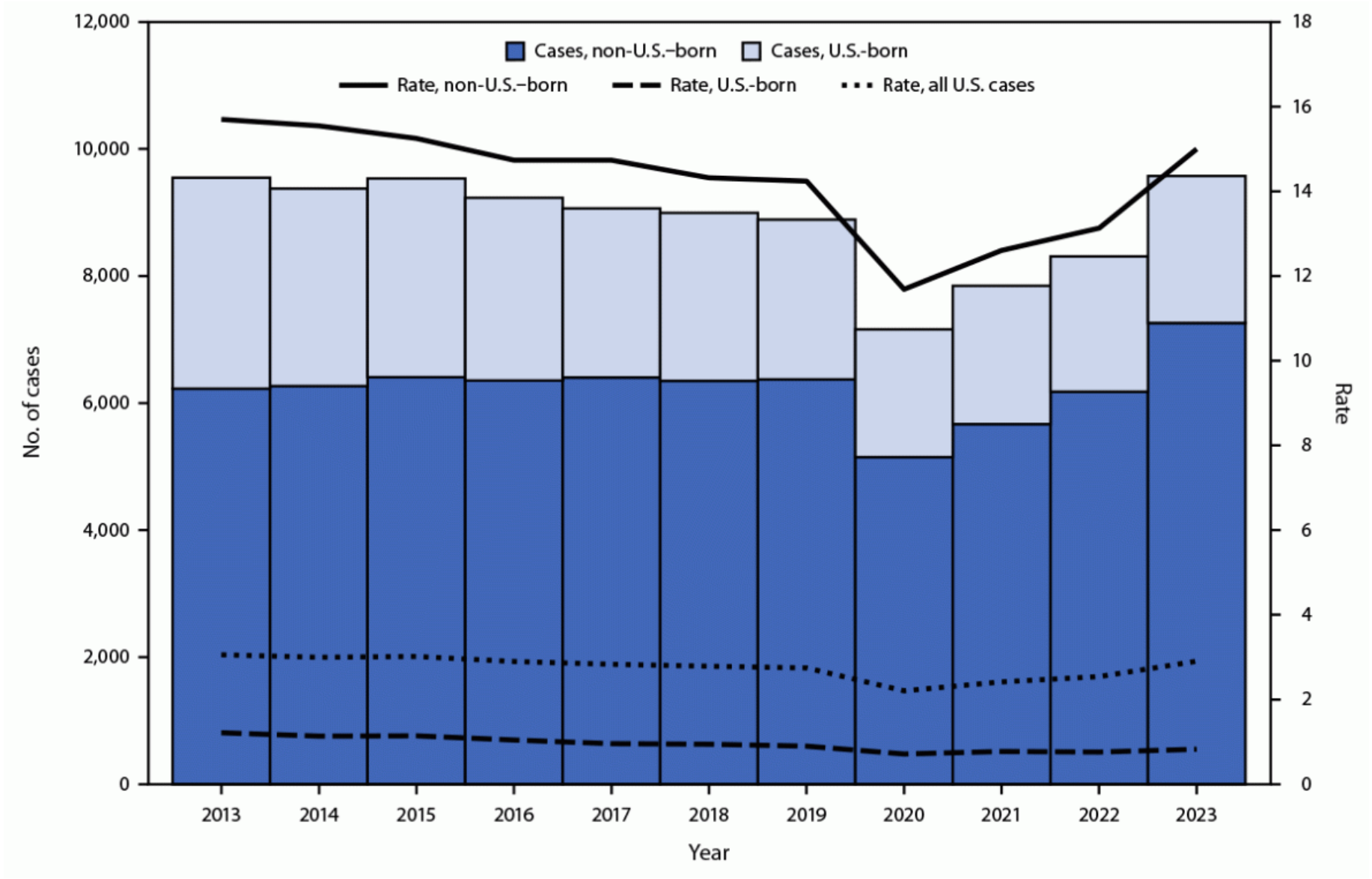


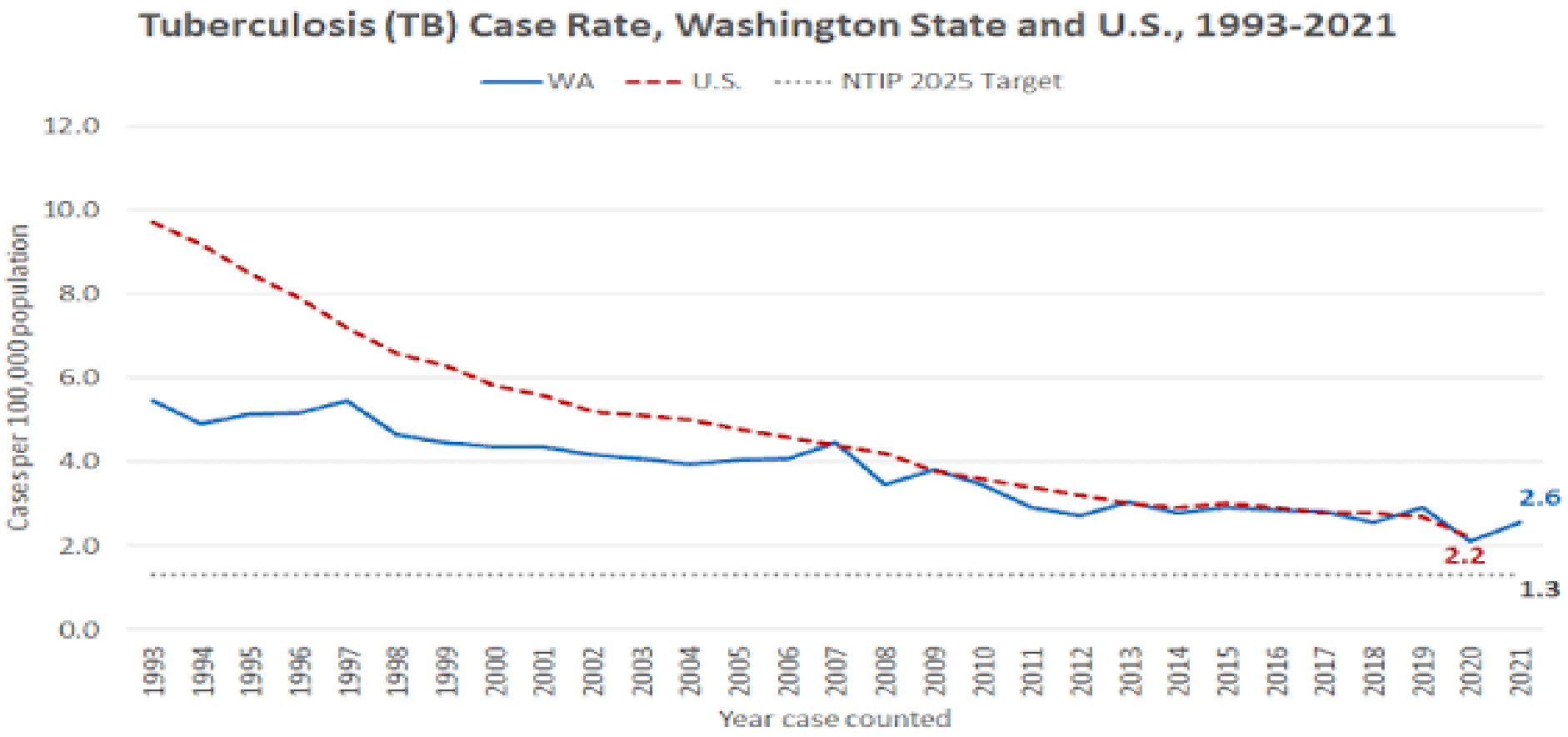
Management Of Latent Tuberculosis Infection

