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Global Tuberculosis Institute
NEW JERSEY MEDICAL SCHOOL

Testing and Treatment of TB Infection (LTBI)

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Disclosures

- None

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Outline

- Definitions
- Diagnosis
- Treatment regimens
  - 3HP
  - 4R
  - 3HR
  - 9H/6H
- Special considerations
  - HIV
  - Pediatrics

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Definition of Terms

- TB Exposure
  - Asymptomatic
  - TST negative
  - CXR normal
- **TB Infection (LTBI = Latent TB Infection)**
  - **Asymptomatic**
  - **TST positive**
  - **CXR normal or calcifications**
- TB Disease
  - Symptomatic
  - TST positive (can be negative)
  - CXR abnormal (usually)

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DIAGNOSIS

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Spectrum of Infection/Disease

- Latent TB Infection
  - Many infections completely unnoticed
  - Asymptomatic
  - Self Limited
- Primary disease
  - Pulmonary disease
  - Dissemination
- Reactivation
- Risk of progression to TB disease absent treatment of LTBI
  - 40 to 50% infants
  - 5 to 15% children
    - Risk highest in the 1 to 2 years after infection
  - Adult data
    - 5 to 10% lifetime risk
    - 50% of the risk in the first 2 years
    - HIV infected 5 to 10% YEARLY risk

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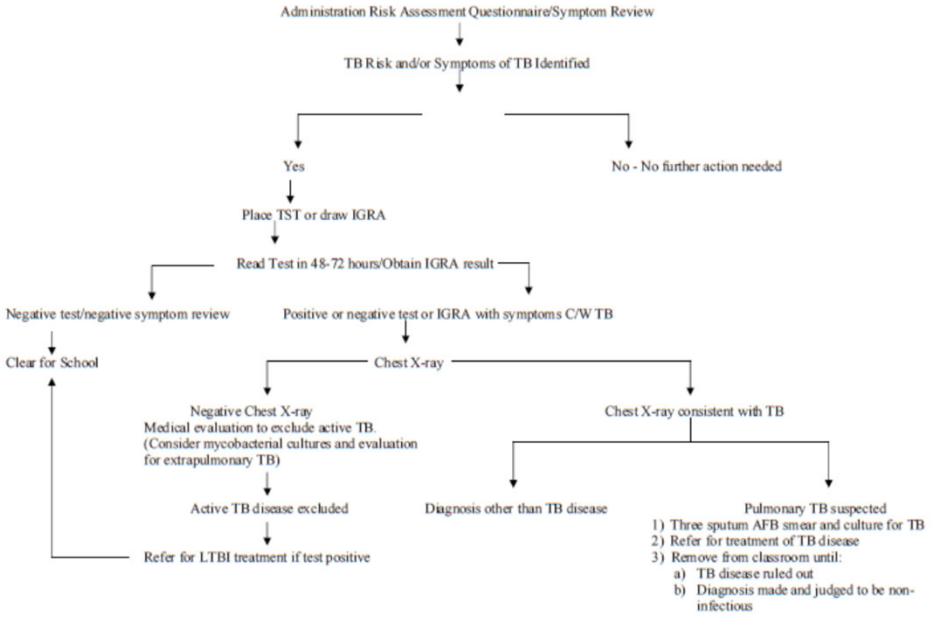
Example of Risk Based Screening in Schools



THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT TYLER
HEARTland NATIONAL TB CENTER
A PARTNERSHIP OF UT HEALTH SCIENCE CENTER AND TCID

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APPENDIX B

Tool for Institutional Use

Part I: Tuberculosis (TB) Screening Questionnaire (to be completed by incoming students)

Please answer the following questions:

Have you ever had close contact with persons known or suspected to have active TB disease? ❑ Yes ❑ No

Were you born in one of the countries or territories listed below that have a high incidence of active TB disease? (If yes, please CIRCLE the country, below) ❑ Yes ❑ No

