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UPDATES IN THE TREATMENT OF ACTIVE TUBERCULOSIS – 2026 WITH BONUS TB POTPOURRI!

CLINICAL & PUBLIC HEALTH GUIDANCE — INDIANA

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Disclosures

- Financial - None
- Medical Consultant, TB Prevention and Care Program Indiana Department of Health
- Owner of a 43 consecutive negative TB screening tests!
- Genuine Iowa farm boy
- Grandfather of Avery Lynn and Kaia Rose

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Objectives

- Understand recent national guideline updates for active TB treatment.
- Review key regimen changes for drug-susceptible and drug-resistant TB.
- Discuss Indiana public health policy and implementation practices.
- Address clinical considerations and next steps for care delivery.

Why This Matters

- Tuberculosis remains a significant public health issue worldwide and in the U.S., requiring effective treatment strategies.
- Shorter, safer regimens improve adherence, outcomes, and reduce transmission.
- New evidence has led to clinical practice guideline updates from major respiratory and infectious disease societies.
- 2025 ATS/CDC/ERS/IDSA Clinical Practice Guidelines (updated Dec 30, 2024)
  - American Thoracic Society, CDC, European Respiratory Society, and Infectious Diseases Society of America.

Core Update: Drug-Susceptible TB in Adults

<u>New Shorter Regimen Option (4 months):</u>

Adults & adolescents (≥12 years) with drug-susceptible pulmonary TB:

- 2HPZM/2HPM — isoniazid (H), rifapentine (P), pyrazinamide (Z), moxifloxacin (M) for 2 months +
- 2HPM — isoniazid, rifapentine, moxifloxacin for 2 months.
- An alternative to the traditional 6-month isoniazid, rifampin, pyrazinamide, and ethambutol (2HRZE) regimen.
  - *HRZE previously known as RIPE*

Implications:

- Reduced treatment duration:
  - may increase adherence
  - will decrease toxicity
  - will decrease interruption of patient's lifestyle AND impact on public health system
- Useful across outpatient and inpatient contexts.

Clinical Implementation Considerations

Before implementing shorter regimens:

- ✓ Evaluate eligibility (severity, drug susceptibility, age).
- ✓ Consult TB specialist
- ✓ Monitor for adverse effects (e.g., QT prolongation with moxifloxacin).
- ✓ Ensure adherence support (DOT, clinic follow-up).
- ✓ Reinforce infection control and isolation criteria per public health rules.

Children & Adolescents (Non-Severe Disease*)

Shortened course possible (4 months):

- Children (3 months — 16 years) with non-severe TB:
- 2HRZE/2HR — isoniazid, rifampin, pyrazinamide, ethambutol for initial 2 months + isoniazid and rifampin for 2 months.
- Alternative to standard 6-month 2HRZE/4HR regimen

* Non-severe TB defined by localized disease without significant airway obstruction or miliary pattern.

Drug-Resistant TB (DR-TB) Updates

Shorter, All-Oral Regimens (6 months):

For rifampin-resistant TB:

- BPaL (bedaquiline, pretomanid, linezolid)
- BPaLM (bedaquiline, pretomanid, linezolid, moxifloxacin)

These regimens shorten treatment from ~15+ months to 6 months, improving tolerability and reducing total treatment time.

Local Public Health Framework

Indiana TB Prevention & Care Program focuses on:

TB elimination through education, surveillance, outreach, and collaboration.

Key points:

- Local health departments coordinate treatment and follow-up.
- Isolation and infection control practices are governed under Indiana Administrative Code rules.
- Close **cooperation between clinicians and health departments is essential** for case management and contact tracing.

Follow-Up & Monitoring

- ✓ Monthly sputum cultures until conversion.
- ✓ Assess for treatment response and side effects.
- ✓ Engagement with local TB control program for contact investigations.
- ✓ Utilize CDC/IDOH resources for guidance and case management tools.

Summary of New Practice Points

- Shorter treatment regimens are now recommended for most drug-susceptible TB cases.
- Regimens for drug-resistant TB are significantly shorter with all-oral options.
- Close collaboration between clinical and public health teams is critical.

