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IGRAs, the TST, and Treatment of TB Infection

Andrea T. Cruz, MD, MPH

September 1, 2022

Pediatrics

Disclosures

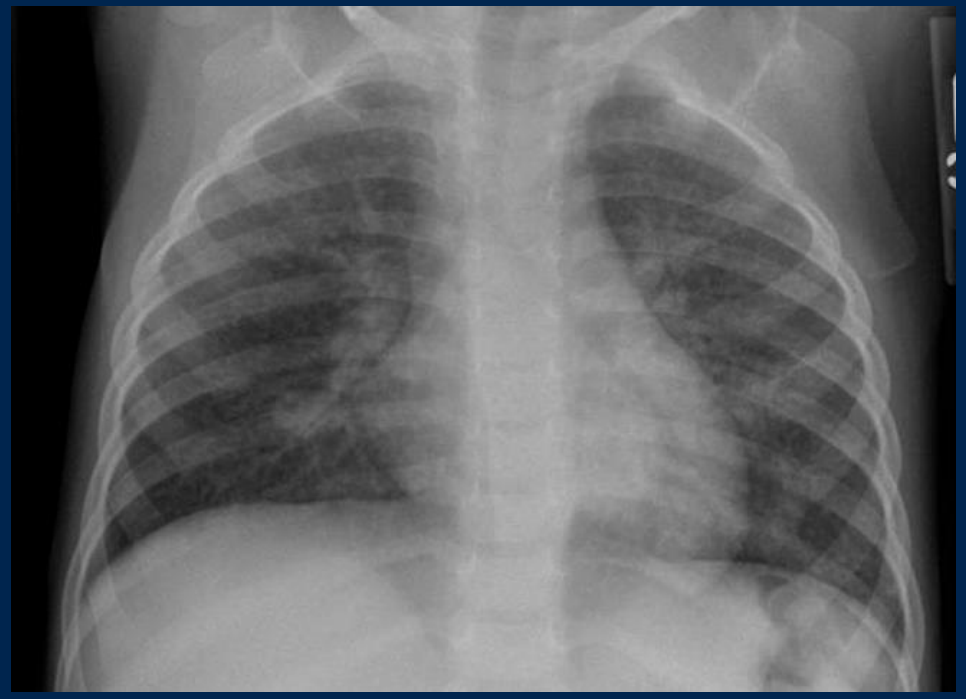
- Associate editor, *Pediatrics*
- Any clinical pictures are included with parental permission

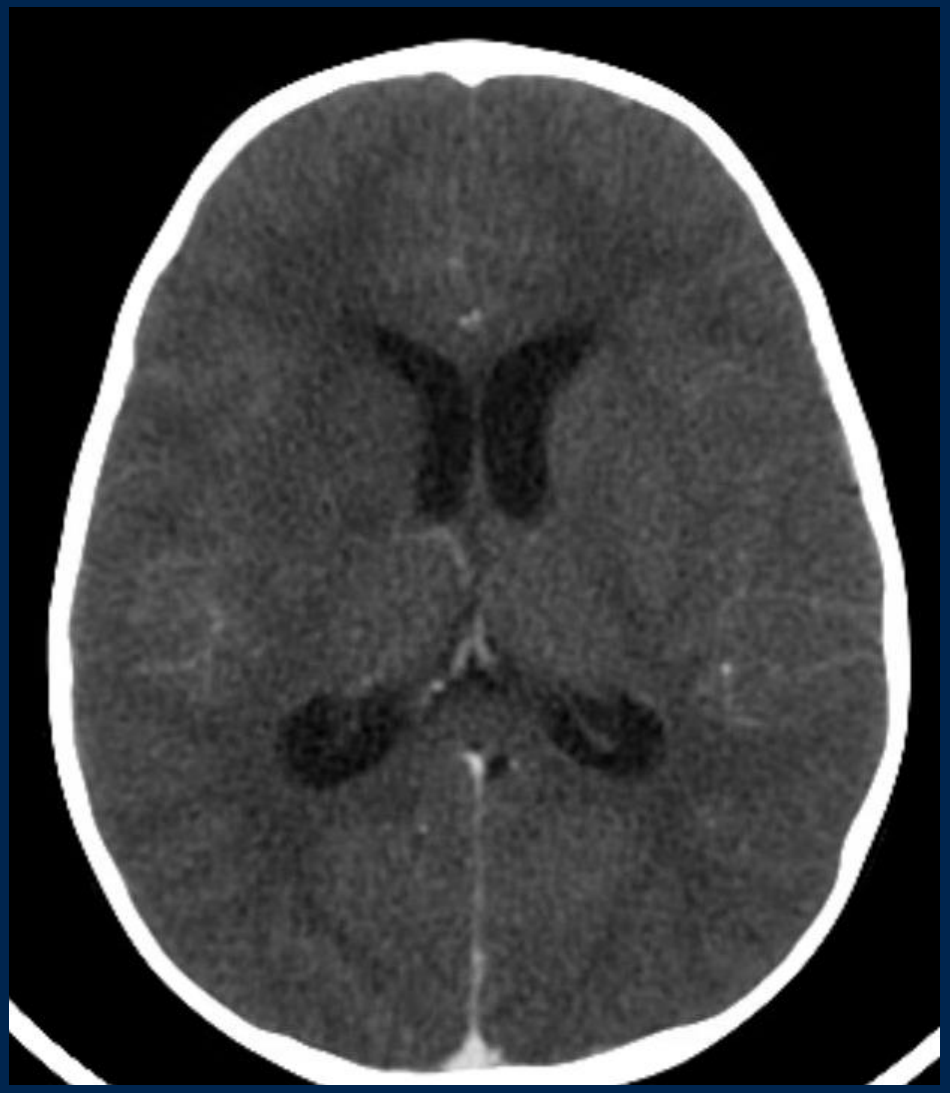
Objectives

- Integrate TB risk factor screening into practice
- Review indications for IGRAs vs TSTs
- Plan a course of therapy for a child with TB infection

Case

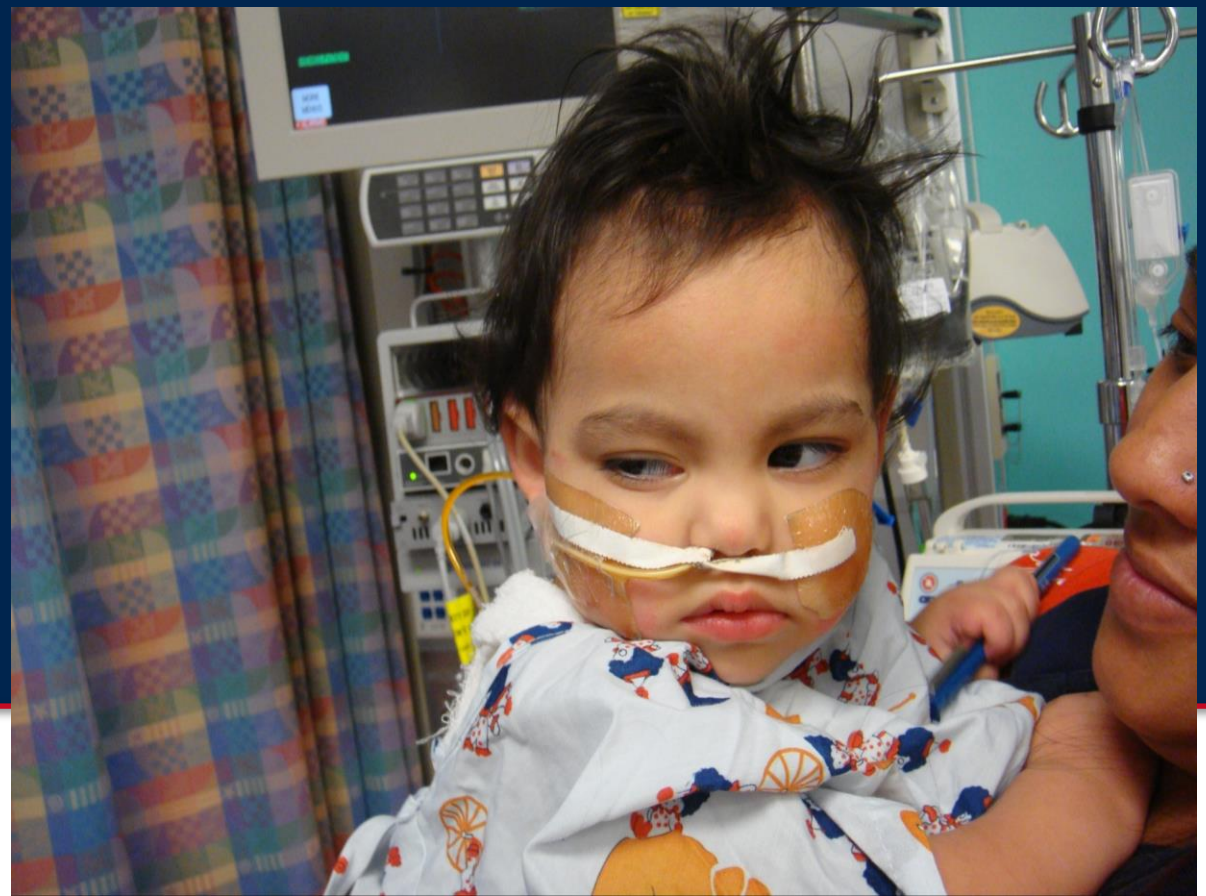
- 14-month-old girl, no medical history, presented to ED with seizures, no return to baseline
- Progressively more altered → intubated
- Fever x 2 weeks, vomiting → prior diagnoses of gastroenteritis
- CT brain (uncontrasted): prominent ventricles, hypoattenuation of R basal ganglia
- CSF: 450 WBC, 2 RBC, protein 800, glucose < 20, Gram stain: no organisms seen





