EVALUATION AND TREATMENT OF LATENT TB INFECTION

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Latent TB Infection Objectives

- Discuss Diagnosis/Testing for LTBI
- Review Risk Factors: LTBI and Progression to TB Disease
- Describe 3 Regimens for LTBI

Latent TB Infection (LTBI)

LTBI is the presence of *M. tuberculosis* organisms (tubercle bacilli) without signs and symptoms or radiographic or bacteriologic evidence of TB disease.

LTBI vs. Pulmonary TB Disease

Latent TB Infection

- Positive TST* or IGRA† result
- Chest radiograph normal

Pulmonary TB Disease

- TST or IGRA is usually positive
- Chest radiograph is usually abnormal

*tuberculin skin test
†Interferon-Gamma Release Assay

LTBI vs. Pulmonary TB Disease

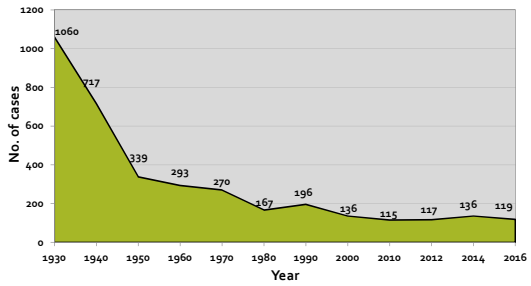
Latent TB Infection

- No symptoms or physical findings suggestive of TB
- If done, respiratory specimens are smear and culture negative and CXR stable.
- Wait for final results before starting LTBI treatment

Pulmonary TB Disease

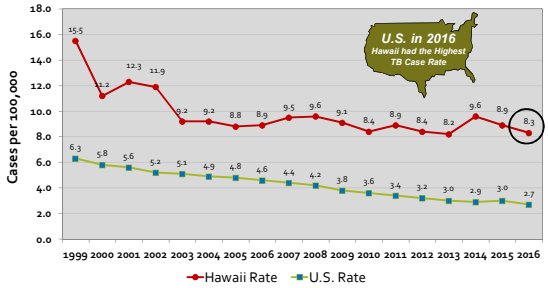
- Symptoms *may* include one or more of the following: fever, cough, night sweats, weight loss, fatigue, hemoptysis, decreased appetite
- Respiratory specimens are usually culture positive (smear positive in about 50% of patients)

Reported TB Cases Hawaii, 1930–2016



Updated as of May 1, 2017

TB Case Rates
Hawaii vs. United States, 1999–2016



Updated as of May 1, 2017

LTBI
TB Elimination?

- US 2016
- 9,272 cases to 300??

- Hawaii
- 116 TB disease 2017
- >150,000 LTBI?

TB Screening

- "Universal testing with TST or IGRA, including programs based at schools, child care centers…is discouraged because it results in either a low yield of positive results or a large proportion of false-positive results…"

- 2015 AAP Red Book

TB Screening

- "However, using a questionnaire to determine risk factors for LTBI can be effective."

2015 AAP Red Book

TB Screening

- "The USPSTF recommends screening for LTBI in populations **at increased risk**."
- "Populations at increased risk for LTBI include persons who were born in, or are former residents of countries with increased tuberculosis prevalence and persons who live in, or have lived in, high-risk congregate settings…"
- US Preventive Services Task Force September 6, 2016

Targeted TB Testing and Treatment of Latent TB Infection

- As TB disease rates in the United States decrease, finding and treating persons at high risk for latent TB infection (LTBI) has become a priority.
- Targeted TB testing is used to focus program activities and provider practices on groups at the highest risk for TB.
- Treatment of LTBI substantially reduces the risk that persons infected with *M. tuberculosis* will progress to TB disease.

Targeted TB Testing

- Essential TB prevention and control strategy
- Detects persons with LTBI who would benefit from treatment
- De-emphasizes testing of groups that are not at high risk for TB
- Can help reduce the waste of resources and prevent inappropriate treatment

LTBI
Who Should We Test?