Afghanistan	Congo	Iran (Islamic Republic of)	Namibia	Singapore
Algeria	Côte d'Ivoire	Iraq	Nauru	Solomon Islands
Angola	Democratic People's Republic of Korea	Kazakhstan	Nepal	Somalia South Africa
Anguilla	Democratic Republic of the Congo	Kenya	Nicaragua	South Sudan
Argentina	Djibouti	Kiribati	Niger	Sri Lanka
Armenia	Dominican Republic	Kuwait	Nigeria	Sudan
Azerbaijan	Ecuador	Kyrgyzstan	Northern Mariana Islands	Suriname
Bangladesh	El Salvador	Lao People's Democratic Republic	Pakistan	Swaziland
Belarus	Equatorial Guinea	Latvia	Palau	Tajikistan
Belize	Eritrea	Lesotho	Panama	Thailand
Benin	Estonia	Liberia	Papua New Guinea	Timor-Leste
Bhutan	Ethiopia	Libya	Paraguay	Togo
Bolivia (Plurinational State of)	Fiji	Lithuania	Peru	Trinidad and Tobago
Bosnia and Herzegovina	French Polynesia	Madagascar	Philippines	Tunisia
Botswana	Gabon	Malawi	Poland	Turkmenistan
Brazil	Gambia	Malaysia	Portugal	Tuvalu
Brunei Darussalam	Georgia	Maldives	Qatar	Uganda
Bulgaria	Ghana	Mali	Republic of Korea	Ukraine
Burkina Faso	Greenland	Marshall Islands	Republic of Moldova	United Republic of Tanzania
Burundi	Guam	Mauritania	Romania	Uruguay
Cabo Verde	Guatemala	Mauritius	Russian Federation	Uzbekistan
Cambodia	Guinea	Mexico	Rwanda	Vanuatu
Cameroon	Guinea-Bissau	Micronesia (Federated States of)	Saint Vincent and the Grenadines	Venezuela (Bolivarian Republic of)
Central African Republic	Guyana	Mongolia	Sao Tome and Principe	Viet Nam
Chad	Haiti	Montenegro	Senegal	Yemen
China	Honduras	Morocco	Serbia	Zambia
China, Hong Kong SAR	India	Mozambique	Seychelles	Zimbabwe
China, Macao SAR	Indonesia	Myanmar	Sierra Leone	
Colombia				
Comoros				

Source: World Health Organization Global Health Observatory, Tuberculosis Incidence 2014. Countries with incidence rates of ≥ 20 cases per 100,000 population. For future updates, refer to http://www.who.int/tb/country/en/.

Have you had frequent or prolonged visits* to one or more of the countries or territories listed above with a high prevalence of TB disease? (If yes, CHECK the countries or territories, above) ❑ Yes ❑ No

Have you been a resident and/or employee of high-risk congregate settings (e.g., correctional facilities, long-term care facilities, and homeless shelters)? ❑ Yes ❑ No

Have you been a volunteer or health care worker who served clients who are at increased risk for active TB disease? ❑ Yes ❑ No

Have you ever been a member of any of the following groups that may have an increased incidence of latent *M. tuberculosis* infection or active TB disease: medically underserved, low-income, or abusing drugs or alcohol? ❑ Yes ❑ No

If the answer is YES to any of the above questions, [insert your college/university name] requires that you receive TB testing as soon as possible but at least prior to the start of the subsequent semester).

If the answer to all of the above questions is NO, no further testing or further action is required.