Case

- Immediately started on steroids and TB therapy
- Discharged on INH, RIF, PZA, ethionamide + steroids



Breakdowns

Exposed — Failure to screen the mother or diagnose her in a timely fashion

Infected — Failure to identify LTBI in siblings, which would have prompted testing the baby

Diseased

Sick — Failure to identify early stages of CNS TB

Diagnosed

Treated

Objectives

- To understand barriers to prevention and strategies to address them, particularly through short-course therapy
- To review the updated TB infection testing, treatment guidelines
- To emphasize importance of collaboration between clinicians and public health departments





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Epidemiology

Pediatrics

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

Old vs New Immigration Guidelines (2007-2018) – countries with incidence > 20 per 100,000

Age (y)	TST/IGRA	CXR	Goal
<2	No	If symptomatic	Entirely unclear; reluctance to use TST in a heavily BCG-immunized population
2-14	Yes	If + TST or IGRA	Identify children with infection

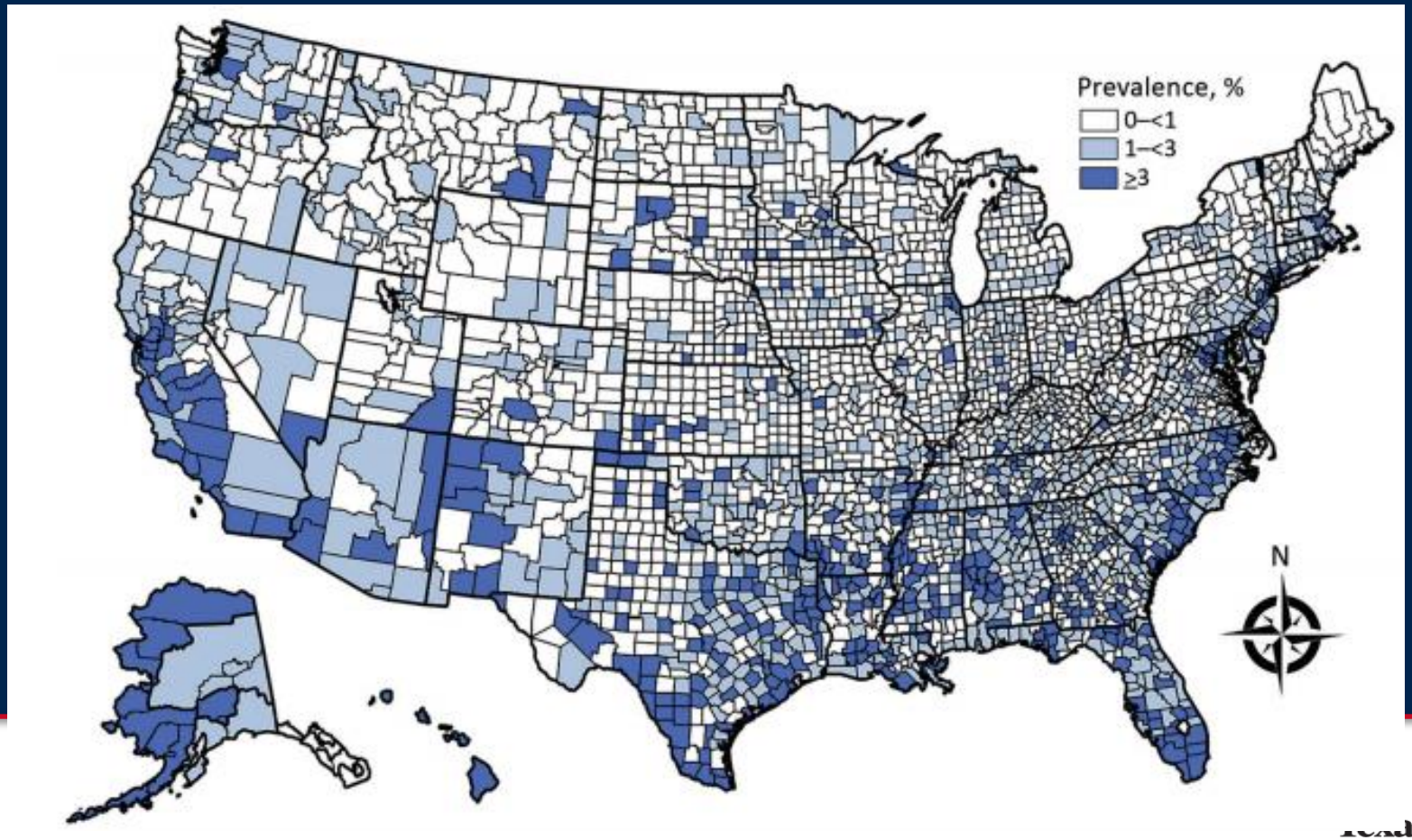
Age (y)	TST/IGRA	CXR	Goal
<2	No	If symptomatic	Entirely unclear; reluctance to use TST in a heavily BCG-immunized population
2-14	IGRA	If + TST or IGRA	Integrate a more specific test to identify children with infection

*All persons > 14yo need CXR, regardless of TB incidence in their country of emigration
Pediatric recommendations only apply to countries with a TB incidence > 20 per 100,000

https://www.cdc.gov/immigrantrefugeehealth/exams/ti/panel/tuberculosis-panel-technical-instructions.html

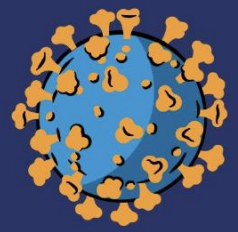
U.S. Data: Infection

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



Emerg Infect Dis 2018;24:1930

The COVID-19 pandemic has reversed years of progress made in the fight to end TB



In 2020

TB DEATHS INCREASED FOR THE FIRST TIME IN OVER A DECADE

FEWER PEOPLE WERE DIAGNOSED AND TREATED OR PROVIDED WITH TB PREVENTIVE TREATMENT

FEWER RESOURCES FOR ESSENTIAL TB SERVICES AND TB R&D

Actions to mitigate and reverse the impact of the COVID-19 pandemic on access to essential TB services are urgently needed

INVEST TO END TB SAVE LIVES

END TB

World Health Organization

Why do we care?

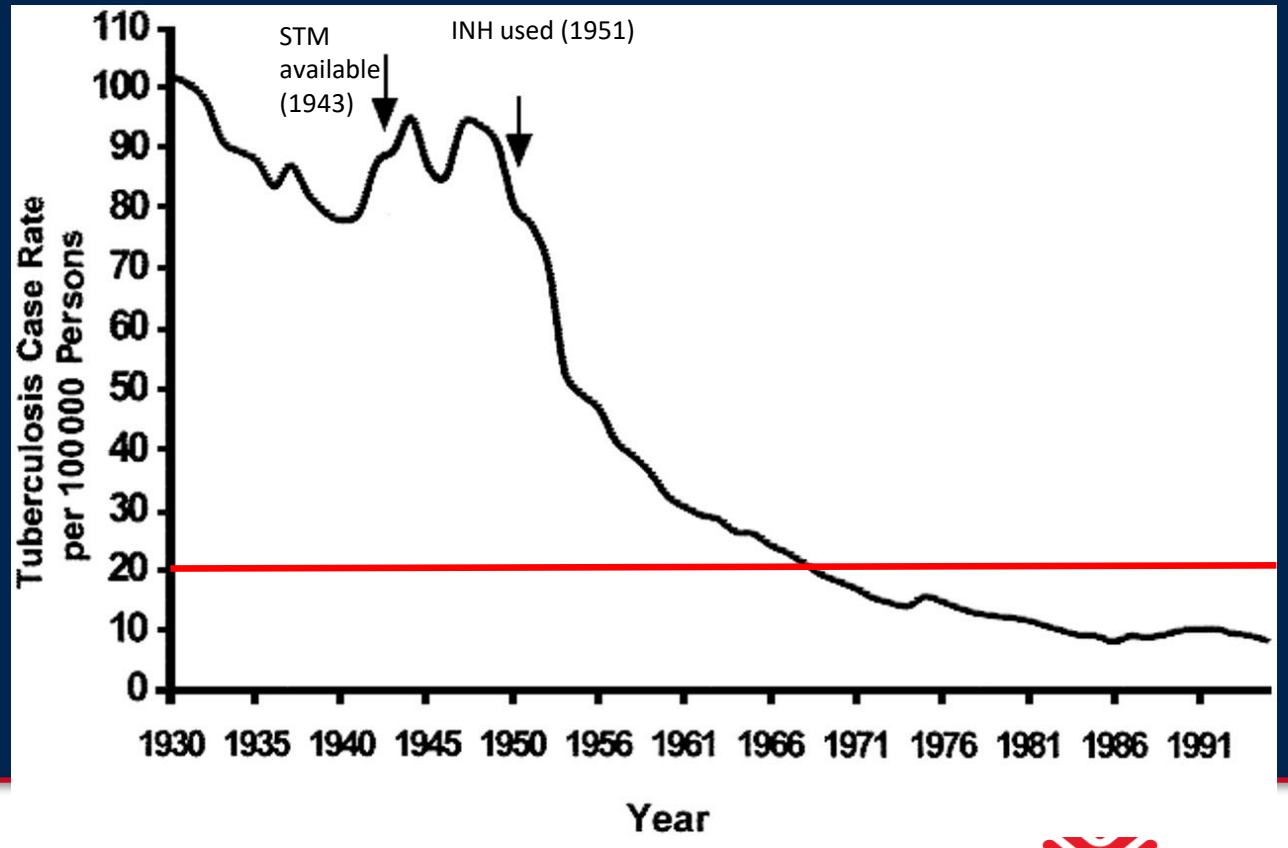
- Risk of progression impacted by age
- Decades of potential benefit from treatment
- Excellent tolerability

