Diagnosis and Treatment of (Latent) Tuberculosis Infection

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Disclosures

- I have no disclosures or conflicts of interest relevant to this topic to report
- I am on the DSMB for a South African study evaluating the efficacy of regiments for MDR-TB infection treatment in children
- I am an associate editor for *Pediatrics*

Objectives

- To discuss the epidemiology of TB globally → nationally
- To understand barriers to prevention and strategies to address them
- To review the updated TB infection testing, treatment guidelines

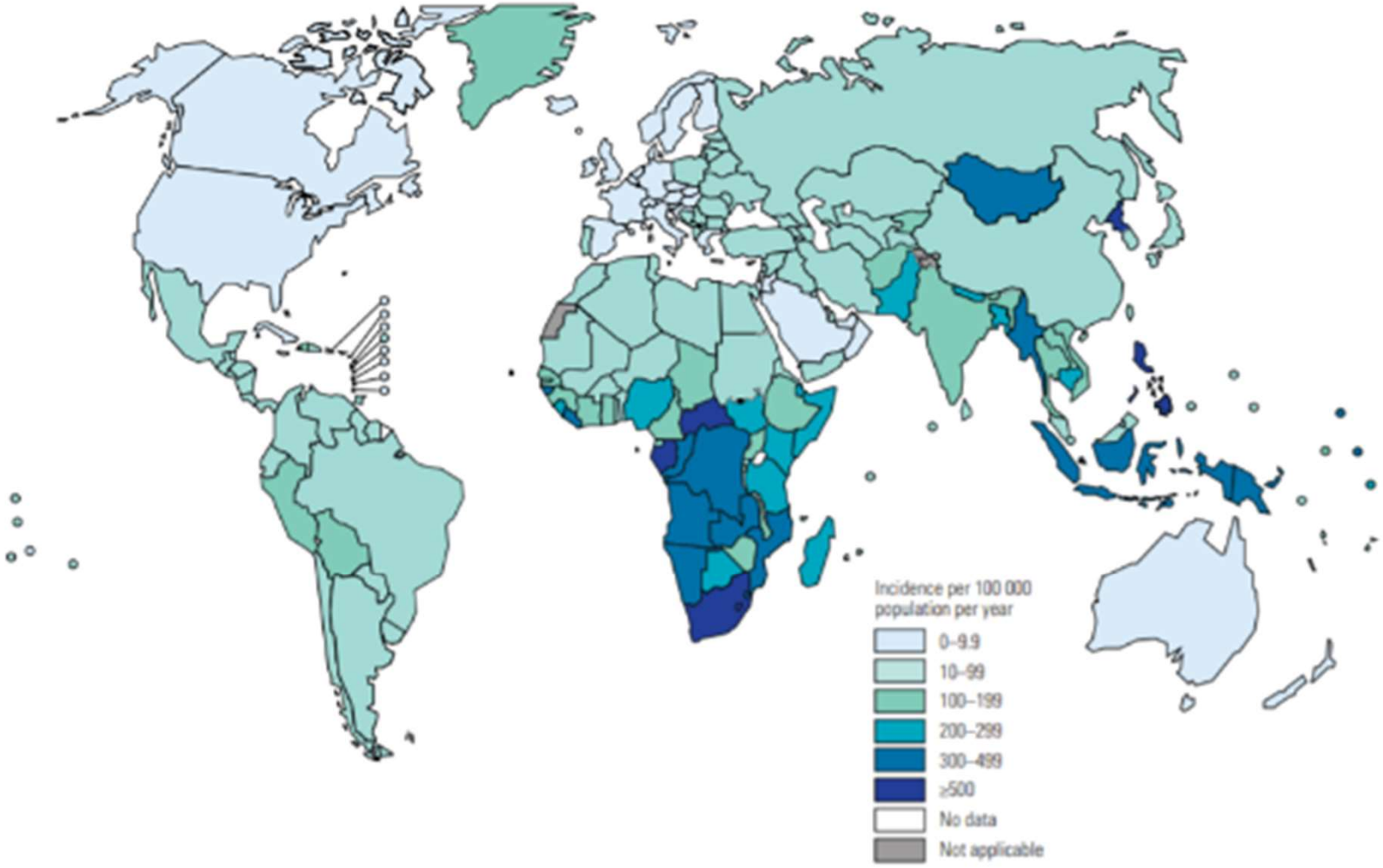
TB Definitions

Category	Sx	Exam	TST/IGRA	CXR	Contagious (kids)	Treatment
Exposure	-	-	-	-	Never	For children < 5yrs old and immunocompromised patients during the 'window period'
Infection	-	-	+	-	Never	Usually 1-2 drugs, given 3-9 months (given by family or health department)
Disease	+	-/+	+/-	+/-	Rare	Multiple drugs (3-4), given 6-12 months (always given by health department)