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Questions & Discussion

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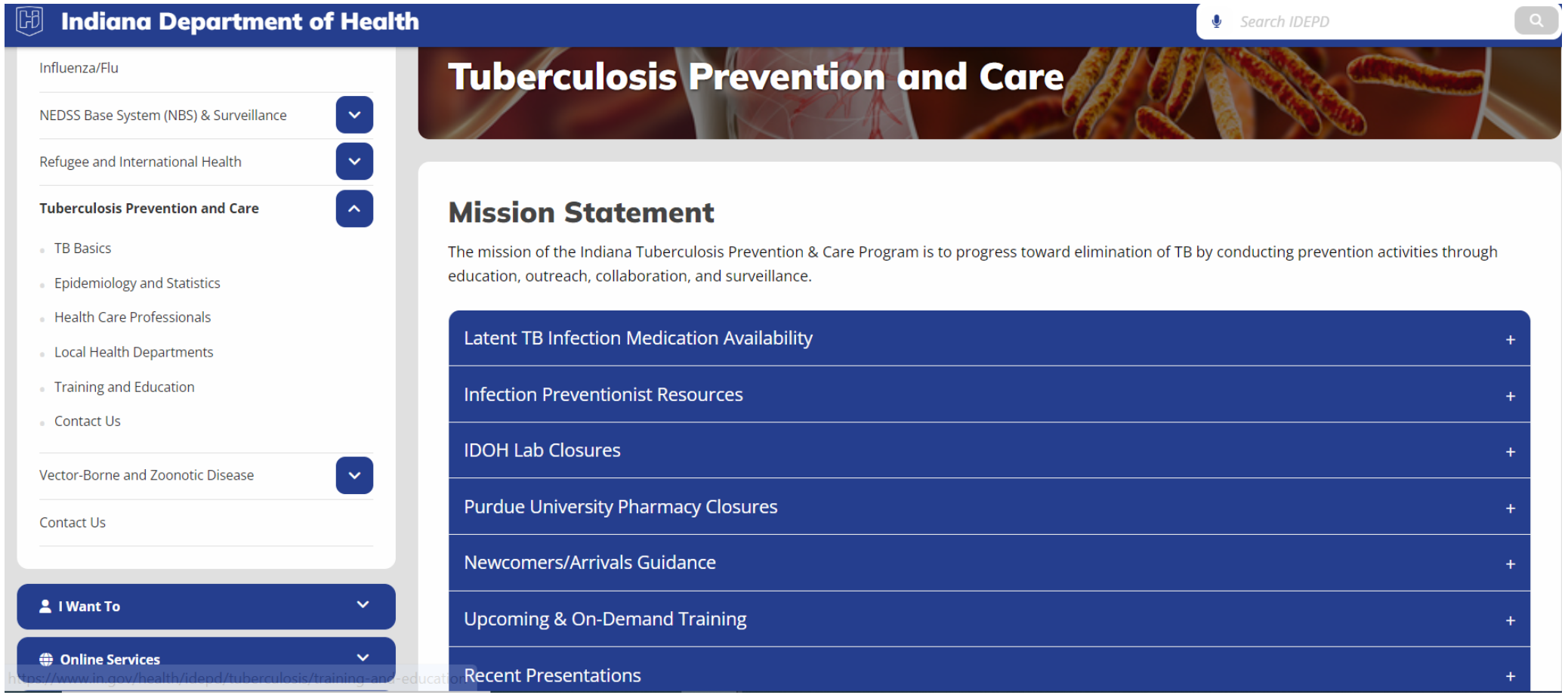
References – accessed March 2026

- Clinical Overview of Tuberculosis | Tuberculosis (TB) | CDC
- Updates on the Treatment of Drug-Susceptible and Drug-Resistant Tuberculosis: An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. J. Saukkonen, et al. American Journal of Respiratory and Critical Care Medicine, Volume 211, Issue 1, January 2025, Pages 15–33, https://doi.org/10.1164/rccm.202410-2096ST
- Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. 2016. P. Nahid, et al. https://academic.oup.com/cid/article/63/7/e147/2196792
- https://www.in.gov/health/idepd/tuberculosis/

IDOH TB Prevention and Care Resources



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https://www.in.gov/health/idepd/tuberculosis/