Age at infection (y)	No disease (%)	Pulmonary TB (%)	CNS TB (%)
<1	50	**30-40**	**10-20**
1-2	75-80	10-20	2.5
2-5	95	5	0.5
5-10	98	2	<0.5
>10	80-90	10-20	<0.5

Peds in Review 2010;31:13

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

- Societal infrastructure changes
- Active surveillance
- Emphasizing prevention



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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

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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**





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Screening for TB Risk Factors

Pediatrics

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





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Testing: TB Infection

Pediatrics

Controversies in tuberculous infection among pediatric infectious disease specialists in North America

- 197/323 members of the Emerging Infectious Network responded; 2015
  - 7% cared for at least 5 children with TB disease annually
  - 34% cared for at least 5 children with TB infection annually
- Substantial variation in:
  - IGRA use low overall, particularly in preschool-aged children
- 86% continued to use 9 months of INH as first-line therapy
- Comment from editor of a domestic journal: “We can’t publish this; it makes it look like the respondents don’t know anything about TB.”

Cruz et al. *Int J Tuberc Lung Dis.* 2016;20:1463

INDETERMINATE QUANTIFERON-TB GOLD IN-TUBE ASSAY RESULTS IN CHILDREN

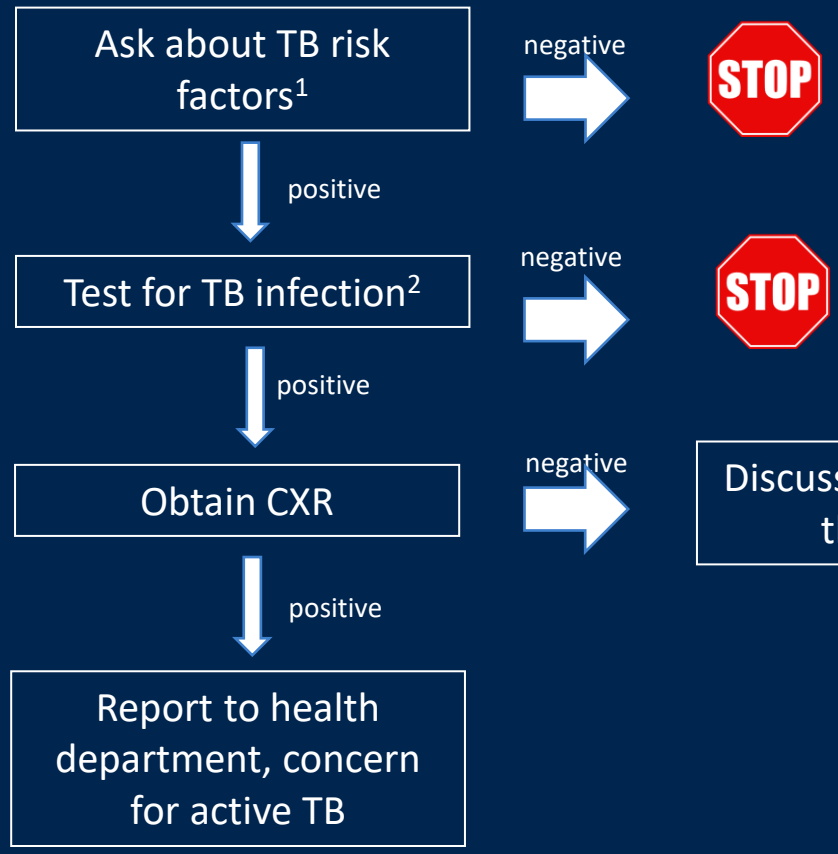
POSSIBLE ASSOCIATION WITH PROCEDURAL SPECIMEN COLLECTION

- 183 children with QFTs; 31% indeterminate, most due to failure of positive control

Variable	Total (n = 183)	Children With Indeterminate QFT-GIT Results (n = 56)	Children With Positive or Negative QFT-GIT Results (n = 127)	OR (95% CI)
	# (%)*	# (%)*	# (%)*	
Demographics				
Male	96 (52%)	26 (46%)	70 (55%)	1
Female	87 (48%)	30 (54%)	57 (45%)	1.4 (0.8–2.7)
Mean age (in years)	11	9.6	11.7	$P = 0.002$
Comorbidities				
Previously healthy	79 (43%)	22 (39%)	57 (45%)	1
HIV	29 (16%)	0	29 (23%	—
Autoimmune†	18 (10%)	9 (16%)	9 (7%)	2.6 (0.9–7.4)
Cancer	16 (9%)	7 (12.5%)	9 (7%)	2 (0.7–6.1)
Inflammatory bowel disease	14 (8%)	6 (11%)	8 (6%)	1.9 (0.6–6.2)
Immunocompromised‡	11 (6%)	6 (11%)	5 (4%)	3.1 (0.9–11.2)
Solid organ transplantation	4 (2%)	1 (2%)	3 (2%)	0.9 (0.09–8.8)
Other comorbidities§	12 (7%)	5 (9%)	7 (6%)	1.9 (0.5–6.5)
Specimen collection				
Outpatient	71 (39%)	6 (11%)	65 (51%)	1
Inpatient	112 (61%	50 (89%)	62 (49%)	8.7 (3.5–21.8)
Phlebotomist	167 (91%)	48 (86%)	119 (94%)	1
Nurse¶	16 (9%)	8 (14%)	8 (6%)	2.5 (0.9–7)

Bui, Cruz, Graviss. *PIDJ* 2014;33:220

Algorithmic Approach to TB Testing



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

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

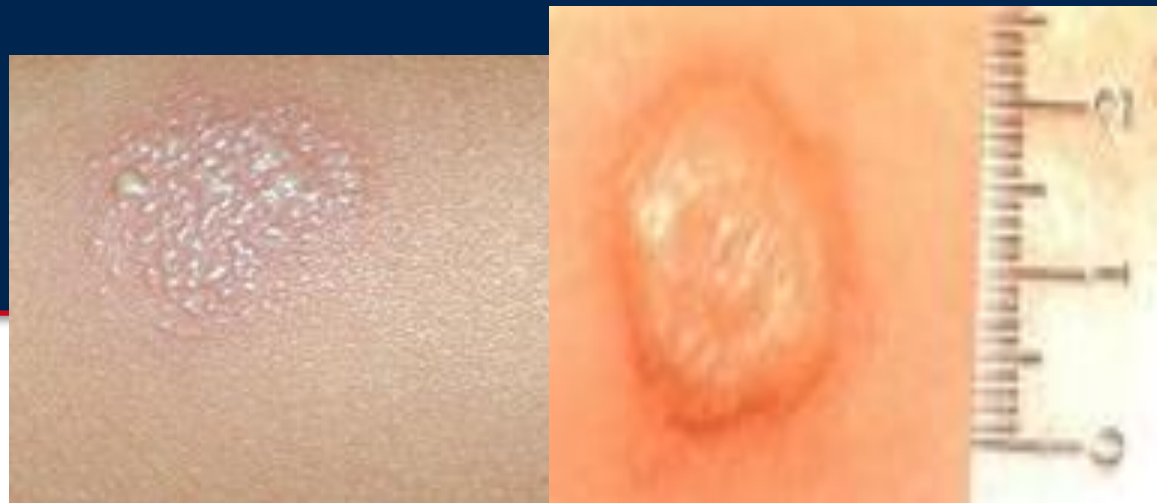
3:
- Isoniazid + rifapentine
- Rifampin
- Rifampin + Isoniazid
- Isoniazid

Comparison of Skin Test & IGRA

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, TB in immunocompetent adults	75-90%	75-95%
Estimated specificity, TB in immunocompetent adults	***70-95%***	***90-100%***
Distinguish between TB infection and TB disease	No	No
Boosting	Yes	No
Patient visits required	Two	One

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



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

PPD Limitations

False positives:

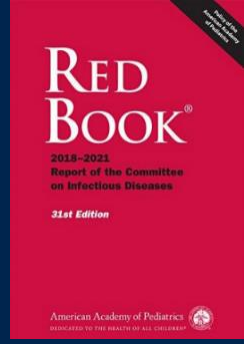
- Exposure to mycobacteria other than TB
- BCG vaccine

False negatives:

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

- Inter-observer variability
- Sliding scale for what is considered positive can be confusing
- **Until very recently**, lack of any confirmatory tests

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

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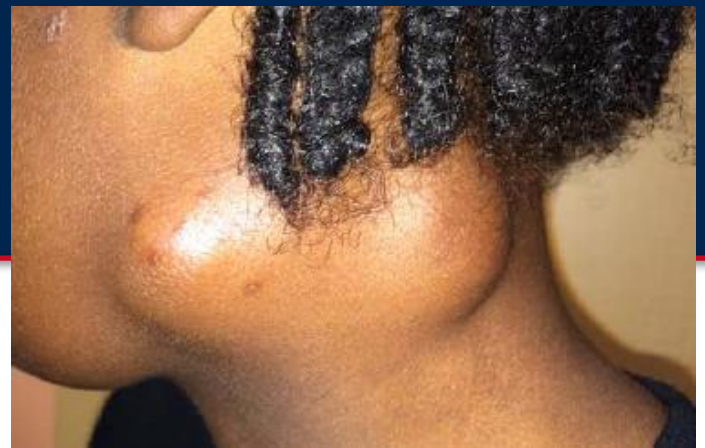
TB Infection: Treatment

Pediatrics

Evaluating for Disease

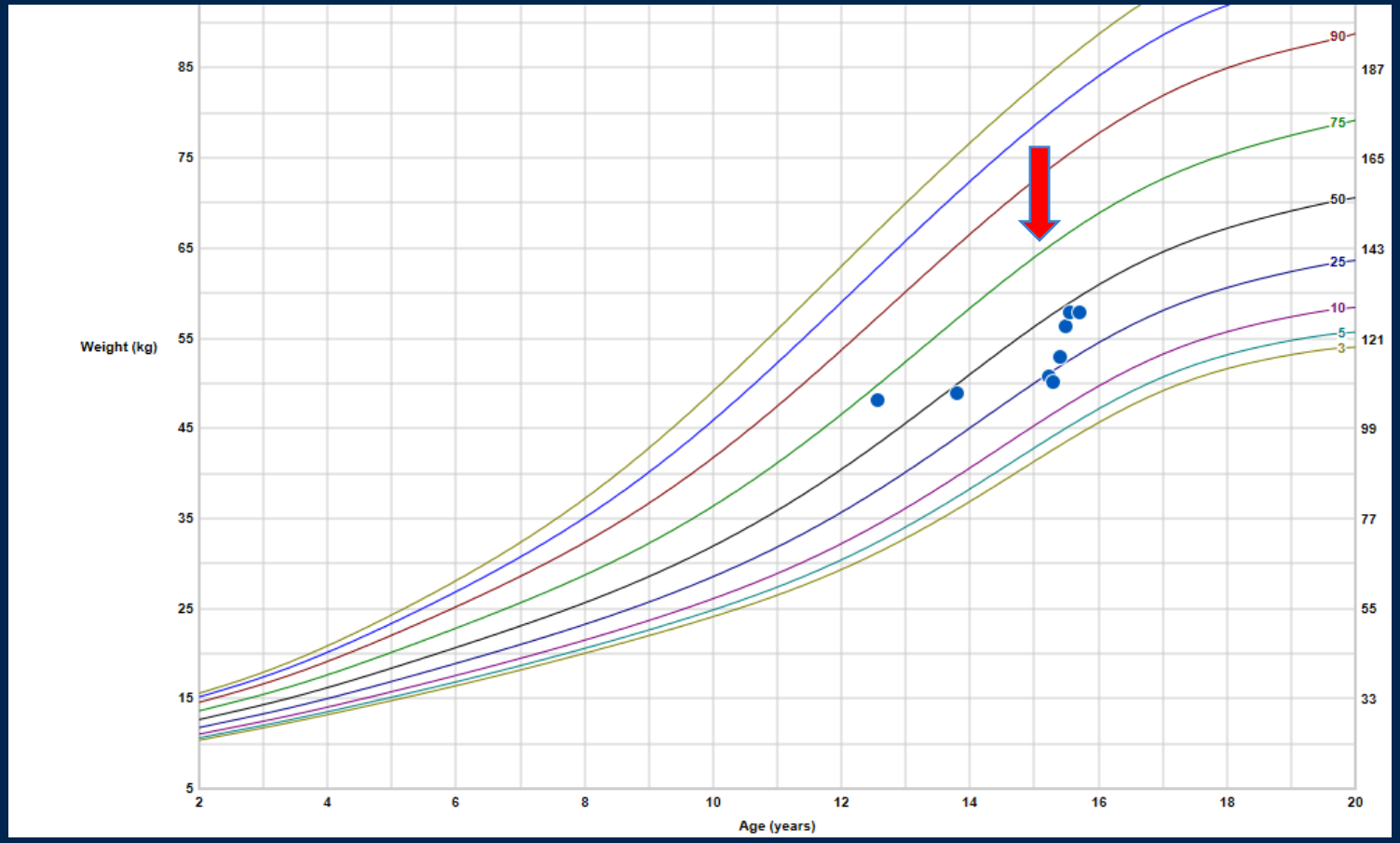
- 2-view CXR (thymus)
- Growth stasis
- Loss of milestones
- Differentiating normal from abnormal lymph nodes

Site	% of cases	Median age (y)
Pulmonary	77.5	6
Lymphatic	13.3	5
Pleural	3.1	16
Meningeal	1.9	2
Bone/joint	1.2	8
Miliary	0.9	1
GU	0.8	16
Peritoneal	0.3	13



Pediatrics 2004;114:333

Assessing growth at each visit



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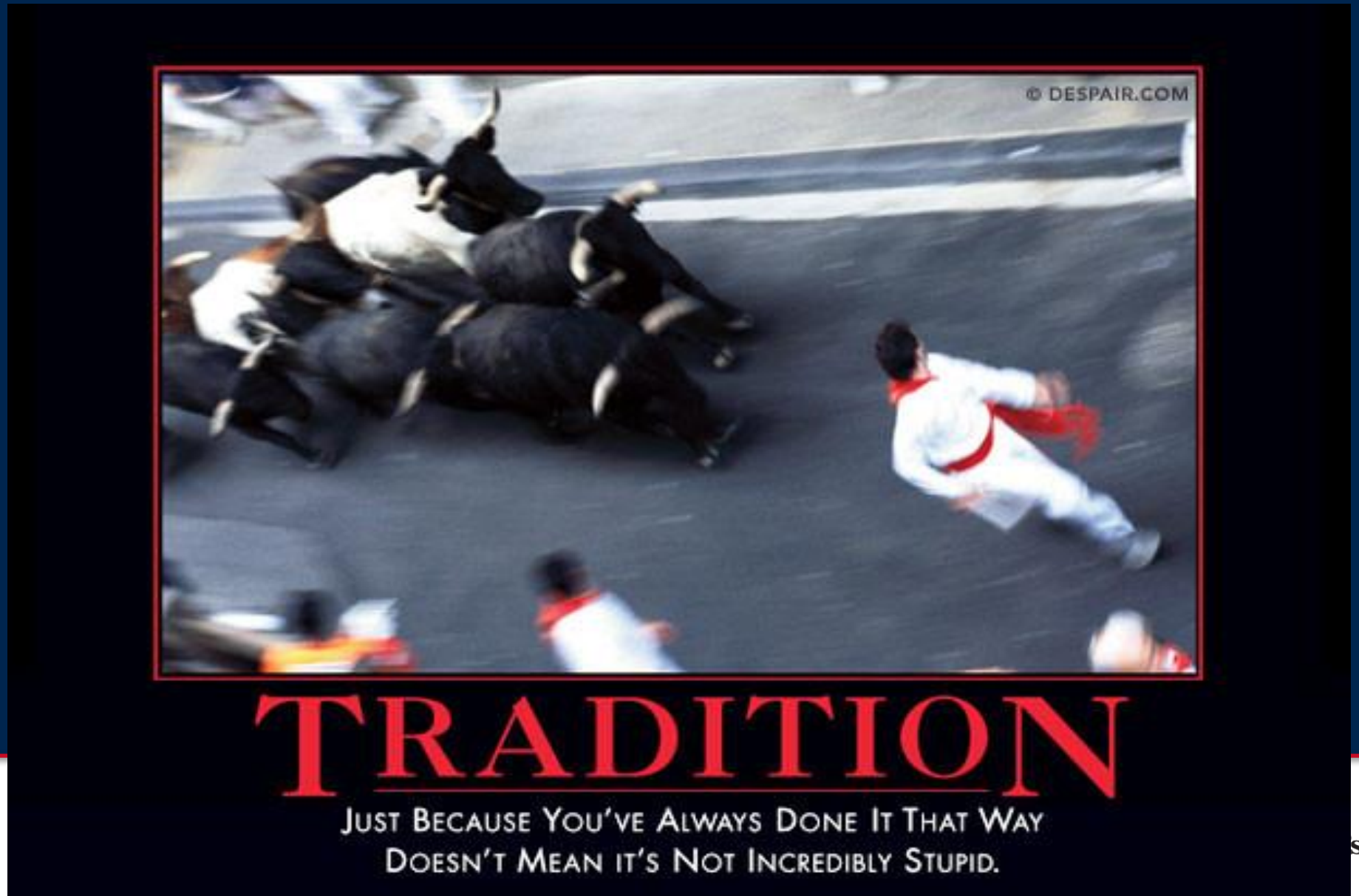
2015 -2021 Red Book: LTBI Regimens