IGRA: interferon gamma release assay; TST: tuberculin skin test

Epidemiology

Estimated TB incidence rates, 2019



https://www.who.int/publications/i/item/9789240013131

Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study

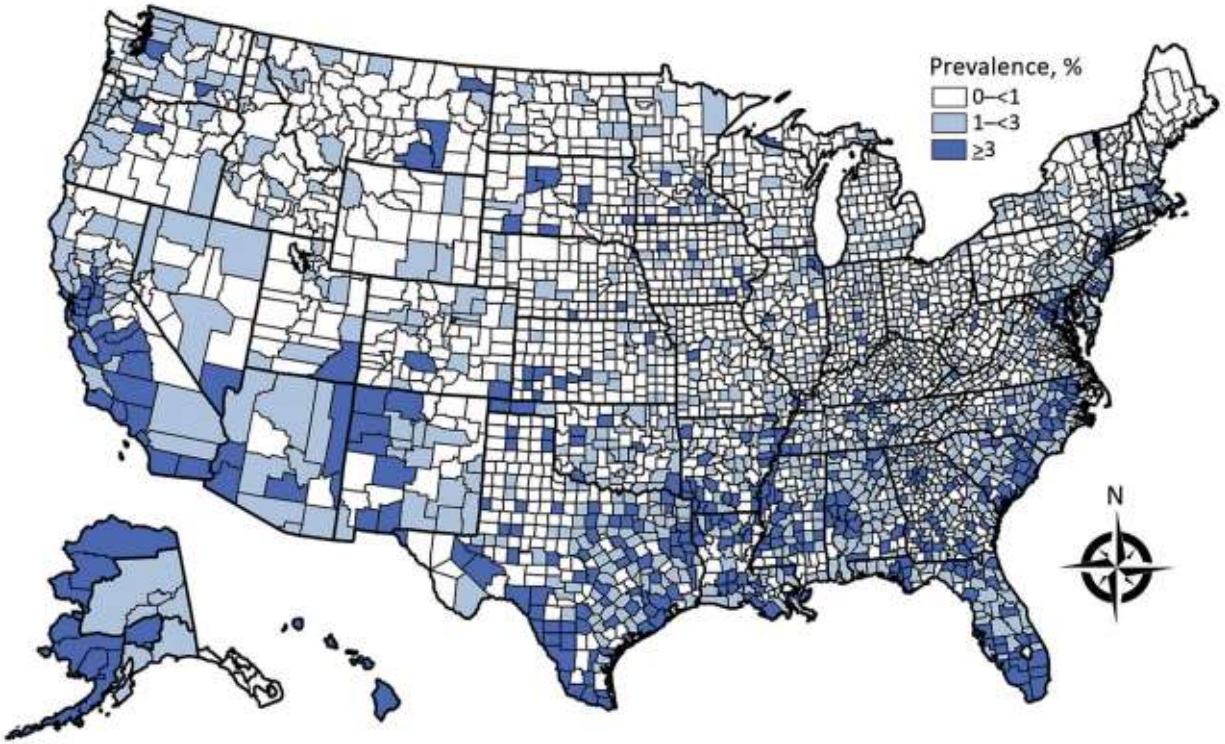
Peter J Dodd, Elizabeth Gardiner, Renia Coghlan, James A Seddon

- 25% of global population infected
- Modeling study in 22 countries accounting for 80% of all TB cases globally
- 15 million children share a household with a person with infectious TB
- Pediatric TB infection:
  - Incidence: 7.6 million
  - Prevalence: 53 million

Lancet Glob Health 2014;2:453

U.S. Data: Infection

- Limited data, as not reportable in all states
- 3.1% estimated to have TB infection (9 million)



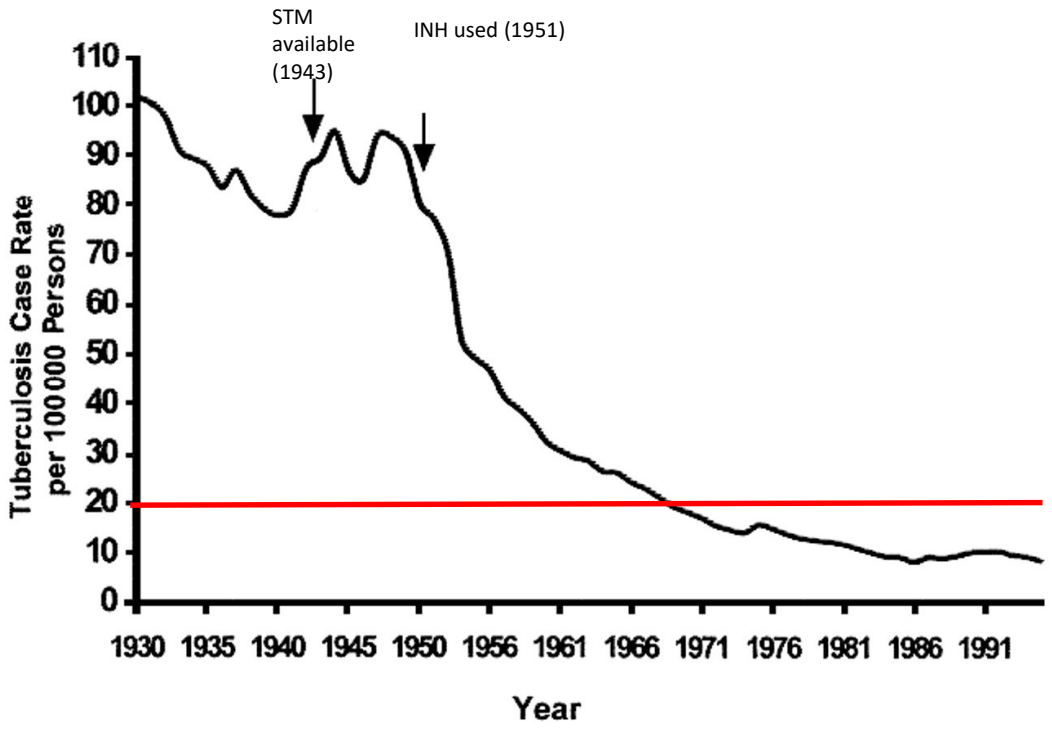
Emerg Infect Dis 2018;24:1930

Why do we treat TB infection?

- Risk of developing TB disease with untreated infection:
  - 5-10% lifetime risk in most patients
  - 40-50% risk in infants
  - 5-10% annual risk in HIV-infected patients
- ½ of lifetime risk in 1st 1-2 yrs after TST conversion
- Remainder of risk evenly spread over lifetime
- We can reduce risk by 90-95% with therapy

How did high-incident countries become low-incident countries (pre-HIV)?

