AAP 2018 Red Book
Tuberculosis: IGRAs and Treatment of TB Infection

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Baylor College of Medicine
Disclosures

Dr. Starke is a member of the Data Safety Monitoring Board of Otsuka Pharmaceuticals for the pediatric studies of delamanid, a new drug for MDR-TB.
Objective

To review important changes in the 2018 American Academy of Pediatrics Report of the Committee on Infectious Diseases [the “Red Book”] about childhood tuberculosis

- Use of IGRAs
- Treatment regimens for tuberculosis infection
- Rifampin dosing
A Case

- 12 yr. old girl from Mexico with IBD needs infliximab
- TST is 0 mm; she is started on infliximab
- She is lost to follow up, but shows up about a year later with worsening IBD
- The GI folks want to put her back on infliximab
- A TST is done and there are 3 notes in the chart about the results:
  1. Nurse #1: “Negative”
  2. Nurse #2: “Some induration, likely positive”
  3. Pedi Resident: “Only redness, negative result”
- Infliximab is started; 2 months later she presents with fever, cough and cavitary tuberculosis
- **Number of positive TSTs previously seen by the resident = 0**
TB Epidemiology Studies Consortium Research Update on Latent Tuberculosis Infection

Christine S. Ho, M.D., M.P.H.
CDC TBESC Project Officer
ACET Meeting
December 12, 2016
TBESC-II Collaborators

CDC-funded collaboration with health departments, academic institutions, and CDC

1. California Department of Public Health
2. Denver Health and Hospitals Authority
3. Duke University, North Carolina
4. Emory University, Atlanta
5. Hawaii Department of Health
6. Seattle-King County Health Department
7. Maricopa County Health Department
8. Maryland Department of Health
9. University of Florida
10. University of North Texas Health Science Center
Research Questions

- Which tests or test combinations can best identify LTBI in specific high-risk populations in the U.S.?

- Can test characteristics be improved
  - By changing cutoff values?
  - By testing sequentially?

- Which test best predicts progression to TB?
Study Design

- Prospective cohort study
- Enrolled from populations at high risk of LTBI
- Each enrollee tested for LTBI with 3 FDA-approved tests:
  - QuantiFERON (QFT) blood test
  - T-SPOT.TB (T-SPOT) blood test
  - Tuberculin skin test (TST)
Study Eligibility Criteria

- Close contact of a person with pulmonary TB
- Foreign-born from a high incidence country
- Foreign-born from a medium incidence country who moved to the U.S. within the past 5 years
- Spent ≥ 30 days in a high incidence country within the last 5 years
- Belongs to a population with a local LTBI prevalence ≥25% (e.g., homeless)
Examine LTBI prevalence in our high risk groups using single and combination test results

Use latent class analysis (LCA) to estimate the “true” prevalence of LTBI in our study population, as well as test sensitivities and specificities

Analysis on clean data from July 2012-September 2014 dataset
Cut Points for Positive Tests

- **TST:**
  - 5mm for HIV-infected persons, close contacts
  - 10 mm for recent immigrants, <5 years of age, injection drug users

- **QFT:** ≥ 0.35 IU/ml

- **TSPOT:**
  - International: Positive: ≥ 6 spots
  - U.S.: Positive: ≥ 8 spots, borderline: 5-7 spots
## Characteristics of 11,962 TBESC Participants

**July 2012-September 2014**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>6,284</td>
<td>53</td>
</tr>
<tr>
<td>Foreign-born</td>
<td>9,643</td>
<td>81</td>
</tr>
<tr>
<td>BCG vaccination</td>
<td>6,332</td>
<td>53</td>
</tr>
<tr>
<td>HIV infection</td>
<td>1,460</td>
<td>12</td>
</tr>
<tr>
<td>Children &lt; 5 years old</td>
<td>516</td>
<td>4.3</td>
</tr>
<tr>
<td>Median age (years, IQR)</td>
<td>31 (19, 46)</td>
<td></td>
</tr>
<tr>
<td>Age Group</td>
<td>TST</td>
<td>QFT</td>
</tr>
<tr>
<td>-----------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>&lt; 5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5+ years</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5+ years</td>
<td>35</td>
<td>40</td>
</tr>
</tbody>
</table>