Rec	2015	2018	2021
Preferred regimen	INH	**No specific preference (this is order in Red Book):** • **3m INH + Rifapentine*** • **4m Rifampin** • **9m INH**	Several regimens are recommended, depending on circumstance: • 3m INH + Rifapentine • 4m Rifampin • **3m INH + Rifampin (if 3HP or 4R not feasible)** • **6-9m INH**
RIF role	Limited: INH intolerance or INH resistance in child's contact	Expanded	Unchanged
3HP	Use in ≥ 12 years	Use in ≥ 2 years	Unchanged

*States that some experts think 3HP is the preferred regimen

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



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

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

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

Completion Rate and Safety of Tuberculosis Infection Treatment With Shorter Regimens

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

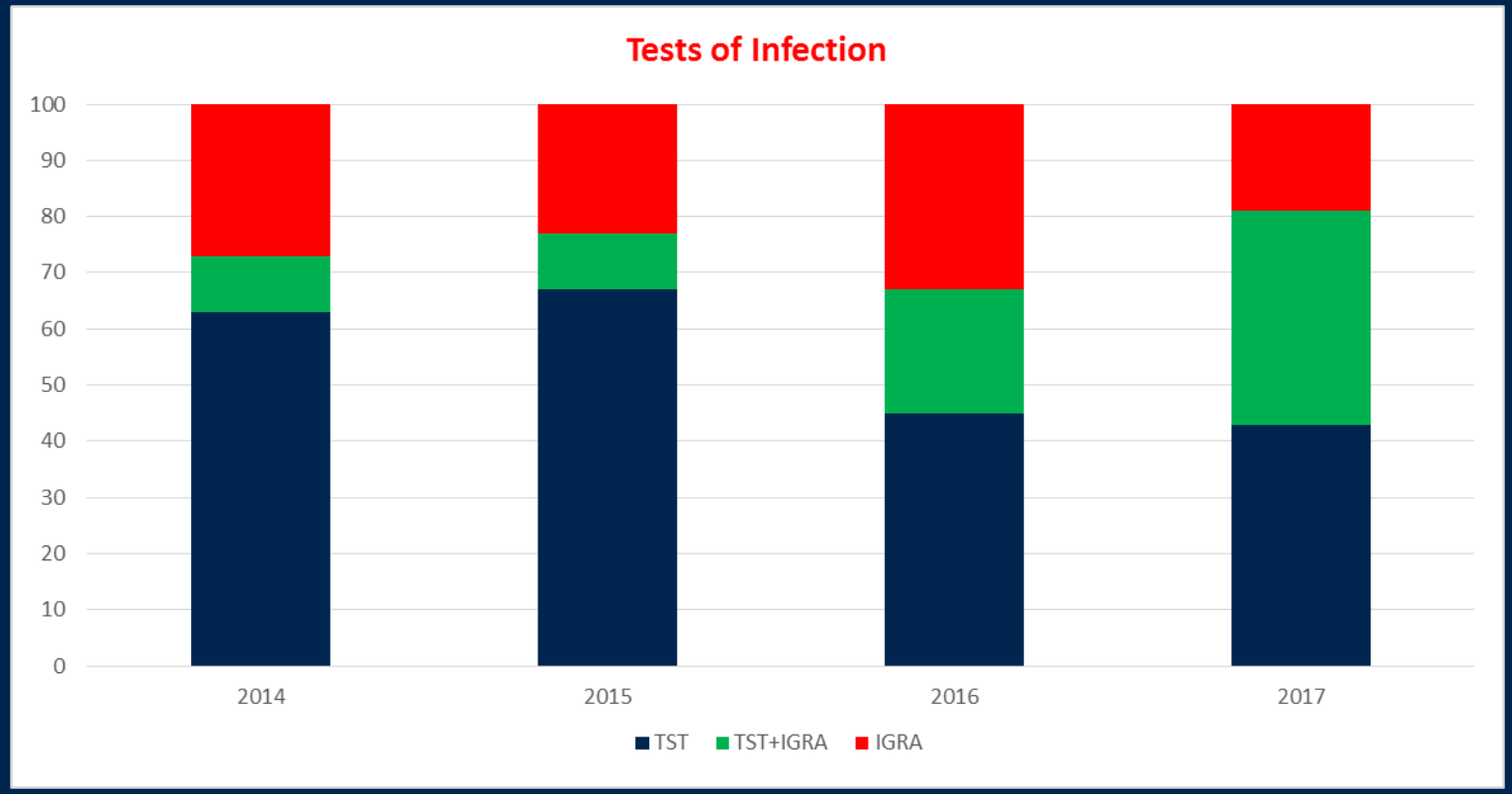
- 3HP vs 4RIF vs 9H, retrospective, non-randomized, 2014-2017
- Completion not associated with race/ethnicity or test of infection
- Completion frequencies:

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)

Cruz & Starke. *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



Diagnosed by TST alone: 65% → 45%

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

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Completion Rate and Safety of Tuberculosis Infection Treatment With Shorter Regimens

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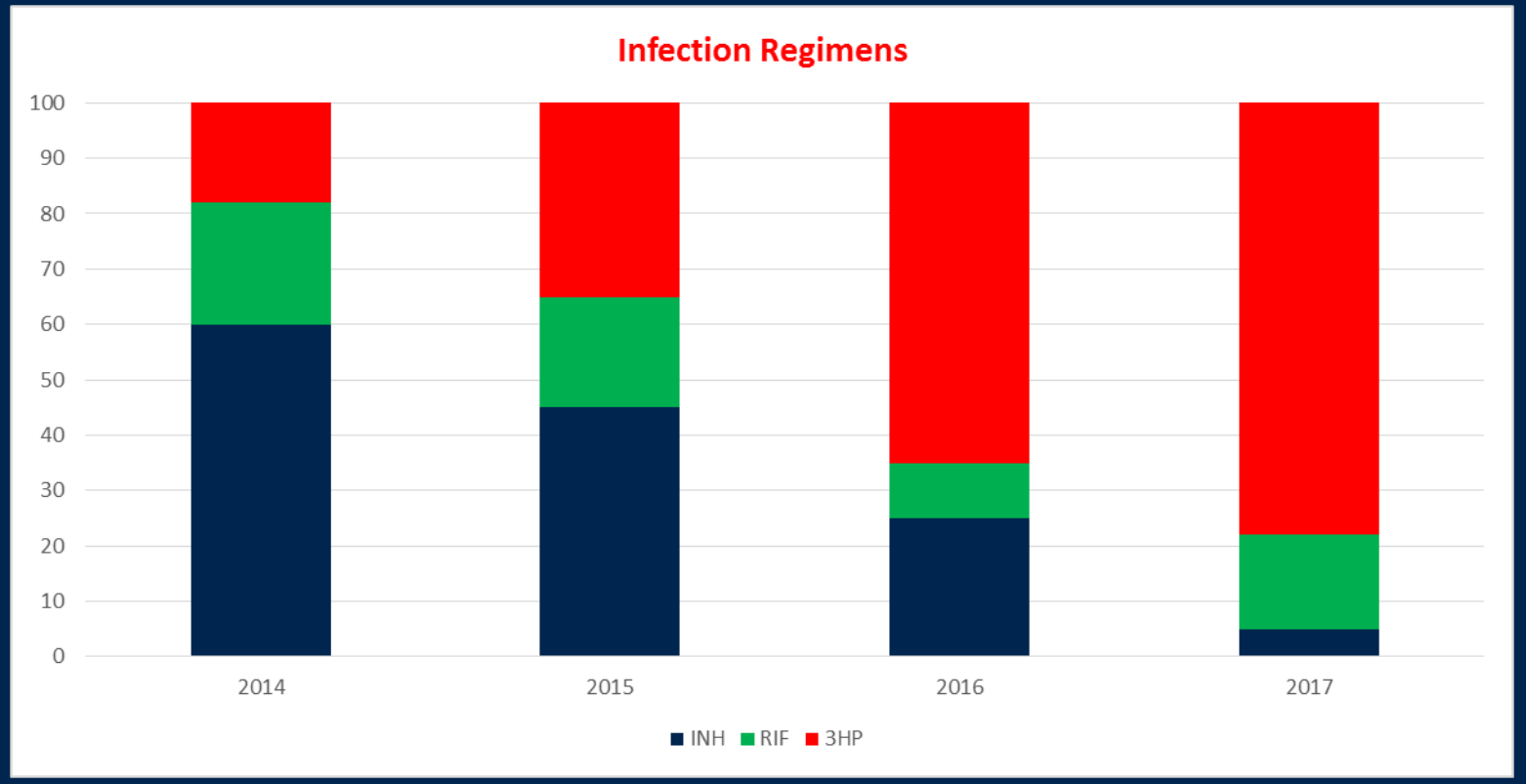

