

LTBI and Pregnancy

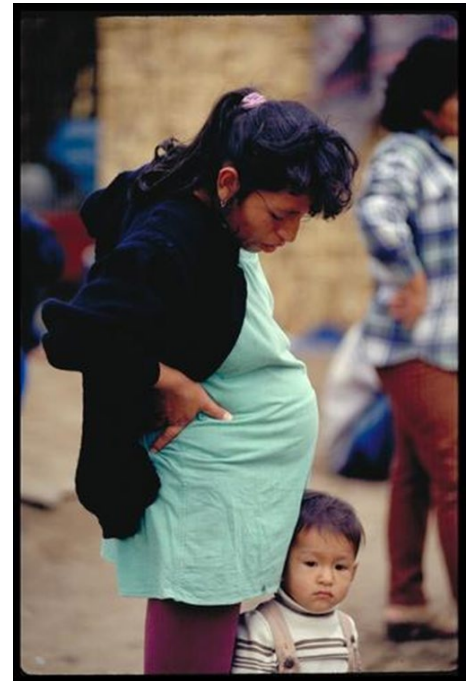
John Bernardo



Session 7
April 15, 2021

Outline

- Epidemiology of TB
- LTBI and Pregnancy
 - Screening
 - Testing
 - Clinical evaluation, radiography
 - Treatment



What is Tuberculosis??

TB is an Infectious Disease

- Endemic in the world today
- Reservoir of infected persons

The disease can involve any organ/system

- Respiratory system (lungs/airways) most common form

Can be spread from person to person (*airborne*)

- *Not* very contagious

May be difficult to diagnose

- *Suspicion* is most important

Is treatable

- Treatment cures the disease

Is preventable

- Reduces reservoir of infected persons

Epidemiology, 2019

Global

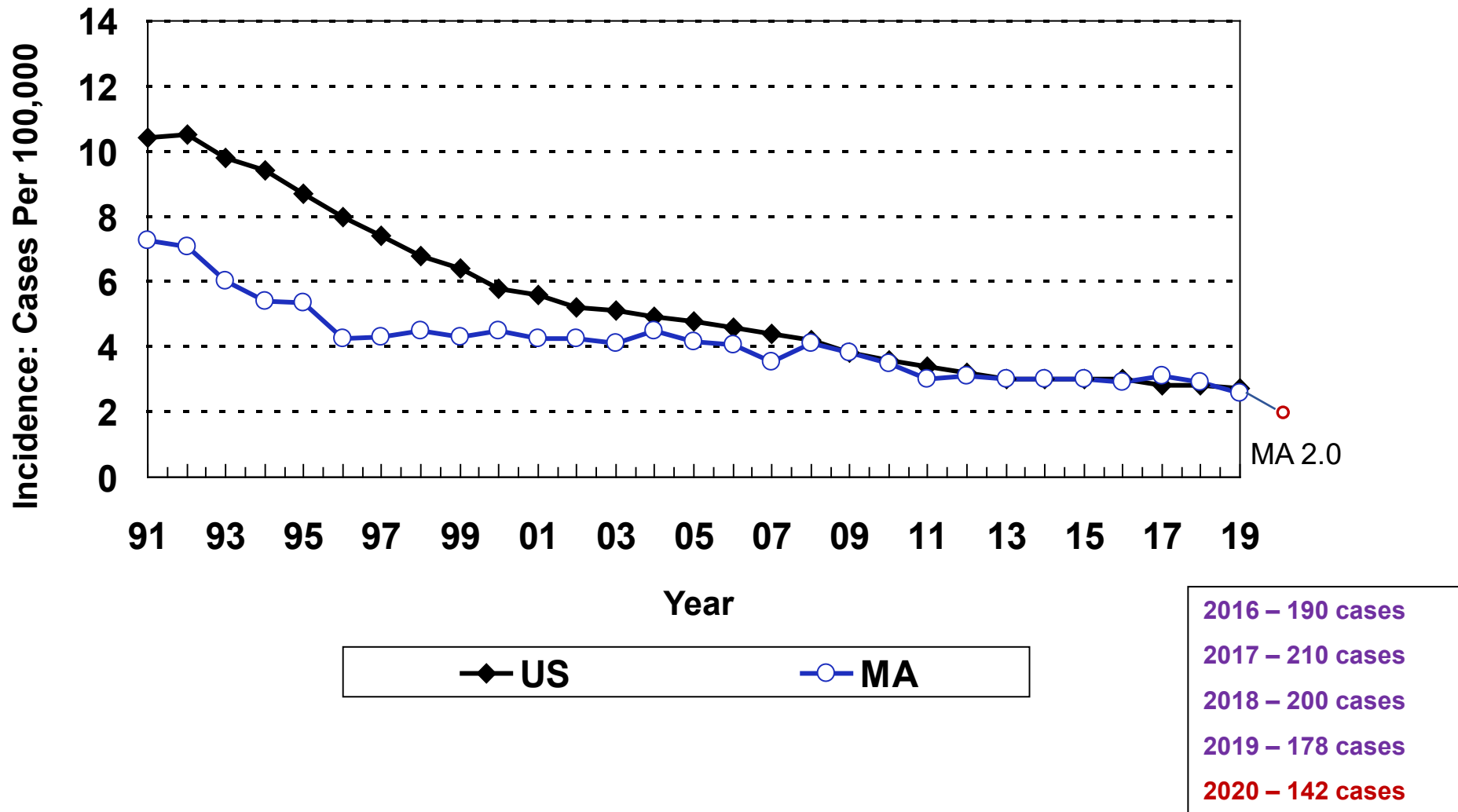
- 10.0 million TB cases (est)
- 7.1 million TB cases notified
 - M 56%
 - F 32%
 - Children <15 12%
- 1.4 million people died
- 456,426 cases with HIV (69% with known HIV results)