** The significance of the travel exposure should be discussed with a health care provider and evaluated.*

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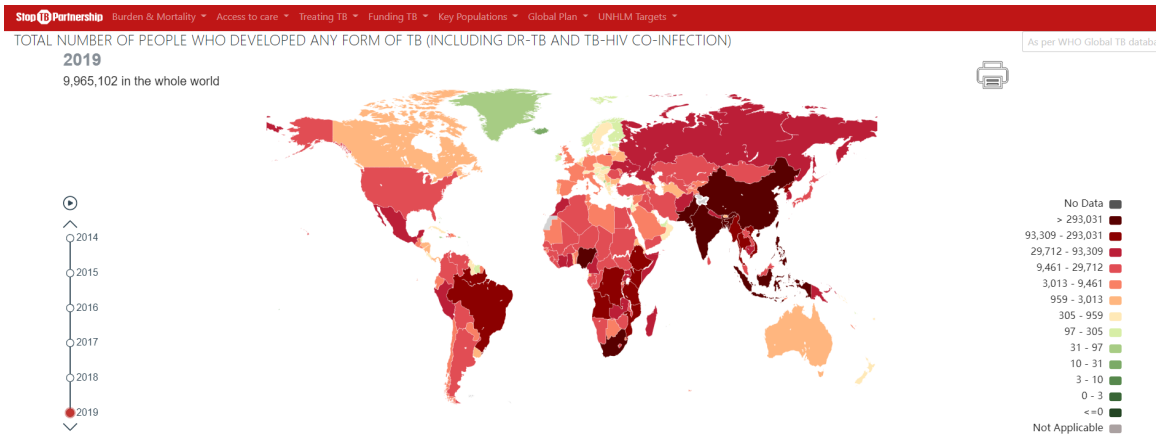
Worldwide TB Diagnoses



WHO.int

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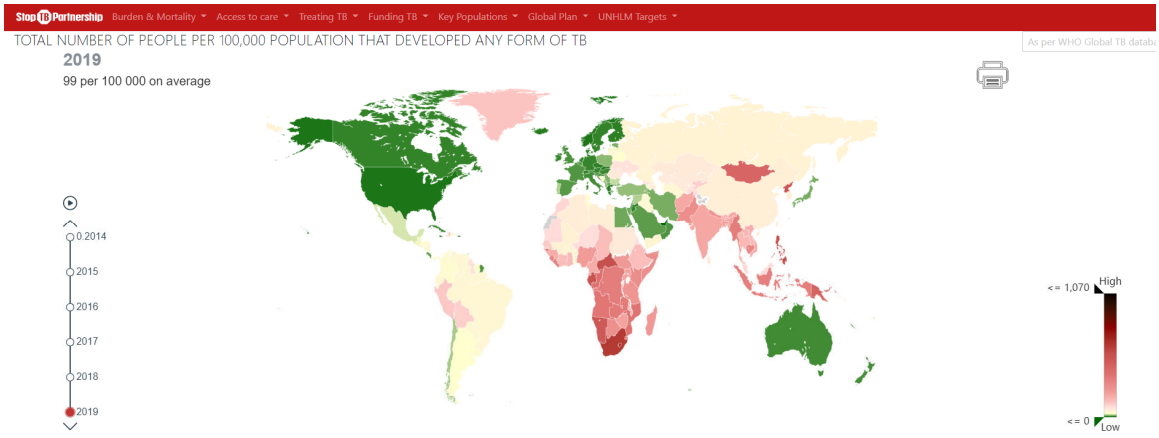
Worldwide TB Diagnosis Rates



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Risk for Progression from TB Infection to TB Disease

Risk Factor and Study	Relative Risk (95% CI)
	%
Advanced, untreated HIV infection	
Moss et al.[10]	9.9 (8.7–11)
Pablos-Méndez et al.[16]	9.5 (3.6–25)
Close contact with a person with infectious tuberculosis†	
Ferebee[17]	6.1 (5.5–6.8)
Radiographic evidence of old, healed tuberculosis that was not treated	
Ferebee[17]	5.2 (3.4–8.0)
Treatment with ≥15 mg of prednisone per day‡	
Jick et al.[18]	2.8 (1.7–4.6)
Chronic renal failure	
Pablos-Méndez et al.[16]	2.4 (2.1–2.8)
Treatment with TNF-α inhibitor	
Askling et al.[19]	2.0 (1.1–3.5)
Poorly controlled diabetes	
Pablos-Méndez et al.[16]	1.7 (1.5–2.2)
Weight ≥10% below normal	
Palmer et al.[20]	1.6 (1.1–2.2)
Smoking	
Bates et al.[21]	1.5 (1.1–2.2)

Medical Hx
Social Hx

Horsburgh and Rubin, NEJM 2011

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Testing for TB Infection

- Limited by inability to identify *Mycobacterium tuberculosis* in people with latent infection
- Diagnosis is indirect and based on detecting host immune response to infection (cell-mediated immunity)
  - Tuberculin skin test (TST)
  - Interferon gamma release assays (IGRA)
- Not able to accurately predict risk of reactivation

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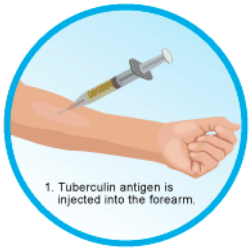
Approved Tests for LTBI

QuantiFERON®-TB Gold In-Tube (Qiagen) measures interferon gamma



Tuberculin Skin Test

T-SPOT®.TB test (Oxford Immunotec) measures peripheral blood mononuclear cells that produce interferon gamma

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TB Testing: How good are our tests?