- Societal infrastructure changes
- Active surveillance
- Emphasizing prevention
- U.S. led/leads way on prevention



Barriers to TB infection treatment

Barrier	Example(s)	Potential solution
Failure to identify who needs testing	Lack of medical home Failure to use AAP risk questionnaire	Screening in non-traditional settings*
Failure to test (appropriately)	Slow uptake of IGRAs TST misinterpretation	IGRAs
Failure to explain reasons for therapy	Fixed beliefs re: BCG Lack of emphasis on LTBI treatment internationally	Standardized information packets for families Caregiver education Provider education
Failure to anticipate barriers to therapy	Prior beliefs & cognitive dissonance Economic Social stigma Logistic	Use of directly-observed therapy (DOT) Make it easy for families

AAP: American Academy of Pediatrics

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Failure to test (appropriately)	**Slow uptake of IGRAs** **TST misinterpretation**	**IGRAs**
Failure to explain reasons for therapy	Fixed beliefs re: BCG Lack of emphasis on LTBI treatment internationally	Standardized information packets for families Caregiver education **Provider education**
Failure to anticipate barriers to therapy	**Prior beliefs & cognitive dissonance** **Economic** **Social stigma** **Logistic**	**Use of directly-observed therapy (DOT)** **Make it easy for families**

*Hatzenbuehler et al. *PIDJ* 2016;35:733

Testing for TB Infection

Who does AAP Recommend Testing?

- Universal skin testing is NOT recommended
- Initial PPD should be done before initiation of immunosuppressive therapy (including prolonged steroid usage, TNF-α antagonists)
- Annual PPDs: HIV+ or incarcerated
- Q2-3yr testing should be considered: high-risk
- Immediate PPD should be placed:
  - As part of contact investigation
  - CXR or clinical findings consistent with TB
  - Children emigrating from endemic countries
  - Children with travel history to or contact with persons from endemic countries

Risk Factor Questionnaire

TABLE 4. ORs and 95% CIs for Logistic Model Predictors of Positive TST Result (≥10 mm) in 29 699 Children

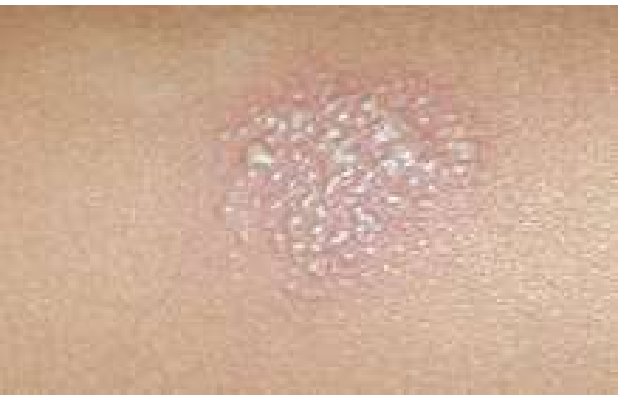
Predictor	OR	95% CI
Child received BCG vaccine	2.31	(1.70,3.13)
Child born outside United States	8.63	(6.16,12.09)
Household member with history of TB	1.53	(1.14,2.04)
Child lived outside United States	2.06	(1.49,2.85)

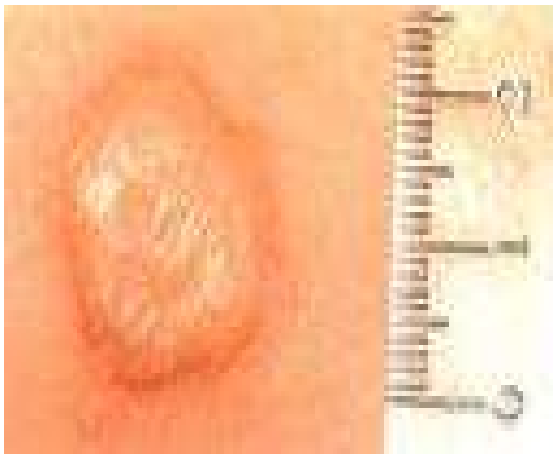
Number of Factors Affirmed	*n*	Sensitivity (%)	Specificity (%)	PPV (%)
1	16 823	83.5	47.5	1.59
2	5297	66.7	83.9	4.04
3	1514	48.9	95.7	10.4
4	471	25.9	98.8	17.6

Pediatrics 2001;107:e54

Positive PPDs

- Generally, skin test conversion occurs within 2 months of contact
- Measure only **induration**
- **Record millimeters of induration (never record “+” or “-”)**
- Any induration seen only in the first 24 hours should be ignored
- Induration after 72 hours counts
- Blistering also counts
- Recognize that many primary care providers may inaccurately place and read TSTs





What *is* a Positive PPD?

≥ 5mm	≥ 10mm	≥15mm
HIV-infected	Children < 4 years of age	Anyone, even without risk factors
Contact to a TB case	Children exposed to high-risk adults†	
Child in whom you suspect TB disease	Immigrants from high-prevalence regions*	
	Children with diabetes or other immunocompromising conditions	

† HIV-infected, incarcerated, IV drug use

**Low* prevalence regions: US, Canada, Scandinavia, Western Europe, Australia, New Zealand

This is really confusing for people who don't do this all the time!