Treated with INH: 60% → 8%

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

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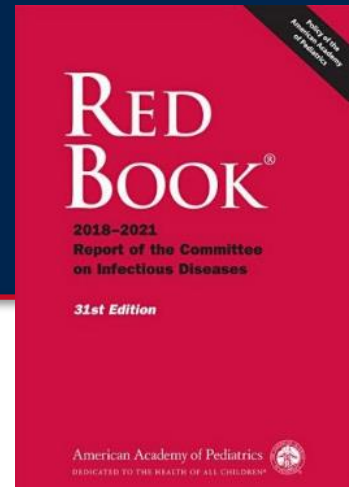
Why don't we use more RIF? Balancing resources

- **National shortage!**
- Cost is $200/month without insurance
- Only way I can get RIF for uninsured kids is under DOPT or enhanced self-administered therapy
- Hard to get suspension form (and 2-week shelf life)

Recommendation	2015	2021
Standard treatment	10-20	**15-20**
TB meningitis	10-20	**20-30**
Non-meningitic TB, infants, toddlers	10-20	**20-30**
Exceed adult maximum (600mg)	No	Yes



Pediatrics

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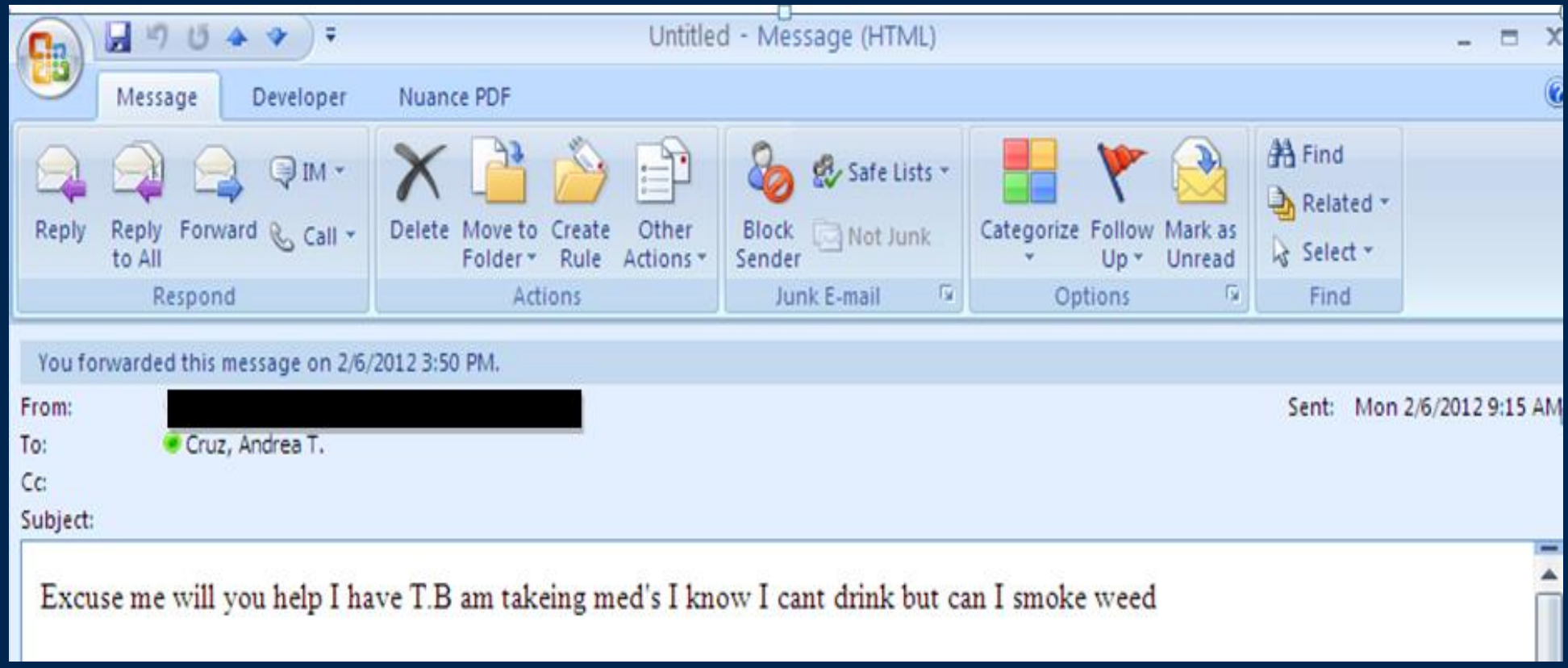
INH

- 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

A transparent therapeutic relationship….



I also get to learn from my patients

Feb 11, 2013, 9:32 AM

What happens if you we're taking the pills for the T-B and you do drugs like lean &dro just once

Dro: hydroponically-grown marijuana

Lean: promethazine + codeine + Sprite +/- Jolly Ranchers

Caveats

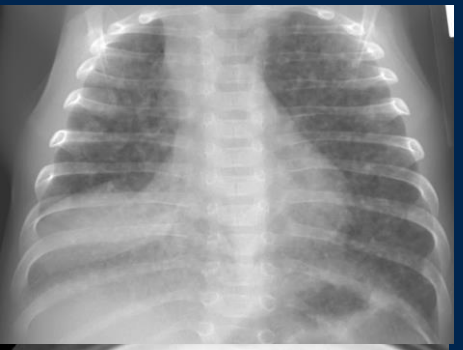
- When a child has problem with the medication, issue is often the parents (buying in to need for treatment, etc)
- INH suspension is often sorbitol based → osmotic diarrhea (use crushed pills)
- Baseline/serial LFTs unnecessary in otherwise healthy children
- Consider baseline LFTs in obese children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

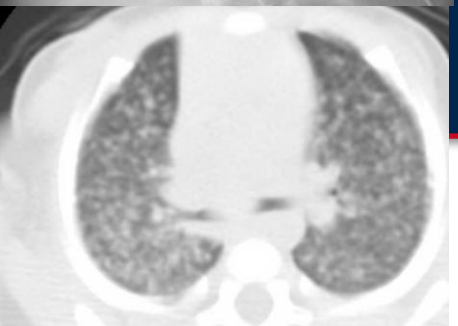
Conclusions

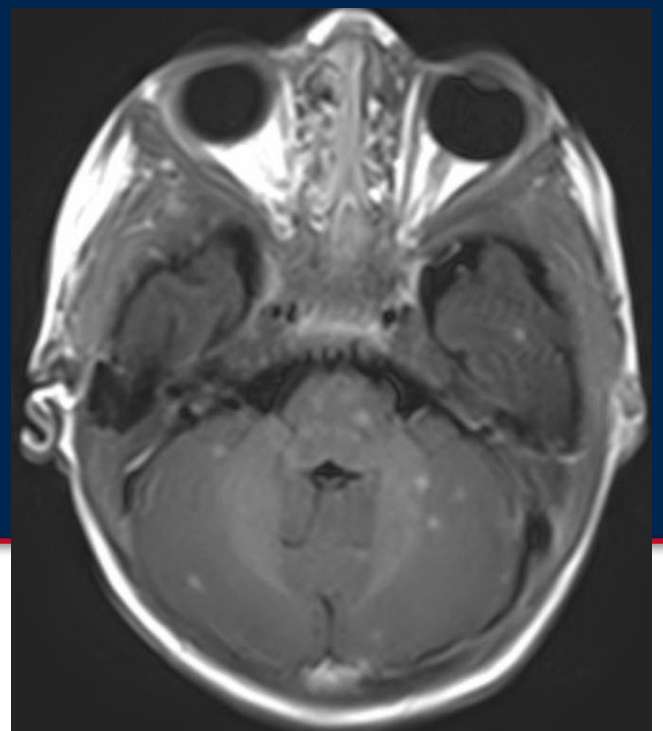
- IGRAs can identify children receiving most benefit from treatment
- IGRAs can reduce unnecessary treatment in BCG-immunized and non-immunized children
- Selecting shorter-course therapy optimizes treatment
- Pull in resources to help families succeed
- Please feel free to call/email with questions: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