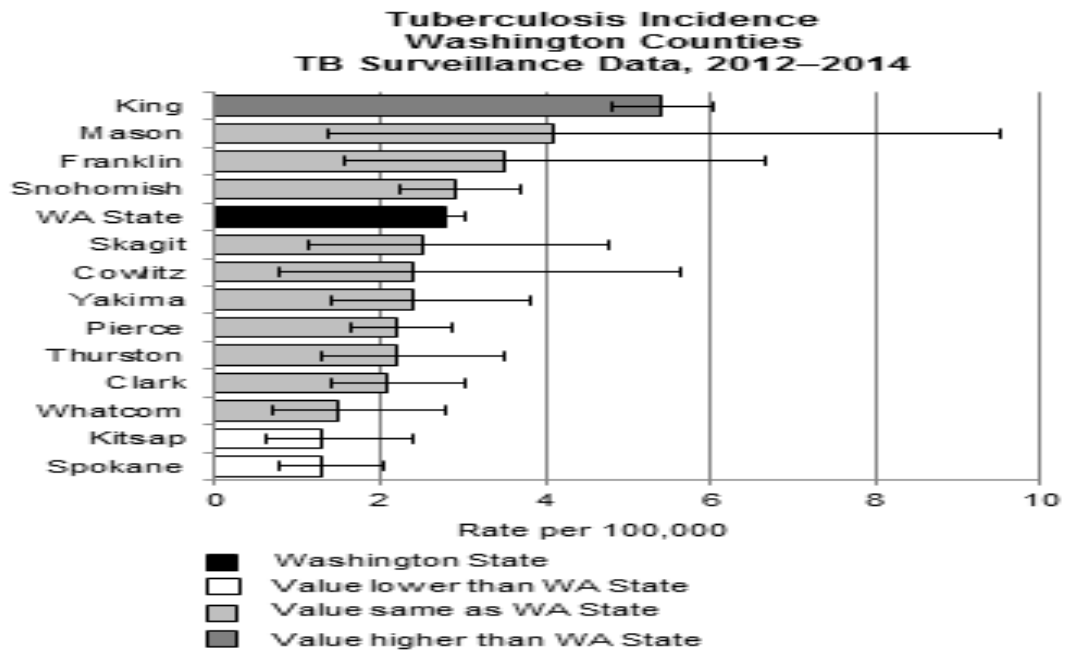
Pallavi Bhargava MD
Franciscan Infectious Disease Associates
SMMC Silverdale