2018 Red Book

PPD Limitations

False positives:
- Exposure to mycobacteria other than TB
- BCG vaccine

False negatives:
- Corticosteroid usage
- Other immunocompromise
- Viral suppression: measles, mumps, influenza

- **20%** don't return for TST interpretation
- Inter-observer variability
- Sliding scale for what is considered positive can be confusing
- **Until recently**, lack of any confirmatory tests

PEDIATRICS PERSPECTIVES

The Case for Retiring the Tuberculin Skin Test

Andrea T. Cruz, MD, MPH,[a] Lee B. Reichman, MD, MPH[b]

The Mantoux tuberculin test (TST) is likely the oldest widely used test in contemporary diagnostics. In the past, when its obvious weaknesses were considered, it always "received a pass" because of the lack of an alternative test. However, with the advent and improvement of interferon γ release assays (IGRAs), we feel it is past time to reconsider the widespread use of TSTs.

CASE

An adolescent with inflammatory bowel disease refractory to steroids was tested for latent tuberculosis infection (LTBI). The TST result was read as positive by a nurse and negative by a physician who had never seen a positive TST result. The patient was not treated for LTBI, received infliximab, and 2 months later developed cavitary pulmonary tuberculosis. Contact tracing identified 2 relatives and several classmates with LTBI and a younger sibling with intrathoracic tuberculosis.

How can we do better? IGRAs, or blood tests for the diagnosis of tuberculosis infection in place of TSTs, have been licensed in the United States since 2001. IGRAs are now recommended for use for children as young as 2 years of age[1] and are recommended by the Centers for Disease Control and Prevention (CDC) for adults in all situations in which a TST has been done.[2] IGRAs have clear advantages over the TST: improved specificity due to absence of false-positive results from Bacillus Calmette-Guérin (BCG) vaccine and most nontuberculous mycobacteria, the need for only 1 patient encounter, and avoidance of boosting (Table 1).[3]

[a]*Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas; and* [b]*Rutgers Global Tuberculosis Institute, Newark, New Jersey*

Dr Cruz conceptualized the article, drafted the initial manuscript, and reviewed and revised the manuscript; Dr Reichman conceptualized the article and critically reviewed and revised the manuscript; and both authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-

IGRAs

- Interferon-γ release assays (IGRAs) detect host response to *Mycobacterium tuberculosis*-specific antigens
- Two main tests currently FDA-approved:
  - T-SPOT.*TB*
  - QuantiFERON Gold Plus
- Offer several potential advantages over tuberculin skin test (TST)

MMWR 2010;59(No.RR-5):1-14

Comparison of TSTs & IGRAs for Children

Characteristic	TST	IGRA
Antigens studied	Many -PPD	ESAT-6, CFP-10, (TB-7.7)
Cross-reactivity with BCG	Yes	**Unlikely**
Cross-reactivity with NTM*	Yes	**Less Likely**
Estimated sensitivity, confirmed TB disease	75-85%	80-85%
Estimated sensitivity, clinical TB disease	50-70%	60-80%
Estimated specificity, BCG-vaccinated children	***49-65%***	***89-100%***
Estimated specificity, BCG-unvaccinated children	***95-100%***	***90-95%***
Distinguish between TB infection and TB disease	No	No
Boosting	Yes	No
Patient visits required	Two	One

*can see cross-reaction with *M. flavescens, M. kansasii, marinum,* and *M. szulgai*

Indeterminate IGRAs

- Reports as high as 30% in newer generation tests, and in younger children
- May be due to specimen handling
- More common in HIV infection
- Overall, seen in 4% of IGRAs done
- Seen very infrequently with TSPOTs (<2%)

Pediatr Infect Dis J 2018;37(4):292; Front Pediatr 2019, e-published 5/29/19

Test characteristics by LCA, HIV-neg, Foreign-born, ≥ 5y (n=7,931)

LTBI prevalence	34% (27.6 to 39.2)		
Sensitivity		**PPV**	
TST	80.7% (72.6-90.5)	TST	**57.9% (52-61.3)**
QFT	78.9% (69-90.2)	QFT	**96.4% (90-99.5)**
TSPOT	73.5% (63.9-86.3)	TSPOT	**98.2% (94.2-99.8)**
Specificity		**NPV**	
TST	70% (68-71)	TST	87.3% (79.9-95)
QFT	98.5% (96.1-99)	QFT	89.9% (83.6-96.3)
TSPOT	99% (98-99.9)	TSPOT	87.7% (81.1-94.9)

Stout et al Thorax 2018:0:1-9.

Test characteristics by LCA, HIV-neg, Foreign-born, **< 5y** (n=463)

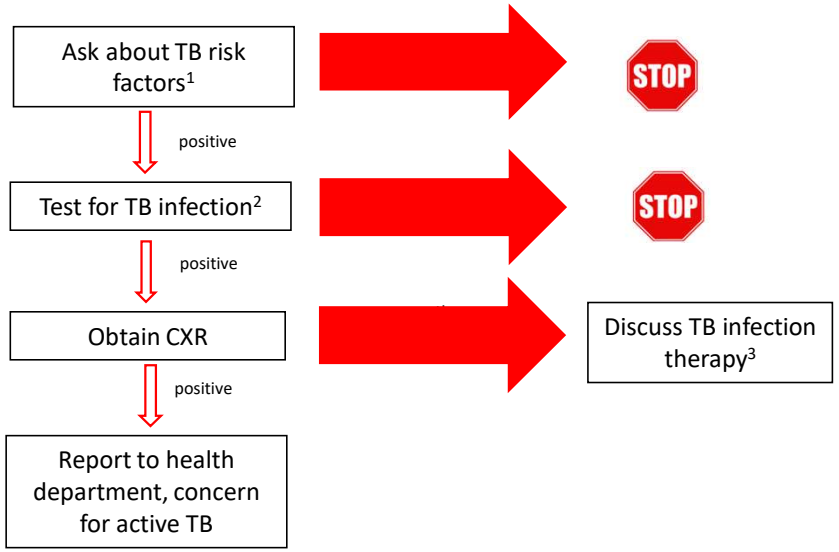
LTBI prevalence	**4.0 % (1.9-6.7)**		
Sensitivity		**PPV**	
TST	69.1% (68.5-79.7)	TST	**10% (5-17)**
QFT	71.2% (55-86)	QFT	**73.1% (41.3-95)**
TSPOT	59% (43-76)	TSPOT	**79.2% (52-96.3)**
Specificity		**NPV**	
TST	73.9% (70-78)	TST	98% (97-99)
QFT	98.9% (97-99%)	QFT	99% (97-99)
TSPOT	99% (98-99)	TSPOT	98% (97-99)

Stout et al Thorax 2018:0:1-9.