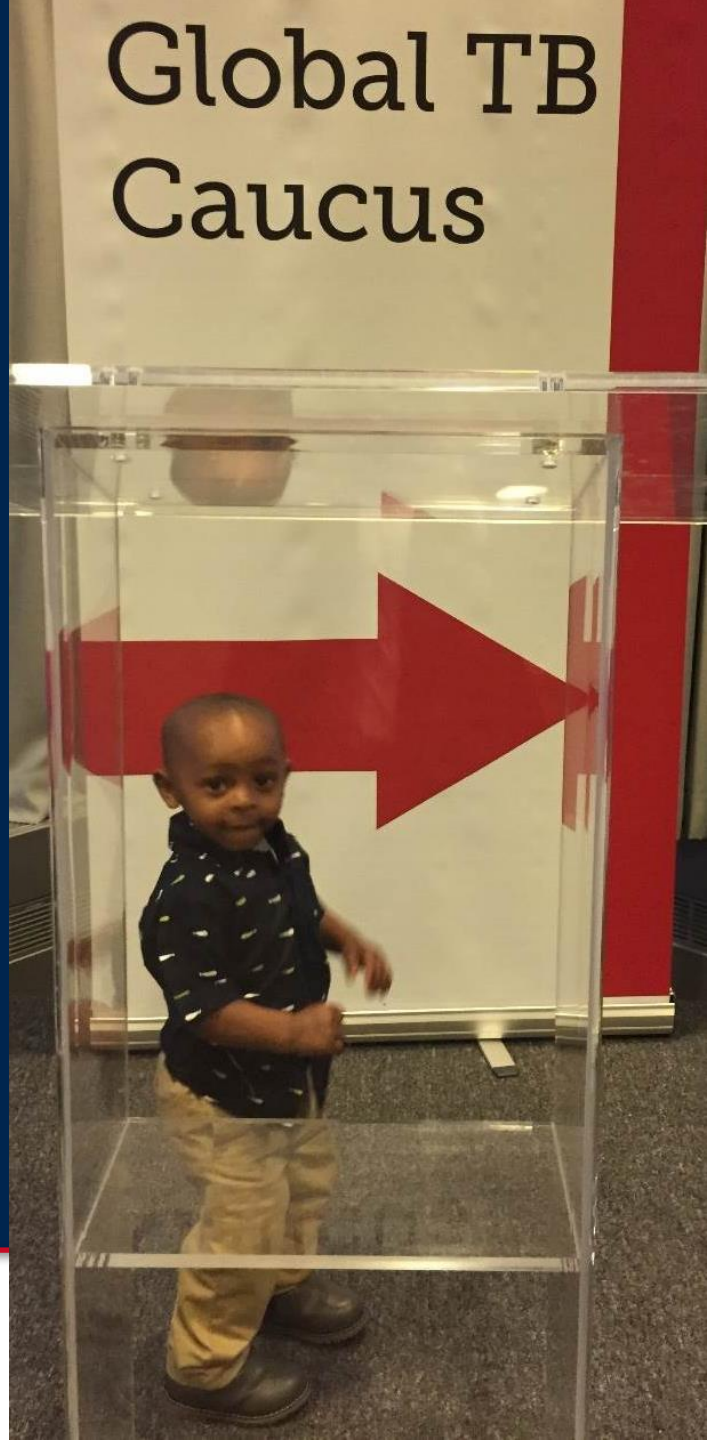
Take-home messages

- TB is often not on the top 5 social problem list for our families
  - Anticipate barriers to care
  - Recognize strategies to circumvent these
- Feel comfortable phoning a friend









Resources: Heartland

- TB screening tests in children: https://www.heartlandntbc.org/wp-content/uploads/2021/12/tb_testing_in_children_booklet_web.pdf

- TB infection treatment in children: https://www.heartlandntbc.org/wp-content/uploads/2021/12/tip_for_treating_LTBI_in_children.pdf

Thank you!

- Thank you for the invitation to talk to your team!

- If I can ever help with a peds case:
  - acruz@bcm.edu
  - Office: (832) 824-5582
  - Cell: (281) 685-2584

- 752 children seen 2007-2017 and started on therapy
- 99% of families agreed to start therapy
- Children tolerated medication exceedingly well
- TST conversion seen in **5%** and associated with parent being the ill individual (OR 3.2, 1.2-8.2)
  - **Not associated with smear- or culture-positivity**

Emerg Infect Dis. 2019;25:523

Why were the rates of progression to LTBI lower in this study?

- Glass ½ full:
  - We are casting the net of contact wider; this reflects better public health control
  - Maybe window prophylaxis prevents progression to infection
- Glass ½ empty:
  - Kids are being identified as contacts later, so most of those who are positive are positive at the time of first testing; this reflects worsening public health control
  - We are snaring all kinds of low-risk kids in contact investigations; we need to be more specific

Cruz & Starke. Accepted, *Emerg Infect Dis*


Treatment of Multidrug-Resistant Tuberculosis Infection in Children

Andrea T. Cruz, MD, MPH, Anthony J. Garcia-Prats, MD,† Jennifer Furin, MD, PhD,‡ and James A. Seddon, MBBS, PhD§*

- In many countries, no attempt made to treat these patients
- Few data on regimens and doses
- Most use a fluoroquinolone, either as monotherapy or in conjunction with a 2nd drug, after TB disease is excluded
- Some children will not be candidates for MDR-LTBI treatment, based on the isolate's drug-susceptibility pattern

Cruz et al. *PIDJ* 2018;37:1061

Adolescents With Tuberculosis

A Review of 145 Cases

Andrea T. Cruz, MD, MPH, Kevin M. Hwang, BA, Gilad D. Birnbaum, BA, and Jeffrey R. Starke, MD

- 145 adolescents, 43% microbiologically confirmed
- 14% identified via contact tracing, 90% of whom were asymptomatic

TABLE 3. Comparison of Adolescents With Cavitary and Noncavitary Pulmonary TB

Variable	Total (n = 118)*	Cavitary (n = 31)	Noncavitary (n = 87)	*P*
Age				
Mean age (yr)	15.3	15.8	15.1	0.047
TST				
TST ≥5 mm	105 (89%)	26 (84%)	79 (90%)	0.32
Microbiology				
Cultures attempted	97 (82%)	31 (100%)	66 (76%)	0.001
AFB smear	24/97 (25%)	13/31 (42%)	11/66 (17%)	0.01
AFB culture	52/97 (54%)	20/31 (65%)	32/66 (48%)	0.19
Duration of therapy				
Mean duration of therapy (mo)	7.6	8.5	7.3	0.20
End-of-therapy radiographic findings				
Radiograph abnormal	63 (53%)	16† (52%)	47 (54%)	0.83
Hilar adenopathy	14	1 (3%)	13 (15%)	0.11
Scarring	37	17 (55%)	30 (34%)	0.06
Calcifications	2	0	2 (2%)	1
Effusions	1	0	1 (1%)	1

PIDJ 2013:32:937

Tuberculosis in Pediatric Oncology and Bone Marrow Transplantation Patients

Andrea T. Cruz, MD, MPH,[1,2]* Gladstone Airewele, MBBS, MPH,[3] and Jeffrey R. Starke, MD[1]

- Currently, no recommendations to test for infection prior to chemo or BMT
- **Many of these patients have epi risk factors that should result in screening aside from their heme-onc diagnosis**

TABLE I. Clinical Course for Five Children With Cancer Or Bone Marrow Transplantation and Tuberculosis

#	Age (years)/sex	Race/ethnicity	Malignancy	Site of disease	Country of birth	TST (mm)	CXR	Culture	TB outcome
1	2/M	Hispanic	Hepatoblastoma	Disseminated (abdominal, pulmonary)	US	16	Infiltrate	Positive	Survived
2	5/M	Asian	ALL	Pulmonary	US	18	Pleural effusion	Negative	Survived
3	10/M	Hispanic	Hodgkin	Lymph node	Mexico	15	Normal	Positive	Survived
4	10/M	Asian	Medulloblastoma	Pulmonary	Vietnam	0	Apical nodules	Positive	Survived
5	18/M	Asian	Hodgkin	Pulmonary	Vietnam	10	Cavity	Positive	Survived
6	18/F	Black	S/p BMT for Hgb SS	Disseminated (pulmonary, bacteremia)	Nigeria	ND	Infiltrates	Positive (blood and lung) at autopsy	Died

Pediatr Blood Cancer 2014;61:1484

Tuberculosis among Families of Children with Suspected Tuberculosis and Employees at a Children's Hospital

- Only 12% of children were contagious, using very liberal definitions
- 17% of children were accompanied to TCH by an adult with previously undiagnosed pulmonary TB

TABLE 1. Cost-Effectiveness of Tuberculin Skin Testing (TST) in a Tuberculosis Screening Program

Population	No. of persons screened	No. of TSTs performed	No. of CXRs obtained	Total cost of evaluation, $	No. of abnormal CXRs (caregivers) or TST conversions (employees)	Cost per identification of 1 abnormal CXR (caregivers) or TST conversion (employees), $	No. of persons screened to identify 1 abnormal CXR (caregivers) or TST conversion (employees)
Caregivers	254	NA[a]	254	54,705	10	5,471	25
Employees: contact investigations	880	498	119	88,323	1[b]	88,323	880
Employees: noncontact investigations	19,883	19,841	87	1,963,553	45	22,570	441
Total	21,017	20,339	460	2,106,581	56	37,618	375

Cruz et al. *Infect Control Hosp Epidemiol* 2011;32:188
Muñoz et al. *Infect Control Hosp Epidemiol* 2002;23:568

Gastric Aspirate Yield For Children With Suspected Pulmonary Tuberculosis

Andrea T. Cruz,[1,2] Paula A. Revell,[3] and Jeffrey R. Starke[1,4]

- 280 children; 11% with culture confirmation and only 3 had positive AFB smears
- Of the 32 with positive cultures:
  - 75% positive on first specimen
  - 2nd and 3rd specimens increased diagnostic yield by 19% and 8%, respectively
- Intermittent positivity requires multiple gastrics