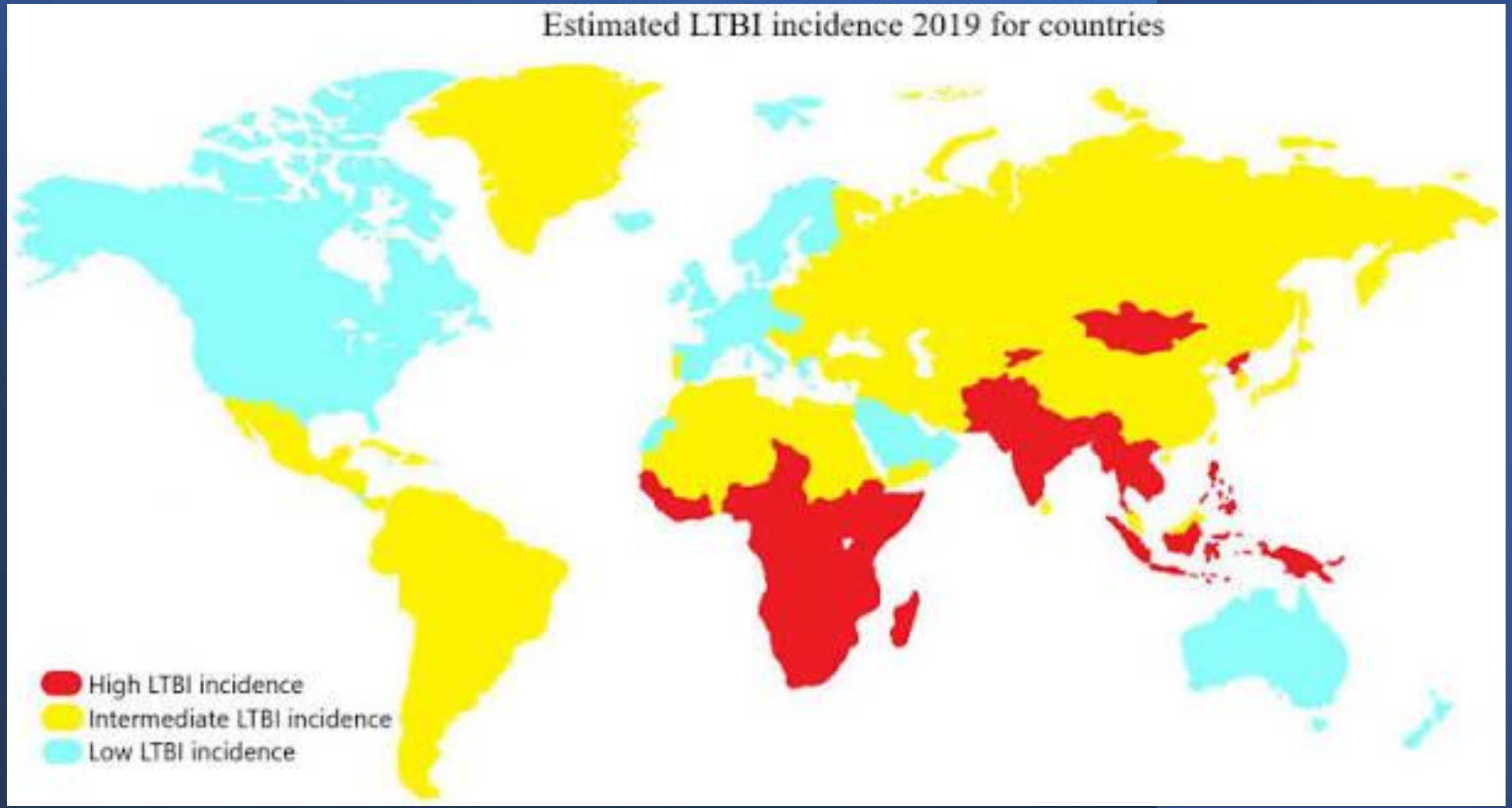
Latent Tuberculosis Infection (LTBI)

INTRODUCTION
AVAILABLE TESTS AND INTERPRETATION OF RESULTS
TARGETED TESTING AND TREATMENT
SOCIETY GUIDELINES
TREATMENT REGIMEN
MONITORING TREATMENT
WHATS IN THE HORIZON
CASES, Q&A


Cases, non-U.S.–born
Cases, U.S.-born
Rate, non-U.S.–born
Rate, U.S.-born
Rate, all U.S. cases
No. of cases
Rate
Year
12,000
10,000
8,000
6,000
4,000
2,000
0
18
16
14
12
10
8
6
4
2
0
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023


Tuberculosis (TB) Case Rate, Washington State and U.S., 1993-2021
WA
U.S.
NTIP 2025 Target
12.0
10.0
8.0
6.0
4.0
2.0
0.0
Cases per 100,000 population
2.6
2.2
1.3
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
Year case counted


Tuberculosis Incidence
Washington Counties
TB Surveillance Data, 2012–2014
King
Mason
Franklin
Snohomish
WA State
Skagit
Cowlitz
Yakima
Pierce
Thurston
Clark
Whatcom
Kitsap
Spokane
0
2
4
6
8
10
Rate per 100,000
Washington State
Value lower than WA State
Value same as WA State
Value higher than WA State


Estimated LTBI incidence 2019 for countries
High LTBI incidence
Intermediate LTBI incidence
Low LTBI incidence

LTBI prevalence

• USA *	4-5 %	13 million
• Globally	25-33 %	2-3 billion
• India	40 %	0.5 billion

Active TB Burden US 3/100,000

Exposure: 30% will develop LTBI

Highest risk in the first 2 years of exposure/conversion

Active TB Life- time risk : 5-10% of those with LTBI

IC Host: Annual 8-10 %

Surveys funded by CDC

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

Published: November 4, 2015 • https://doi.org/10.1371/journal.pone.0140881

LTBI

- Active Tuberculosis is largely a preventable disease.
- Identification and treatment of LTBI has been the key strategy to reduce progression to active TB.
- LTBI treatment efficacy 80-90 %
- Newer regimens have higher completion rates and are safe
- **Traditionally with Public Health but has become a mainstream Primary Care issue.**

World TB day marks the day Robert Koch announced his discovery of Tubercle bacteria causing MTB disease