Single Test Prevalence for Foreign-Born, HIV-negative Persons, by Age Group
Test Characteristics by LCA for Foreign-Born Participants >5 years (n=8,018)

| LTBI prevalence | 37.9% (32.6-42.9) |
| Sensitivity      |                  |
| TST             | 74.8% (67.2-82.4) | PPV  |
| QFT             | 71.6% (63.3-79.9) | TST  | 60.0% (56.4-62.7) |
| T-SPOT*         | 70.3% (61.4-79.1) | QFT  | 97.6% (94.0-99.6) |
|                 |                  | T-SPOT* | 98.6% (95.8-99.8) |
| Specificity     |                  |
| TST             | 69.6% (67.7-71.4) | NPV  |
| QFT             | 98.9% (97.8-99.9) | TST  | 81.8% (78.5-91.1) |
| T-SPOT*         | 99.4% (98.6-100) | QFT  | 85.0% (73.8-89.3) |
|                 |                  | T-SPOT* | 84.5% (77.8-91.0) |

PPV = positive predictive value, true positive /true positive + false positive; NPV = negative predictive value, true negative/true negative + false negative

* For LCA we used ≥5 spots as a positive T-SPOT result
What This Means for the Clinician: Population ≥5 Years at High Risk for LTBI

Hypothetical cohort of 1000 foreign-born patients ≥5 years (38% LTBI prevalence)

<table>
<thead>
<tr>
<th></th>
<th>LTBI</th>
<th>No LTBI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TST +</strong></td>
<td>285</td>
<td>186</td>
<td>471</td>
</tr>
<tr>
<td><strong>TST -</strong></td>
<td>95</td>
<td>434</td>
<td>529</td>
</tr>
<tr>
<td></td>
<td>380</td>
<td>620</td>
<td>1000</td>
</tr>
</tbody>
</table>

- Sensitivity of 75%
- Specificity of 70%
Of 1000 people—
- 39% (186/471) with TST+ don’t have LTBI
- Positive predictive value (PPV) is 61%
- 25% (95/380) of LTBI missed

<table>
<thead>
<tr>
<th></th>
<th>LTBI</th>
<th>No LTBI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IGRA+</strong></td>
<td>270</td>
<td>6</td>
<td>276</td>
</tr>
<tr>
<td><strong>IGRA-</strong></td>
<td>110</td>
<td>614</td>
<td>724</td>
</tr>
<tr>
<td></td>
<td>380</td>
<td>620</td>
<td>1000</td>
</tr>
</tbody>
</table>

- Sensitivity of 71%
- Specificity of 99%
Of 1000 people—
- 2% (6/276) with IGRA+ don’t have LTBI
- PPV is 98%
- 29% (110/380) of LTBI missed
## LTBI Test Characteristics by LCA for Foreign-Born Children <5 Years (n=463)

<table>
<thead>
<tr>
<th>LTBI prevalence</th>
<th>4.2% (1.9-6.7)</th>
</tr>
</thead>
</table>

### Sensitivity

<table>
<thead>
<tr>
<th>Test</th>
<th>Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>74.8% (67.2-82.4)</td>
</tr>
<tr>
<td>QFT</td>
<td>70.4% (54.4-86.1)</td>
</tr>
<tr>
<td>T-SPOT*</td>
<td>58.9% (42.5-75.7)</td>
</tr>
</tbody>
</table>

### Specificity

<table>
<thead>
<tr>
<th>Test</th>
<th>Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>74.0% (69.7-78.0)</td>
</tr>
<tr>
<td>QFT</td>
<td>98.9% (97.7-99.9)</td>
</tr>
<tr>
<td>T-SPOT**</td>
<td>99.0% (98.1-99.9)</td>
</tr>
</tbody>
</table>