United States

- 8,916 TB cases*
 - M 60%
 - F 40%
 - Children <15 4%
- 542 people died (2018)
- 373 cases with HIV (87% with known HIV results)

*7,163 in 2020 (20% decr vs 2-3%/yr since 2010)

Incidence, United States and Massachusetts, 1991-2020



High Risk Groups, Massachusetts, 2020

$n = 142$

Non-U.S. born	125 (88%)
Children < 15 years	3 (2%)
Prison/jail	1 (1%)
Homeless	5 (4%)
Substance use*	5 (4%)
HIV positive	8 (6%)

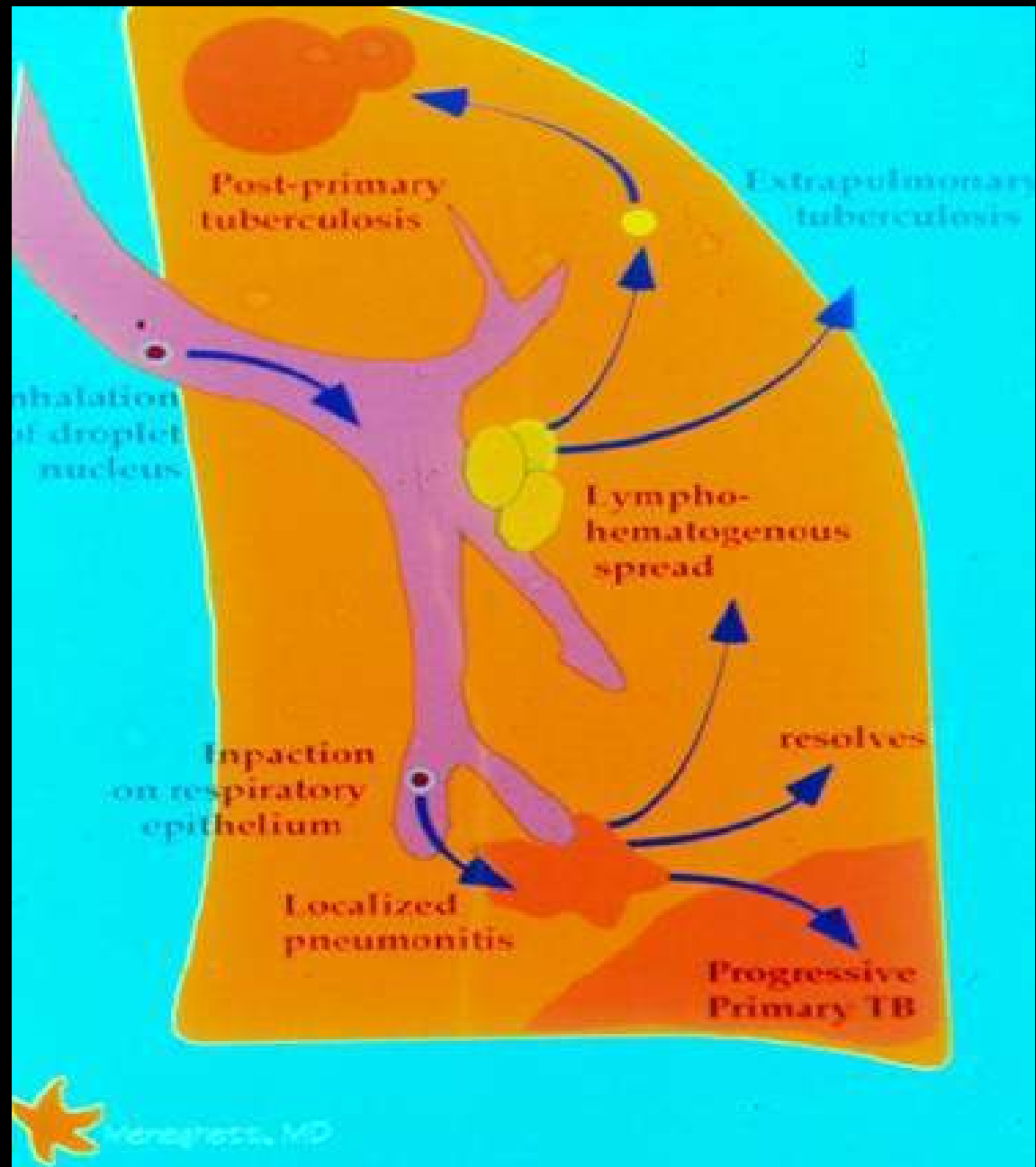
* Alcohol, injecting and/or non-injecting drug use

