Tuberculosis (TB) 101

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Tierney Hall
Wisconsin TB Program
August 24th, 2021

TB 101

History and pathophysiology

Epidemiology

Latent TB vs. active TB

Diagnosis and treatment

Brief overview of WI TB Program functions

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TB Disease

Airborne disease caused by the bacterium *Mycobacterium tuberculosis*

Usually considered a respiratory disease but can affect many other parts of the body

THE CAUSE OF TUBERCULOSIS

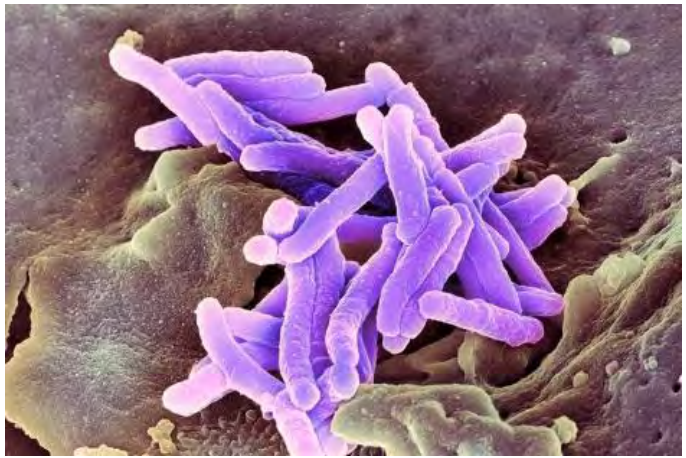
Robert Koch
(1843-1910)

Bacteria: aerobic, non-spore forming, rod-shaped microbe found in water, soil, plants, animals, milk, with zombie-like characteristics

Characteristics:

- Size: 0.3 X 1.0µm
- Waxy coat/Acid Fast –AFB
- Slow growing (q 15-20h)
- Adapts (tropism) dormant-like
- 40% genes unknown function

THE CAUSE OF TUBERCULOSIS



Species: *Mycobacterium tuberculosis, M. bovis, M. Africanum & M.microti =* **MTB Complex**, *M. leprae*

Other Names: consumption, kings evil, scrofula, Potts disease, phthisis, lupus vulgaris, white plague.

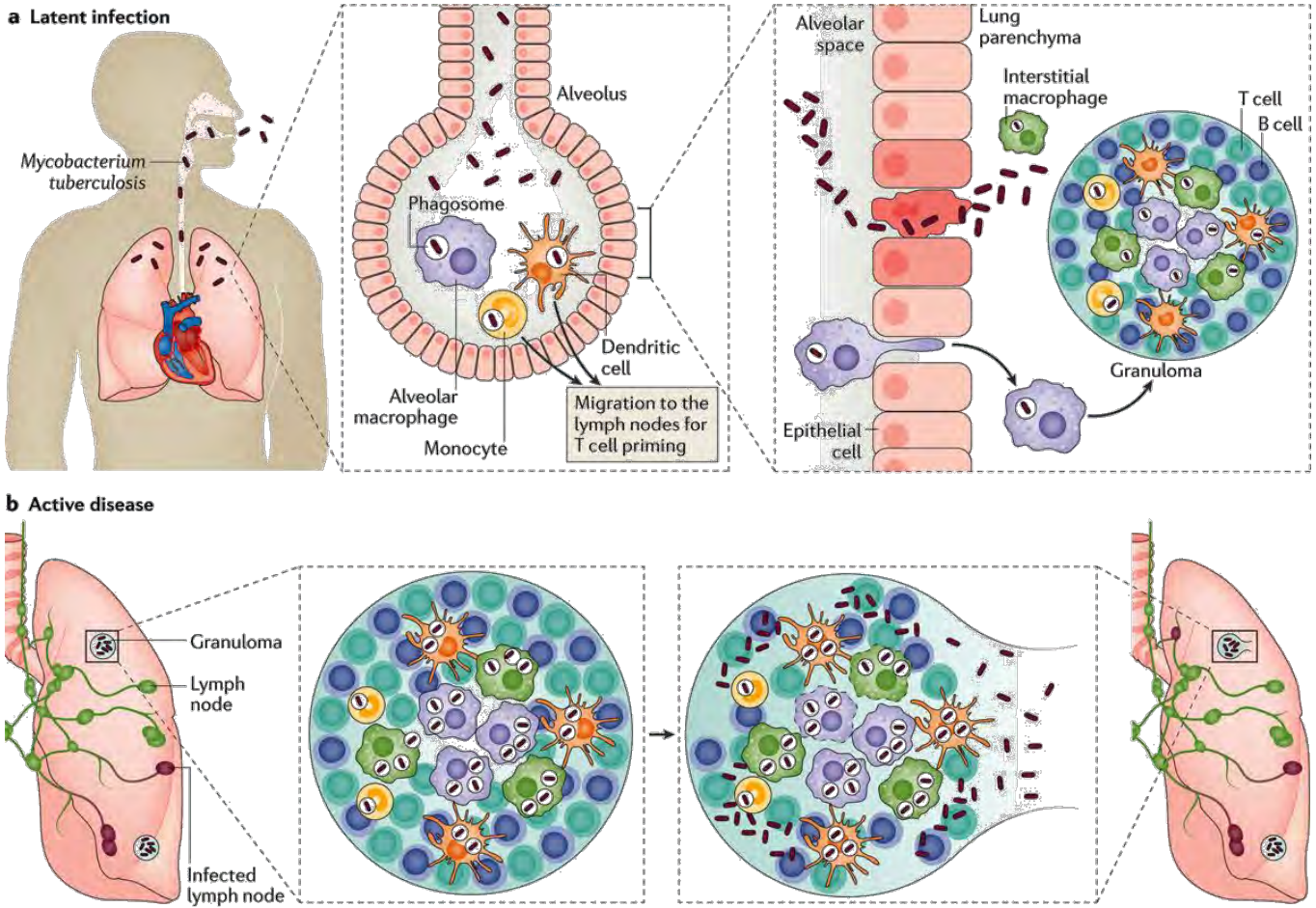
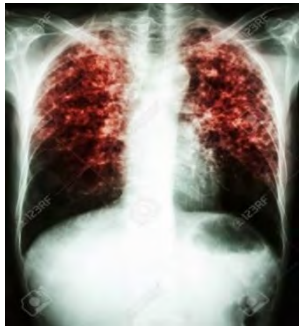


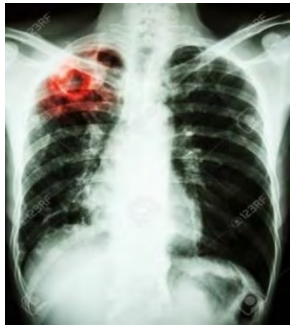
Figure 3 *Mycobacterium tuberculosis* infection

Pathophysiology of LTBI from " Tuberculosis" in Nature Reviews vol. 2 (2016) by Pai, M. et. al.

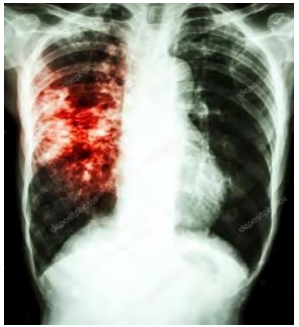
TB on radiograph varies:



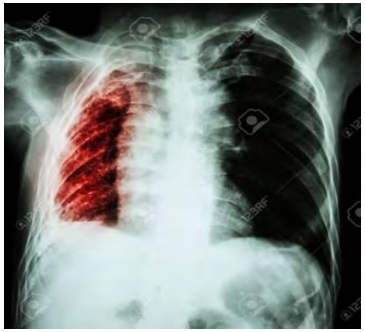
Interstitial infiltration



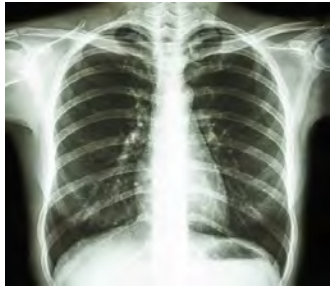
Cavity



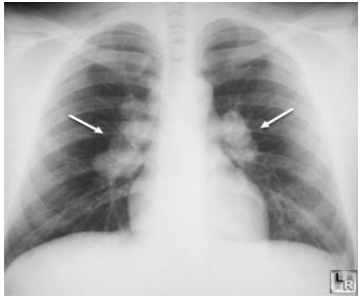
Patchy infiltrate



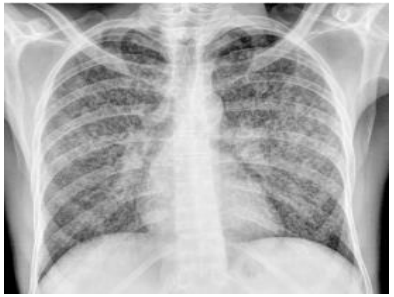
Pleural effusion



Nodules



Hilar lymphadenopathy



Miliary

Possible TB Disease Symptoms

Night Sweats

Fever

Chills

Weakness or fatigue

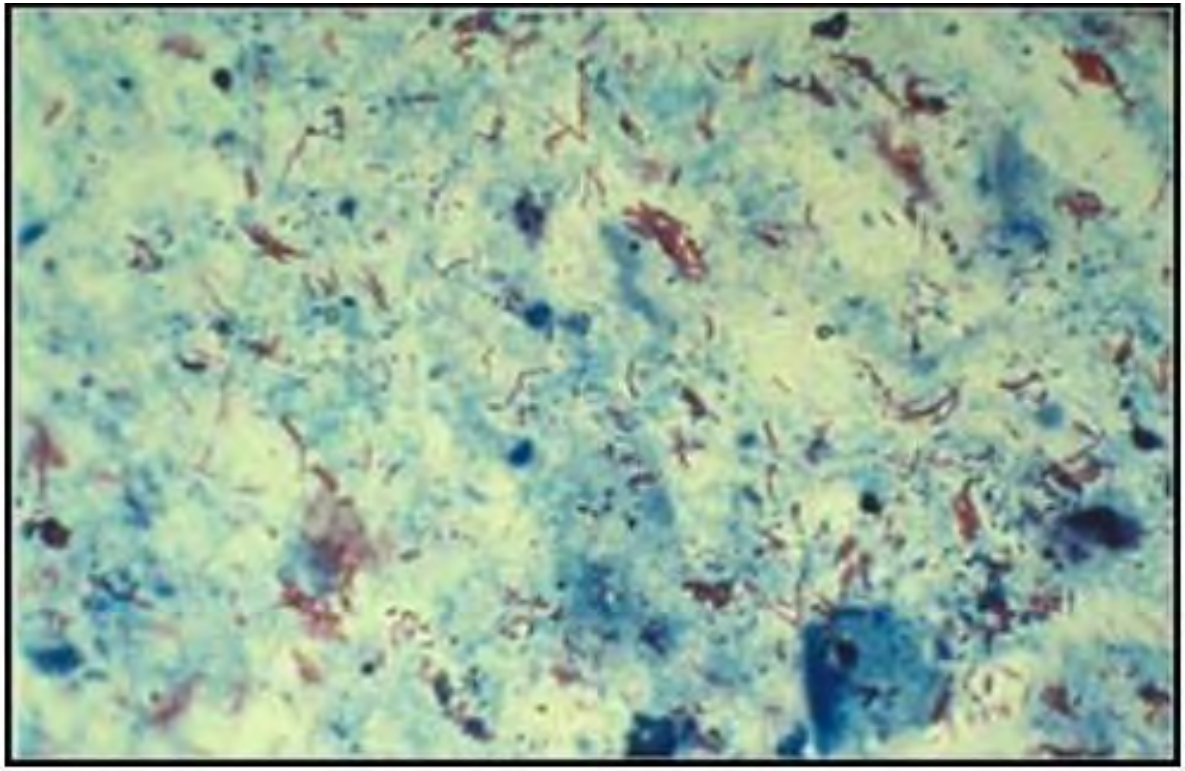
Weight loss

No appetite

Cough lasting longer than 3 weeks

Pain in the chest

Coughing up blood or sputum (phlegm from inside the lungs)

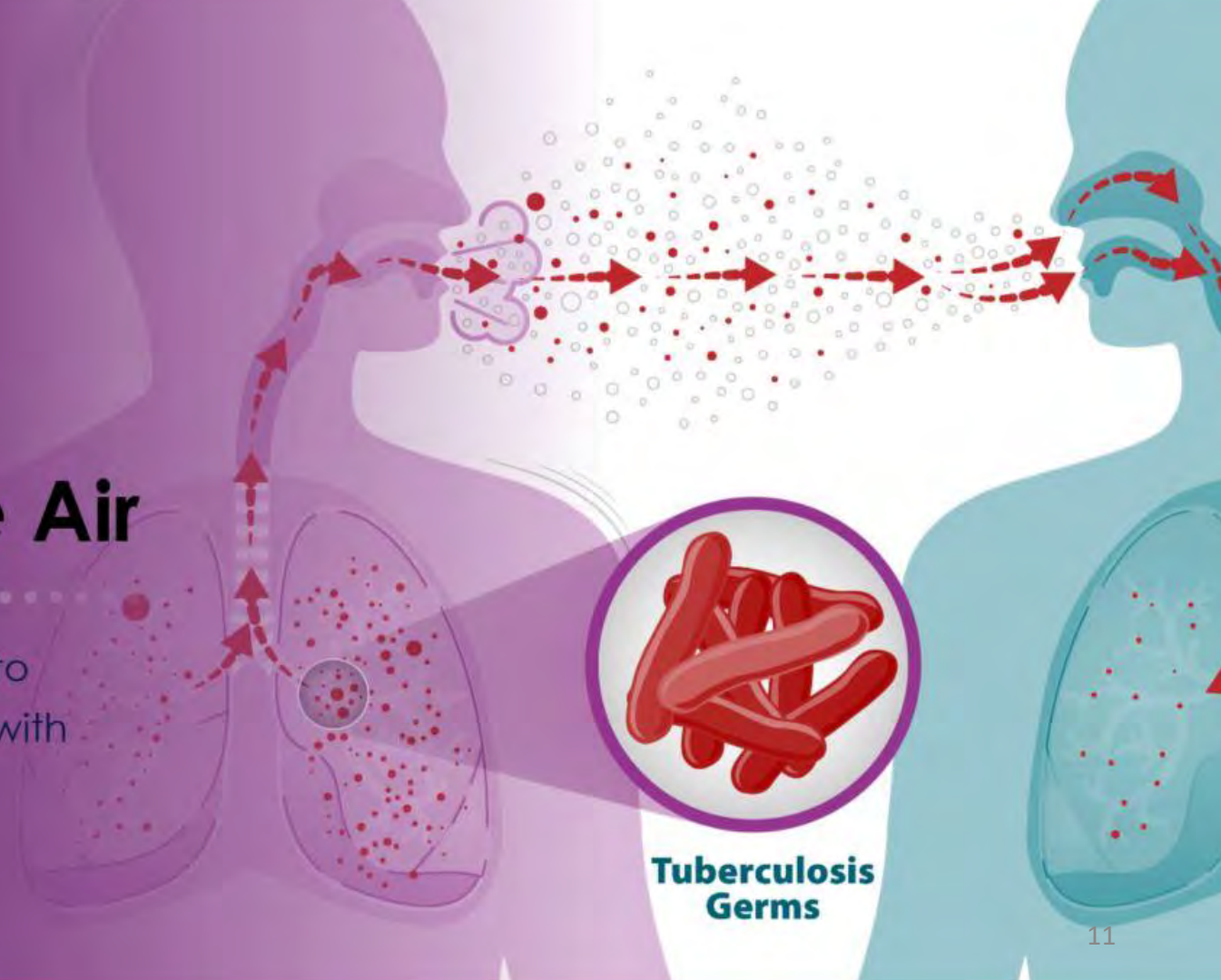


Acid-Fast bacilli stained in smear
Tubercle bacilli are shown in red

Tuberculosis can be diagnosed by collecting specimens for smear, culture, and PCR examination

TB Spreads Through the Air

TB spreads from person to person when someone with contagious TB coughs, speaks, or sings.



TB is NOT Spread by

Sharing toothbrushes

Saliva from kissing

Shaking someone's hand

Touching bed linens or toilets

Sharing food, drink, or utensils

How infectious is TB?

Nature of Exposure	Risk of Infection (from TB)	
None Known (baseline)	1 in 100,000 *	
Contact with Infectious Person +		
Casual social contact	1 in 100,000	
School, workplace	Up to 50 to 1 in 3	
Bar, social club		Up to 1 in 10
Dormitory	1 in 5	
Home		1 in 3
Nursing home		1 in 20

* Values are estimates, based on available medical literature, of the likelihood that under the conditions indicated, exposure to a person with…tuberculosis will cause another infection. Clearly, the duration of the exposure is a major factor in interpreting these data.

+ Susceptibility to tuberculosis reflects the intensity of the exposure, which in turn, is determined by the number of organisms aerosolized by the index patient and by the closeness of the conditions of exposure (e.g., size of space and adequacy of ventilation).

TABLE.RISK OF INFECTION: ACCORDING TO THE CONDITIONS OF EXPOSURE ; MUSHER, HOW CONTAGIOUS ARE COMMON RESPIRATORY TRACT INFECTIONS? (2003)NEJM VOL.348,P.1257,2003

Factors associated with transmission

Factors Associated with More Infectiousness	Factors Associated with Less Infectiousness
Presence of a cough	No cough
Cavity in the lung	No cavity in the lung
Acid-fast bacilli on sputum smear	No acid-fast bacilli on sputum smear
TB of the lungs, airway, or larynx	Most extrapulmonary (non-respiratory) TB
Patient no covering the mouth or nose when coughing	Patient covering mouth or nose when coughing
Not receiving adequate treatment or having prolonged illness	Receiving adequate treatment for 2 weeks or longer
Undergoing cough-inducing procedures	Not undergoing cough-inducing procedures
Positive sputum cultures	Negative sputum cultures