Latent TB/TB Infection

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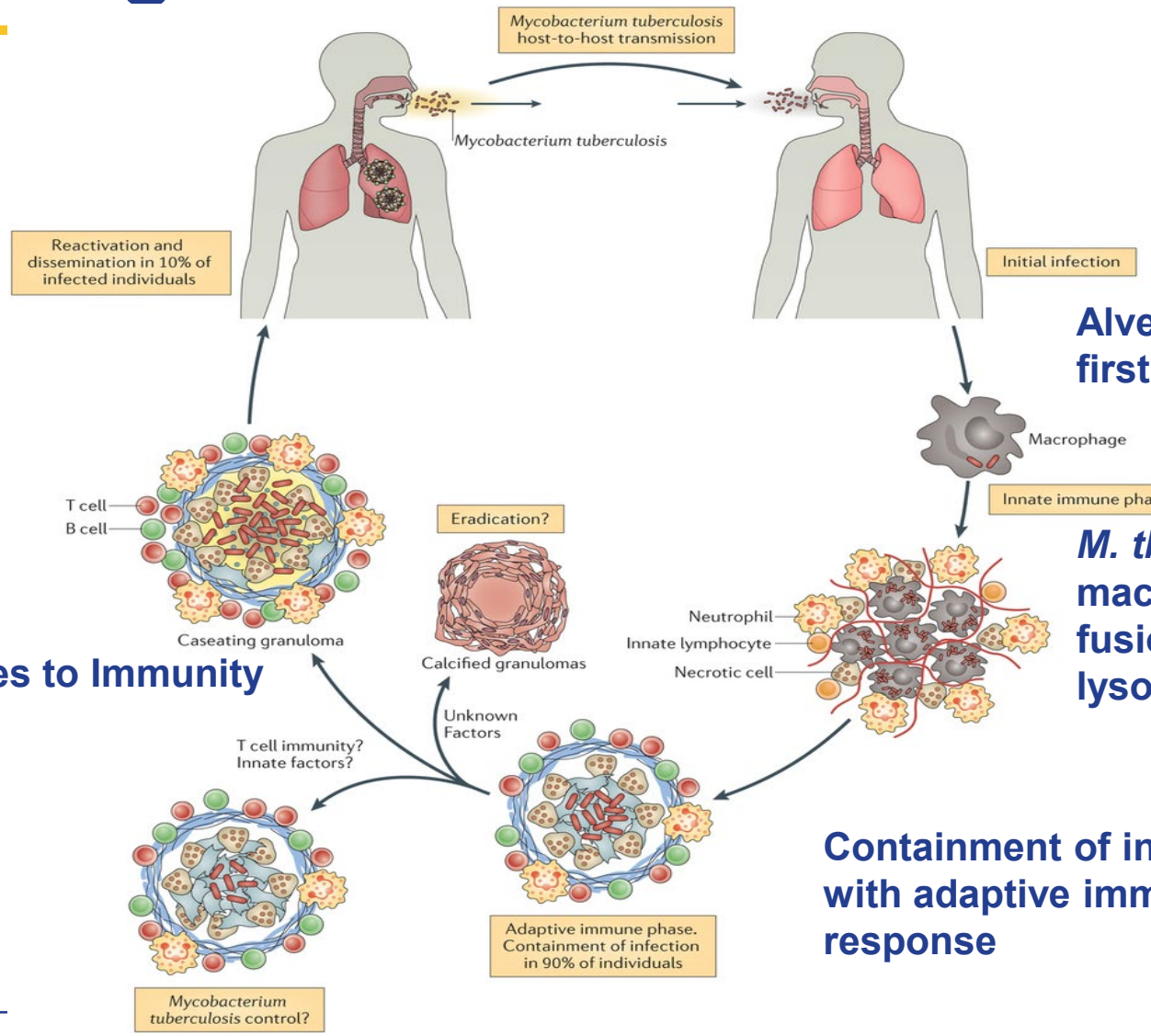
Pathogenesis Overview