MDPH - ISIS

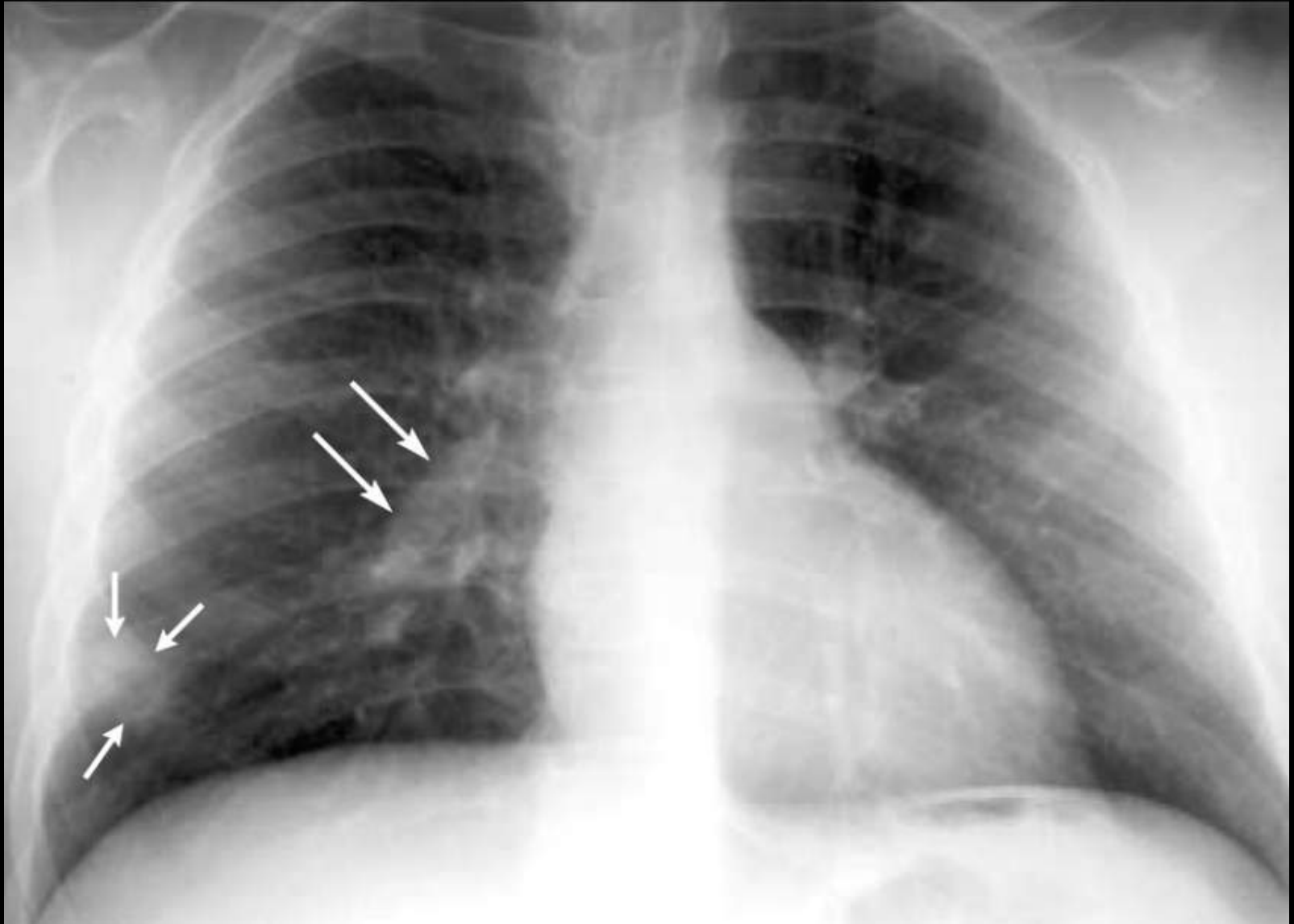
Transmission and Pathogenesis



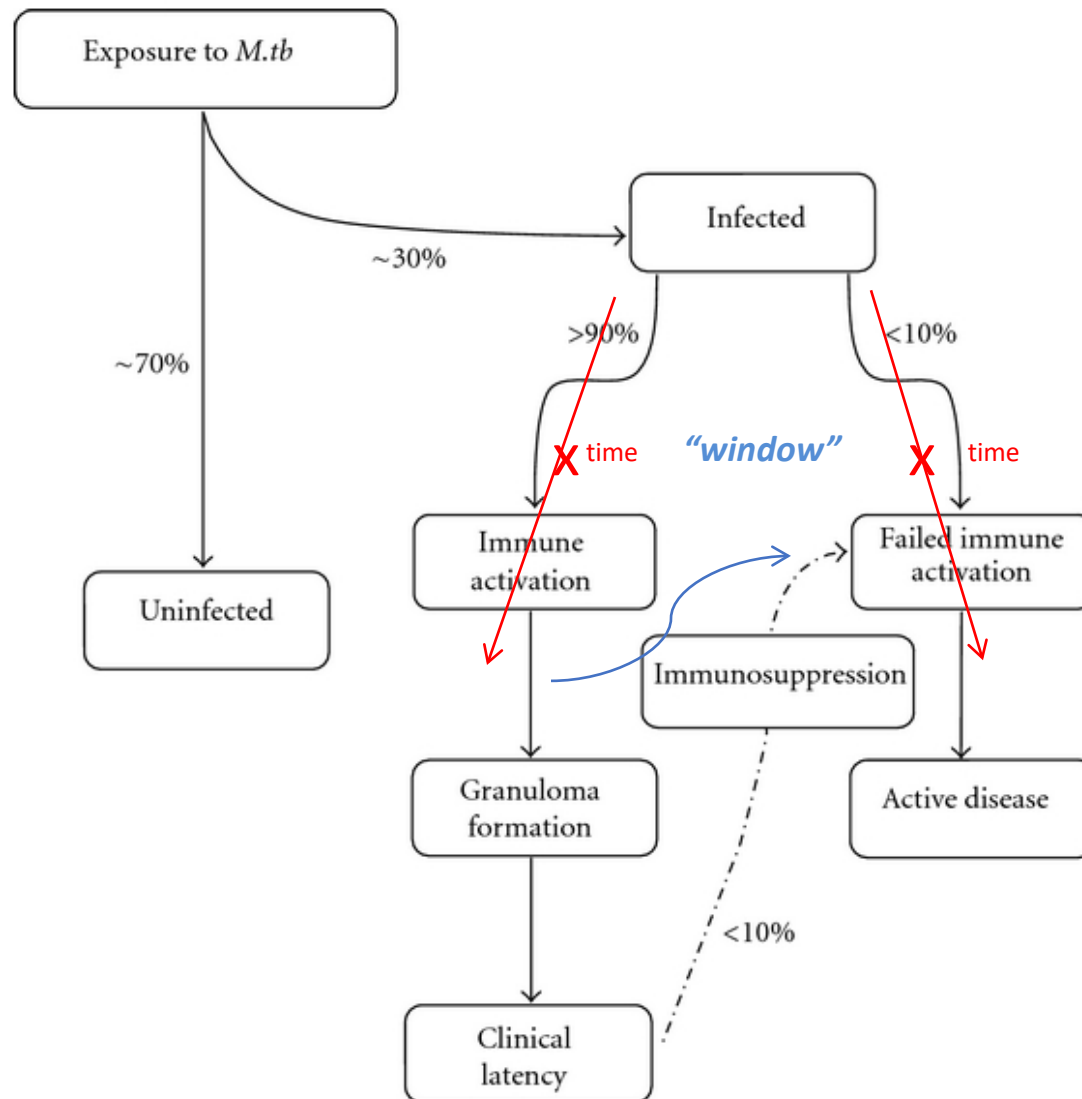
Primary Infection



Primary TB in a Child



TB disease progression and major events leading to protection



TB infection *versus* TB Disease...

What is the difference between the two?

