Participant Questions

The following questions were submitted by participants following the Pediatric Tuberculosis: The Essentials Webinar. The responses have been provided by the presenter, Ann Loeffler and relate to information presented during the training. To view the archived recording of the 10/8/14 training, please visit the following web address: http://www.currytbcenter.ucsf.edu/training/webarchive/pedtb2014/arch_pedtb2014.cfm

Questions:

1. Why do some children have false positive TSTs?

   Some false positive tuberculin skin tests (TSTs) are from technical aspects such as incorrect placement, incorrect reading, using the wrong solution, etc. Some false positive TSTs are from infection with nontuberculous mycobacteria, vaccination with BCG (especially multiple BCCs or BCG outside the newborn period), and boosting with serial TSTs within a one-year time frame.

2. You said: "Don't test folks who you won't treat if positive." Why would you not treat a positive?

   Many providers do not treat individuals with positive TSTs because they believe the reaction is actually caused by a prior BCG vaccine (especially in foreign-born patients). Once they have ruled out tuberculosis disease, many providers choose to ignore the positive TST and do not treat for LTBI.

3. So, the recommendation would be not to test low-risk populations because you are more likely to get a false positive?

   True. You should not test children who have a low risk for TB exposure or disease. You should not test adults who have low risk for TB disease and no recent exposure.

4. And if you wouldn't trust the positive result well enough to treat, you shouldn't test in the first place

   Correct!
5. Is this because you would choose not to treat an older person at risk for liver toxicity? Or someone who is otherwise not a good candidate for LTBI treatment?

_I think that a lot of providers would be willing to treat if the chest radiograph was suggestive of TB disease, but are disinclined to treat LTBI because they're not sure if the positive reaction is true (and to some extent because they worry about hepatotoxicity and other side effects of LTBI treatment)._ 

6. At what age are IGRAs recommended versus TSTs? Can TSTs be used for children younger than 5 years? And are IGRAs recommended only for children older than 5 years of age?

_IGRA tests can be used interchangeably with TST in children 5 years and over. Many providers prefer IGRA for children who have received BCG in the past. You can draw an IGRA blood test on any child of any age. Insurance companies sometimes decline to pay for it for children under 5 years of age. There is an increased likelihood of false negative or indeterminate IGRA results in young children because of their immature immune system. This is also true for the TST. A negative IGRA and a negative TST do not rule out tuberculosis infection or disease. A positive test is suggestive of tuberculosis infection and a positive IGRA is more specific than a positive TST._

7. What does the American Academy of Pediatrics (AAP) say regarding the use of QuantiFERON TB Gold test applicability?

_“QuantiFERON-TB Gold, T-SPOT.TB, and Gold In-Tube are IGRAs and are the preferred tests in asymptomatic children older than 4 years of age who have been immunized against BCG. These FDA-approved tests measure ex vivo interferon-gamma production from T lymphocytes in response to stimulation with antigens that are fairly specific to _M tuberculosis_ complex. As with TSTs, IGRAs cannot distinguish between latent infection and disease, and a negative result from these tests cannot exclude the possibility of tuberculosis disease in a patient with findings that raise suspicion for these conditions. The sensitivity of these blood IGRA tests is similar to that of TSTs for detecting infection in adults and children who have untreated culture-confirmed tuberculosis. The specificity of IGRAs is higher than that for TSTs, because the antigens used are not found in BCG or most pathogenic nontuberculous mycobacteria (eg, are not found in _M avium_ complex but are found in _Mycobacterium kansasii_, _Mycobacterium szulgai_, and _Mycobacterium marinum_). IGRAs are recommended by the CDC, and some experts prefer IGRAs for use in adults in all circumstances in which a TST would have been used. The published experience testing children with IGRAs is less extensive than for adults, but a number of studies have demonstrated that IGRAs perform well in children 5 years of age and older. Some children who received BCG vaccine can have a false-positive TST result, and LTBI is overestimated by use of the TST in these circumstances. The negative predictive value of IGRAs is not clear, but in general, if the IGRA result is negative and the TST result is positive in an asymptomatic child, the diagnosis of LTBI is unlikely.”_
At this time, neither an IGRA nor the TST can be considered a "gold standard" for diagnosis of LTBI. Current recommendations for use of IGRA in children are in Table 3.78:

**Table 3.78. Recommendations for Use of the Tuberculin Skin Test (TST) and an Interferon-Gamma Release Assay (IGRA) in Children**

<table>
<thead>
<tr>
<th>TST preferred, IGRA acceptable</th>
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<tbody>
<tr>
<td>Children &lt;5 y of age&lt;sup&gt;a&lt;/sup&gt;</td>
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</table>

<table>
<thead>
<tr>
<th>IGRA preferred, TST acceptable</th>
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<tbody>
<tr>
<td>Children &gt;5 y of age who have received BCG vaccine</td>
<td></td>
</tr>
<tr>
<td>Children &gt;5 y of age who are unlikely to return for TST reading</td>
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</tbody>
</table>

**TST and IGRA should be considered when:**

The initial and repeat IGRA are indeterminate
The initial test (TST or IGRA) is *negative* and:
- Clinical suspicion for TB disease is moderate to high<sup>b</sup>
- Risk of progression and poor outcome is high<sup>b</sup>

The initial TST is *positive* and:
- >5 y of age and history of BCG vaccination
- Additional evidence needed to increase compliance
- Nontuberculous mycobacterial disease is suspected

<sup>a</sup>Positive result of either test is considered significant in these groups.
<sup>b</sup>IGRAs should not be used in children <2 years of age unless tuberculosis disease is suspected. In children 2 through 4 years of age, there are limited data about the usefulness of IGRAs in determining tuberculosis infection, but IGRA testing can be performed if tuberculosis disease is suspected.

Children with a positive result from an IGRA should be considered infected with *M. tuberculosis* complex. A negative IGRA result cannot be interpreted universally as absence of infection.

Indeterminate IGRA results do not exclude tuberculosis infection and may necessitate repeat testing and should not be used to make clinical decisions."

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8. Can you treat an adult patient who should have been treated for LTBI as a child but never received treatment?

*You can certainly treat adults for LTBI. The risk-benefit balance changes as the patient becomes older and after it is more than 2 years since infection. We generally do not treat adults for LTBI more than 2 years after the exposure/infection unless they have any risk for progression to TB disease including renal*
impairment, diabetes mellitus, transplant, HIV, chemotherapy, chronic steroids, etc.

9. Is INH/RIFAPENTINE approved for children? How young is too young for INH/RPT x 12 weeks?

MMWR December 9, 2011 / 60(48);1650-1653 describes the recommendations for use of INH and rifapentine in Children 12 years and older.

In addition “INH-RPT can be considered on a case-by-case basis when both 1) the circumstances make the completion of 9 months of daily INH unlikely and 2) the likelihood or the hazard of TB is great (e.g., recent M. tuberculosis infection in a preschool-aged child).” Also see NEJM 2011 365;23

3HP arm
Rifapentine: Persons weighing > 50.0 kg received rifapentine 900 mg once-weekly Persons weighing < 50.0 kg were dosed once-weekly according to the following scale:

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Dose</th>
</tr>
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<tbody>
<tr>
<td>10.0-14.0 kg</td>
<td>300 mg</td>
</tr>
<tr>
<td>14.1-25.0 kg</td>
<td>450 mg</td>
</tr>
<tr>
<td>25.1-32.0 kg</td>
<td>600 mg</td>
</tr>
<tr>
<td>32.1-50.0 kg</td>
<td>750 mg</td>
</tr>
</tbody>
</table>

Isoniazid: Persons 2-11 years old received isoniazid 25 mg/kg (rounded up to the nearest 50 or 100 mg; 900 mg max) once-weekly Persons > 12 years old received isoniazid 15 mg/kg (rounded up to nearest 50 or 100 mg; 900 mg max) once-weekly

10. What is the age limit of treatment with rifampin for 6 months? What age is considered adolescent?

Age 0-14 is considered a child in tuberculosis studies. I predict that the next set of guidelines will use rifampin for 4 months for all LTBI.

11. What if parent wants to wait until child is old enough for IGRA before starting LTBI?

No one is forced to take LTBI treatment. I explain the risks and benefits to the parents, especially for the youngest children who have a high rate of progression from LTBI to TB disease. I often draw an IGRA test for young children whose parents are reluctant to use LTBI treatment. Even if the test is positive, the parents still have to agree to LTBI treatment