March 24th 1882

Latent and Active TB (*Mtb*) Diagnosis and Management

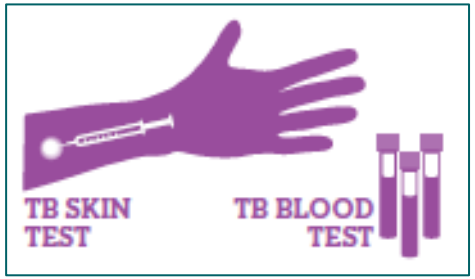
IDSA,ATS,CDC 2017

23 evidence-based recommendations

6 strong

1 7 conditional

Latent TB Infection (LTBI)



TST Tuberculin Skin Test

PPD, Montoux (cutoffs vary)

IGRA Interferon Gamma Release Assays EST 6 CFP 10

-Quantiferon Plus

-Ellispot (T-spot)

Positive PPD/TST

Likely Infected and High risk for progression or IC patients

> or = 5mm

Likely to be infected but Low to Intermediate risk of progression

> or =10mm

Unlikely to be Infected and No risk > or =15 mm

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**

IGRA

- Quantiferon 2001
- Quantiferon Gold 2005
- Quantiferon Gold In tube 2007
- Quantiferon TB Gold Plus 2018

Advantages of IGRA

No BCG Vaccine Interference

Less cross reactivity with NTM

Single Patient Visit

No Booster Phenomenon

Objective Laboratory Results

Quantiferon

Mitogen – Positive Control
Low response may indicate inability to generate IFN-γ

Nil – Negative Control
Adjusts for background IFN-γ

TB1 – Primarily detects CD4 T cell response

TB2 – Optimized for detection of CD4 and CD8 T cell responses



Interpretation of IGRA Test Results

IGRA Test	Results Reported as
QFT-GIT	Positive, negative, indeterminate
T-Spot	Positive, negative, indeterminate, borderline

Note: Laboratory should provide both quantitative and qualitative results

NIL	IU/mL	0.033
Mitogen NIL	IU/mL	9.550
TB Ag NIL	IU/mL	<0.001
TB Ag 2 NIL	IU/mL	<0.001
Resulting Agency		HFAH

NIL	IU/mL	0.039
Mitogen NIL	IU/mL	8.780
TB Ag NIL	IU/mL	3.610
TB Ag 2 NIL	IU/mL	1.790

NIL	IU/mL	0.081
Mitogen NIL	IU/mL	0.240
TB Ag NIL	IU/mL	<0.001
TB Ag 2 NIL	IU/mL	<0.001

NIL	IU/mL	>10.000
Mitogen NIL	IU/mL	0.920
TB Ag NIL	IU/mL	<0.001
TB Ag 2 NIL	IU/mL	0.440

NIL	IU/mL	0.039
Mitogen NIL	IU/mL	0.060
TB Ag NIL	IU/mL	<0.001
TB Ag 2 NIL	IU/mL	<0.001

Latent versus Active

IGRA and TST testing provide evidence for infection with MTB, cannot distinguish active from latent TB.

- The tests do not turn negative after treatment.
- Must assess presence or absence of symptoms, imaging

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

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)
- Recent immigrants from TB-endemic regions of the world (within 5 years of arrival to the United States)

Latent Tuberculosis Infection: Screening

Release Date: September 2016

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Asymptomatic adults at increased risk for infection	The USPSTF recommends screening for latent tuberculosis infection (LTBI) in populations at increased risk.	

Increased Risk for Progression to TB Disease - 1

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

- HIV-infected persons
- Those with a history of prior, untreated TB or fibrotic lesions on chest radiograph
- Children ≤ 5 years with a positive TST



Increased Risk for Progression to TB Disease - 2

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

Increased Risk for Progression to TB Disease - 3

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

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

LTBI Diagnosis: ATS guidelines

Recommendations for diagnostic testing for LTBI are based upon the likelihood of infection with *Mtb* and the likelihood of progression to TB disease if infected

IGRA preferred over TST
Strong recommendation

- Five years or older
- Those likely to be infected with TB
- Have a low or intermediate risk of disease progression
- It has been decided that testing for latent TB infection is warranted and who are also BCG-vaccinated, or unlikely to return to have their TST read

High risk of progression to disease

There are insufficient data to recommend a preference for either a TST or an IGRA as the first-line diagnostic test in individuals 5 years or older who are likely to be infected with *Mtb*

Children less than 5 yrs

- We suggest performing a TST rather than an IGRA in healthy children <5 years of age for whom it has been decided that diagnostic testing for LTBI is warranted (*conditional recommendation, very low-quality evidence*).

- Remarks: In situations in which an IGRA is deemed the preferred diagnostic test, some experts are willing to use IGRAs in children over 3 years of age.