- TST and IGRAs are indirect methods and are dependent on a healthy immune system
- No gold standard to compare for LTBI
- Accuracy of tests depends on the prevalence of infection
- Association of IGRA to exposure risk and risk of progression are indirect but important measures

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Overall Test Performance → More Specific

	Sensitivity**	Specificity (BCG vaccinated population)	Specificity (non-BCG vaccinated population)
TST	71-82%	*60%	97%
QFT	81-86%	> 95%	> 95%
T-SPOT.*TB*	90-95%		98%

* Variable, depends on when and how often BCG was given
**Sensitivity wanes in HIV or young children

Advantages: one visit, blood test, more specific

Pai, M etal. Clinical Microbiology Reviews, 2014
King et al., AJRCCM, 2015

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General Recommendations for Using IGRAs

- May be used in place of (but not in addition to) a TST in all situations for which CDC recommends tuberculin skin testing
- IGRA preferred
  - Hard to reach populations (e.g., homeless, migrant workers)
    - Only one visit required
  - People who have received BCG (either as vaccine or cancer therapy)
    - TB specificity higher
- Both TST and IGRA may be considered
  - At high risk for infection or progression (e.g., HIV)
  - Suspicion for TB disease exists
  - Further evaluation of positive TST results in individuals at low risk for infection and progression
    - Confirming questionable TST results
  - Other reasons: immediate hypersensitivity to PPD, convincing high risk patient with strongly positive TST to take LTBI treatment, indeterminate/borderline IGRA
- TST preferred
  - Children < 2 yrs

MMWR, June 25, 2010/59

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Tuberculin Skin Test Interpretation

- Induration of > 5 mm is considered positive for:
  - People living with HIV
  - Recent contacts of people with infectious TB
  - People with chest x-ray findings suggestive of previous TB disease
  - People with organ transplants
  - Other immunosuppressed patients
- Induration of > 10 mm is considered a positive reaction for:
  - People who have recently come to U.S. from areas where TB is common
  - People who use drugs
  - Mycobacteriology laboratory workers
  - People who live or work in high-risk congregate settings
  - People with certain medical conditions that increase risk for TB (e.g., silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, and certain intestinal conditions)
  - **Children younger than 5 years of age**
  - Infants, children, or adolescents exposed to adults in high-risk categories
- Induration of > 15 mm is considered a positive reaction for people who have no known risk factors for TB

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TREATMENT PLANNING

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LTBI Treatment

- Initiating treatment
- Choosing a treatment regimen
- Monitoring
- Completion

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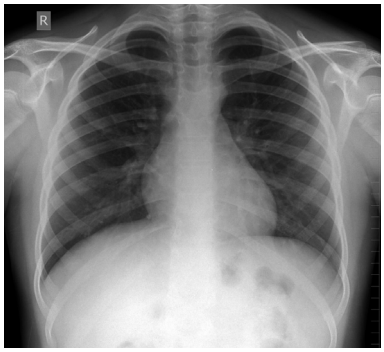
Treatment of TB Infection

- Rule out TB disease
  - History, exam, chest radiograph, bacteriology if needed
- Assess risks and benefits of treatment
- Educate and counsel patient
  - Why treatment is indicated
  - Potential side effects
  - Duration of therapy
- Completion of treatment is low
  - Maximize with shorter regimen, selecting right population



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Baseline Laboratory Evaluation

- Not indicated routinely
- Indicated for:
  - Persons with HIV infection
  - Pregnant & postpartum women (up to 2-3 mos. after delivery)
  - Individuals with history/risk of liver disease
    - Regular alcohol use
    - Chronic hepatitis
    - History of injection drug use
  - Consider in older individuals with other chronic medical conditions/medications