TST/IGRA Summary Data

- Foreign-born, ≥ 5 yrs
  - TST had roughly same performance as coin flip for predicting LTBI
  - Both QFT and TSPOT had high PPVs
- Foreign-born, < 5 yrs
  - LTBI prevalence by LCA was 4%
  - For TST ≥10mm as positive, PPV was 10%
  - Almost all + TST results were false positives

Algorithmic Approach to TB Testing

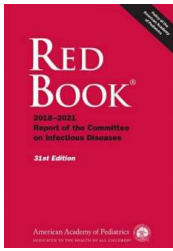


1:
- *Epidemiologic risk factors:* birth in or prolonged travel to a high-prevalence nation, contact to TB case
- *Medical risk factors:* HIV+ or immunocompromised

2:
- Interferon gamma release assays (IGRAs)
- Tuberculin skin test (TST)

3: Regimens
- Isoniazid + rifapentine (3m)
- Rifampin (4m)
- Isoniazid + Rifampin (3m)
- Isoniazid (6-9m)

Red Book Guidelines: IGRAs

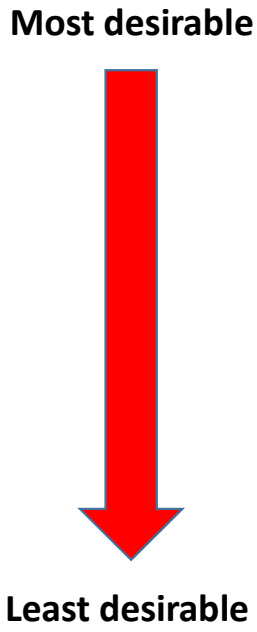


Recommendation	2015	2018	2021
Age*	≥ 5 years	≥ 2 years	TST recommended for <2y, IGRA acceptable
Preferred test for BCG-immunized children	Yes	Unchanged	Unchanged
Use in immunocompromised children	Cautiously	Unchanged	Unchanged

*States that some experts use down to 1 year of age; any negative result (IGRA or TST) should be interpreted cautiously in infants < 3 months of age

Treatment: LTBI

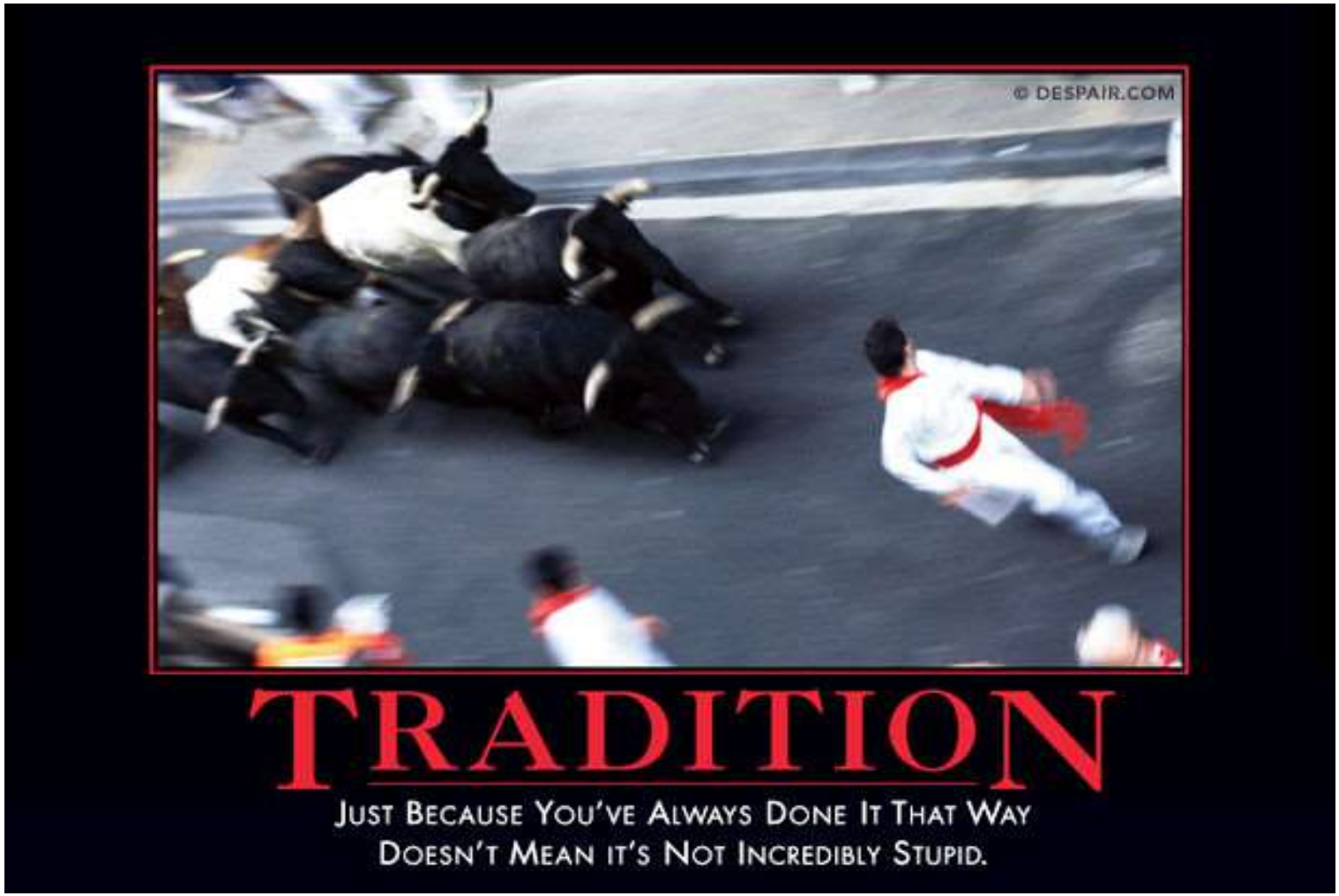
Regimen	Pros	Cons
INH/RFP x 12 doses	Adherence; most experts consider to be the preferred regimen for children >=2yrs old	Availability; requirement for DOPT
RIF x 4m	Adherence, availability	Cost if uninsured; drug interactions
INH/RIF x 3m	Adherence	Slightly increased risk of side effects compared to monotherapy
INH x6-9	~20% benefit over INH x 6m	Adherence (<50% completion)