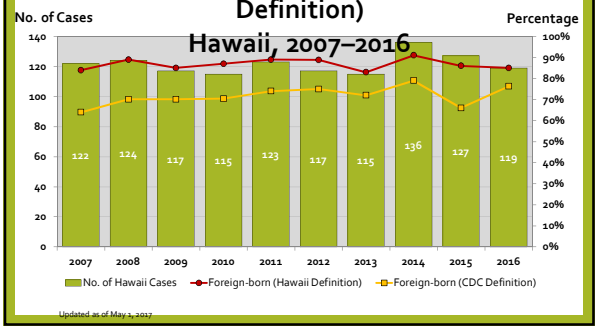
- Risk of Exposure
- Risk of Progression

Persons at Risk for Developing TB Disease

Persons at high risk for developing TB disease fall into 2 categories:

- Those who have an increased likelihood of exposure to persons with TB disease
- Those with clinical conditions that increase their risk of progressing from LTBI to TB disease

Trends in TB Cases and Percentage of Foreign-born Persons (Hawaii vs. CDC Definition) Hawaii, 2007–2016



Updated as of May 1, 2017

Increased Likelihood of Exposure to Persons with TB Disease

Persons at risk for exposure to persons with TB disease include:

- Close contacts to person with infectious TB
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, homeless shelters, health care facilities)
- Immigrants from TB-endemic regions of the world
- Children with household members from TB-endemic areas

Increased Risk for Progression to TB Disease

Persons more likely to progress from LTBI to TB disease include:

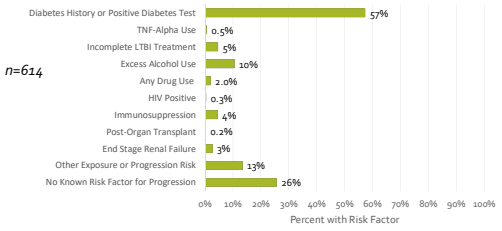
- Underweight or malnourished persons
- Substance abusers (such as smoking, alcohol abusers, or injection drug use)
- Those receiving TNF-α antagonists for treatment of rheumatoid arthritis or Crohn's disease
- HIV Infection
- X-rays consistent with prior untreated TB disease
- Children <5 years of ago with + skin test

Increased Risk for Progression to TB Disease

Persons more likely to progress from LTBI to TB disease include:

- Those with certain medical conditions such as:
  - Silicosis
  - Diabetes mellitus
  - Chronic renal failure or on hemodialysis
  - Solid organ transplantation (e.g., heart, kidney)
  - Carcinoma of head or neck
  - Gastrectomy or jejunoilial bypass

Risk Factors for TB Progression
All Hawaii TB Cases, 2012-2016



Priority Groups for LTBI Treatment

Persons with Highest Risk

- Recent contact to someone with infectious TB (within previous 2 years)
- Skin test converter i.e. TST negative within previous 2 years and increase of 6 mm to at least 10mm†
- Persons living with HIV

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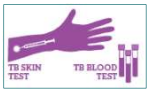
- Persons with diabetes, especially when newly diagnosed or poorly controlled
- Persons with fibrotic changes on chest X-ray consistent with prior TB disease (Class 4)
  - Excludes calcified lymph nodes, small granulomas, apical pleural capping or thickening, basal pleural thickening, blunting or scarring
- Persons receiving prednisone the equivalent of 15 mg/day for 21 month
- Persons receiving tumor necrosis factor (TNF) inhibitors
  e.g. Remicade (infliximab), Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab pegol), and Simponi (golimumab). (FDA black box warning)
- Children less than 5 years of age

Other Risks

- Persons born in high-prevalence areas outside the USA
  - e.g. Africa, Asia (includes India and Philippines), Eastern Europe, Latin America, Middle East, Pacific Islands
- Persons with other medical conditions that increase the risk for progression of TB
  - e.g. chronic renal failure/dialysis, organ transplant, silicosis, certain types of cancer (leukemia and lymphomas, or cancer of the head, neck or lung), gastrectomy or jejunoileal bypass, and weight loss of at least 10% below body weight
- Children 5 years or older and adolescents exposed to adults in high-risk categories;
  - Locally we recommend treatment of adolescents and young adults from Pacific Islands and Philippines
- Other
  - Cigarette smokers and persons who abuse drugs and/or alcohol
  - Residents and employees of high-risk congregate settings (correctional facilities, nursing homes, homeless shelters, hospitals, or other health-care facilities)