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Treatment Initiation: Patient Education

- Counsel and educate patient
  - Discuss patient's risk for progressing to TB disease
  - Emphasize benefits of treatment
  - Assess whether patient willing to be treated for full treatment period
- Review common side effects
- Establish treatment and monitoring plan
- Instruct patient to immediately report signs and symptoms of adverse drug reactions:
  - Fever
  - Headache
  - Rash
  - Anorexia, nausea, vomiting, or abdominal pain in right upper quadrant
  - Fatigue or weakness
  - Dark urine
  - Persistent numbness in hands or feet

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LTBI Treatment Regimens

TABLE 3. Recommendations for regimens to treat latent tuberculosis infection

Priority rank*	Regimen	Recommendation (strong or conditional)	Evidence (high, moderate, low, or very low)
Preferred	3 mos isoniazid plus rifapentine given once weekly	Strong	Moderate
Preferred	4 mos rifampin given daily	Strong	Moderate (HIV negative)†
Preferred	3 mos isoniazid plus rifampin given daily	Conditional	Very low (HIV negative)
		Conditional	Low (HIV positive)
Alternative	6 mos isoniazid given daily	Strong§	Moderate (HIV negative)
		Conditional	Moderate (HIV positive)
Alternative	9 mos isoniazid given daily	Conditional	Moderate

Sterling, et al. MMWR 2020

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3HP Short Course Regimen: INH + Rifapentine 12 Dose Regimen

PROs

- INH + Rifapentine + B6 once a week x 12 weeks
- Adherence better

CONs

- Pill burden (10 pills)
- DOT
- Rifapentine information lacking for some groups

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3HP Recommendations

- Equal alternative to 9 months INH in otherwise healthy individuals ≥ 12 years old + high risk for TB disease:
  - Close contact
  - Recent PPD conversion
  - Fibrotic changes on CXR
  - HIV not on ART, otherwise healthy
- Others considered on an individual basis if circumstances deem INH-RPT to be a better choice (likelihood of completion should be considered)

Recommendations for Use of an INH-RPT Regimen with DOT to Treat LTBI. *MMWR* / December 9, 2011 / Vol. 60 / No. 48

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INH and Rifapentine for 12 weeks (3HP)

- Efficacy was similar
- 82% in INH-RPT vs. 69% completion in standard therapy group
- Fewer adverse events in INH-RPT arm
- More hepatotoxicity in INH alone group
- More 'possible hypersensitivity' reactions in INH-RPT

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INH-RPT NOT Recommended

- Children < 2 years old
- HIV on ART if drug interactions
- Pregnancy, or likely to become pregnant during treatment
- Presumed INH or RIF resistance
- Prior adverse effects with INH or rifamycins

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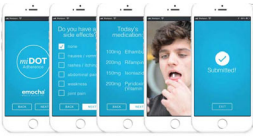
Self Administration or Modified DOT



- iAdhere Study
- SAT in the US was non-inferior to DOT
- Discontinuation due to adverse events was similar among groups
- Video DOT
- Use of recorded or video visits being studied at several sites
- Convenient, well accepted

→ **Such strategies may improve initiation and adherence to therapy**

Belknap et al., CROI, 2015
Gold et al., Open Forum Infectious Diseases, 2016

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Rifapentine Adverse Effects

- Reddening of secretions
- Uncommon
  - Hepatotoxicity (0.4%)
  - Leukopenia
  - Thrombocytopenia
  - Hypersensitivity seen with other rifamycins (3.8%)
    - Fever, 'flu-like', pruritus, hypotension, headache, petechiae
- Hepatic induction of drug metabolism
- Be observant of other potential adverse effects as regimen more widely used

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INH-RPT Monitoring

- Assess for fever, dizziness, rash, jaundice, muscle aches, abdominal pain, nausea, vomiting, loss of appetite at each encounter
- Educate patients to report above symptoms
- Monthly clinical assessment at a minimum

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Other Short-Course Regimens for TB Infection