### PPV*

<table>
<thead>
<tr>
<th>Test</th>
<th>Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>10.2% (5.0-16.9)</td>
</tr>
<tr>
<td>QFT</td>
<td>73.8% (43.3-95.5)</td>
</tr>
<tr>
<td>T-SPOT</td>
<td>71.9% (45.4-93.2)</td>
</tr>
</tbody>
</table>

### NPV*

<table>
<thead>
<tr>
<th>Test</th>
<th>Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>98.3% (96.7-99.3)</td>
</tr>
<tr>
<td>QFT</td>
<td>98.7% (97.3-99.6)</td>
</tr>
<tr>
<td>T-SPOT</td>
<td>98.2% (96.5-99.4)</td>
</tr>
</tbody>
</table>

PPV = positive predictive value, true positive /true positive + false positive; NPV= negative predictive value, true negative/true negative + false negative

**For LCA we used ≥5 spots as a positive T-SPOT result**
LTBI Test Characteristics by LCA in Foreign-Born Children <5 Years (n=463)

For LCA we used ≥5 spots as a positive T-SPOT result.
What This Means for the Clinician: Population < 5 Years at High Risk for LTBI

Hypothetical cohort of 1000 foreign-born children < 5 yrs (4% LTBI prevalence)

<table>
<thead>
<tr>
<th></th>
<th>LTBI</th>
<th>No LTBI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST+</td>
<td>30</td>
<td>284</td>
<td>314</td>
</tr>
<tr>
<td>TST-</td>
<td>10</td>
<td>676</td>
<td>686</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>960</td>
<td>1000</td>
</tr>
</tbody>
</table>

- Sensitivity of 74.8%
- Specificity of 74.0%
- Of 1000 people—
  - 90% (284/314) with TST+ don’t have LTBI
  - Positive predictive value (PPV) is ~10% (30/314)
  - 25% (10/40) LTBI missed

QFT
- Sensitivity of 70.4%
- Specificity of 98.9%
- Of 1000 people—
  - 26% (10/38) with positive QFT don’t have LTBI
  - PPV is 74% (28/38)
  - 30% (12/40) LTBI missed

T-SPOT
- Sensitivity of 58.9%
- Specificity of 99.0%
- Of 1000 people—
  - 29% (10/34) with positive T-SPOT don’t have LTBI
  - PPV is 71% (24/34)
  - 40% (16/40) LTBI missed
Summary

Foreign-born persons ≥5 years
- TST was little better than a coin flip in predicting who had LTBI
- Both the QFT and TSPOT had high positive predictive values of 97.6 and 98.6

Foreign-born persons <5 years
- LTBI prevalence by LCA was 4%
- For TST ≥10 mm as positive, the PPV was 10%; almost all positive TST results were false positives
- Our data support recommendations preferring either serial testing (TST followed by a QFT/T-SPOT) or use QFT/T-SPOT as the initial screening test in foreign-born persons <5 years
T-Spot. *TB* Data From Oxford Imm.
Anna Mandalakas and Heather Highsmith

- Anonymous data from ~ 44,000 T-Spot. *TB* results
- No epidemiologic data available – cannot validate sensitivity, specificity, PPV or NPV
- Most invalid results from high nil response – higher in spring!
- 1.3% could not perform due to low lymphocyte counts