Low risk for *Mtb* infection and disease progression

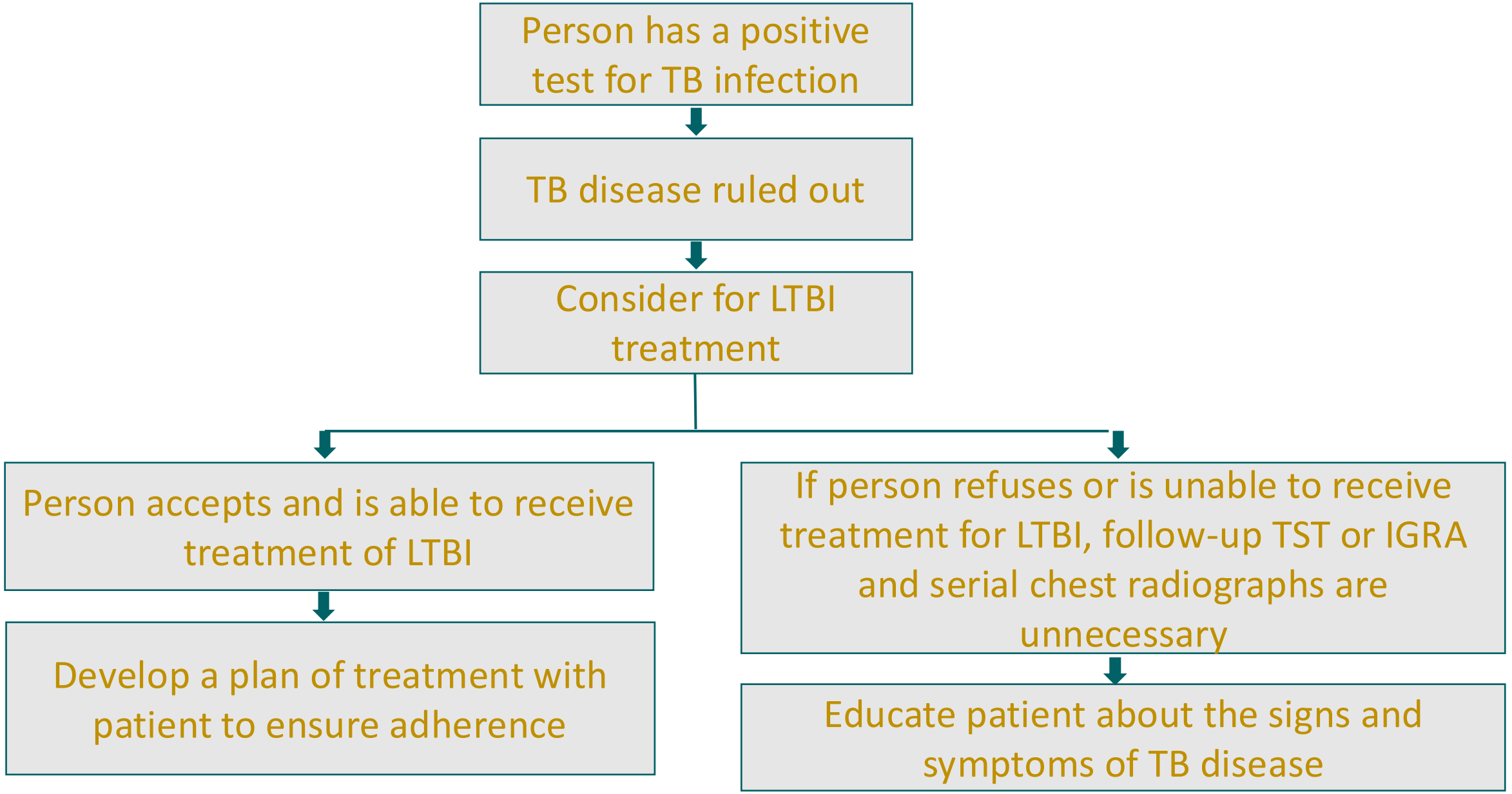
- NOT be tested for *Mtb* infection*
- A TST is an acceptable alternative in settings where an IGRA is unavailable, too costly, or too burdensome.

- We suggest a second diagnostic test if the initial test is positive in individuals 5 years or older (*conditional recommendation, very low-quality evidence*).
- The confirmatory test may be either an IGRA or a TST. When such testing is performed, the person is considered infected only if both tests are positive.

***law or credentialing bodies may require**

American Thoracic Society (ATS) emerged from American Sanatorium Association founded in 1905

Evaluation of Persons with Positive TB Test Results



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
- Determine current and previous drug therapy

Treatment Regimens for Latent TB Infection

Drug(s)	Duration	Interval	Minimum Doses
Isoniazid	9 months	Daily	270
		Twice weekly	76
	6 months	Daily	180
		Twice weekly	52
Isoniazid & Rifapentine	3 months	Once weekly	12
Rifampin	4 months	Daily	120

Note: Rifampin (RIF) and Pyrazinamide (PZA) should not be offered to persons with LTBI. RIF and PZA should continue to be administered in multidrug regimens for the treatment of persons with TB disease.

ORIGINAL ARTICLE

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Timothy R. Sterling, M.D., M. Elsa Villarino, M.D., M.P.H., Andrey S. Borisov, M.D., M.P.H., Nong Shang, Ph.D., Fred Gordin, M.D., Erin Bliven-Sizemore, M.P.H., Judith Hackman, R.N., Carol Dukes Hamilton, M.D., Dick Menzies, M.D., Amy Kerrigan, R.N., M.S.N., Stephen E. Weis, D.O., Marc Weiner, M.D., et al., for the TB Trials Consortium PREVENT TB Study Team*

December 8, 2011
N Engl J Med 2011; 365:2155-2166
DOI: 10.1056/NEJMoa1104875

Abstract

BACKGROUND

Treatment of latent *Mycobacterium tuberculosis* infection is an essential component of tuberculosis control and elimination. The current standard regimen of isoniazid for 9 months is efficacious but is limited by toxicity and low rates of treatment completion.