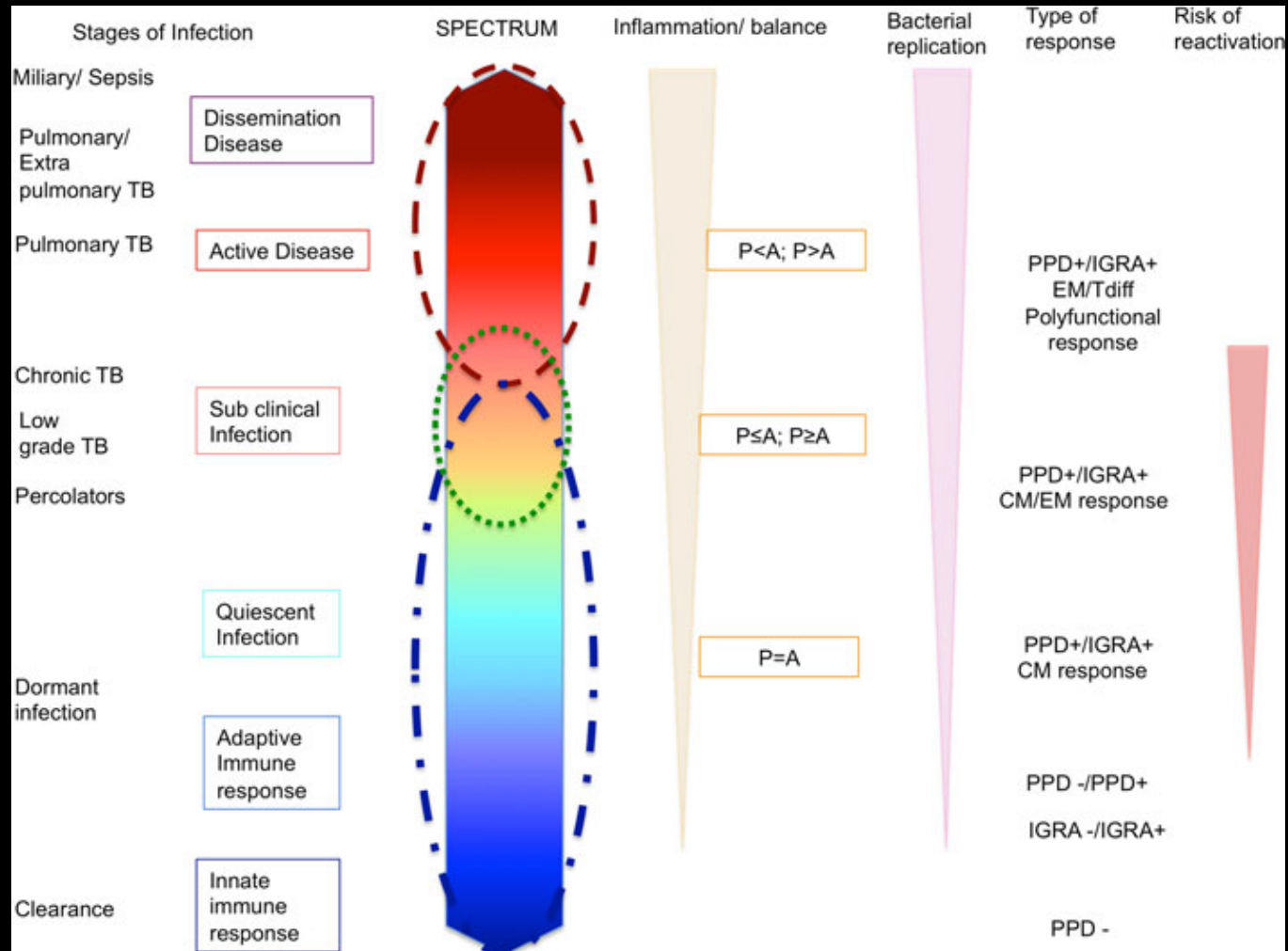
TB Infection

- Positive TB test (TST/IGRA)
- Not sick (feels well)
- Negative x-ray
- Cannot spread infection
- Treat with 1 medicine
- 1/4 World population
 - *Reservoir for future TB Disease* (5-10% lifetime risk)

TB Disease

- Usually TB skin test is positive
- Symptoms may be present or absent:
 - cough, fevers, sweats, weight loss
- Abnormal x-ray
- Can spread infection (family, friends, work, ...)
- Treat with multiple drugs
- 10,000,000 cases/yr (World)

Outcome of TB Infection



Risk of TB in Pregnancy

- Cohort series with case control
- All pregnancies in General Practitioner Data base in England over 12 years
- 192,801 women with a total of 264,136 pregnancies
- 177 TB events – 22 during pregnancy and 22 during 180 days postpartum
 - Incident rate ratios higher than no pregnancy
 - 1.29 pregnancy and 1.95 postpartum
 - Administrative, immunologic or medical factors

TB and Women

Pregnancy and the Post Partum State

- ? Due to fact that women are in care at this time
 - Prenatal care
 - Prevention of mother child transmission (PMTCT) programs
- ? Biologic differences during pregnancy that influence infection
 - Th1 pro-inflammatory responses are suppressed in pregnancy = masking of symptoms, increased susceptibility of new infection or progression to disease
 - Postpartum Th1 suppression reverses (similar to IRIS) which may exacerbate symptoms

Screening for LTBI in Pregnancy Risk Assessment

- CDC, ACOG suggest screening for LTBI to *target testing*
 - Those *at risk* (US):
 - Foreign born; travel
 - Contact to active TB
 - HIV infected
 - Co-morbid disease that predisposes to TB
 - Other locally defined high risk