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>N</th>
<th>Positive (%)</th>
<th>Negative (%)</th>
<th>Borderline (%)</th>
<th>Invalid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>455</td>
<td>11 (2.4)</td>
<td>433 (95.2)</td>
<td>3 (0.7)</td>
<td>8 (1.8)</td>
</tr>
<tr>
<td>1 to &lt;2</td>
<td>964</td>
<td>13 (1.3)</td>
<td>937 (97.2)</td>
<td>7 (0.7)</td>
<td>7 (0.7)</td>
</tr>
<tr>
<td>2 to &lt;3</td>
<td>1047</td>
<td>31 (3.0)</td>
<td>1000 (95.5)</td>
<td>7 (0.7)</td>
<td>9 (0.9)</td>
</tr>
<tr>
<td>3 to &lt;5</td>
<td>2591</td>
<td>106 (4.1)</td>
<td>2453 (94.7)</td>
<td>19 (0.7)</td>
<td>13 (0.5)</td>
</tr>
<tr>
<td>5 to &lt;10</td>
<td>10746</td>
<td>463 (4.3)</td>
<td>10101 (94.0)</td>
<td>112 (1.0)</td>
<td>70 (0.7)</td>
</tr>
</tbody>
</table>
Question
If the IGRAs had come first, and we were now considering whether and how to use the TST, what would we say?
TECHNICAL REPORT

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

**TABLE 1** Comparison of the TST and IGRA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TST</th>
<th>IGRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigens used</td>
<td>Many; PPD</td>
<td>3 (QFT) or 2 (T-SPOT)</td>
</tr>
<tr>
<td>Sample</td>
<td>Intradermal injection</td>
<td>Blood draw</td>
</tr>
<tr>
<td>Patient visits required</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Distinguish between LTBI and TB disease</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cross-reactivity with BCG</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cross-reactivity with NTM</td>
<td>Yes</td>
<td>Only rare species(^a)</td>
</tr>
<tr>
<td>Differing positive values by risk</td>
<td>Yes (5-10-15)</td>
<td>No</td>
</tr>
<tr>
<td>Causes boosting</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Subject to boosting by previous TST</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td>Durability over time (stays positive with or without treatment)</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>Difficulties with test reproducibility</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Relative cost</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>Location of need for trained staff</td>
<td>“Bedside”</td>
<td>Laboratory</td>
</tr>
<tr>
<td>Estimated specificity in BCG-unvaccinated children</td>
<td>95% to 100%</td>
<td>90% to 95%</td>
</tr>
<tr>
<td>Estimated specificity in BCG-vaccinated children</td>
<td>49% to 65%</td>
<td>89% to 100%</td>
</tr>
<tr>
<td>Estimated sensitivity (confirmed TB disease)</td>
<td>75% to 85%</td>
<td>80% to 85%</td>
</tr>
<tr>
<td>Estimated sensitivity (clinical TB disease)</td>
<td>50% to 70%</td>
<td>60% to 80%</td>
</tr>
</tbody>
</table>

\(^a\) *M. marinum, M. kansasii, M. szulgai, and M. flavescens.*
IGRAs AND THE 2018 AAP “RED BOOK”

- Can use IGRAs in immunocompetent children \( \geq 2 \) years of age [previously \( \geq 5 \) years of age] in all situations when a TST would be used; some experts down to 1 year of age
- Particularly useful/preferred for children who have received a BCG vaccination
- Same recommendations as TST for risk factors and frequency of testing
- Use with caution in immunocompromised children

Neither IGRAs nor the TST are perfect; always need clinical judgment!
**TABLE 2** Suggested Uses of TST and IGRA in Children

<table>
<thead>
<tr>
<th>TST preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Children younger than 5 y(^a)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IGRA preferred, TST acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Children 5 y or older who have received BCG vaccine</td>
</tr>
<tr>
<td>• Children 5 y or older who are unlikely to return for the TST reading</td>
</tr>
</tbody>
</table>

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-\(\alpha\) 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

---

**TNF-\(\alpha\), tumor necrosis factor \(\alpha\)**

\(^a\) Some experts will use an IGRA in children 2 to 4 years of age, especially if they have received a BCG vaccine but have no other significant risk factors. Most experts do not use an IGRA for children younger than 2 years because of lack of data for this age group and the high risk of progression to disease.