Related Articles

EDITORIAL DEC 8, 2011
Practical Preventive Therapy for Tuberculosis?
C. Dye

CORRESPONDENCE APR 12, 2012

NEJM Dec 8 2011

Sterling et al

	INH 3745	3HR 3986
TUBERCULOSIS	**15** (0.43)	**7** (0.19)
ADVERSE EFFECTS	**4.6 %**	**3.9 %**
COMPLETION RATES	**69 %**	**82 %**
HEPATOTOXICITY	**2.7 %**	**0.4 %**

NEJM Dec 8 2011

Sterling et al

	INH 3745	3HR 3986	
TUBERCULOSIS	**15** (0.43)	**7** (0.19)	
ADVERSE EFFECTS	**4.6 %**	**3.9 %**	**<.001**
COMPLETION RATES	**69 %**	**82 %**	**<.001**
HEPATOTOXICITY	**2.7 %**	**0.4 %**	**<.001**

ORIGINAL ARTICLE

Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults

Dick Menzies, M.D., Menonli Adjobimey, M.D., M.P.H., Rovina Ruslami, M.D., Ph.D., Anete Trajman, M.D., Ph.D., Oumou Sow, M.D., Heejin Kim, M.D., Joseph Obeng Baah, M.D., Guy B. Marks, Ph.D., F.R.A.C.P., Richard Long, M.D., Vernon Hoeppner, M.D., Kevin Elwood, M.D., Hamdan Al-Jahdali, M.D., et al.

August 2, 2018
N Engl J Med 2018; 379:440-453

Four months Rifampin versus 9 months INH

Higher completion rates and better safety

	INH 3416	RIFAMPIN 3443
Tuberculosis Infection	**4 4/7732 PYS**	**4 5 /7652**
Noninferiority		**Noninferior**
Superiority		**Not superior**
ADR grade 3-5	**59 (2.1)**	**24 (0.8)**
Hepatic 3-4	**50 (1.8)**	**8 (0.3)**

Original Article

One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis

Susan Swindells, M.B., B.S., Ritesh Ramchandani, Ph.D., Amita Gupta, M.D., Constance A. Benson, M.D., Jorge Leon-Cruz, M.S., Noluthando Mwelase, M.B., Ch.B., Marc A. Jean Juste, M.D., Javier R. Lama, M.D., M.P.H., Javier Valencia, M.D., Ayotunde Omoz-Oarhe, M.D., Khuanchai Supparatpinyo, M.D., Gaerolwe Masheto, M.D., Lerato Mohapi, M.D., Rodrigo O. da Silva Escada, M.D., Sajeeda Mawlana, M.B., Ch.B., Peter Banda, M.B., B.S., Patrice Severe, M.D., James Hakim, M.B., Ch.B., M.Med., M.Med.Sc., Cecilia Kanyama, M.B., B.S., Deborah Langat, M.B., Ch.B., Laura Moran, M.P.H., Janet Andersen, Sc.D., Courtney V. Fletcher, Pharm.D., Eric Nuermberger, M.D., Richard E. Chaisson, M.D., for the BRIEF TB/A5279 Study Team

The NEW ENGLAND JOURNAL of MEDICINE

- A 1-month regimen of rifapentine plus isoniazid was noninferior to 9 months of isoniazid alone for preventing tuberculosis in HIV-infected patients.
- The percentage of patients who completed treatment was significantly higher in the 1-month group.

The NEW ENGLAND JOURNAL of MEDICINE

PLOS Medicine

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RESEARCH ARTICLE

Acceptability and safety of one versus three months of rifapentine and isoniazid to prevent tuberculosis in people exposed in the household or workplace in Brazil: The Ultra-Curto randomized controlled trial

Betina Durovni, Marcelo Cordeiro-Santos, Solange Cesar Cavalcante, Renata Spener-Gomes, Jamile Garcia, Silvia Cohn, Valeria Saraceni, Beatriz Kohler, Lawrence H. Moulton, Alexandra Brito da Souza, Abiye Berihun, Mark Marzinke, Richard E. Chaisson, the Ultra Curto Study Team

Published: February 10, 2026 • https://doi.org/10.1371/journal.pmed.1004758

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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 approved.

Latent TB Infection Treatment Regimens for Specific Situations – Fibrotic Lesions

Persons with Fibrotic Lesions Suggesting Previous TB

- Should be treated for LTBI if they have
  - A positive TST reaction (at least 5 mm) or IGRA result
  - No symptoms of infectious TB disease
  - No history of treatment for TB disease
- Treat only after active disease excluded with sputum testing
- Acceptable regimens include
  - 9 months of INH
  - 4 months of RIF (with or without INH)
  - 3 months of INH and RPT (12-dose regimen)

Latent TB Infection Treatment Regimens for Specific Situations – Multidrug-Resistant TB

Contacts of Persons with Multidrug-Resistant TB

- Consider risk for progressing to MDR disease before recommending LTBI treatment
- When prescribing treatment for these contacts, consult an MDR TB expert
- Moxifloxacin or levofloxacin for 6-12 months if S (with or without ETM)
- PZA plus ETM if susceptible and resistant to FQ

Latent TB Infection Treatment Regimens for Specific Situations - Pregnancy

Pregnancy and Breast-Feeding

- **Rifampin daily for 4 months**
- **9 months of INH daily or twice weekly; give with vitamin B6**

- Women at high risk for progression to TB disease should not delay LTBI treatment; monitor carefully
- Breast-feeding not contraindicated

Monitoring

- Adherence
- Weekly report 3HP
- Side effects
- DDI
- Watch for active TB
- HSR
- Hepatotoxicity
- Baseline CBC LFTs : selected patients
- Follow Up: baseline abnormal or symptomatic