JPIDS 2013;2:171

Emergency Department Presentation of Children With Tuberculosis

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

- N=60 (35% of all cases)
- 76% diagnosed at time of first ED visit
- 73% intrathoracic; 12% with meningitis
- Screening tools validated for adults were 77-98% sensitive for intrathoracic and 50-100% sensitive for extrathoracic TB

Table 1
Frequency of Documentation of TB Risk Factors and Symptoms among 60 Pediatric ED Patients With TB

Historical Finding	Frequency Documented (Positive)
Risk factor*	
Any TB risk factor documented	31 (78)
History of exposure to person with TB	20 (57)
Birth abroad	10 (50)
Personal history of TB in past	2 (18)
Prior positive TB skin test	4 (36)
Contact with persons with history of incarceration	2 (29)
Contact with HIV-infected persons	0
Contact with homeless persons	0
Symptoms	
Fever	50 (86)
Cough	44 (82)
Subjective weight loss	15 (41)
Night sweats	6 (23)
Hemoptysis	7 (35)

Acad Emerg Med 2011:18:726

Pediatric dialysis patients

- 49/50 patients completed TB risk factor questionnaires and were tested by both TST and QuantiFERON
- 51% had any TB risk factor, most commonly parental (45%) or child (22%) foreign birth
- 12% previously tested positive and completed therapy
- 2% with indeterminate QuantiFERONs
- 2 children with + IGRAs had no discernable risk factors

Cruz et al. *JPIDS* 2015;4:84

Childhood Pleural Tuberculosis

A Review of 45 Cases

Andrea T. Cruz, MD, Lydia T. Ong, PA, and Jeffrey R. Starke, MD

- Mean age: 11 years
- Contacts identified for 44%
- 73% with concomitant parenchymal disease or intrathoracic adenopathy
- Several children had multiple VATS prior to TB being diagnosed

TABLE 2. Historical and Microbiologic Findings Associated With Childhood Pleural Tuberculosis in a Series of 45 Patients

Findings	No. Patients (%)
Known source case before diagnosis	8 (17.8%)
Other epidemiologic risk factors	35 (77.8%)
TST Positive	40/45 (88.9%)
AFB smear positive	
Total	3/40 (7.5%)
Pleural fluid	0/9
Other sites	3/31 (9.7%)
M. tuberculosis culture-positive by site	
Total	20/40 (50%)
Pleural fluid	5/9 (55.6%)
Nonpleural fluid	15/31 (48.4%)
Pleural biopsy	8/16 (50%)
Gastric aspirate	4/8 (50%)
Sputum	3/4 (75%)
Pericardial fluid	0/2
Peritoneal lymph node	0/1
PCR–pleural fluid	3/5 (60%)
Histopathology of pleural tissue*	
AFB smear positive	4/16 (25%)
Caseating granulomas	8/16 (50%)
Necrosis	1/16 (6.3%)
Nonspecific inflammation	5/16 (31.3%)
Nondiagnostic	3/16 (18.8%)

PIDJ 2009;28:981

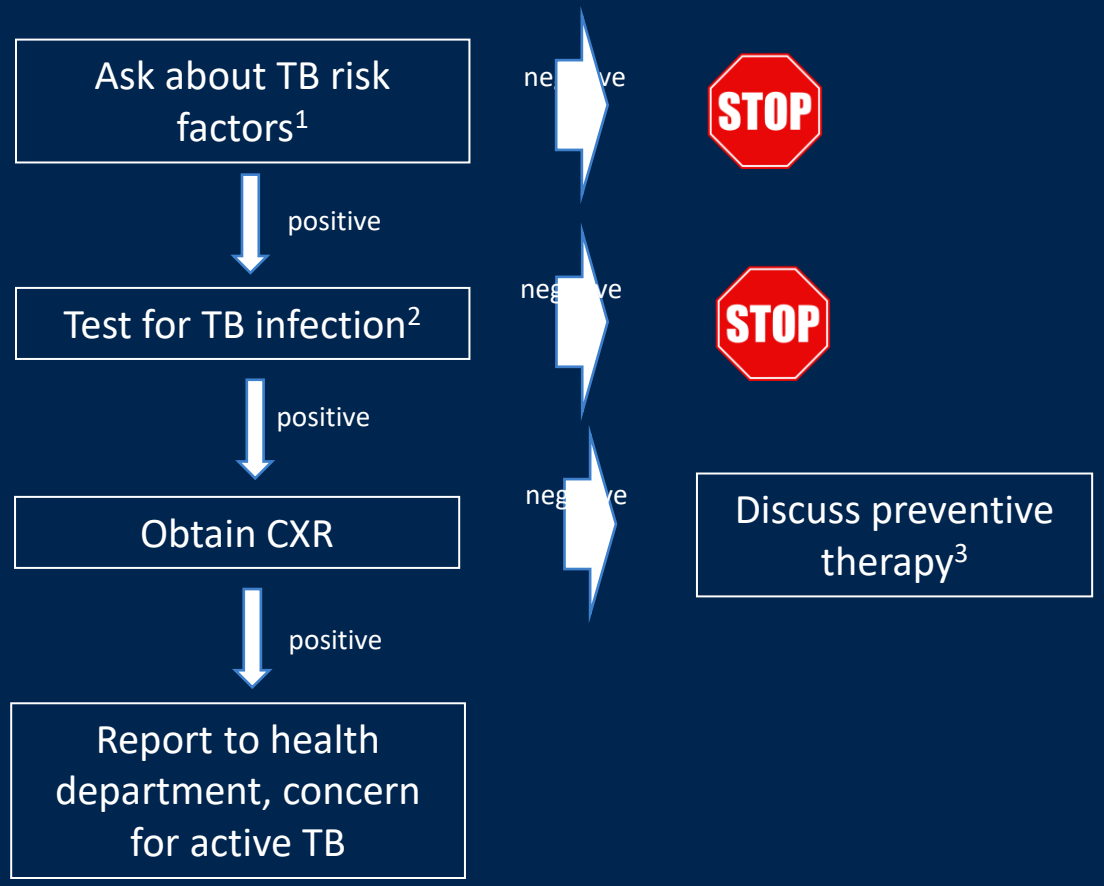
Validated Questions to Determine LTBI Risk

- Has a relative or contact had:
  - TB disease
  - A positive TB skin test (TST) or TB blood test (IGRA)
- Was the child:
  - Born in a high-risk country
  - Traveled to a high-risk country for > 1 week

- *No one recommends universal TB screening, but instead screening those with risk factors*

Pediatrics 2001;107:e54; Red Book 2015

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

3:
- Isoniazid + rifapentine
- Rifampin
- Isoniazid






Texas Children's Hospital®

Baylor College of Medicine

TB Exposure

Pediatrics

Why do we care about TB exposure?

- Window between exposure and time to TST or IGRA becoming positive
- In young (<5 yo) children, this can be shorter than the time to development of symptoms
- Intervene to start preventive therapy until you have the results of the definitive TST or IGRA (usually done 8-10 weeks after contact is broken)

Twice-weekly therapy for children with tuberculosis infection or exposure

- 1383 children treated intermittently: 68% exposure, 32% infection

	Exposure (n=935)	Infection (n=448)
Person-years of follow-up	4663	3148
Completion	99.5%	95.8%
# who progressed to infection	**13.8%**	N/A
# who progressed to disease	0	2 (0.4%)
Estimated efficacy	N/A	98%
Adverse events (any)	1.3%	6.7%
Elevated LFTs	1 (0.1%)	2 (0.4%)

Cruz & Starke. *Int J Tuberc Lung Dis* 2013;17:1

TECHNICAL REPORT

Interferon-γ Release Assays for Diagnosis of Tuberculosis Infection and Disease in Children

TABLE 2 Suggested Uses of TST and IGRA in Children

TST preferred
- Children younger than 5 y[a]

IGRA preferred, TST acceptable
- Children 5 y or older who have received BCG vaccine
- Children 5 y or older who are unlikely to return for the TST reading

Both the TST and an IGRA should be considered when:
- The initial and repeat IGRA results are indeterminate/invalid
- The initial test (TST or IGRA) result is *negative* and:
  - There is clinical suspicion of TB disease[b]
  - The child has a TB risk factor and is at high risk of progression and poor outcome (especially therapy with an immunomodulating biologic agent, such as a TNF-α antagonist)[b]
- The initial TST is *positive* and:
  - The patient is 5 years or older and has a history of BCG vaccination
  - Additional evidence is needed to increase adherence with therapy

Pediatrics 2014;134:e1763

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- TST conversion seen in **5%** and associated with parent being the ill individual (OR 3.2, 1.2-8.2)
  - **Not associated with smear- or culture-positivity**

Emerg Infect Dis. 2019;25:523

Comparison of TST & IGRA

Characteristic	TST	IGRA
Antigens studied	Many	ESAT-6, CFP-10, (TB-7.7)
Cross-reactivity with BCG	Yes	Unlikely
Cross-reactivity with NTM	Yes	Less Likely
Estimated sensitivity, TB in immunocompetent adults	75-90%	75-95%
Estimated specificity, TB in immunocompetent adults	***70-95%***	***90-100%***
Distinguish between TB infection and TB disease	No	No
Boosting	Yes	No
Patient visits required	Two	One

Pediatr Infect Dis J 2006;25:941

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.