- RIF daily for 4 months (4R)
  - INH resistant or intolerant
  - Patient unlikely to be adherent for longer treatment period
  - 80-85% treatment completion rates
- Rifabutin may be substituted
- Increases completion rate, lessens burden on public health clinic
- Be aware of drug interactions
  - Methadone, prednisone, protease inhibitors, oral contraceptives, many others
- INH and RIF daily for 3 months (3HR)
  - Equivalent to 6 months INH
  - Including children and HIV
  - Decreased hepatotoxicity
- Consider B6 if increased risk for neuropathy

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3RH Short Course Regimen for TB Infection

- INH and RIF daily for 3 months
- Equivalent to 6 months INH
  - Including children and HIV
- Decreased hepatotoxicity

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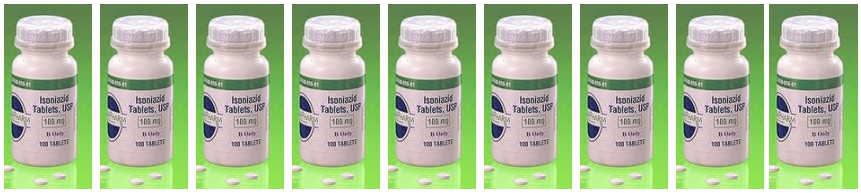
TB Infection Treatment and Duration: INH 9 months

- Completion of Isoniazid for 9 months (9H) is variable, but poor even in controlled situations
  - 53% in NJ (Lardizabal et al., 2006)
  - 69% in CDC INH – RPT trial



- Follow up costs

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Choice of Treatment Regimen Summarized

- Short course preferred over 9H
- 3HP if able to provide
- 4R might be most practical/cost-efficient for patient and clinic
- 3HR in limited settings
- 6H/9H if on essential medications or other contraindication to rifamycin

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Monthly Monitoring During Treatment

- Reinforce patient's understanding of LTBI and its treatment
- Evaluate for signs and symptoms of active TB and drug reactions
- Monitor adherence to prescribed regimen
- Educate patient about signs and symptoms of hepatotoxicity
- Review all medications and assess for potential drug interactions

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- Repeat liver function tests (if done initially):
  - Patients with abnormal baseline
  - Persons with HIV infection
  - Pregnant and post-partum women
  - History/risk of liver disease
    - Heavy alcohol ingestion
    - Chronic hepatitis
    - History of injection drug use
    - On two or more meds

Table 4.4 – Common Adverse Reactions to TB Drugs.

Caused by	Adverse Reaction	Signs and Symptoms	Significance of Reaction*
Any drug	Allergic	• Skin rash	May be serious or minor
Ethambutol	Eye damage	• Blurred or changed vision • Changed color vision	Serious
Pyrazinamide Isoniazid Rifampin	Hepatitis (liver toxicity)	• Abdominal pain • Abnormal liver function test results • Brown urine, light colored stool • Fatigue • Fever for 3 or more days • Flu-like symptoms • Lack of appetite • Nausea • Vomiting • Yellow skin or eyes	Serious
Isoniazid	Nervous system damage	• Dizziness • Tingling or numbness around the mouth	Serious
	Peripheral neuropathy	• Tingling sensation, numbness, or pain in hands and feet	Serious
Pyrazinamide	Stomach upset	• Stomach upset, vomiting, lack of appetite	May be serious or minor
	Gout	• Abnormal uric acid level • Joint aches	Serious
Rifampin	Bleeding problems due to low platelets	• Easy bruising • Slow blood clotting	Serious
	Discoloration of body fluids	• Orange urine, sweat, or tears • Permanently stained soft contact lenses	Minor
	Drug interactions	• Interferes with many medications, such as birth control pills or implants, blood thinners, some HIV medicines, and methadone	May be serious or minor

*Patients should stop medication for serious adverse reactions and consult a clinician immediately. Patients can continue taking medication if they have minor adverse reactions.