Alveolar macrophages are first line of defense

M. tb survives inside the macrophage- prevents fusion of phagosome and lysosome

Containment of infection with adaptive immune response

Changes to Immunity

Nature Reviews | Microbiology

Barry, Nat Rev Microbiol, 2009

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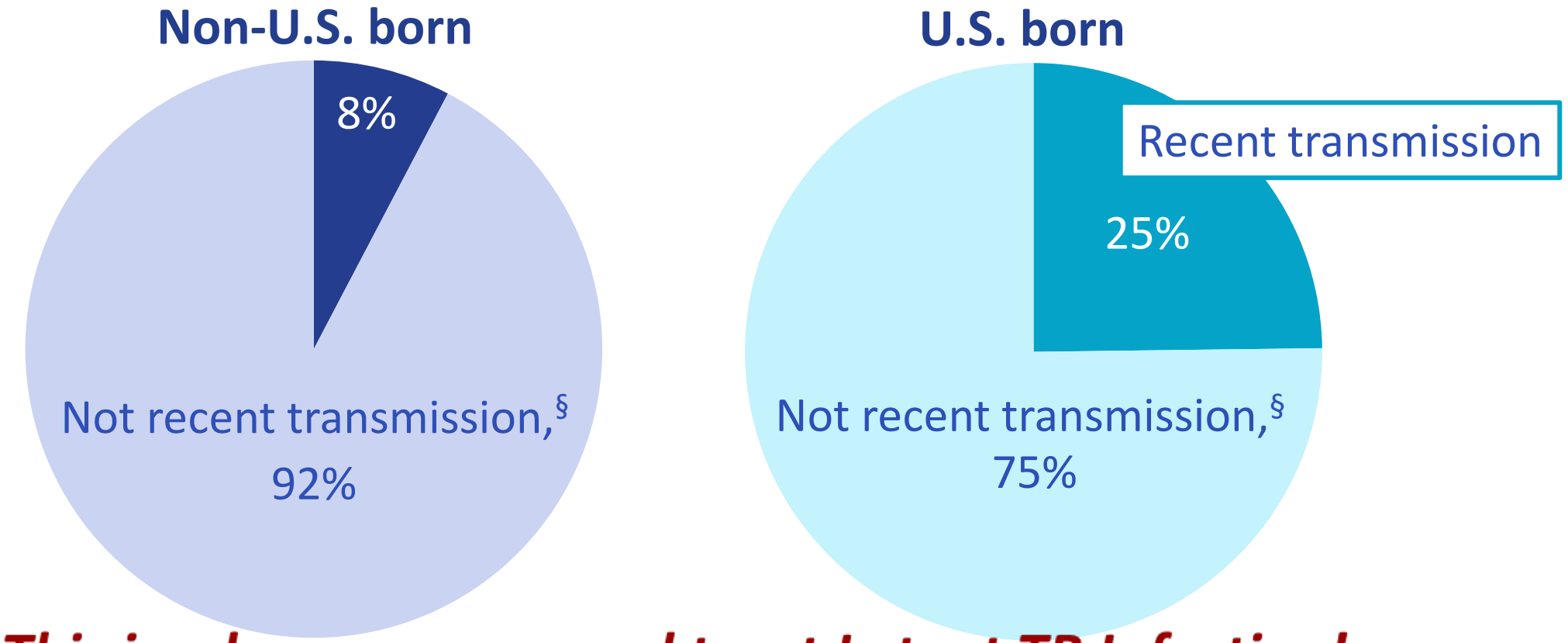
Percentages of TB Cases Estimated to be Attributed and Not Attributed to Recent Transmission* by Origin of Birth,† 2020–2021



This is why we screen and treat Latent TB Infection!

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* Cases with unknown origin of birth not shown (n=40).
† A TB case is designated as attributed to recent transmission if a plausible source case can be identified in a person who i) has the same *M. tuberculosis* genotype, ii) has an infectious form of TB disease, iii) resides within 10 miles of the TB case, iv) is 10 years of age or older, and v) was diagnosed within 2 years before the TB case.
§ Cases not attributed to recent transmission may be misclassified in children <5 years old or indeterminate in persons with a recent U.S. arrival due to limitations of the plausible-source case method.