\(^b\) A positive result of either test is considered significant in these groups.
IGRAs IN CHILDREN – SOME CLINICAL ISSUES

BCG-vaccinated child

- **Strategy 1**: TST: if negative, no more testing; if positive, follow with an IGRA
- **Strategy 2**: Do only the IGRA
- **Note**: If TB exposure, child should be considered infected if either test is positive

Child about to be immune compromised

- No TB risk factor: do either a TST or an IGRA
- TB risk factor: do both a TST and an IGRA and evaluate and treat if either test result is positive [RISK and BENEFIT]
Treatment of Tuberculosis Infection in Children: 2015 Red Book

- 9H the *preferred* regimen
- 4R to be used only when there is isoniazid resistance or intolerance; “some experts would chose to treat children younger than 12 years with 6R.”
- 3HP “should not be used routinely for children younger than 12 years of age but can be considered when the likelihood of completing another regimen is low.”
Part of a larger trial of ~7,800 patients

Included children ages 2 to 17 years

905 children evaluable for effectiveness

12 weekly doses of 3HP vs. 9 months daily doses of INH

Completion rates: 3HP – 88%  INH – 91%

Development of TB: 3HP – 0/471  INH – 3/434

No child experienced hepatotoxicity, Grade 4 adverse event

Grade 3 Adverse Effect: 3HP – 3 of 539  INH – 1 of 493

Conclusion: 3HP was at least as effective, safe and had a higher completion rate than 9 months of INH
Cruz and Starke. Completion rate and safety of tuberculosis infection treatment with shorter regimens. *Pediatrics* 2018; 141: e20172838

- Retrospective review of actual practice: N = 667
- 3HP: 283  4R: 132  9H: 252
- Completion rates: 3HP: 97%  4R: 88%
- 9H completion: SAT: 53%  ESAT: 76%  DOPT: 89%
- Multivariate analysis: completion associated with DOPT, increasing age, absence of any AE
- AEs were more common with 9H, including 2 children with significant hepatotoxicity [none with 3HP or 4R]
- One case of TB disease: 16 year old developed culture confirmed pulmonary TB 7 months after completing 3HP; great concern that she “cheeked” and spit out the medications after the HCW left the house
FIGURE 1
4R [N=395] vs. 9H [N=779] from 2016 to 2015 in children
- Retrospective, nonrandomized observational study
- Drug toxicity [all dermatologic]: 4R – 1.5%, 9H-0.7% [NS]
- No known treatment failures
- Completion rates were higher when IGRA was used and when known contact with a TB case was present

### Table 2. LTBI Treatment Completion Rates Stratified by Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Age Range (years)</th>
<th>Treatment Regimen</th>
<th>Completion (proportion, %)</th>
<th>p-value $^{a}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4R (n=395)</td>
<td>%</td>
<td>9H (n=779)</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td>330/395</td>
<td>83.5</td>
</tr>
<tr>
<td>0-1</td>
<td>29/38</td>
<td>76.3</td>
<td>19/37</td>
</tr>
<tr>
<td>2-4</td>
<td>17/26</td>
<td>65.4</td>
<td>75/102</td>
</tr>
<tr>
<td>5-9</td>
<td>58/65</td>
<td>89.2</td>
<td>116/153</td>
</tr>
<tr>
<td>10-14</td>
<td>99/113</td>
<td>87.6</td>
<td>222/305</td>
</tr>
<tr>
<td>15-17</td>
<td>127/153</td>
<td>83</td>
<td>104/182</td>
</tr>
</tbody>
</table>
### TABLE 2. Impact on LTBI Treatment Completion: Multivariable Logistic Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR of Treatment Completion</th>
<th>95% CI</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact with active case</td>
<td>1.82</td>
<td>1.13–2.93</td>
<td>0.013</td>
</tr>
<tr>
<td>4-month rifampin regimen</td>
<td>1.64</td>
<td>1.07–2.52</td>
<td>0.023</td>
</tr>
<tr>
<td>Speaking any of common languages†</td>
<td>1.58</td>
<td>1.02–2.45</td>
<td>0.040</td>
</tr>
<tr>
<td>IGRA‡ tested</td>
<td>1.39</td>
<td>0.91–2.11</td>
<td>0.129</td>
</tr>
<tr>
<td>Nepali language</td>
<td>1.20</td>
<td>0.60–2.37</td>
<td>0.606</td>
</tr>
<tr>
<td>Age</td>
<td>0.97</td>
<td>0.95–1.00</td>
<td>0.073</td>
</tr>
<tr>
<td>Region of origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>1.28</td>
<td>0.79–2.06</td>
<td>0.315</td>
</tr>
<tr>
<td>Africa</td>
<td>0.99</td>
<td>0.60–1.63</td>
<td>0.968</td>
</tr>
<tr>
<td>Other global region</td>
<td>0.56</td>
<td>0.29–1.06</td>
<td>0.075</td>
</tr>
</tbody>
</table>

