug susceptible organisms
  - Restart treatment with standard RIPE regimen
- Patients with a history of poor adherence or self administration should have additional sputum collected and careful selection of a treatment regimen

M. bovis

- Often disseminated disease that is highly associated with the abdomen (abdominal lymph nodes, abscesses, enteritis/colitis)
- Unpasteurized milk products
  - Travel, gifts from foreign places
- Bladder instillation with BCG
  - Fever, sterile pyuria!
- Resistant to PZA, susceptible to INH, rifampin and EMB
  - Note: PZA monoresistance likely *M. bovis* or *M. kansasii*

Medical Factors Associated With Relapse of Tuberculosis

- Cavitary TB
- Extensive disease on CXR; bilateral infiltrates
- Positive 2 month culture
- Associated medical conditions
  - Diabetes
  - HIV
  - Malabsorption of TB drugs
- Tuberculous lymphadenitis
- Underweight at diagnosis and failure to gain
- Drug resistant disease
- Prior treatment for tuberculosis

TB in the Elderly

- Hepatotoxicity as well as other medication toxicities are more common
- Drug-drug interactions are more common
- May want to weigh the risk/benefit of using PZA

TB and HIV Co-infection: Active TB Treatment Principles

- The treatment of active TB disease in patients with HIV infection should follow the same principles as for the treatment of persons without HIV infection
  - Start with 4 drugs, watch for drug-drug interactions with the rifamycin
- Initiate TB treatment immediately
  - Directly observed therapy is strongly recommended
- Initiate or optimize ART
  - Concomitant therapy for both TB and HIV shown to reduce mortality
    - Low CD4 count is risk factor for mortality
    - IRIS more common if ART is initiated early in course of TB treatment, but not associated with mortality

http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/

Initiation of ART in patients with HIV/TB

- In patients with CD4 counts <50 cells/mm^3: Initiate ART as soon as possible, but within 2 weeks of starting TB treatment (AI).
- In patients with CD4 counts ≥50 cells/mm^3: Initiate ART within 8 weeks of starting TB treatment (AIII).
- In all HIV-infected pregnant women: Initiate ART as early as feasible, for treatment of maternal HIV infection and to prevent mother-to-child transmission (MTCT) of HIV (AIII).
- In patients with tuberculous meningitis: Caution should be exercised when initiating ART early, as high rates of adverse events and deaths have been reported in a randomized trial (AI).

http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/

Active TB During Pregnancy

- Diagnosis:
  - If you are suspecting TB in a pregnant woman, shield the abdomen and get a CXR. You could be saving 2 lives
- Treatment:
  - INH, Rifampin, Ethambutol x 9 months
    - Stop ethambutol if susceptible to INH and rifampin
  - PZA is regarded as safe by most countries in world (only US and Australia don't). Discuss the benefits of treatment with the patient and strongly consider adding to the regimen
- Follow carefully for hepatotoxicity
  - During pregnancy
  - Three months postpartum

Treatment shortening regimen – Drug Sensitive TB

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

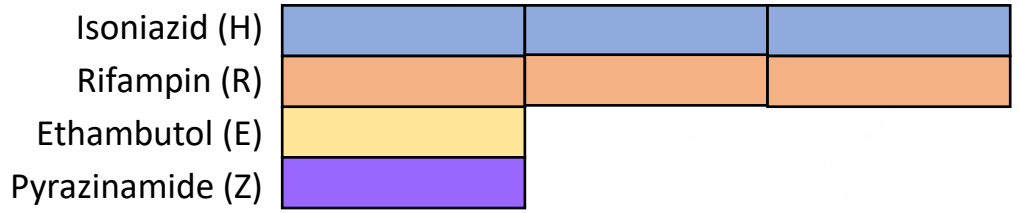
S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

2234 participants (194 PLHIV, 1703 with cavity on CXR)
Randomized 1:1:1 to 3 arms
Noninferiority study

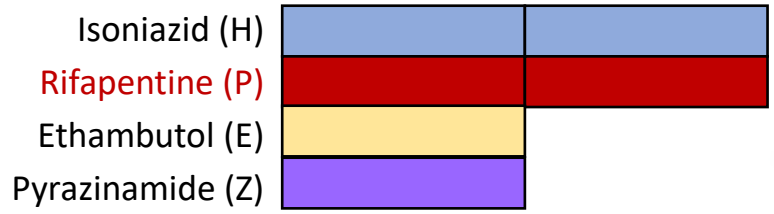
N Engl J Med 2021;384:1705-18.