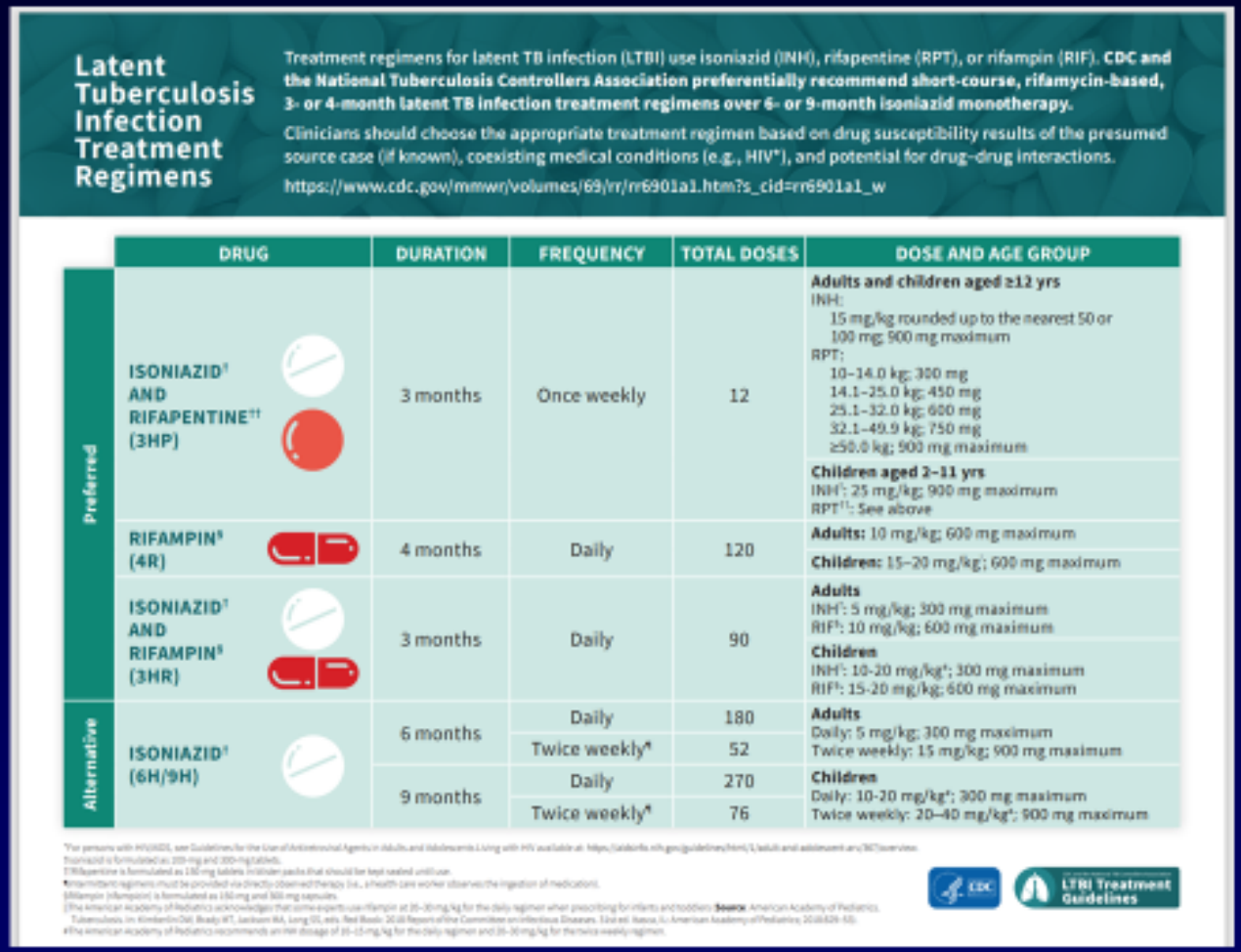
Latent TB Treatment:

Several options

Drug availability is sometimes a factor

Assess for possible **drug interactions**

What will the patient take? **DOT**?



Latent Tuberculosis Infection Treatment Regimens

Treatment regimens for latent TB infection (LTBI) use isoniazid (INH), rifapentine (RPT), or rifampin (RIF). **CDC and the National Tuberculosis Controllers Association preferentially recommend short-course, rifamycin-based, 3- or 4-month latent TB infection treatment regimens over 6- or 9-month isoniazid monotherapy.**

Clinicians should choose the appropriate treatment regimen based on drug susceptibility results of the presumed source case (if known), coexisting medical conditions (e.g., HIV*), and potential for drug–drug interactions.

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

	DRUG	DURATION	FREQUENCY	TOTAL DOSES	DOSE AND AGE GROUP
Preferred	ISONIAZID† AND RIFAPENTINE†† (3HP)	3 months	Once weekly	12	**Adults and children aged ≥12 yrs** 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 yrs** INH†: 25 mg/kg; 900 mg maximum RPT††: See above
Preferred	RIFAMPIN§ (4R)	4 months	Daily	120	**Adults:** 10 mg/kg; 600 mg maximum **Children:** 15–20 mg/kg; 600 mg maximum
Preferred	ISONIAZID† AND RIFAMPIN§ (3HR)	3 months	Daily	90	**Adults** INH†: 5 mg/kg; 300 mg maximum RIF§: 10 mg/kg; 600 mg maximum **Children** INH†: 10–20 mg/kg*; 300 mg maximum RIF§: 15–20 mg/kg; 600 mg maximum
Alternative	ISONIAZID† (6H/9H)	6 months	Daily	180	**Adults** Daily: 5 mg/kg; 300 mg maximum Twice weekly: 15 mg/kg; 900 mg maximum **Children** Daily: 10–20 mg/kg*; 300 mg maximum Twice weekly: 20–40 mg/kg*; 900 mg maximum
			Twice weekly¶	52	
		9 months	Daily	270	
			Twice weekly¶	76	