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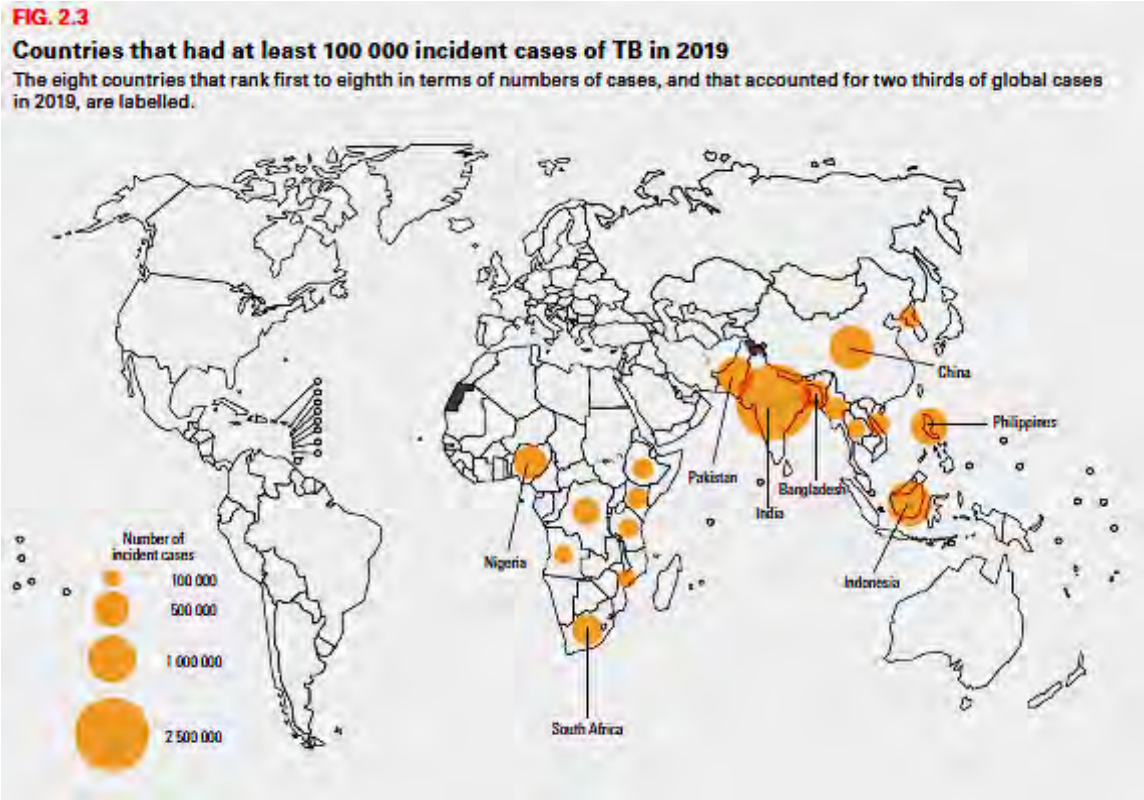
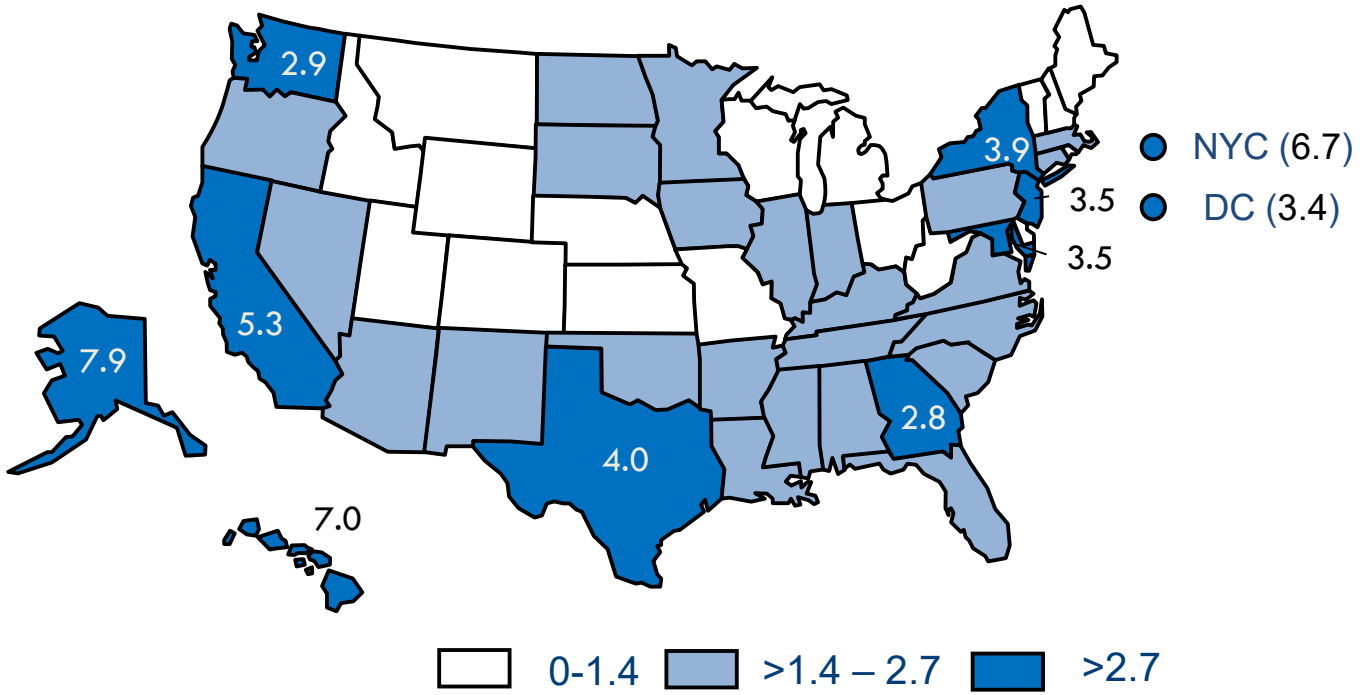
Global Burden of TB 2019



Source: WHO Global Tuberculosis Report 2020

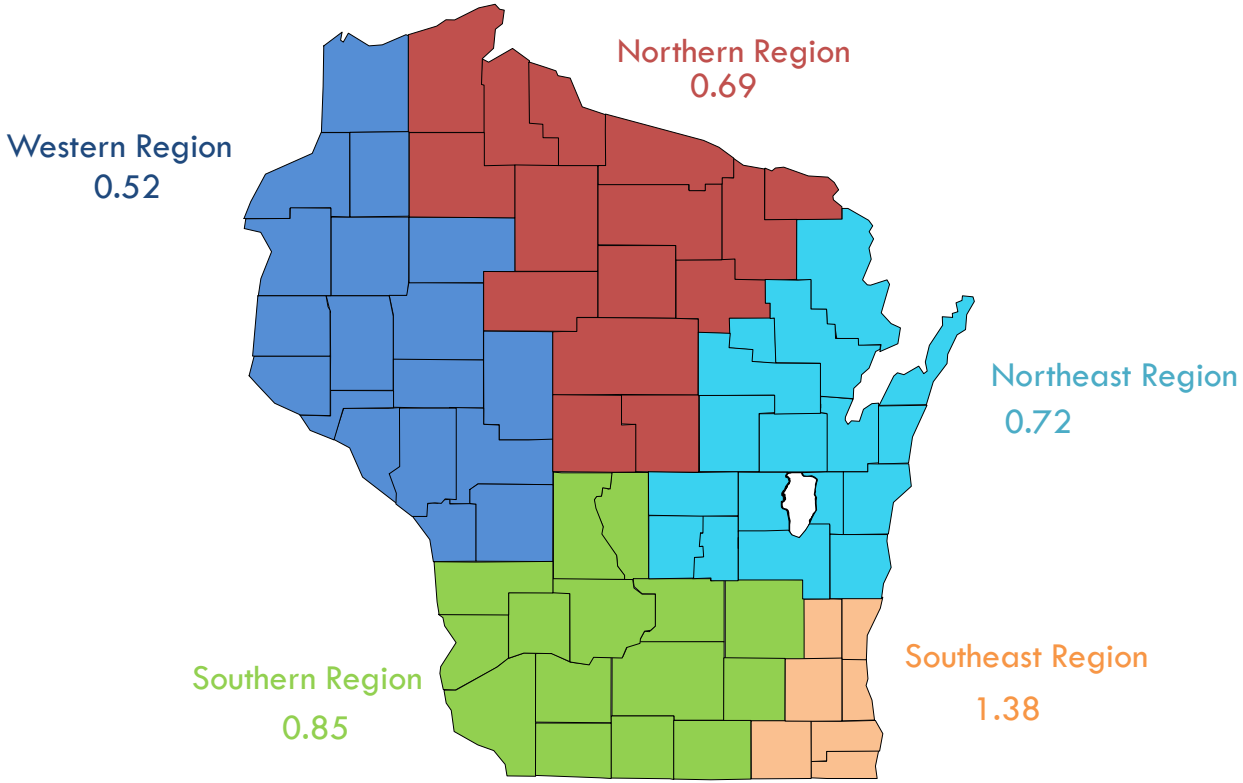
US TB Case Rates 2019



DC, District of Columbia; NYC, New York City (excluded from New York state)

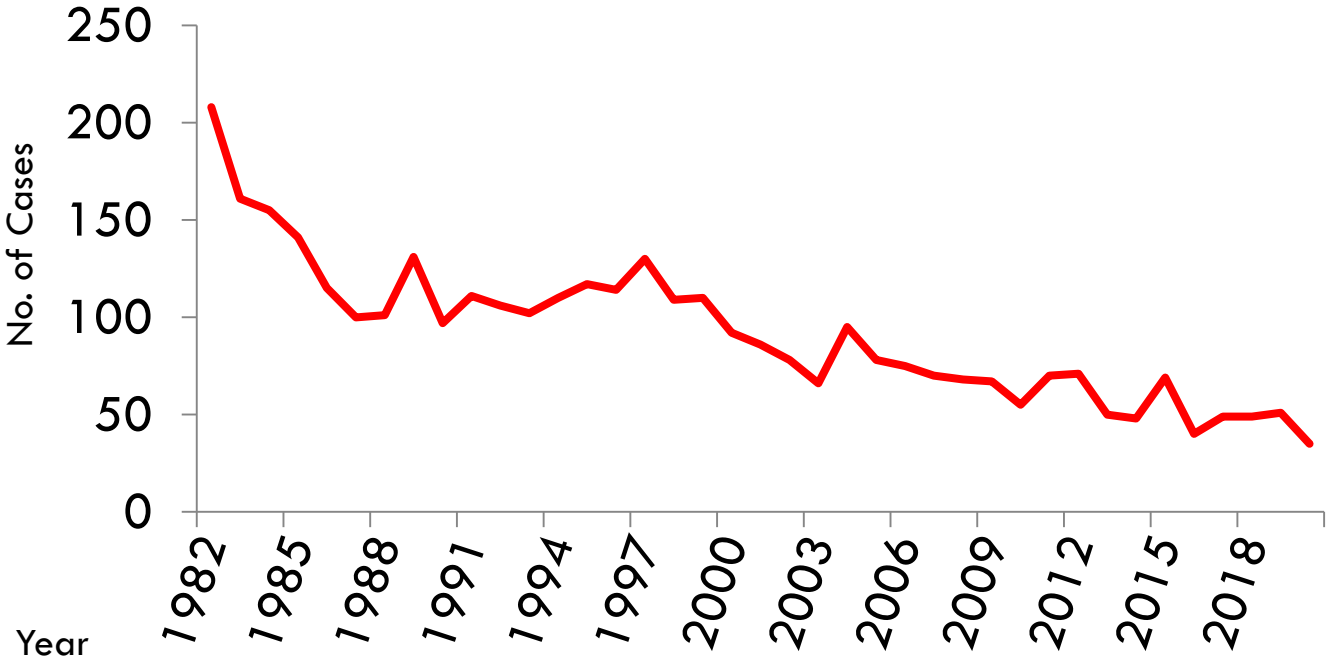
Average TB Incidence rates by Region

Wisconsin 2010-2019

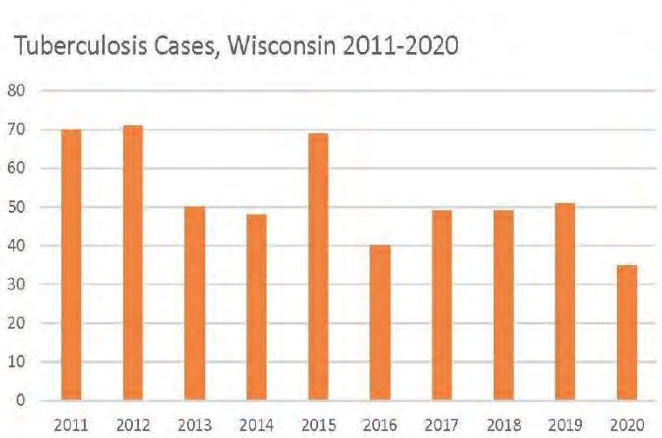


Reported TB Cases WI

1982–2020



Tuberculosis Disease in WI



35
cases of tuberculosis were reported in Wisconsin in 2020

Case average

Wisconsin has had an average of 53 TB cases per year during the past 10 years.