Study 31/A5349

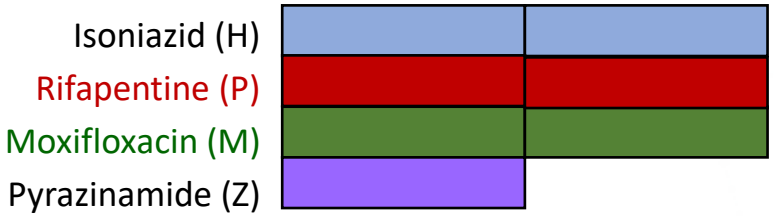
Control
(2HRZE/4HR)



RPT
(2HPZE/2HP)

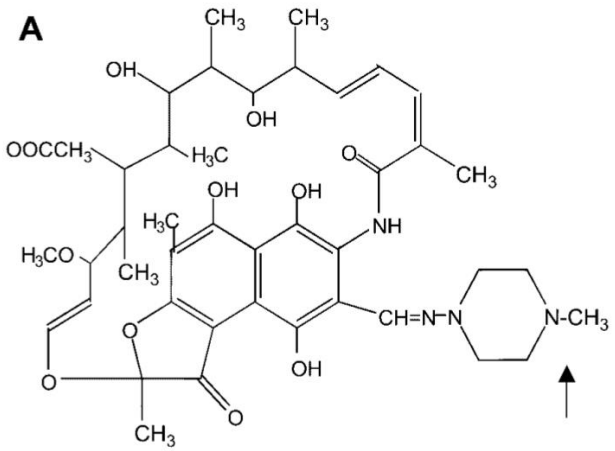


Control
(2HPZM/4HPM)



Notes:

- HRZE dosed at standard doses
- Dosed daily, 7 days/week, observed 5 days/week
- Rifapentine 1200 mg (8 tablets)
- Moxifloxacin 400 mg



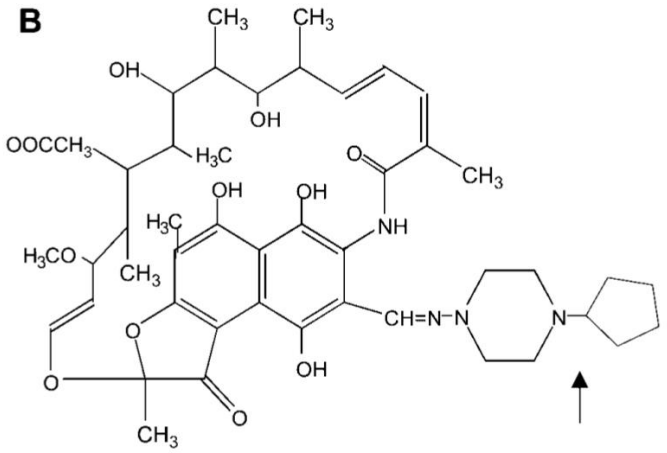


Table 1. Comparing features of rifampin versus rifapentine.

	Rifampin	Rifapentine
MIC	0.125–0.25 µg/mL	0.01–0.06 µg/mL
Half-life	2 h	15 h
Protein binding	80–85%	97–99%
Food requirement	No	Yes
Kinetic	Nonlinear (Michaelis–Menten)	Nonlinear (saturable absorption)
Hepatic enzyme induction	3-fold	4.5-fold
Flat vs. mg/kg dosing	mg/kg	Flat
Cavitary penetration	Good	Poor
Access	Global	Limited
Efficacy	Comparative efficacy at high doses is to be determined	

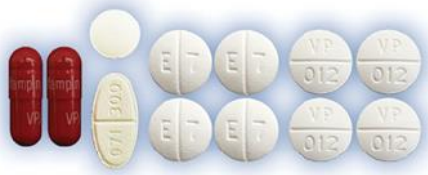
MIC: Minimum inhibitory concentration.

Expert Rev Clin Pharmacol. 2017 Oct;10(10):1027-1036.

Potential Challenges

- Pill burden
  - 1 INH, 8 rifapentine, 1 moxifloxacin, 1 pyridoxine (everybody gets these) + PZA for weight
- Tolerability (versus safety, efficacy)
- Familiarity with the regimen
  - Substitutions?
    - There is no guidance on substituting any of the drugs
  - EOT and they need more treatment?
    - There is no real guidance on how long to extend treatment
- Drug shortages!

Pill Burden

	Standard Regimen (HRZE) >75Kg	Short course regimen (HPMZ) >75Kg
Intensive Phase	**8 weeks**  Isoniazid Rifampin Pyrazinamide Ethambutol Vitamin B6	**8 weeks**  Isoniazid Rifapentine Moxifloxacin Pyrazinamide Vitamin B6
Continuation Phase	**16-28 weeks**  Isoniazid Rifampin Vitamin B6	**9 weeks**  Isoniazid Rifapentine Moxifloxacin Vitamin B6

Photos courtesy of George Lee, RN

New TB Drugs

- Bedaquilline
  - First drug since….ever
  - QT prolongation (watch with FQs, other drugs causing QT prolongation like clofazimine, moxifloxacin)
  - Use in NTMs:
    - benefit in extrapulmonary NTM disease
    - benefit was NOT seen in pulmonary NTM disease
- Delamanid
  - Not yet available in US
- Pretomanid (only approved for use as part of BPaL)

Treatment for MDR-TB

- BPaL(M) x 6 months
  - Bedaquiline
  - Pretomanid
  - Linezolid
  - (Moxifloxacin)
- BPaL(C) has clofazimine
- BPaL

Thank you for your dedication
Thank you for everything you do for your patients every single day

Questions?

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Or

1-800-TEX-LUNG