Test for Infection

- Test those *at-risk*
- Tuberculin Skin Test (TST) or Interferon-gamma Release assay (IGRA) ?
 - Screening thresholds do not change
 - CDC guidelines do not specifically describe IGRA use in pregnancy although data published post guideline date are consistent in ability to use in this population
 - Lighter-Fischer *Obstet Gynecol* 2012;119:1088–95
 - Chehab BM *Kansas J Med* 2010; 3:24–30
 - Jonnalagadda *Infectious Diseases in Obstetrics and Gynecology* 2012, Article ID 950650, doi:10.1155/2012/950650

If test is positive ...

Clinical Evaluation: Exclude Active Tuberculosis Disease

- History and Physical Examination
 - Symptoms: Cough, fevers, sweats, weight loss, ... none
 - Physical findings: For active TB, relate to site of disease
- CXR for those who are found to have a *positive test or are symptomatic*
 - Radiation from a single view shielded CXR is not problematic
 - *But usually can wait* until past 1st trimester unless symptoms are present
- Airborne isolation, laboratory studies if disease is suspected
 - Sputum smear, culture, PCR (Xpert®), pathology

LTBI Treatment in Pregnancy

- Risk for side effects appear to be elevated
 - Concomitant factors in pregnancy?
- For most patients, defer treatment until 3 months post delivery
- Treatment should *not* be deferred to the postpartum period:
 - Contact to active case
 - Documented new conversion (2 years)
 - HIV infected (especially if CD4<350 or not on ART)
 - Diabetes
 - Interpretation of other “high risk” is left open-ended
- **Regimens:**
 - Daily INH (9 or 6 mos); **Rifampin (4 mos)**; INH + Rif (3 mos)
 - 3HP (3 mos weekly INH + Rifapentine) *not recommended* in pregnancy

But ...