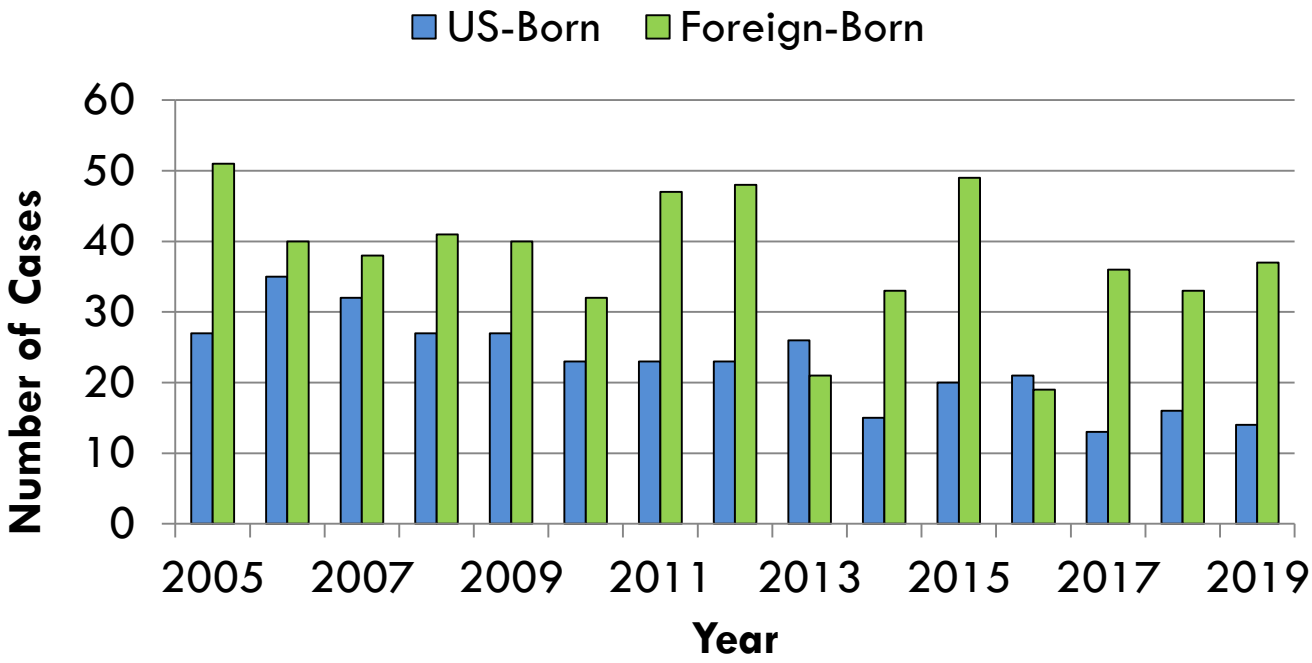
Multi-drug resistance

Wisconsin's rate of multi-drug resistant TB is one of the highest in the U.S. Wisconsin treated 19 patients with MDR-TB in the past 10 years.

Deaths

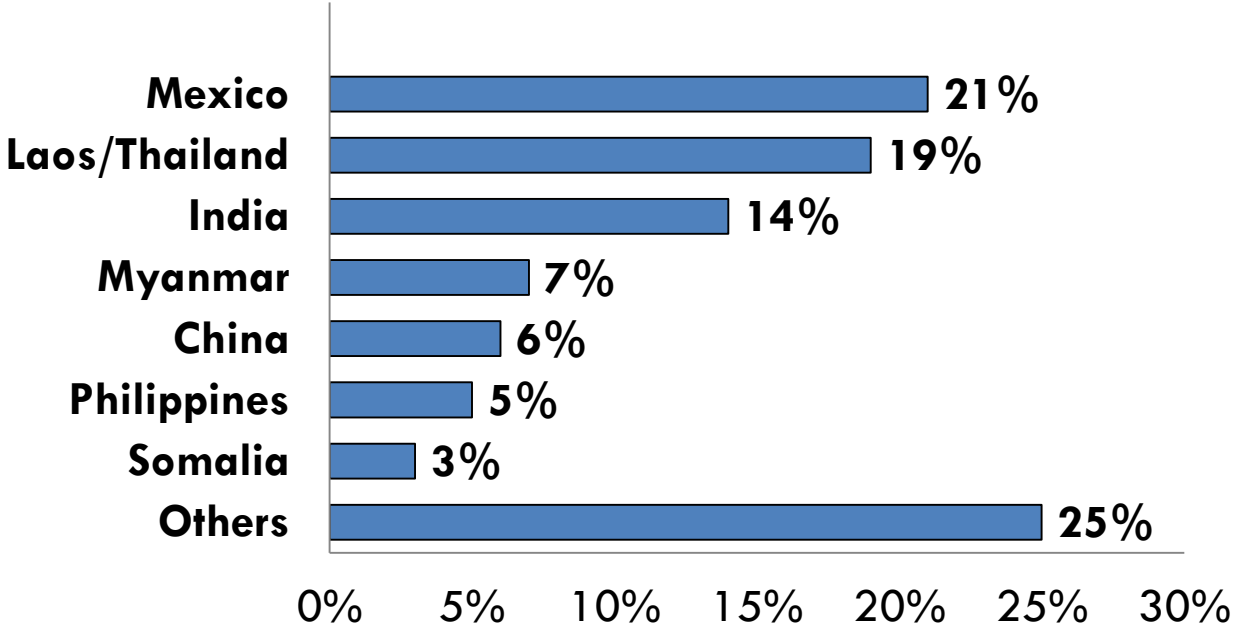
In 2020, five people died from TB or complications of the disease.

No. of TB Cases
U.S.-born vs. Foreign-born Persons
WI 2005–2019



Countries of Birth Among Non-U.S. Born Persons with TB

WI 2010–2019



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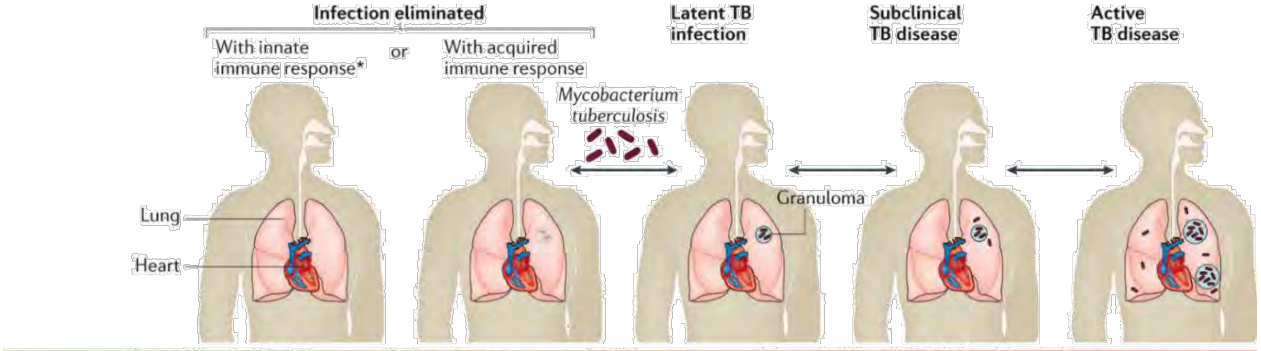
Spectrum of Latent TB (LTBI)



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

Nature Reviews | Disease Primers

Figure 1 The spectrum of TB — from *Mycobacterium tuberculosis* infection to active (pulmonary) TB disease
" Tuberculosis" in Nature Reviews vol. 2 (2016) by Pai, M. et. al.

LTBI versus TB Disease

Person with LTBI (Infected)	Person with TB Disease (Infectious)
Has a **small** amount of TB bacteria in his/her body that are alive, but *inactive*	Has a **large** amount of *active* TB bacteria in his/her body
Cannot spread TB bacteria to others	**May** spread TB bacteria to others
Does not feel sick, but may become sick if the bacteria become active in his/her body	**May** feel sick and may have symptoms such as a cough, fever, and/or weight loss

LTBI versus TB Disease

Person with LTBI (Infected)	Person with TB Disease (Infectious)
Usually has a TB skin test or TB blood test reaction **indicating TB infection**	Usually has a TB skin test or TB blood test reaction **indicating TB infection**
Radiograph is typically **normal**	Radiograph may be **abnormal**
Sputum smears and cultures are **negative**	Sputum smears and cultures may be **positive**

LTBI versus TB Disease

Person with LTBI (Infected)	Person with TB Disease (Infectious)
Category II communicable disease	**Category I** communicable disease
Report within **72 hours** to patient's local health department	Report within **24 hours** to patient's local health department

LTBI versus TB Disease

Person with LTBI (Infected)	Person with TB Disease (Infectious)
Encourage treatment for LTBI to prevent TB disease	**Needs** treatment for TB disease
Does **not** require respiratory isolation	May require respiratory isolation

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TB Screening and Diagnosis

Risk Assessment: form (F-02314)

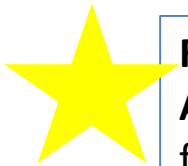
Symptom evaluation

Test for TB Infection: tuberculin skin test (TST) or interferon gamma release assay (IGRA) blood test

Chest Imaging: Chest x-ray (CXR) or computed tomography (CT)