https://www.cdc.gov/tb/topic/treatment/pdf/LTBITreatmentRegimens.pdf

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TB Testing/Screening

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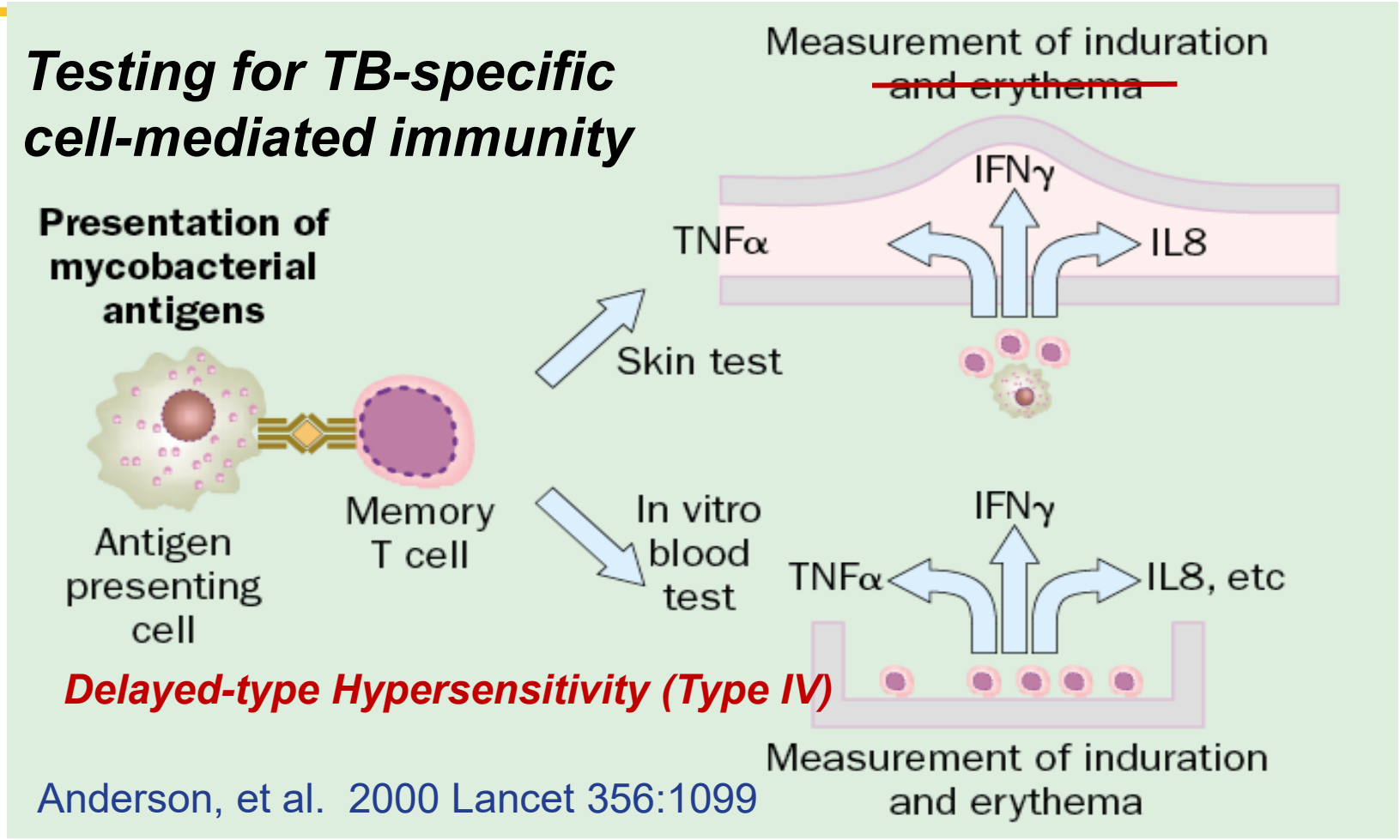
Immune background of TB tests