Rifamycins and Nitrosamines

- Class of compounds commonly found in water and foods and some medications, may be associated with some cancers following long exposures
 - e.g., cured and grilled meats, dairy products and vegetables, ranitidine (Zantac) ...
- 6/18/2020: Notification of rifapentine (Priftin®, Sanofi) nitrosamine impurity (CPNP)
 - Temporary suspension of production
 - FDA: Continue treatment in persons receiving the drug, if available
 - Do not start new rifapentine-based regimen until shipments resume and local supplies are reestablished
- 8/26/20: Impurities identified in rifampin (MNP)
 - Manufacturers should notify FDA when testing shows levels that exceed the acceptable intake limits of 0.16 ppm for MNP (Rif) and 0.10 ppm for CPNP (RPT).
 - FDA will determine on a case-by-case basis whether those drugs should be released for distribution
 - In order to *maintain supply of these drugs*, FDA raised the maximum acceptable limits of contamination with these impurities for rifampin (0.16 -> 5) and rifapentine (0.10 -> 14)
- 9/11/20: CDC-DTBE recommends that providers continue prescribing rifampin and rifapentine for all TB and latent TB infection (LTBI) treatment per existing [guidelines](#)
- 10/29/20: FDA increased max limit CPNP (rifapentine) to 20ppm
- **For now, consider:** NO rifampin for LTBI in pregnancy; use alternate regimen (INH).
 - If on treatment, continue rifampin (only following discussion with patient): Benefits outweigh possible risks

Isoniazid and Hepatitis

- Increased risk during pregnancy (especially 3d trimester) and 3-4 months postpartum
 - Especially
 - Hispanic or Black women
 - Underlying liver disease
 - Substance abuse (e.g., EtOH)

Franks, A.L., *et al.* Public Health Rep. 104:151-155, 1989. PMID: 2495549

So:

Monitoring During Treatment

- Pregnancy and postpartum: Increased risk for INH hepatotoxicity
 - Especially in Hispanic and African-American women
- Baseline
 - General evaluation for chronic liver disease, EtOH use, and exposure to other hepatotoxins
 - Transaminases, Bili, CBC
 - HIV and hepatitis B and C
- Monthly
 - Clinical evaluation, transaminases, CBC
- EDUCATION
 - STOP medication(s) if AE is SUSPECTED

Breastfeeding

- Breastfeeding does not transmit TB
 - No documented cases of transmission from breast milk
- Formula fed infants remain at high risk of infection
- Anti-tuberculous drugs cross into breast milk in small amounts
 - Serum level no more than 20% of the therapeutic level for INH
 - Less than 11% for others
 - Administer pyridoxine (B6) to infant if mom is taking INH
 - Milk will be orange with rifampin
 - No toxic effects reported in infants breast fed
 - No indication to advise mom to “pump and dump”

Snider D.E., and Powell K.E.: Should women taking antituberculosis drugs breast-feed? Arch. Intern. Med. 1984; 144: pp. 589-590

February 14, 2020
CDC



Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020

MMWR Recommendations and Reports / February 14, 2020 / 69(1);1–11

Timothy R. Sterling, MD¹; Gibril Njie, MPH²; Dominik Zenner, MD³; David L. Cohn, MD⁴; Randall Reves, MD⁴; Amina Ahmed, MD⁵; Dick Menzies, MD⁶; C. Robert Horsburgh Jr., MD⁷; Charles M. Crane, MD⁸; Marcos Burgos, MD^{8,9}; Philip LoBue, MD²; Carla A. Winston, PhD²; Robert Belknap, MD^{4,8}

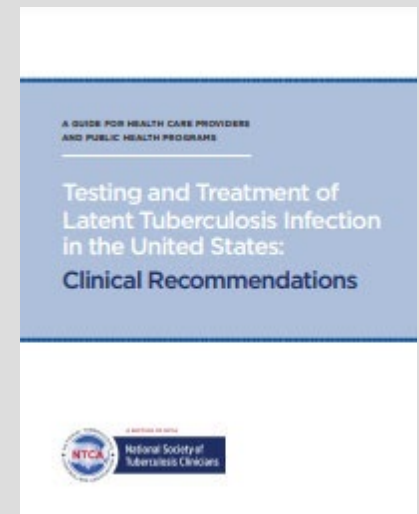
Pages: 8 (excluding references); 3 pages to describe and justify methods

https://www.cdc.gov/mmwr/volumes/69/rr/rr6901a1.htm?s_cid=rr6901a1_w

Testing and Treatment of Latent Tuberculosis Infection in the United States: Clinical Recommendations A Guide for Health Care Providers and Public Health Programs 2021

AKA
The Companion Statement

Pages: 120 (includes references)



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<http://www.tbcontrollers.org/resources/tb-infection/clinical-recommendations/#.YEfA2TZYbcs>