Ending TB Through Prevention

Accepted Regimens

1HP month regimen

3HP: 12 weeks INH Rifapentine DOT or SEA

4R: 4 months of rifampin

6H or 9H: 6 or 9 months INH

81 year old female with positive QFN Gold

- Loss of appetite, weight loss accompanying ventral hernia mesh repair infection
- TB quantiferon done by PCP in March
- No fever or chills
- Known exposure in 1970 from boyfriend, daughter and niece both received 6 months of multiple pills
- CXR unremarkable
- Forgetful per visiting home health RN

Case 1: 81 year old resident of kitsap county

- QuantiFERON Mitogen minus NIL 9.95
- QuantiFERON NIL 0.05
- Quantiferon Plus TB1 minus NIL 7.26 High
- Quantiferon Plus TB2 minus NIL 9.12 High

- Quantiferon TB Gold Plus Positive Abnormal

Canceled appointment, refusing to take Rifampin

- Symptom based monitoring
- Fever
- Night sweats
- Loss of appetite
- Weight Loss
- Organ specific symptoms

Chronic cough

LN enlargement

Back pain

66 yr old former Certified Nurse attendant born in ElSalvador

- QuantiFERON Mitogen minus NIL 9.94
- QuantiFERON NIL 0.06
- Quantiferon Plus TB1 minus NIL 0.02
- Quantiferon Plus TB2 minus NIL 0.05
- Quantiferon TB Gold Plus Negative

Systemic sclerosis sent by Rheumatology

- Positive RPR 1:1, negative TPPA
- We got talking

- Visit Diagnosis

ASB

LTBI

Stop cephelexin and begin rifampin 600 mg daily for 4 months

66 year old female from Guam with new diagnosis of RA

- Positive IGRA
- Amlodipine, Omeprazole, Apixaban

28 yr old Nursing student born in India referred with positive PPD

- PPD 25 mm
- Received BCG
- No known contact
- Asymptomatic
- Normal CXR
- Travels frequently to visit family in India

56 yr old male from Liberia, reports a positive PPD 20 yrs ago. Annual visits back home.

	8/8/2017	9/20/19
Nil	0.050	0.089
MITOGEN NIL	9.1	>10
TB NIL	0.389	0.330
TB AG 2 NIL		0.060

43 yr old from Bangladesh with a 15 mm TST

- Applied for a job in a child-care center.
- Asymptomatic
- BCG at birth
- No known contact
- Immigrated as a young adult to Canada followed by USA
- CXR normal

Case 1 Why should patients receive a medical evaluation before starting treatment for LTBI

A. To exclude the possibility of TB disease
B. To determine if there is a history of prior treatment for LTBI or TB disease
C. To determine existing medical conditions
D. A, B, and C are all correct.
E. Only A and B are correct.

Baseline laboratory testing is routinely indicated for which of the following patients?

- **A.** HIV-infected persons
- **B.** Pregnant women
- **C.** Teenagers
- **D.** A, B, and C are all correct.
- **E.** Only A and B are correct.

Loretta is receiving LTBI treatment and is evaluated each month by her public health nurse. What should she be evaluated for?

- **A.** Adherence to the prescribed regimen
- **B.** Signs and symptoms of TB disease
- **C.** Signs and symptoms of adverse effects, especially hepatitis
- **D.** A, B, and C are all correct.
- **E.** Only A and B are correct.

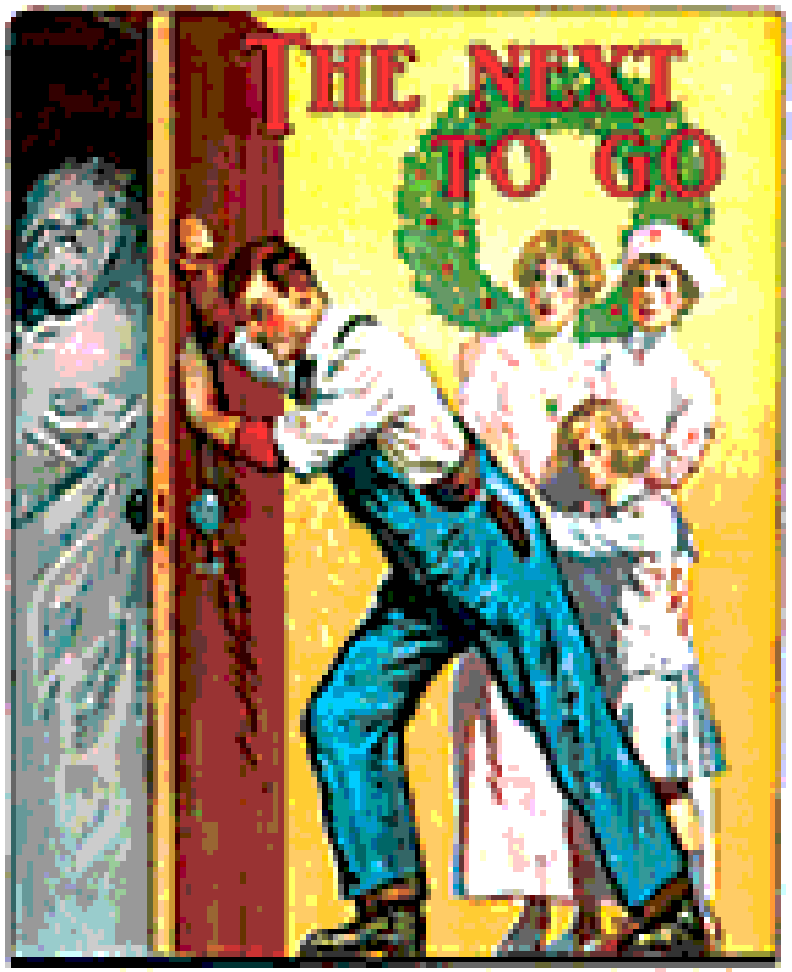
Routine laboratory monitoring is recommended for which of the following patients with LTBI?