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Management of the Patient Who Misses Doses

- Extend or re-start treatment for frequent or prolonged interruptions that preclude completion within recommended time frame
- Examine patients to rule out TB disease when treatment interruption > 2 months
- Recommend and arrange for DOT as needed
- Completion of therapy is based on the total number of doses administered, not on duration alone

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Completion of Therapy (Rule Book)

Regimen	Duration	Doses	Complete Within
Daily INH	9 months	270	12 months
Twice weekly INH	9 months	76	12 months
Daily INH	6 months	180	9 months
Twice weekly INH	6 months	52	9 months
Rifampin	4 months	120	6 months
INH-RPT	3 months	11-12	16 weeks

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PEDIATRIC TB DIFFERENCES

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Evaluation of Contacts

Contacts at High Risk for Rapid Development of TB Disease

Sometimes LTBI treatment is given to people who have a negative TST or IGRA result. For example, some contacts at high risk for rapidly developing TB disease should start LTBI treatment even if they have a negative test and less than 8 to 10 weeks have passed since they were last exposed to TB. These contacts include

- Children who are younger than 5 years of age (some TB programs may have different age cutoff guidelines)
- People living with HIV

Some contacts may start taking LTBI treatment if they have a negative TST or IGRA result but less than 8 to 10 weeks have passed since they were last exposed to TB.

Once TB disease is ruled out, these contacts should start LTBI treatment to prevent them from rapidly developing TB disease. They also should be retested 8 to 10 weeks after they were last exposed to TB. If the contact has a positive TST or IGRA result, he or she should continue to take LTBI treatment. Contacts living with HIV may be given a full course of LTBI treatment even if their second TST or IGRA result is negative.

TB contacts living with HIV may be given a full course of LTBI treatment even if their second TST or IGRA result is negative.

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TB Disease by Age

	Risk of disease following primary infection			Comments
	Disseminated tuberculosis/ tuberculosis meningitis	Pulmonary tuberculosis	No disease	
<1 years	10–20%	30–40%	50%	High rates of morbidity and mortality
1–2 years	2–5%	10–20%	75–80%	High rates of morbidity and mortality
2–5 years	0·5%	5%	95%	..
5–10 years	<0·5%	2%	98%	"Safe school years"
>10 years	<0·5%	10–20%	80–90%	Effusions or adult-type pulmonary disease

Adapted from reference 30.

Table 1: Risk of pulmonary and extrapulmonary disease in children following infection with ***Mycobacterium tuberculosis***

Newton, et al Lancet ID 2008

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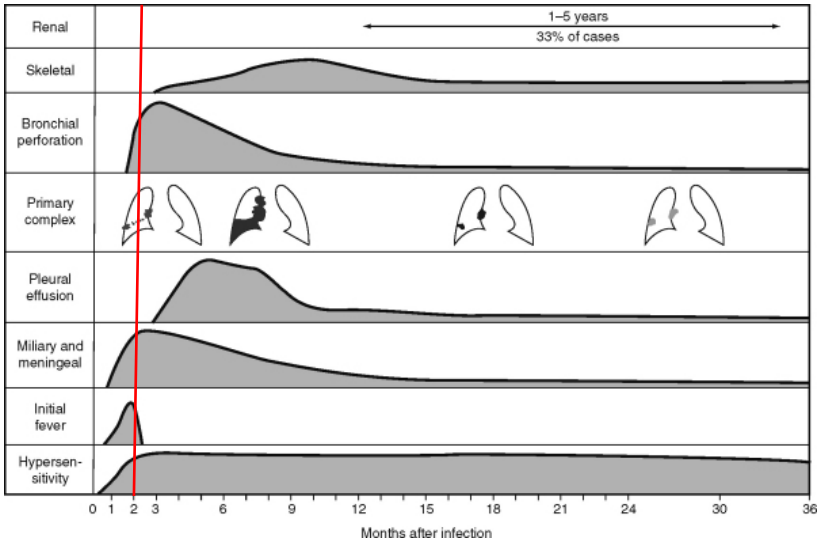
Reason for Window Prophylaxis



From Starke Chapter 107 in Textbook of Pediatric ID 2009

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Summary

- Prior to initiating LTBI treatment, assess for presence of TB disease
- Choose treatment regimen based on individualized evaluation of each patient
- Monthly clinical assessments and ongoing patient education important
- Use DOT for high-priority patients

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