*Comparator is variable/characteristic not present.
†Any language spoken by >5% of patients.
‡Interferon-gamma releasing assay used to diagnose LTBI.
The AAP Red Book Committee was shown the data but I am not allowed to show it to you as it is, as yet, unpublished and remains blinded.

- ~ 400 children in 4R and 9H groups
- 4R well tolerated and higher completion rates than 9H
Order in the book and in the Table will be 3HP, 4R, and 9H.

Only limitation stated is that 3HP cannot be used in children under 2 years of age because of lack of pK data for rifampentine.

Will not state a specific preference but will say that “some experts” think that 3HP is the preferred regimen.
Rifampin Dosing

- Target serum concentration of 8μg/ml
- CSF to serum ratio: 0.04-0.11
- **Schaaf et al, BMC Med, 2009**: only 9% of children achieved this level at 2 hrs post dose [South Africa]
- **Verhagen et al, Trop Med Int Health, 2012**: only 23% of children achieved this level [Venezuela]
- **Savic et al, Clin Pharm Ther, 2015**: study of pK of rifampin and levofloxacin in adults and children with TBM [Indonesia]

* Takes at least an oral dose of 30 mg/kg and an IV dose of 15 mg/kg of rifampin to reach the target AUC of 92 mg*h/L; even higher doses required to ensure that every child reaches this exposure
Pullen et al: Pharmacokinetics of intravenous rifampin in neonates. Ther Drug Monit 2006; 5:654
21 neonates treated for *Staphylococcus aureus* infections

**FIGURE 1.** Plasma concentrations of rifampicin (RIF) and 25-O-desacetyl rifampicin (DES) plotted against the time after rifampicin administration.

**FIGURE 2.** Rifampicin peak plasma concentrations after the second dose plotted against the rifampicin dose.
Pullen et al: Pharmacokinetics of intravenous rifampin in neonates. Ther Drug Monit 2006; 5:654
21 neonates treated for *Staphylococcus aureus* infections

**FIGURE 3.** Plasma concentrations of rifampicin (RIF) and 25-O-desacetyl rifampicin (DES) plotted against the time after rifampicin administration at the beginning of the rifampicin therapy (A) and after two weeks of therapy (B) in eight study patients.
Treatment of Tuberculosis Infection in Children: 2018 Red Book: Rifampin Dosing

**Standard Treatment**

2015: 10-20 mg/kg/day

2018: 15-20 mg/kg/day

**Infants, Toddlers and TBM [any age]**

2015: 10-20 mg/kg/day

2018: 20-30 mg/kg/day
Summary

1. IGRAs routinely age 2 years and above; some experts down to 1 year

2. 3HP [age 2 years and above], 4R and 9H all acceptable regimens for treatment of tuberculosis infection in children

3. Increases in recommended rifampin doses: Routine: 15-20 mg/kg/d Young Children: 20-30 mg/kg/d TB Meningitis: 20-30 mg/kg/d