DOPT: directly-observed preventive therapy; INH: isoniazid; RIF: rifampin; RFP: rifapentine

MMWR 2020;69(1):1-8

Adherence with 9 months of INH is < 50% for adults & children with LTBI



Treatment for Preventing Tuberculosis in Children and Adolescents

A Randomized Clinical Trial of a 3-Month, 12-Dose Regimen of a Combination of Rifapentine and Isoniazid

M. Elsa Villarino, MD, MPH; Nigel A. Scott, MS; Stephen E. Weis, DO; Marc Weiner, MD; Marcus B. Conde, MD; Brenda Jones, MD; Sharon Nachman, MD; Ricardo Oliveira, MD; Ruth N. Moro, MD, MPH; Nong Shang, PhD; Stefan V. Goldberg, MD; Timothy R. Sterling, MD; for the International Maternal Pediatric and Adolescents AIDS Clinical Trials Group (IMPAACT) and the Tuberculosis Trials Consortium (TBTC)

- 905 children (2-17-yrs-old) from US, Canada, Brazil, China, Spain
- Pediatric cohort nested within PREVENT RCT

Variable	3HP	9INH	p=
Progression to disease	0%	0.74%	0.11
Treatment completion	88.1%	80.9%	0.003
Discontinuation due to AE	0.6%	0.2%	0.63
Drug-related hepatotoxicity	0%	0%	-

Villarino et al. *JAMA Pediatr* 2015;169(3):247

SAFETY AND ADHERENCE FOR 12 WEEKLY DOSES OF ISONIAZID AND RIFAPENTINE FOR PEDIATRIC TUBERCULOSIS INFECTION

Andrea T. Cruz, MD, MPH, and Jeffrey R. Starke, MD

- 80 children received 3HP (mean: 13y) in 2014-15
  - 25 were < 12-years-old
- 99% completed therapy
- 94% reported no adverse events
  - 1 with RUQ pain and AST/ALT 90/145
  - 3 nausea/vomiting, normal LFTs
  - 1 with transient rash
  - Contrast to adult data: 63% with flu-like illness, 17% with rash
- *1 adolescent developed cavitary TB 7 months after completion of therapy*

Pediatr Infect Dis J 2016;35:811

Safety and Side Effects of Rifampin versus Isoniazid in Children

- 829 children <18yo, 4RIF vs 9INH
- No hepatotoxicity in either arm; only disease seen in INH arm; *not* powered for efficacy

Table 2. Completion of Treatment.

Variable	Rifampin (N=422)	Isoniazid (N=407)	All Participants (N=829)	Adjusted Difference (95% CI)*
	number (percent)			*percentage points*
Treatment completed: ≥80% of doses	365 (86.5)	314 (77.1)	679 (81.9)	13.6 (7.9 to 19.3)
Treatment completed within allowed time: per protocol	360 (85.3)	311 (76.4)	671 (80.9)	13.4 (7.5 to 19.3)
Received 80–89% of doses	7 (1.7)	8 (2.0)	15 (1.8)	
Received 90–100% of doses	353 (83.6)	303 (74.4)	656 (79.1)	
Treatment completed but not within time allowed per protocol	5 (1.2)	3 (0.7)	8 (1.0)	
Treatment not completed	57 (13.5)	93 (22.9)	150 (18.1)	

NEJM 2018;379:454

Safety and completion of a 4-month course of rifampicin for latent tuberculous infection in children

A. T. Cruz,*† J. R. Starke*

- 404 treated for TBI; 80% 9INH, 20% 4RIF
- Completion rates:
  - 4RIF/self-meds vs 9 INH/DOPT: OR 0.6, 0.2-1.7
  - **4RIF/self-meds vs 9 INH/self-meds: OR 7.9, 2.7-32.2**
  - *Cost consequences:
    - RIF more expensive than INH
    - But, cost of DOPT is substantial, and DOPT not available for all children
- Adverse events: (none serious)
  - 4RIF: 3%
  - 9INH: 6%

