The Most Widely Misunderstood Test of All

Lee B. Reichman, MD, MPH
NJMS Global Tuberculosis Institute
Subject: TB in Thailand
Date: Wed 3 Sep 1996 11:06:50 EDT
From: NIH National Tuberculosis Center
To: Reichman

Dear Reichman,

I am a physician in Muangmai and have a 30-year-old patient who recently passed away. The patient was a resident of a slum area and contracted TB. His symptoms include coughing, fever, and weight loss. He was hospitalized and treated for TB in a local clinic. However, he died in the past few weeks.

I am aware of the general recommendations in the WHO and other guidelines for the treatment of TB. However, I would like to know if there are specific guidelines for TB treatment in Thailand.

What are your recommendations for this patient?

Thank you.

Sincerely,

[Name]
Medical Officer

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Subject: TB
Date: Wed 3 Sep 1996 11:06:50 EDT
From: NIH National Tuberculosis Center
To: Reichman

Dear Reichman,

My sixty-year-old daughter is tested positive for TB. I am really very much worried. She is advised to take INH, PZA, and rifampicin for six months. Is it really necessary to go through this? She has no symptoms. According to my physician, she tested positive because of some immunization shot given in India. What are the side effects of the medicine? Is there any long-term effect of this medicine?

Please guide us.

Thank you.
For more than 4 decades, treatment of persons with latent *Mycobacterium tuberculosis* infection to prevent active disease has been an essential component of TB control in the US.

1965: First recommended for use in the US for previously untreated TB, PPD converters, and all children <3 years with a positive tuberculin test.

1967: Recommendations broadened to include all PPD + (>10 mm) and close contacts.

1970: 2 deaths and 19 developed liver disease out of 2000 contacts exposed to an infectious case on Capitol Hill.

1974: Development of guidelines regarding pretreatment screening and monitoring to minimize risk for hepatitis and exclusion of low-risk persons older than 35 as candidates for treatment.
### History of Treatment of Latent Tuberculosis Infection

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>Guidelines further revised to recommend routine clinical and laboratory monitoring for persons older than 35 or with increased risk for hepatotoxicity</td>
</tr>
<tr>
<td>1998</td>
<td>2 months of RIF + PZA recommended for HIV+, subsequently HIV-</td>
</tr>
<tr>
<td>2000</td>
<td>9 months Isoniazid decreed better than 6</td>
</tr>
<tr>
<td></td>
<td>2RZ decreed equal to 9 Isoniazid</td>
</tr>
<tr>
<td>2001</td>
<td>2RZ deemphasized due to liver toxicity in favor of 9 month Isoniazid</td>
</tr>
<tr>
<td>2004</td>
<td>4R suggested as effective advantageous regimen</td>
</tr>
</tbody>
</table>

### U.S. Guidelines for FDA-Approved IGRAs

<table>
<thead>
<tr>
<th>Year</th>
<th>Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>Guidelines for Using the Quantiferon®-TB Test for Diagnosing Latent Mycobacterium Tuberculosis Infection</td>
</tr>
<tr>
<td>2005</td>
<td>Guidelines for Using the Quantiferon®-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, United States</td>
</tr>
</tbody>
</table>

**Recent FDA Approvals**

- Oct 2007 Quantiferon®-TB Gold-In-Tube (QFT-GIT)
- July 2008 T-Spot®.TB test (T-spot)

### Targeted Tuberculin Testing and Treatment of Latent TB Infection

As the rate of active TB in the United States has decreased, identification and treatment of persons with latent infection who are at high risk for active TB have become essential components of the TB elimination strategy.
Change in Nomenclature

- To focus on groups at the highest risk for TB, the term targeted tuberculin testing is used to encourage directed program activities
- Treatment of latent TB infection (LTBI) rather than preventive therapy or chemoprophylaxis to promote greater understanding of the concept for both patients and providers resulting in better implementation of this TB control strategy

Targeted Testing

- Targeted testing identifies persons at high risk for TB who would benefit by treatment of LTBI
- Screening of low-risk persons should be replaced by targeted testing

Purpose of Targeted Testing

- Find persons with LTBI who would benefit from treatment
- Find persons with TB disease who would benefit from treatment
- Groups that are not high risk for TB should NOT be tested routinely
Incidence of Active TB in Persons with Selected Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>TB cases/1000 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent TB infection</td>
<td>12.9</td>
</tr>
<tr>
<td>Infection &lt;1 yr past</td>
<td>1.6</td>
</tr>
<tr>
<td>Infection 1-7 yr past</td>
<td>0.6</td>
</tr>
<tr>
<td>HIV Infection</td>
<td>35.0 – 162</td>
</tr>
<tr>
<td>Injection Drug Use</td>
<td>76.0</td>
</tr>
<tr>
<td>HIV seropositive or unknown</td>
<td>10.0</td>
</tr>
<tr>
<td>Silicosis</td>
<td>2.0 – 13.6</td>
</tr>
<tr>
<td>Underweight (non-standard)</td>
<td></td>
</tr>
<tr>
<td>Underweight by &gt; 15%</td>
<td>2.6</td>
</tr>
<tr>
<td>Underweight by 15% – 10%</td>
<td>2.6</td>
</tr>
<tr>
<td>Underweight within 5% of standard</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Groups at Risk / Risk Factors for Infection -1