Microbiology: AFB smear, culture, nucleic acid amplification testing (NAAT)

TB Screening and Diagnosis



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Wisconsin TB Risk Assessment

Recently updated to align with national recommendations

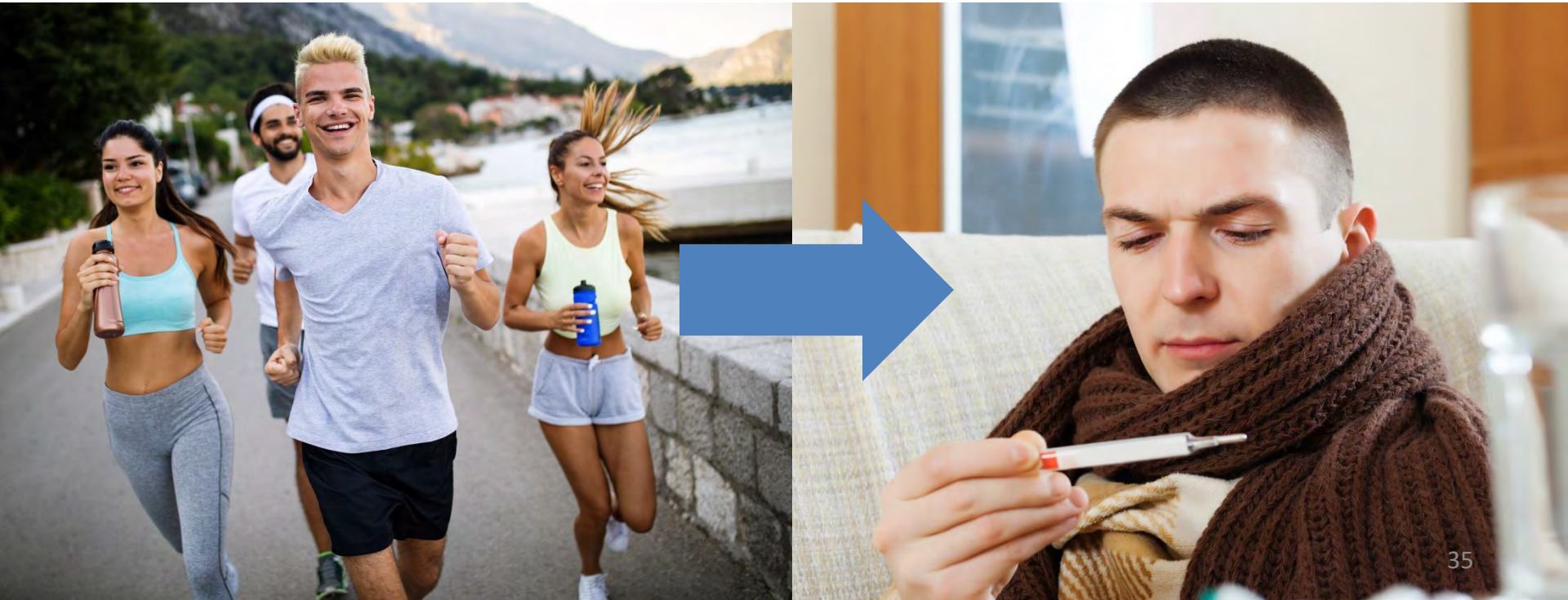
Includes risk for TB infection and risk for progression if infected

TB testing recommended for patients with any of the following risks:

Birth, travel, or residence in TB endemic countries

Close contact with someone who has TB

Immunocompromising conditions:



Immunocompromising conditions:

Cancer

HIV

Tumor necrosis factor (TNF) alpha antagonists, high-dose steroids, organ transplantation

NOT A RISK (IN WISCONSIN):

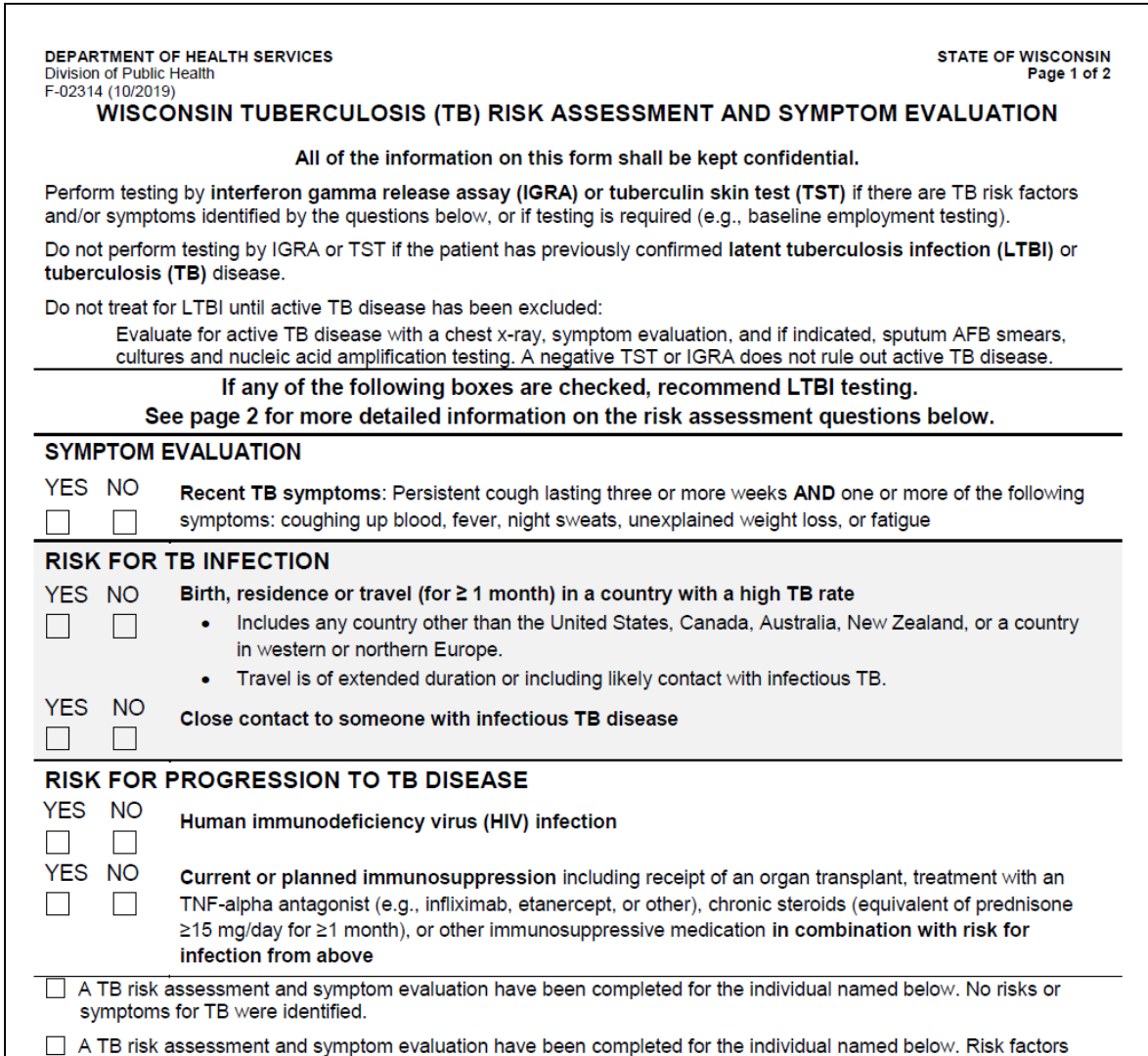
Nursing homes, health care facilities

Jails, Prisons

Homeless shelters

Wisconsin TB Risk Assessment Questionnaire

https://www.dhs.wisconsin.gov/tb/index.htm



DEPARTMENT OF HEALTH SERVICES
Division of Public Health
F-02314 (10/2019)

STATE OF WISCONSIN
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WISCONSIN TUBERCULOSIS (TB) RISK ASSESSMENT AND SYMPTOM EVALUATION

All of the information on this form shall be kept confidential.

Perform testing by **interferon gamma release assay (IGRA) or tuberculin skin test (TST)** if there are TB risk factors and/or symptoms identified by the questions below, or if testing is required (e.g., baseline employment testing).

Do not perform testing by IGRA or TST if the patient has previously confirmed **latent tuberculosis infection (LTBI)** or **tuberculosis (TB)** disease.

Do not treat for LTBI until active TB disease has been excluded:

Evaluate for active TB disease with a chest x-ray, symptom evaluation, and if indicated, sputum AFB smears, cultures and nucleic acid amplification testing. A negative TST or IGRA does not rule out active TB disease.

If any of the following boxes are checked, recommend LTBI testing.
See page 2 for more detailed information on the risk assessment questions below.

SYMPTOM EVALUATION

YES ☐ NO ☐ **Recent TB symptoms**: Persistent cough lasting three or more weeks **AND** one or more of the following symptoms: coughing up blood, fever, night sweats, unexplained weight loss, or fatigue

RISK FOR TB INFECTION

YES ☐ NO ☐ **Birth, residence or travel (for ≥ 1 month) in a country with a high TB rate**

- Includes any country other than the United States, Canada, Australia, New Zealand, or a country in western or northern Europe.
- Travel is of extended duration or including likely contact with infectious TB.

YES ☐ NO ☐ **Close contact to someone with infectious TB disease**

RISK FOR PROGRESSION TO TB DISEASE

YES ☐ NO ☐ **Human immunodeficiency virus (HIV) infection**

YES ☐ NO ☐ **Current or planned immunosuppression** including receipt of an organ transplant, treatment with an TNF-alpha antagonist (e.g., infliximab, etanercept, or other), chronic steroids (equivalent of prednisone ≥15 mg/day for ≥1 month), or other immunosuppressive medication **in combination with risk for infection from above**

☐ A TB risk assessment and symptom evaluation have been completed for the individual named below. No risks or symptoms for TB were identified.