Cruz & Starke. *Int J Tuberc Lung Dis* 2014;18(9):1057

INCREASING ADHERENCE FOR LATENT TUBERCULOSIS INFECTION THERAPY WITH HEALTH DEPARTMENT–ADMINISTERED THERAPY

Andrea T. Cruz, MD, MPH,† and Jeffrey R. Starke, MD**

Variable	Subcategory	All Patients N (%)*†	Completed N (%)*‡	Defaulted N (%)*‡
Total		248	186 (75%)	62 (25%)
Age, y	Mean	7.4	7.2 (6.5–7.8)	8.2 (7–9.4)
	Median	7	7	7
Race/ethnicity	Hispanic	145 (58%)	108 (74%)	37 (26%)
	Asian	58 (23%)	43 (74%)	15 (26%)
	Non-Hispanic Black	38 (15%)	30 (79%)	8 (21%)
	Non-Hispanic White	7 (3%)	5 (71%)	2 (29%)
Region of country of origin	United States	91 (37%)	73 (80%)	18 (20%)
	Latin America	48 (19%)	34 (71%)	14 (29%)
	Asia	33 (13%)	24 (73%)	9 (27%)
	Africa	17 (7%)	10 (59%)	7 (41%)
	Middle East	7 (3%)	3 (43%)	4 (57%)
	N.D.	47 (19%)	37 (79%)	10 (21%)
No. medications used	1 drug	245 (99%)	184 (65%)	61 (25%)
	2 drugs	3 (1%)	2 (67%)	1 (33%)
	INH	242 (98%)	183 (76%)	59 (24%)
	RIF	1 (0.4%)	1 (100%)	0
	PZA + FQ	3 (1%)	2 (67%)	1 (33%)
	Changed from INH to RIF§	2 (0.8%)	0	2 (%)
How medications administered	Self-medicated	99 (40%)	49 (49%)	50 (51%)
	ESAT	20 (8%)	17 (85%)	3 (15%)
	DOPT	129 (52%)	120 (93%)	9 (7%)
	ESAT or DOPT	149 (60%)	137 (92%)	12 (8%)
How identified	Contact investigation	82 (33%)	75 (91%)	7 (9%)
	Other	166 (67%)	111 (67%)	57 (34%)

Multivariate: **only the use of DOPT** was associated with completion of therapy (OR 7.2, 95% CI 3.8-13.8)

Cruz & Starke. *PIDJ* 2012;31:193

Completion Rate and Safety of Tuberculosis Infection Treatment With Shorter Regimens

Andrea T. Cruz, MD, MPH, Jeffrey R. Starke, MD

- 3HP vs 4RIF vs 9H, retrospective, non-randomized, 2014-2017
- Completion not associated with race/ethnicity or test of infection
- Completion frequencies:

Regimen	% completion	OR (CI)
9H (given by families)	**53%**	REF
9H (given by DOT)	89%	7.1 (3.5-14.3)
4RIF (given by families)	84%	4.6 (2.1-10.1)
4RIF (given by DOT)	97%	30.6 (3.9-239)
3HP (given by DOT)	97%	27.4 (11.8-63.7)

Pediatrics 2018;141(2):e20172838

Completion Rate and Safety of Tuberculosis Infection Treatment With Shorter Regimens