Persons or groups with presumed recent MTB infection
- Close contacts to infectious TB
- Skin test or IGRA conversion within 2 years
- Immigrant from endemic countries (within 5 years of arrival)
- Children <5 years with + TST or + IGRA

Groups at Risk / Risk Factors for Infection -2

Clinical conditions associated with progression to active TB
- HIV infection
- Prior, untreated TB, with fibrotic lesions on CXR
- Underweight, malnourished persons
### Groups at Risk / Risk Factors for Infection -3

**Other medical conditions**
- Silicosis
- Diabetes mellitus
- Chronic renal failure/hemodialysis
- Solid organ transplantation (*heart, kidney*)
- Carcinoma of head/neck
- Gastrectomy/jejunoilial bypass

### Chest Radiograph

- Abnormalities often seen in apical or posterior segments of upper lobe or superior segments of lower lobe
- May have unusual appearance in HIV-positive persons
- Cannot confirm diagnosis of TB
- Has **NO** role in screening for LTBI or TB disease
Administering the Tuberculin Skin Test

- Inject intradermally 0.1 ml of 5 TU PPD tuberculin
- Produce wheal 6mm to 10mm in diameter
- Do not recap, bend, or break needles, or remove needles from syringes
- Follow universal precautions for infection control
PHRENOLOGY

The study of the mind and character from the shape of the skull

- Read reaction 48-72 hours after injection
- Measure only induration
- Record reaction in millimeters
Concentric-Circle Approach to Contact Tracing

Criteria for TST Positivity by Risk Group - 1

Induration 5mm or more
- HIV+
- Close contacts
- Chest radiograph consistent with prior untreated TB
- Patients with organ transplants and other immunosuppressed patients (i.e. prednisone 15 mg/d x 1 mo.)
Criteria for TST Positivity by Risk Group - 2

Induration 10 mm or greater

• Recent immigrants (within the past 5 years) from high prevalence countries

• Injection drug users

• Resident and employees of the high-risk congregate settings (prisons, nursing homes, hospitals, shelters, residential facilities for AIDS patients)

Criteria for TST Positivity by Risk Group - 3

Induration 10 mm or greater

• Mycobacteriology lab personnel

• Persons with clinical conditions (silicosis, diabetes, chronic renal failure, malignancies and hematologic disorders, malnutrition)

• Children < 4yrs, infants, children, and adolescents exposed to adults at high risk

Criteria for TST Positivity by Risk Group - 4

Positive skin test result ≥ 15 mm

• Persons with no known risk factors for TB may be considered

• Targeted skin testing programs should only be conducted among high risk groups
Occupation Exposure to TB

Appropriate cutoff depends on

• Individual risk factors for TB
• Prevalence of TB in the facility

Factors that May Cause False-Positive and False-Negative Reactions to the Tuberculin Skin Test

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Possible Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>False-positive</td>
<td>Nontuberculous mycobacteria</td>
</tr>
<tr>
<td></td>
<td>BCG vaccination</td>
</tr>
<tr>
<td>False-negative</td>
<td>Anergy</td>
</tr>
<tr>
<td></td>
<td>Recent TB infection</td>
</tr>
<tr>
<td></td>
<td>Very young age: &lt; 8 mos. old</td>
</tr>
<tr>
<td></td>
<td>Live-virus vaccination</td>
</tr>
<tr>
<td></td>
<td>Overwhelming TB disease</td>
</tr>
<tr>
<td></td>
<td>Poor TST technique</td>
</tr>
</tbody>
</table>

BCG – Fantasy and Fact

**FANTASY**

• BCG protects against getting TB infection
• BCG provides lifetime protection against developing active TB
• BCG causes the tuberculin skin test (TST) to be positive for life
• In a BCG-vaccinated person, a positive TST is most likely due to BCG
• A positive TST in a person of any age from any country is most likely due to BCG, not TB infection
• There is no need for a BCG-vaccinated person with a positive TST to be treated