Interferon–Gamma Release Assays (IGRAs)

Advantages of IGRAs:

- Requires a single patient visit, ready in 24 hrs
- Do not cause booster phenomenon
- Test reading not affected by reader's perception or bias
- Not impacted by BCG / most NTB mycobacteria#

Limitations of IGRAs include:

- Blood processing needed
- Limited data on use in children < 5, recent TB exposures, immunocompromised persons

- Species *kansasii*, *marinum*, and *szulgei* still cross-react

Interferon gamma release assays

Sensitivity may not be greater than TST
- both 70–75% range

IGRA tests – greater specificity than TST

- IGRA are *not* affected by BCG or most NTMB

Not useful in severe lymphopenia

No test distinguishes active from latent disease ☹

Meta-analysis: New Tests for the Diagnosis of Latent Tuberculosis Infection: Areas of Uncertainty and Recommendations for Research Menzies, et al Ann Int Med 2007, **146:340-354**

Interpretation of Quantiferon Gold IGRA Results

Test	Rationale	Expected	Range
NIL	Baseline state of cells	Should be low	Less than 1
Mitogen minus NIL	Artificial stimulation	Should be high	Usually > 10
TB minus NIL	TB antigen-specific stimulation	May be high if infected with TB	Current positives are 0.35 to >10

It is important to make sure the IGRA test is:

- Blood sample is collected and processed according to the manufacturer
- The test run in a laboratory familiar with the test
- Discuss the results with your local expert if there are any questions

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Concerns with IGRA as a screening tool in HCWs

QFT reversions – initial positive, followed by negative

- Baseline TST+/QFT+: only 7% [N=28]
- Baseline TST-/QFT+: 70% [N=10]

Baseline QFT result	Retested (n)	Treated(n)	Reversions (n)	Reversions (%)
0.35-0.69	11	1	6	55%
0.7-1.0	2	0	1	50%
1.1-5.0	9	3	1	11%
> 5.0	16	9	1	6%

Pai M et al, Serial testing of health care workers for tuberculosis using interferon-g assay. AJRCCM 2006

Delineating a Retesting Zone Using Receiver Operating Characteristic Analysis on Serial QuantiFERON Tuberculosis Test Results in US Healthcare Workers – Thanassi, et al 2012

Validated model on a sample of 862 HCWs from three US hospitals to define a QuantiFERON Gold In-Tube retesting zone between 0.35 and 1.11 IU/mL

Looked to maximize separation between HCWs

- who have two consecutive positive tests, and
- those who have reversions

HCWs had a 75% risk for reversion if initial positive test fell within the 0.35 to 1.11 range

Thanassi, et al. 2012. Pulmonary Medicine. Article ID 291294

Delineating a Retesting Zone Using Receiver Operating Characteristic Analysis on Serial QuantiFERON Tuberculosis Test Results in US Healthcare Workers

Determined 0.35–1.11 IU/mL as optimal retesting zone

Similar to the clinical situation much like the 5, 10, and 15 mm tuberculin skin test cut-off points

Using higher cut-off values for QFT retesting could:

- lessen patient anxiety
- decrease unnecessary radiographs
- prevent unnecessary exposure investigations
- Possibly spare patients from inappropriate medical treatment due to a transiently “positive” QFT test

Thanassi, et al. 2012. Pulmonary Medicine. Article ID 291294

Interferon gamma release assays

Summary

- Use in low-incidence populations, including HCW may be complicated by current “false-positive” rates
- Use in high-risk groups warranted, but care needed with immunocompromised pts with low white counts

Selecting a Test to Detect TB Infection

IGRAs are the preferred for:

- People who have poor rates of return for TST reading and interpretation (e.g., unhoused)
- Persons who have received BCG vaccination or are known to have NTBM infection