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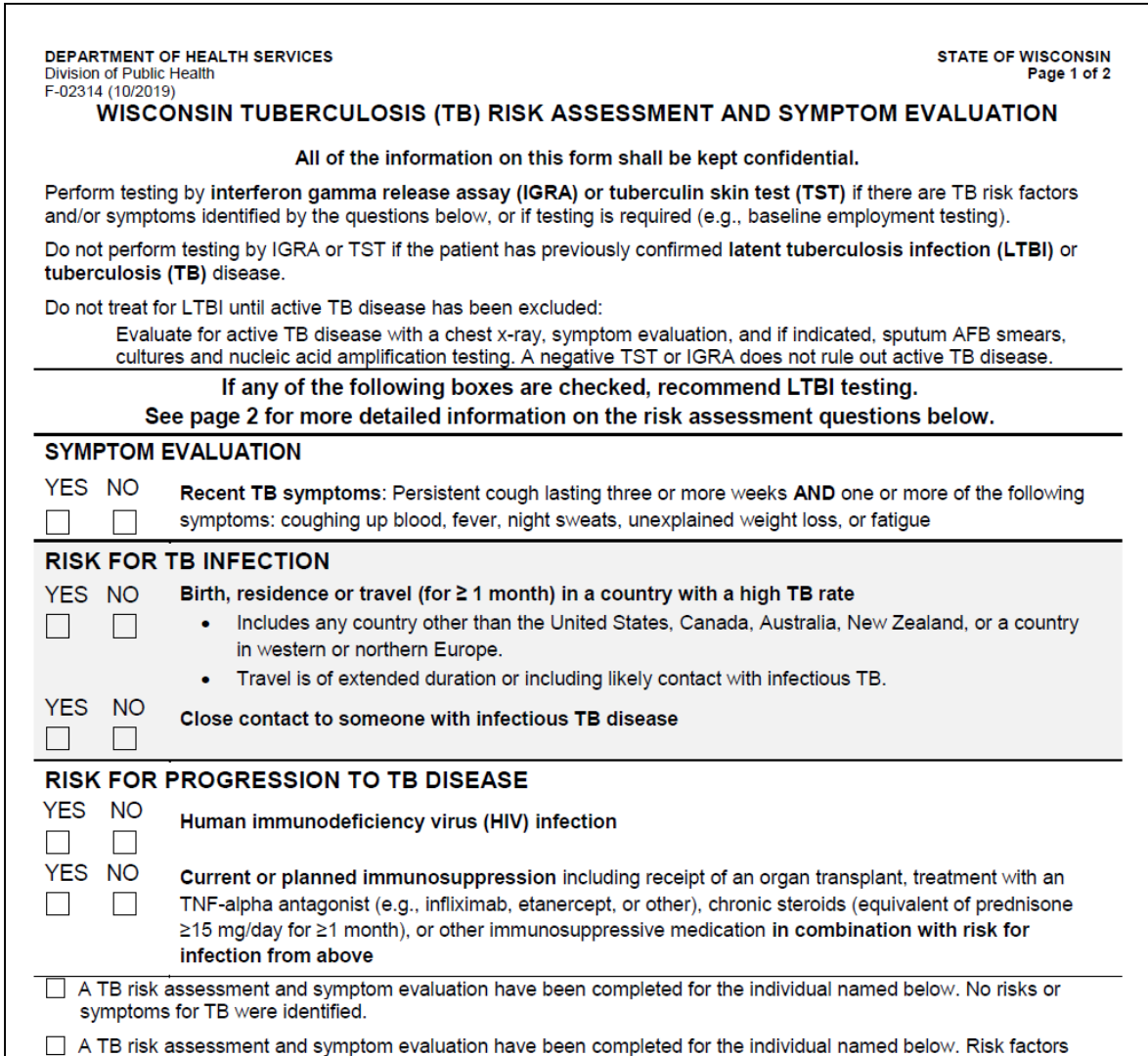

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INTERFERON GAMMA RELEASE ASSAYS (IGRAs)

Interferon Gamma Release Assays (IGRAs)

Detect the presence of *M. tuberculosis* infection by measuring the immune response to TB proteins (antigens) in whole blood.

Cannot differentiate between LTBI and active TB disease. Additional tests are needed to diagnose or rule out TB disease.

Can be used in all situations in which CDC recommends tuberculin skin test (TST) as an aid in diagnosing *M. tuberculosis* infection.

Interferon Gamma Release Assays (IGRAs)

Two IGRAs are commercially available and approved by the U.S. Food and Drug Administration (FDA) as aids in diagnosing *M. tuberculosis* infection:

QuantiFERON®-TB Gold In-Tube test (Qiagen)

T-SPOT®.*TB* test (Oxford Immunotec)

How IGRAs Work

A whole blood sample is collected from the patient. During the assay:

Blood cells are exposed to TB-specific antigens (ESAT-6, CFP-10, TB7.7).

Interferon gamma is released from patient's activated white blood cells (T-cells) and measured.

The amount of interferon gamma detected indicates whether the patient has been exposed to *M. tuberculosis* complex.

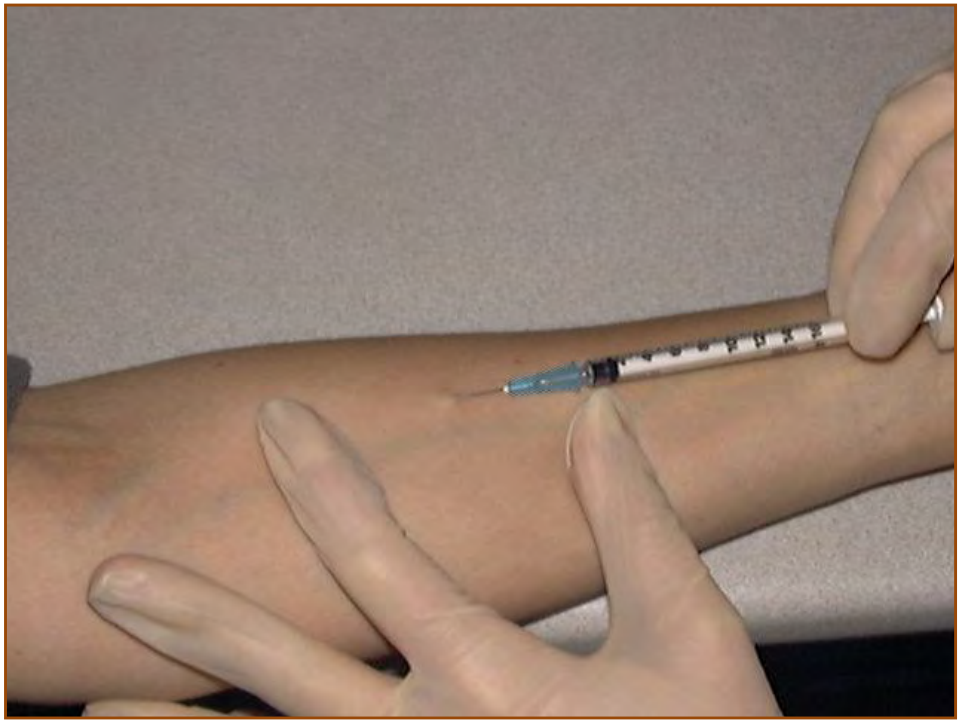
IGRA Results

Result	Description	Acceptable Value (IU/mL)	Significance
Mitogen	Positive Control	≥ 0.5 ≥ 20 spots	Addresses the immune competence of the patient's immune cells. A low mitogen result indicates inability to respond to an antigen.
Nil	Negative Control	≤ 8.0 ≤ 10 spots	Indicates the presence of any residual gamma interferon found in the patient's blood due to an ongoing immune response (infection) that can cause a false-positive result.
Patient Result	TB Antigen Minus Nil	See next slide	Quantitation of interferon gamma: Indicates patient's response to TB antigens.

IGRA Results

IGRA Test Result	QuantiFERON	T-SPOT	Notes
Positive	≥ 0.35	≥ 8 spots	Infection is likely
Negative	< 0.35	≤ 4 spots	Infection unlikely
Indeterminate or invalid	High nil value or low mitogen value	High nil value or low mitogen value	Not clinically interpretable. Occurs if controls do not perform as expected. Collect another specimen for retesting.
Borderline (equivocal)	Not applicable	5, 6 or 7 spots	Uncertain likelihood of TB infection. Collect another specimen for retesting.

Tuberculin Skin Test (TST)



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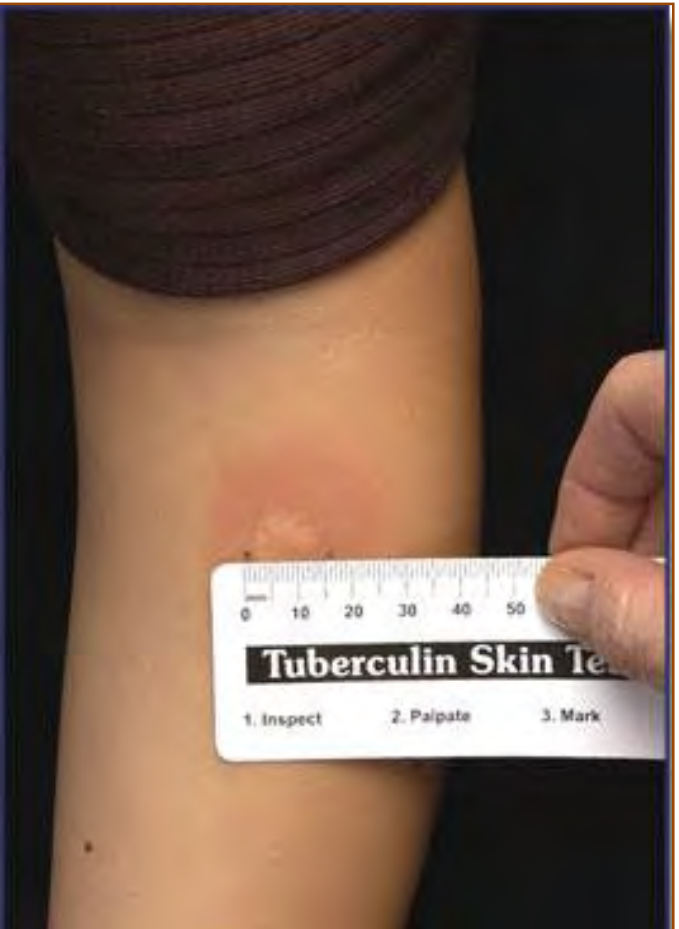
Tuberculin Skin Testing (TST)



- Five Tuberculin Units (TU) of Purified Protein Derivative (PPD)
- Read at 48-72 hours
- False positives include:
  - Non-Tuberculosis Mycobacteria (NTM)
  - Recent Bacillus Calmette-Guérin (BCG) vaccination
- Interpretation depends on person's risk factors

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TST Interpretation

≥ 5 mm induration is considered positive for:

Persons infected with HIV*

Recent contact of a person with infectious TB disease

Persons with fibrotic changes on chest radiograph consistent with prior TB; and

Patient with organ transplants and other immunosuppressed patients (including patients receiving the equivalent of ≥15mg/day of prednisone for ≥ 1 month or those taking TNF-a° antagonists.