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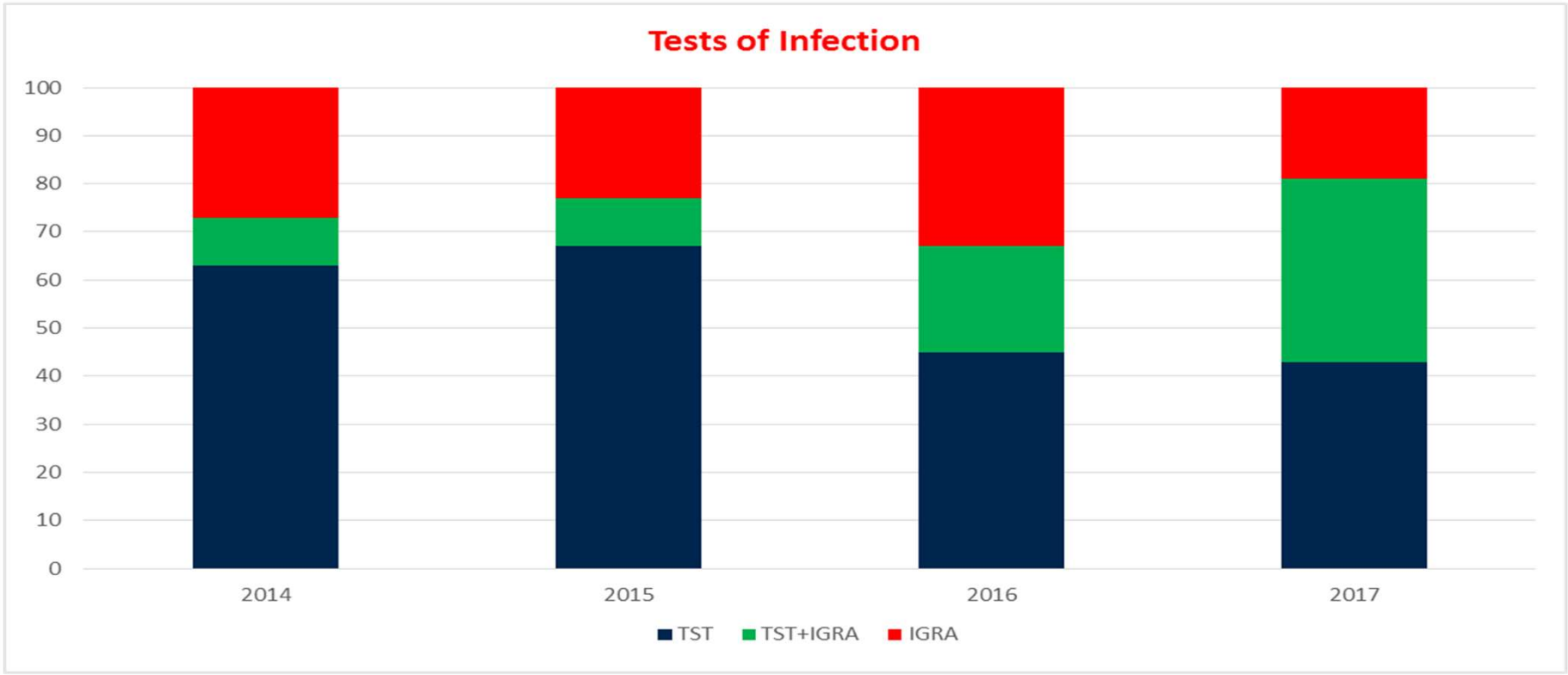
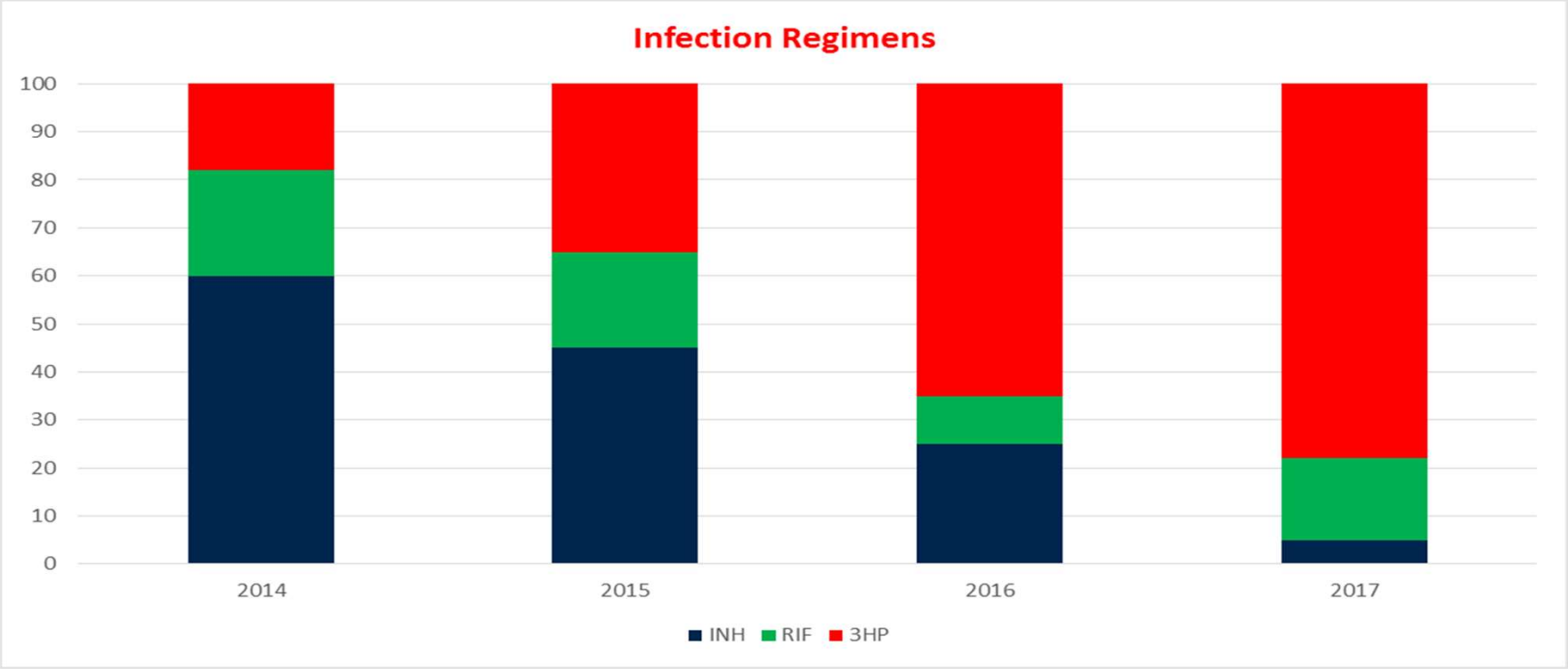


Diagnosed by TST alone: 65% → 45%

Pediatrics 2018;141(2):e20172838

Completion Rate and Safety of Tuberculosis Infection Treatment With Shorter Regimens

Andrea T. Cruz, MD, MPH, Jeffrey R. Starke, MD



Cruz & Starke. *Pediatrics* 2018;141(2):e20172838

Treated with INH: 60% → 8%

INH

- If you are reaching for INH as your first-line treatment for TB infection in all kids, you need to ask yourself **why**
- Most common reasons we now use it:
  - Child receiving medication precluding rifamycin use
  - Parents don’t want DOPT and can’t afford RIF

Caveats

- When a child has problem with the medication, issue is often the parents (buying in to need for treatment, etc)
- INH suspension is often sorbitol based → osmotic diarrhea (use crushed pills)
- Baseline/serial LFTs unnecessary in otherwise healthy children
- Consider baseline LFTs in obese children who may have NAFLD
- If suspected side effect: stop meds, then check LFTs (in that order)

Conclusions

- IGRAs can identify children receiving most benefit from treatment
- IGRAs can reduce unnecessary treatment in BCG-immunized and non-immunized children
- Selecting shorter-course therapy optimizes treatment
- Pull in resources to help families succeed
- Please feel free to call/email with questions:
  - Office: 832-824-5582
  - Cell: 281-685-2584
  - Email: acruz@bcm.edu