Testing for *M. tuberculosis* Infection

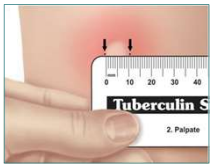
- There are two testing methods available for the detection of *M. tuberculosis* infection in the United States:
  - Mantoux tuberculin skin test (TST)
  - Interferon-gamma release assays (IGRA)
- These tests do not exclude LTBI or TB disease



- Decisions about medical and public health management should include other information, and not rely only on TST or IGRA results

Reading the TST

- Measure reaction in 48 to 72 hours
- Measure induration, not erythema
- Record reaction in millimeters, not "negative" or "positive"
- Ensure trained health care professional measures and interprets the TST



Reading the TST

- Educate patient and family regarding significance of a positive TST result
- Positive TST reactions can be measured accurately for up to 7 days
- Negative reactions can be read accurately for only 72 hours

TST Interpretation

≥ 5 mm induration is interpreted as positive in

- HIV-infected persons
- Close contacts to an infectious TB case
- Persons with chest radiographs consistent with prior untreated TB

TST Interpretation

≥ 10 mm induration is interpreted as positive in

- Recent immigrants
- Injection drug users
- Residents or employees of congregate settings
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that place them at high risk
- Children<4 years; infants, children, and adolescents exposed to high risk adults

TST Interpretation

≥ 15 mm induration is interpreted as positive in

- Persons with no known risk factors for TB.

- Although skin testing programs should be conducted only among high-risk groups, certain individuals may require TST for employment or school attendance.
- Diagnosis and treatment of LTBI should always be tied to risk assessment.

Factors That May Cause False-Positive TST Reactions

- Nontuberculous mycobacteria
  - Reactions caused by nontuberculous mycobacteria are usually ≤10 mm of induration
- BCG vaccination
  - Reactivity in BCG vaccine recipients generally wanes over time; positive TST result is likely due to TB infection if risk factors are present

Factors That May Cause False-Negative TST Reactions -1

- Anergy: Inability to react to a TST because of a weakened immune system.
- Recent TB infection (< 10 weeks since exposure)
- Very young age
- Recent live viral vaccine
- Overwhelming TB disease
- Poor TST administration technique

Boosting

- Some people with LTBI may have a negative skin test reaction when tested years after infection because of a waning response.
- An initial skin test may stimulate (boost) the ability to react to tuberculin.
- Positive reactions to subsequent tests may be misinterpreted as new infections rather than "boosted" reactions.

Two-Step Testing

- For baseline testing of persons who will be retested periodically
  Health care workers or patients admitted to long term care
- 2 methods: 3 visit and 4 visit
- Done only once per lifetime
- 2 tests done within 12 months=valid 2-step test

Interferon-Gamma Release Assays (IGRAs)

- Whole-blood test used to detect *M. tuberculosis* infection
- Two U.S. Food and Drug Administration (FDA) approved IGRAs are commercially available in the U.S.:
  - QuantiFERON®-TB Gold-in-tube test (QFT-GIT)
  - T.SPOT®.*TB* test (T-Spot)

How IGRAs Work

- Blood test that measures and compares amount of interferon-gamma (IFN-γ) released by blood cells in response to antigens
- Entails mixing blood samples with antigens from *M. tuberculosis* and controls
- Cells that recognize the antigen release interferon-gamma
- Amount of interferon release is compared to amount release in response to other antigens

Advantages of IGRAs

- Requires a single patient visit to conduct test
- Results can be available within 24 hours
- Does not boost responses measured by subsequent tests
- Prior BCG vaccination does not cause false-positive IGRA test result
- More specific and possibly more sensitive

Disadvantages/Limitations of IGRAs

- Errors in collecting and transporting blood, or in interpreting assays can decrease accuracy of IGRAs
- Limited data on use of IGRAs to predict who will progress to TB disease in the future
- Limited data on use for children, contacts, immunosuppressed
- Cost
- Accessibility
- Not FDA approved for children <5 years of age
- Cut point variability

Selecting a Test to Detect TB Infection

- IGRAs are preferred method of testing for
  - Groups of people who have poor rates of returning to have TST read
  - Persons who have received BCG vaccine
- TST is the preferred method of testing for
  - Children under the age of 5

Use of Skin Test and IGRA

+TST:

- Consider ordering IGRA to increase patient compliance
- To evaluate low risk patient

-TST:

- Consider IGRA to evaluate high risk patient
- Evaluation of patient suspected of having active TB disease

Treatment of LTBI – Milestones

TB Control strategy chooses LTBI treatment over BCG

1965: American Thoracic Society (ATS) recommends treatment of LTBI for those with previously untreated TB, tuberculin skin test (TST) converters, and young children.