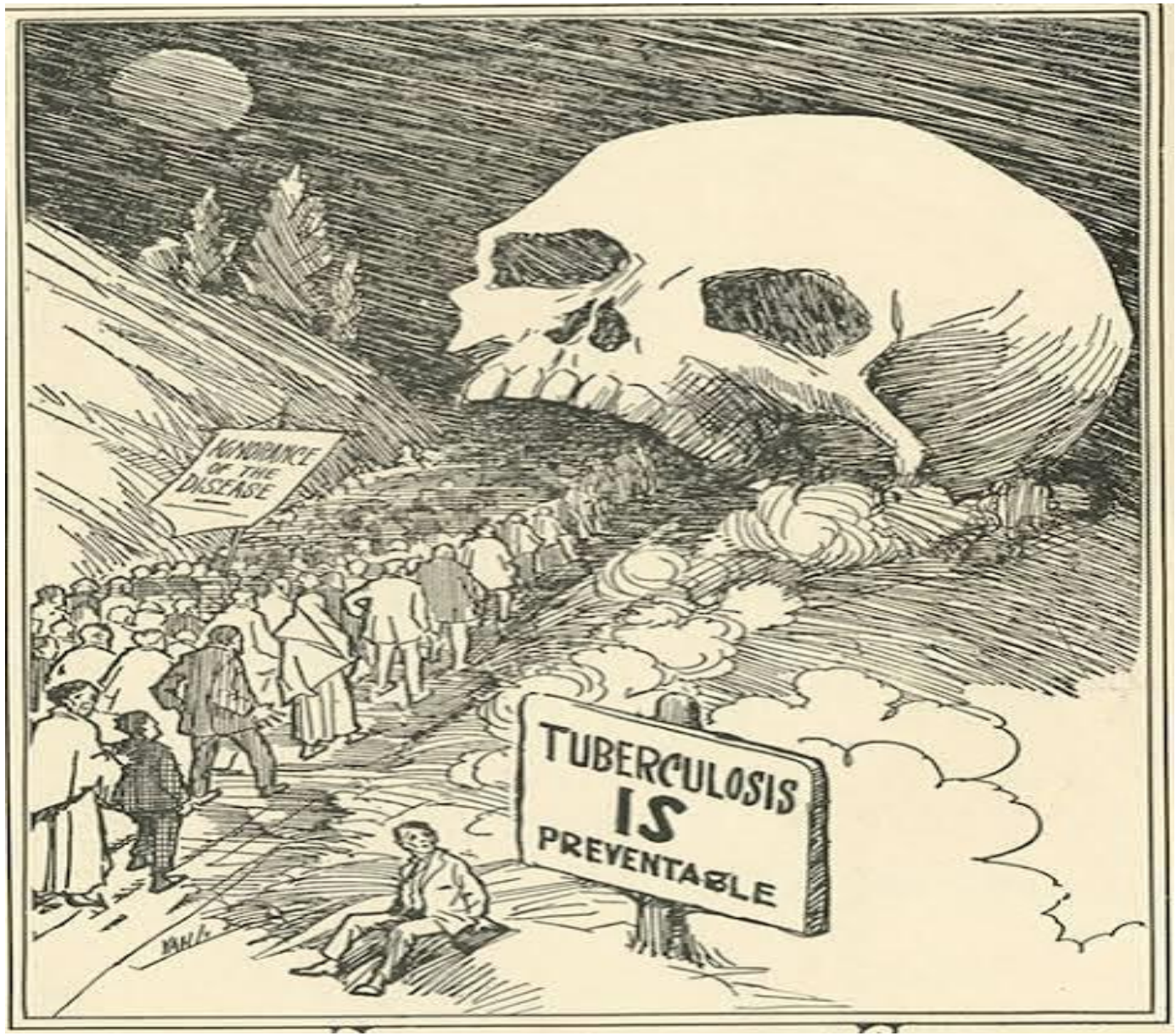
- **A.** Persons whose baseline liver function tests are abnormal
- **B.** Persons with a risk of hepatic disease
- **C.** All patients receiving LTBI
- **D.** A, B, and C are all correct.
- **E.** Only A and B are correct.

The "Consumptive Chic" Aesthetic

In 18th- and 19th-century Europe and America, tuberculosis (then commonly known as "consumption" or the "romantic disease") was paradoxically idealized as a fashionable and artistic aesthetic


PARKERS' TONIC
THE GREAT HEALTH & STRENGTH
RESTORER.
CURES COUGHS,
CONSUMPTION,
ASTHMA.
Are you weary in Brain and Body
AVOID INTOXICANTS AND RELY ON


THE NEXT TO GO
FIGHT TUBERCULOSIS!
Red Cross Christmas Seal Campaign


IGNORANCE OF THE DISEASE
TUBERCULOSIS IS PREVENTABLE

REFERENCES

CDC
WHO
USPSTF JAMA 2016
IDSA and ATS GUIDELINES 2017
NEJM Dec 20011 Aug 2018 Mar 2019
Others since 2019