* Human immunodeficiency virus.

°Tumor Necrosis Factor –alpha inhibitor

TST Interpretation

≥ 10 mm induration is considered positive for:

Recent arrivals from high-prevalence countries

Injection drug users

Residents and employees of high-risk congregate settings

Mycobacteriology laboratory personnel

Children < 4-years-old or child and youth exposed to adults at high-risk

Persons with conditions that increase risk for progressing to TB disease including: silicosis, diabetes mellitus, chronic renal failure, certain types of cancer, gastrectomy or jejunoileal bypass, and weight loss of at least 10% below ideal body weight

TST Interpretation

≥ 15 mm induration is considered positive for:

Persons with no known risk factor for TB disease

Health care personnel who are otherwise at low risk for TB disease

Although TST testing programs should be conducted only among high-risk groups, certain individuals may required testing for employment or school attendance. An approach independent of risk assessment is not recommended by the Centers of Disease Control and Prevention (CDC).

TB Screening and Diagnosis

Risk Assessment: form (F-02314)	**Symptom evaluation**	**Test for TB Infection**: tuberculin skin test (TST) or interferon gamma release assay (IGRA) blood test	**Chest Imaging**: Chest x-ray (CXR) or computed tomography (CT)	**Microbiology:** AFB smear, culture, nucleic acid amplification testing (NAAT)

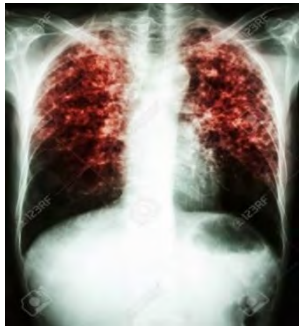
Chest Imaging

Chest radiographs (x-ray or CT) are performed when there is a positive TST, IGRA or symptom screening evaluation.

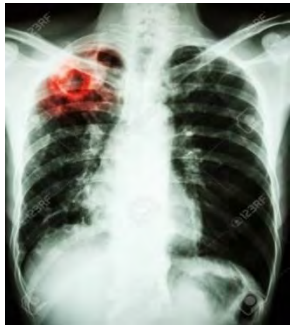
Findings suggestive of TB disease vary.

These findings often warrant sputum collection.

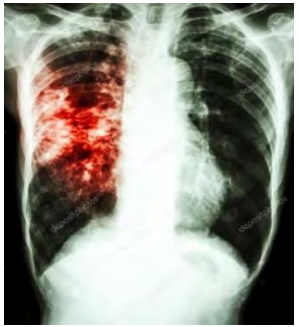
TB on radiograph varies:



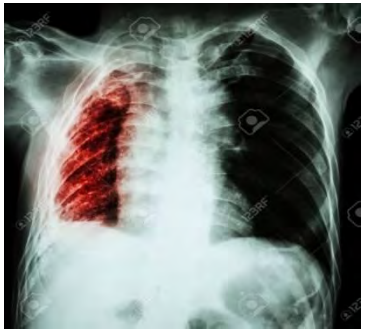
Interstitial infiltration



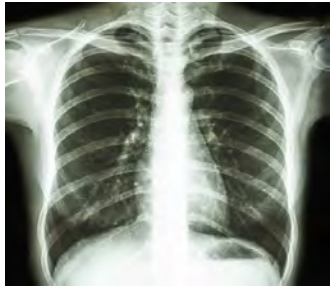
Cavity



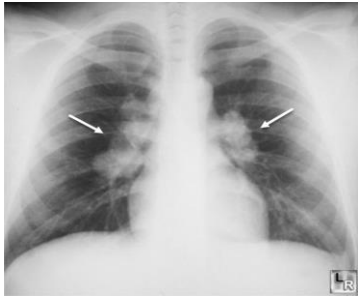
Patchy infiltrate



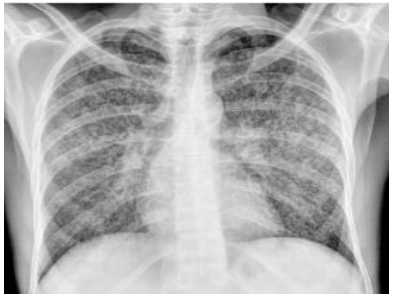
Pleural effusion



Nodules



Hilar lymphadenopathy



Miliary

TB Screening and Diagnosis

Risk Assessment: form (F-02314)	**Symptom evaluation**	**Test for TB Infection**: tuberculin skin test (TST) or interferon gamma release assay (IGRA) blood test	**Chest Imaging**: Chest x-ray (CXR) or computed tomography (CT)	**Microbiology:** AFB smear, culture, nucleic acid amplification testing (NAAT)

Indications for Sputum Collection

Initial diagnosis of TB: Collect a series of three sputum specimens, 8-24 hours apart, at least one of which is an early morning specimen.

Optimally, diagnostic sputum should be collected *before* the initiation of drug therapy.

Monitoring of therapy: Obtain sputum specimens for culture at least monthly until cultures convert to negative.

Centers for Disease Control and Prevention. Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Settings, MMWR 2005:54, RR-17

Methods of Diagnosis: Microbiology

Method	Sensitivity for TB	What positive result looks like	Interpretation
Smear (view bacteria by microscope)	Poor	AFB smear positive # organisms per field Few/moderate/many	Does not confirm tuberculosis
Culture (growth of bacteria)	Very good	Isolated: *M. tuberculosis* complex	Confirms tuberculosis disease
PCR (detection of DNA)	Good	"*M. tuberculosis* complex DNA detected"	Confirms tuberculosis disease

TB TREATMENT

ACTIVE: Through PH, prevents transmission

LTBI: Through public health or private clinicians, 90% risk reduction

Treatment of TB Disease

Intensive Phase	• First 8 weeks of treatment • Most bacilli killed during this phase • 4 drugs used
Continuation Phase	• After first 8 weeks of TB disease treatment (4, 7 or more months) • Bacilli remaining after intensive phase are treated with at least 2 drugs
Relapse	• Occurs when treatment is not continued for long enough • Surviving bacilli may cause TB disease at a later time

Treatment of TB Disease

Intensive phase should contain the following four drugs:

Isoniazid (INH)

Rifampin (RIF)

Pyrazinamide (PZA)

Ethambutol (EMB)

Example of pills used to treat TB disease. From left to right: isoniazid, rifampin, pyrazinamide, and ethambutol

DIRECTLY OBSERVERD THERAPY (DOT)

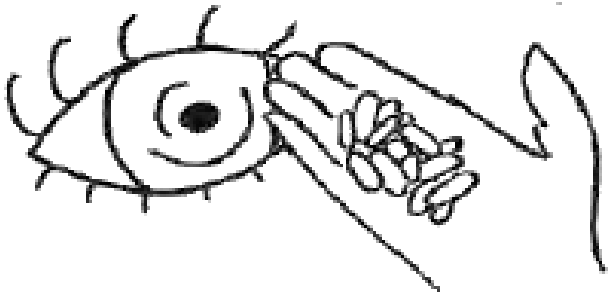
Prevents detention and quarantine by chemical quarantine thereby reducing the risk to the public–allows outpatient treatment

DOT is…

- Observing patient take & swallowing ALL medications to end of treatment
- When patient is actually OBSERVED swallowing each and every dose
- Provided ONLY by trained healthcare worker (under RN -outreach worker or others) -documented & reported side- effects
- Reported daily all doses taken & missed

The responsibility for successful TB treatment is on the provider not the patient

DIRECTLY OBSERVERD THERAPY (DOT)



DOT is NOT…

Given by family or friends

Parent or guardian giving to child or adolescent

Leaving medication at the home or bedside

By means of pill-counts

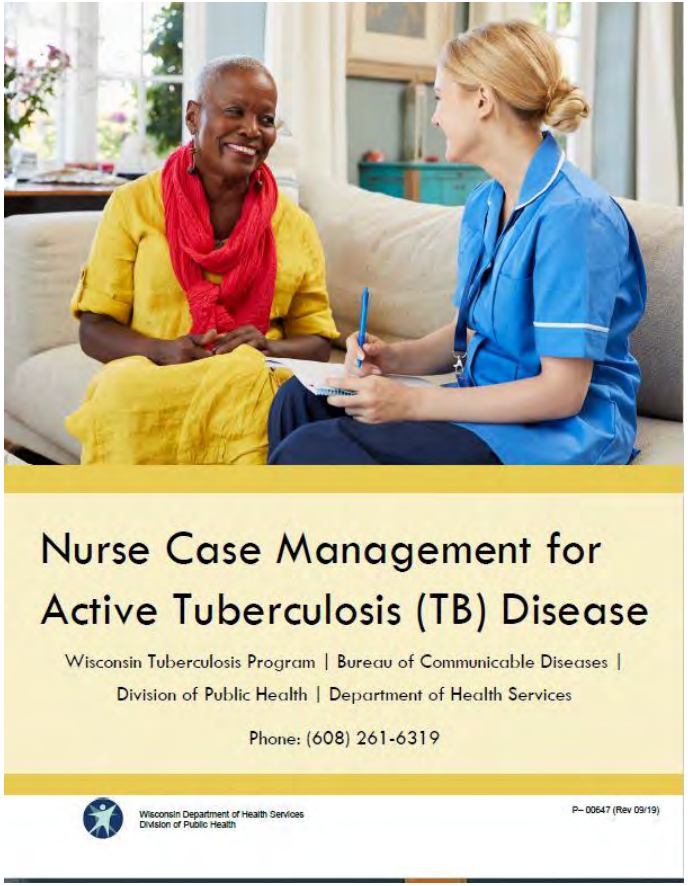
Allowing medical professionals to self-administer medications