1967: Recommendations expanded to include all TST positive reactors (≥ 10 mm).

Treatment of LTBI – Milestones

1974: CDC and ATS guidelines established for pretreatment screening to decrease risk of hepatitis associated with treatment

Treatment recommended for persons ≤ 35 years of age

Treatment of LTBI – Milestones

1983: CDC recommends clinical and laboratory monitoring of persons ≥ 35 who require treatment for LTBI

1998: CDC recommends 2 months of rifampin (RIF) plus pyrazinamide (PZA) as an option for HIV-infected patients (later changed)

Treatment of LTBI – Milestones

2000: CDC and ATS issue updated guidelines for targeted testing and LTBI treatment[1]

9-month regimen of isoniazid (INH) is preferred

2-month regimen of RIF and PZA and a 4 month regimen of RIF recommended as options (later changed)

[1] *MMWR* June 9, 2000; 49(No. RR-6)
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm

Treatment of LTBI – Milestones

2001: Owing to liver injury and death associated with 2-month regimen of RIF and PZA, use of this option de-emphasized in favor of other regimens[2]

2003: 2-month regimen of RIF and PZA generally not recommended — to be used only if the potential benefits outweigh the risk of severe liver injury and death[3]

[2] *MMWR* August 31, 2001; 50(34): 733-735 - http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5034a1.htm
[3] *MMWR* August 8, 2003; 52(31): 735-739 - http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm

Treatment of LTBI – Milestones

2011: CDC recommends 12-doses (3 months) of isoniazid (INH) and rifapentine (RPT) as an option equal to the standard 9-month INH regimen for certain groups*

2016: U.S. Preventive Services Task Force recommends testing for TB as a part of standard preventive care for certain at-risk groups**

*MMWR. Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w
**USPSTF. Latent Tuberculosis Infection: Screening
http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryDraft/latent-tuberculosis-infection-screening

Initiating Treatment

Before initiating treatment for LTBI

- Rule out TB disease by history, physical examination, chest radiography and, when indicated, bacteriologic studies
- Determine prior history of treatment for LTBI or TB disease
- Assess risks and benefits of treatment (www.tstin3d.com)
- Determine current and previous drug therapy

Latent TB Infection Treatment Regimens for Specific Situations – HIV-Infected Persons

HIV-Infected Persons

- Consult an expert in managing HIV and TB
- INH daily for 9-mo, rather than 6-mo, is optimal: 270 doses within 12 months
- RIF is generally contraindicated for persons taking protease inhibitors or delavirdine
- Rifabutin with dose adjustments can sometimes be substituted for RIF
- INH/RPT regimen not recommended for HIV-infected people taking antiretroviral therapy

Latent TB Infection Treatment Regimens for Specific Situations - Pregnancy

Pregnancy and Breast-Feeding

- 9 months of INH daily or twice weekly; give with vitamin B6
- If cannot take INH, Rifampin is alternative
- Rifapentine/INH regimen not currently recommended
- Women at high risk for progression to TB disease should not delay LTBI treatment; monitor carefully
- Breast-feeding not contraindicated

Clinical Monitoring

Instruct patient to stop meds and report any

- Fever
- Headache
- Rash
- Severe GI distress
- Anorexia, nausea, vomiting* or RUQ abdominal pain
- Fatigue or weakness
- Dark urine
- Persistent numbness or tingling in hands/feet

- *1 day of nausea or vomiting and 2 days of decreased appetite

Laboratory Monitoring

- Baseline liver function tests (ALT,AST, T.Bili) not necessary except for patients with risk factors.
- HIV Infection
- History of liver disease
- Regular alcohol use
- Other medication with liver side effects
- Pregnancy or early postpartum period
- History of chronic hepatitis
- Age over 50 years