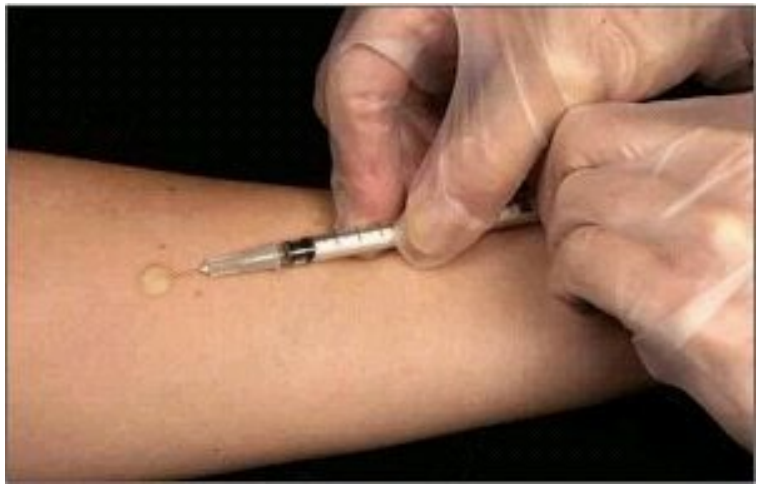
TST is the preferred method for testing for:

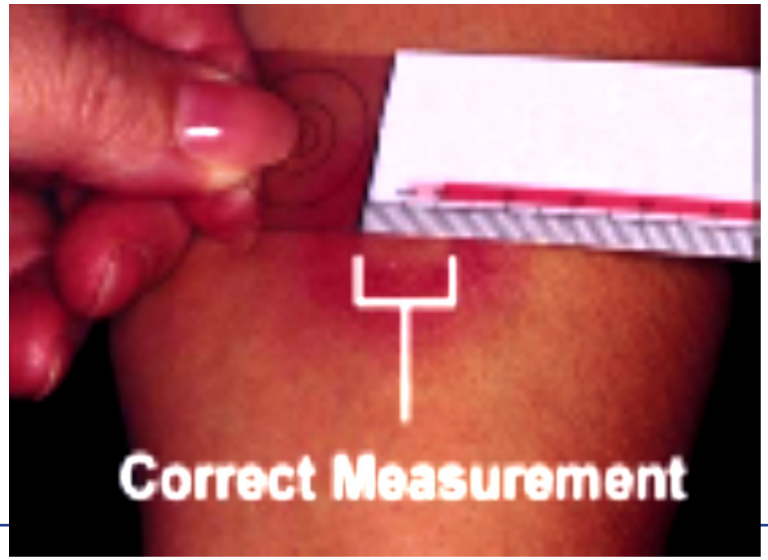
- Children under the age of 5 yrs

Routine testing with **both** TST and IGRAs is **NOT** recommended (with certain exceptions)

Administration and reading of the Tuberculin Skin Test

- Inject intradermally
  - 0.1 ml of 5 TU PPD
- Read reaction 48-72 hrs
- Measure only induration
- Record diameter of reaction in millimeters





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Limitations of TST

False positive due to cross-reactivity with NTBM:

- BCG, wanes over time
- Non-tuberculous mycobacteria, usually < 10 mm

False negative:

- Recent TB infection, peak response at 6 weeks
- Overwhelming active tuberculosis
- Very young age (<6 months old)
- Immuno-compromised: HIV, immunosuppressed
- Severe illness
- Poor technique*

CDC TST Interpretation Recommendations

Training is *essential* to gain proficiency in the administration and interpretation of the TST

The TST should not be performed on a person with written documentation of previous positive TST or treatment for TB

Patients or family members should never measure TST results; only *trained* HCWs

Interpretation of the TST result is the same for persons who have had BCG vaccination

- most BCG cross-reactivity wanes with time

A TST that was not measured and recorded in millimeters (mm) of induration in a timely manner *must* be repeated

BCG Vaccination and Tuberculin Skin Testing

- Bacillus Calmette Guérin – strain of *M.bovis*
- Infant vaccination in high TB endemic areas
- Cross-reactivity of surface proteins leads to enhanced cell-mediated immunity for TB
- Same process impacts the delayed-type (type IV) reaction of a PPD/TST or IGRAs response
- Immunity wanes over time
- Half of vaccinated people lose skin reaction by teen years

BCG Vaccination and Tuberculin Skin Testing

- Tuberculin skin testing NOT contraindicated for BCG-vaccinated persons
- LTBI diagnosis and treatment considered for any BCG-vaccinated person whose skin test reaction is **≥10 mm**, if any of these circumstances are present:
    - Contact with infectious case of TB
    - Born or visit to high TB prevalence area
    - Is continually exposed to populations where TB prevalence is high (HCW, homeless, etc.)