ENCOURAGE TREATMENT

Address beliefs, concerns

Consider costs, flexibility of care

Nurse Care Management



WTBP document (P-00547) on webpage

WTBP webinar on Sept 28, 2021

Treatment of LTBI

Choose shortest, most tolerable regimen:

INH and rifapentine x12 weeks (“3HP”)*

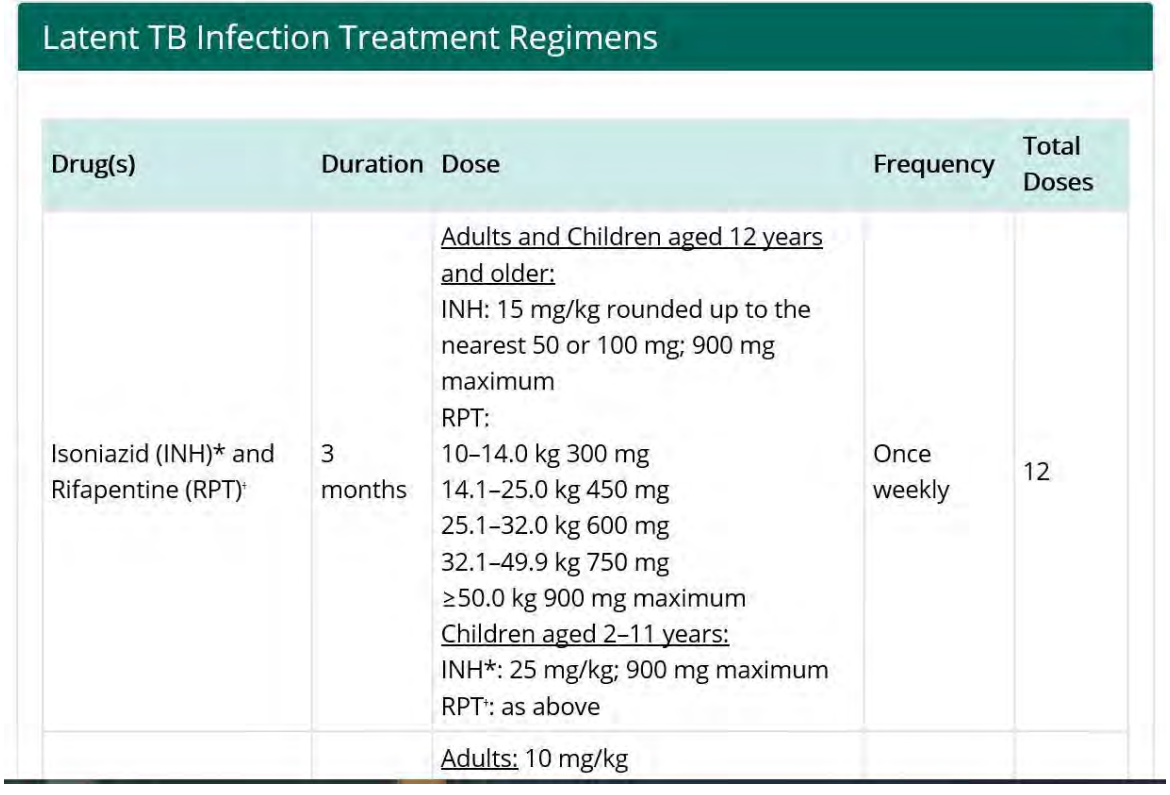
Rifampin x4 mo (“4R”)

INH and rifampin x 3mo

INH x6-9mo

*DOT recommended for regimens containing less than daily INH

Go to CDC webpage



Latent TB Infection Treatment Regimens

Drug(s)	Duration	Dose	Frequency	Total Doses
Isoniazid (INH)* and Rifapentine (RPT)[†]	3 months	Adults and Children aged 12 years and older: INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum RPT: 10–14.0 kg 300 mg 14.1–25.0 kg 450 mg 25.1–32.0 kg 600 mg 32.1–49.9 kg 750 mg ≥50.0 kg 900 mg maximum Children aged 2–11 years: INH*: 25 mg/kg; 900 mg maximum RPT[†]: as above	Once weekly	12
		Adults: 10 mg/kg		

Latent Tuberculosis Infection (LTBI) Treatments

Once a person is diagnosed with latent TB infection (LTBI), treatment should be offered. We recommend that all treatment be done in collaboration with the patient's local health department. Assistance with costs of care and treatment may be available through the local health department.

Isoniazid + Rifapentine once weekly x 12 weeks (3HP)

- Preferred regimen for its high completion rate
- Directly observed therapy (DOT) is highly recommended, or required if Wisconsin TB Dispensary Program is used.
- For patients at least 2 years old. Not recommended for window prophylaxis.
- Dosing for adults over 50kg is isoniazid (INH) 900mg + rifapentine 900mg.

3HP Dosing

⇒ INH 25mg/kg fpr ages 2-11; 15 mg/kg, for ages 12 and up; Round up to nearest 50 or 100mg; 900mg max

⇒ Rifapentine

10.0-14.0 kg	300 mg
14.1-25.0 kg	450 mg
25.1-32.0 kg	600 mg
32.1-49.9 kg	750 mg
≥ 50.9 kg	900 mg max

See CDC website for more information

Rifampin daily x 4 months

- Preferred regimen for those unable to take 3HP or contacts to INH resistant cases
- Usually self-administered with patient picking up medications monthly
- Can be prescribed for infants and for window prophylaxis
- Dosing is 15-20 mg/kg infants & children; 10mg/kg up to 100 lbs/ 45.5 kg adults; 600mg max.

Isoniazid daily x 6-9 months

- Acceptable regimen but has very low completion rates; consider patient reliability
- Usually self-administered with patient picking up medications monthly
- Can be prescribed for infants and for window prophylaxis
- Dosing is 10-15 mg/kg infants & children; 5 mg/kg up to 100 lbs/ 45.5 kg adults; 300mg max.

Isoniazid, Rifampin, Pyrazinamide, & Ethambutol daily x 2 months

- For patients for whom a diagnosis of TB disease is still a possibility
- Start standard four-drug treatment by DOT; at the end of two months, reassess patient and laboratory results:
  - If culture is positive OR patient improves on treatment, consider active TB disease confirmed and treat accordingly.
  - If culture is negative OR the patient does not improve on treatment, end treatment and consider other diagnoses as appropriate. Treatment for latent TB infection is complete.

WI TB Program LTBI Regimens Fact Sheet

RECOMMEND TREATMENT FOR ALL CONFIRMED LTBI?

Strongly encouraged for new LTBI or old untreated LTBI

For previously treated LTBI, rarely retreat

TB 101

History and pathophysiology

Epidemiology

Latent TB vs. active TB

Diagnosis and treatment

Brief overview of WI TB Program functions

Functions of the Wisconsin State TB Program

- Ensure that patients with suspected or confirmed TB disease have ready access to diagnostic and treatment services that meet national standards
- Provide consultation, technical assistance, education and training in the clinical and public health aspects of TB
- Plan and develop state-wide TB control policies and procedures

Functions of the Wisconsin State TB Program (2)

- Oversee interjurisdictional TB contact investigations or medical facility exposures
- Assure statewide TB surveillance: collection of TB and LTBI data and tracking of results

  Federal (CDC) reporting requirements

- Monitor and evaluate TB program activities to enhance TB control strategies

Wisconsin TB Dispensary Program (WTBDP) Purpose Statement

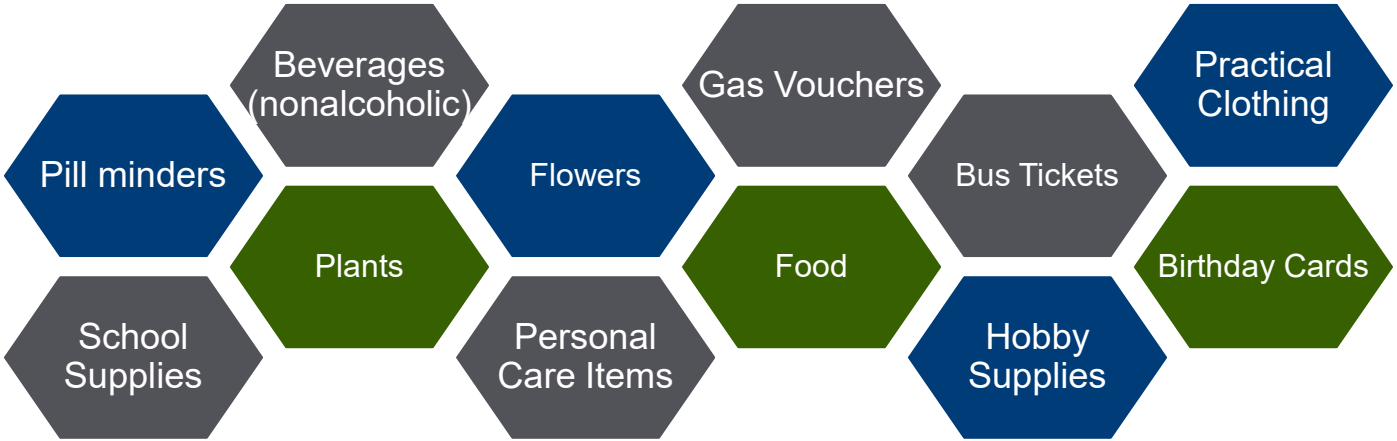
To ensure that all persons in Wisconsin with suspected or confirmed active TB disease or latent TB infection (LTBI) can receive appropriate evaluation, treatment, and monitoring, regardless of insurance availability.

The WTBDP reimburses services for the uninsured and underinsured.

Wisconsin TB Treatment Assistance Program

Designed to encourage and support TB clients through the completion of TB treatment by providing funding to purchase treatment assistance aids.

Aids up to $50 for LTBI patients and $200 for active patients can be provided.



TB Program Contact Information

Phone: 608-261-6319

Fax: 608-266-0049

Email: dhswitbprogram@dhs.wisconsin.gov

Website:

https://www.dhs.wisconsin.gov/tb/index.htm

Questions?