Laboratory Monitoring

- Repeat laboratory monitoring if patient has
- Abnormal baseline results
- Current or recent pregnancy
- High risk for adverse reactions
- Symptoms of adverse reaction
- Liver enlargement or tenderness during exam

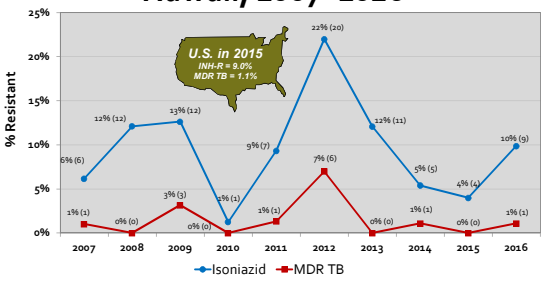
Laboratory Monitoring

- Asymptomatic elevation of hepatic enzymes seen in 10%-20% of people taking INH
  - Levels usually return to normal after completion of therapy
- Discontinue treatment if transaminase level exceeds 3 times the upper limit of normal if patient has symptoms of liver toxicity, and 5 times the upper limit of normal if patient is asymptomatic

LTBI Treatment Regimens

Drug	Duration	Dose	Frequency	Total Doses
Isoniazid	9 months	Adult: 5mg/kg	Daily	270 (within 12 months)
		Children: 10-20mg/kg Max dose: 300mg		
		Adult: 15mg/kg	2X a week	76
		Children: 20-40mg/kg Max dose:900mg		
Isoniazid	6 months	Adult: 5mg/kg	Daily	180 (within 9 months)
		Adolescents: 5mg/kg		
		Max dose: 300mg		

Primary Anti-TB Drug Resistance* Hawaii, 2007–2016



*Cases are culture positive with initial drug susceptibility testing done. Isolates may be resistant to other drugs. Excludes cases with susceptibility testing not done or unknown for isoniazid and rifampin.

Updated as of May 1, 2017

LTBI Treatment

Drug	Dose	Duration	Frequency	Total Doses
Rifampin	Adults: 10mg/kg. Max Dose: 600mg	4 months	Daily	120 (by 6 mos)
	Children: 10-20mg/kg Max Dose: 600mg	6 months 4 mos OK		180

LTBI Treatment

Drug	Dose	Duration	Frequency	Total Doses
Isoniazid	Age ≥12 years: 15 mg/kg. Max dose: 900mg	12 weeks	Once weekly	12 Min: 11 in 16 wks
Plus				
Rifapentine (RPT)	10-14kg: 300mg 14.1-25kg: 450mg 25.1-32Kg: 600mg 32.1-49.9kg: 750mg 50kg+: 900mg			

Table 2 CDC Approved Treatment for LTBI

Medication	Frequency	Duration	Comments
Isoniazid (INH)	Daily	6-9 months	• 6 months is acceptable for Class 1 HIV-negative persons who are ≥15 years of age • 9 months recommended for Class 4 and PLWH and persons less than 15 years of age • CCMD can individualize length of treatment for persons with medical conditions known to increase risk for TB
	2x/week	6-9 months	• Recommend DOPT. • Not recommended for PLWH or Class 4
Rifampin (RIF)	Daily	4-6 months	• Rifampin drug interactions may preclude use, check "Facts and Comparisons" • 4 months for persons less than 15 years of age . • Consider 6 months for PLWH
INH and RIF	Daily	4 months	• Some experts recommend for Class 4 adults with no history of treatment see "Special Populations" section below • 8wks of RIPE also completes Class 4 Tx
INH and Rifapentine (RPT)	Once Weekly	12 doses (3 months)	• Approved in 2011 • Recommend administration by direct observation • See program pilot description

LTBI Treatment with INH: B6

- Persons with diabetes
- Pregnant or breastfeeding women
- Exclusively breastfed infants and other children/adolescent with poor diets
- Patients with nutritional deficiencies/malnutrition
- HIV infection
- Renal failure
- Patients with pre-existing neuropathies
- Alcoholism
- Patient request

Latent TB Infection Treatment Special Populations

- "Class 4"
- Patients using hormonal contraceptives
- Other medications
- History of depression or other mental illness
- Pregnancy or Breastfeeding
- Infants and Children
- Renal disease
- HIV

Table 4 Indications for DOPT

- Child contacts on window prophylaxis or full treatment LTBI, at least until apparently reliable parents are comfortable giving doses
- Intermittent treatment regimens
  - For once-weekly INH-rifapentine regimen
  - Intermittent treatment with INH alone e.g. 2x or 3x/weekly
- Consider for following
  - Contacts to drug resistant TB

Table 3 Duration of Window Period Treatment

High risk category	Duration of treatment
Children 6 months to 5 years	• Can stop window treatment if negative TST or IGRA 8-12 weeks after last exposure to contagious TB • CCMD or other MD may elect to continue treatment on case-by-case basis considering intensity of exposure, contagiousness of source case
Infants under 6 months of age	• Can stop treatment if negative TST or IGRA after 6 months of age AND 8-12 weeks after last exposure • CCMD or other MD may elect to continue treatment on case-by-case basis considering intensity of exposure, contagiousness of source case
HIV infected and other immunosuppressed	Consider recommending a full course of LTBI treatment, regardless repeat skin test results.

Table 8 Managing Missed Doses and Treatment Interruptions

Prescribed course	Maximum duration of treatment course
INH x 9 months	12 months
INH x 6 months	9 months
Rifampin x 4 months	6 months
INH and rifampin x 4 months	6 months
Rifampin x 6 months	9 months
INH-RPT 12 doses/3 months	11. doses within 16 weeks

Case Study A (1)

Patient History

- 47-year-old Hispanic male
- Moved to U.S. from Bolivia 4 years ago
- Known contact of infectious TB case
- TST = 5 mm of induration
- 3 months later TST = 23 mm of induration
- No symptoms of TB disease
- Normal CXR, CBC, AST, and bilirubin

Case Study A (2)

Questions

1. What are this patient's risk factors for TB infection or disease?
2. Has the management of this patient to date been appropriate?

Case Study A (3)

Discussion of risk factors

- Patient is a contact of an infectious TB case
- Recent immigrant to the US from a country with a high prevalence of TB
- If the patient had not been a contact, the 5-mm reaction would not be considered positive
- Lifetime risk is 4.9% and hepatitis risk is 1.2%

Case Study B (1)

Patient History

- 24-year-old Asian female
- Moved to U.S. from Philippines > 5 years ago
- Plans to work in a correctional facility
- TST result negative (0 mm) 1 year ago
- TST for pre-employment physical = 26 mm of induration
- CXR normal
- No symptoms of TB disease
- No known contact with a TB patient

Case Study B

- What are this patient's risk factors for TB infection or disease?
- What is the appropriate management for this patient?

Case Study B

- 1. Immigrant from high incidence country
- 2. Recently converted skin test
- 3. Going to be working in congregate setting
- Lifetime risk is 5.2% and hepatitis risk is 0.3%

Case Study C

- 18 year old male, enrolling in UH Manoa
- Born and raised in Montana
- No known exposures
- No foreign travel
- TB skin test read at 12 mm
- What are his TB risks?
- What is appropriate management?

Case Study C

- No TB risks
- TB skin test is <15mm in this low risk individual and would be read as negative.

LTBI: The Future?

- TB Clearance Changes
- Changes at Department of Health, TB Branch
- New tests?
- New Drug Regimens?

Resources

- Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection *MMWR* 2000; 49 (No. RR-6) http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm
- Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w
- CDC TB Website http://www.cdc.gov/tb
- Latent Tuberculosis Infection: A Guide for Primary Health Care Providers http://www.cdc.gov/tb/publications/LTBI/default.htm

Additional TB Resources Available Online

- CDC's Morbidity and Mortality Weekly Report http://www.cdc.gov/tb/publications/reportsarticles/mmwr/default.htm
- American Thoracic Society http://www.thoracic.org/statements/
- U.S. Preventive Services Task Force http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryDraft/latent-tuberculosis-infection-screening
- Bright Futures Recommendations for Pediatric Preventive Health Care https://www.aap.org/en-us/Documents/periodicity_schedule.pdf

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