**FACT**

• BCG will not protect against becoming infected with TB
• BCG protects against severe complications of TB disease in young children, but provides little or no protection in adolescents and adults
• BCG causes the TST to be positive for a few years and then the TST reaction becomes much weaker. Generally, no reaction is present after 5 years.
• There is no way to tell whether a positive TST is due to BCG or to TB infection
• A positive TST in an adolescent or adult from a TB high-burden country is almost always due to TB infection, not BCG
• Persons with a positive TST from TB high-burden countries are at high risk of developing active TB and should be treated
Boosting

• Some people with LTBI may have negative skin test reaction when tested years after infection
• Initial skin test may stimulate (boost) ability to react to tuberculin
• Positive reactions to subsequent tests may be misinterpreted as a new infection

Two Step Testing

Use two step testing for initial skin testing of adults who will be retested periodically
• If first test positive, consider the person infected
• If first test negative, give second test 1-3 weeks later
• If second test positive, consider person infected
• If second test negative, consider person uninfected

Tuberculin Testing

True Infection vs Booster Effect (mm induration)

<table>
<thead>
<tr>
<th>Situation</th>
<th>Time</th>
<th>0</th>
<th>1 week</th>
<th>1 year</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>4</td>
<td>2</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>C</td>
<td>4</td>
<td>12</td>
<td></td>
<td>14</td>
</tr>
</tbody>
</table>
"I am constantly astounded by the faith that clinicians have in this procedure... Under the best of circumstances these tests are worthless, and under the worst of circumstances they’re delusional."

RE Chaisson, Clinical Infectious Diseases, 1996; 22:668

The Folly of Anergy Testing


Interferon Gamma Release Assays
Quantiferon® - TB GOLD
TB Spot TB®

• Approved by FDA
• Uses antigens not found in BCG or MAC (ESAT-6 CFP-10)
• More specific, no cross reactors
• CDC Guidelines, 2005: Use in place of TST for all indications
**Comparison of IGRAs and TST**

**IGRAs**
- *In vitro* test
- Specific antigens
- No boosting
- 1 patient visit
- Minimal inter-reader variability
- Results possible in 1 day
- Requires phlebotomy

**TST**
- *In vivo* test
- Single antigen
- Boosting
- 2 patient visits
- Inter-reader variability
- Results in 2-3 days

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**TB Infection Prevalence By Test and Clinic Type, San Francisco 2001-2009**

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>TST</td>
<td>26%</td>
<td>~50%</td>
<td>10%</td>
<td>37%</td>
</tr>
<tr>
<td>QFT-1</td>
<td>17%</td>
<td>48%</td>
<td>18%</td>
<td>37%</td>
</tr>
<tr>
<td>QFT-2</td>
<td>7%</td>
<td>23%</td>
<td>4%</td>
<td>14%</td>
</tr>
<tr>
<td>QFT-3</td>
<td>7%</td>
<td>23%</td>
<td>-</td>
<td>-</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Homeless</th>
<th>TB Clinic</th>
<th>Methadone</th>
<th>Immigrant</th>
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</thead>
<tbody>
<tr>
<td>2001</td>
<td>n=1848</td>
<td>n=292</td>
<td>n=346</td>
<td>n=344</td>
</tr>
<tr>
<td>2002</td>
<td>n=9166</td>
<td>n=4042</td>
<td>n=1281</td>
<td>n=2505</td>
</tr>
<tr>
<td>2003</td>
<td>n=483</td>
<td>n=813</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Homeless</th>
<th>TB Clinic</th>
<th>Methadone</th>
<th>Immigrant</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td></td>
<td>7%</td>
<td>23%</td>
<td>4%</td>
</tr>
<tr>
<td>2002</td>
<td></td>
<td>7%</td>
<td>23%</td>
<td>-</td>
</tr>
<tr>
<td>2003</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Decline in positive rate from TST:
- 73%
- >54%
- 60%
- 82%

Updated: 12/09/08

**QFT Gold® for Predicting Active Tuberculosis**

- 601 contacts to active TB screened with TST and QFT Gold®
- 40% (243) + TST
- 11% (66) + QFT Gold
- All patients followed for 2 years
- 6 people developed TB disease all QFT+ who had declined treatment
- QFT predictive value of developing TB disease 15%
- TST predictive value of developing TB disease 2.3%

- Diel R et al, Am J Respir Crit Care Med, 2008
Boosting of IGRAs after TST

- Antigen specific response in IGRA+ & IGRA - subjects are influenced by result of TST
- Boosting evident by day 7 but not day 3
- 3 days is safe window to perform IGRA after TST

- Van Zyl-Smit et al, AJRCCM, 2009, 180

Provisional Recommendations - 1

- TST or IGRAs (QFT-G; QFT-GIT; T-Spot) used as aids to diagnose infection with *M. tuberculosis*
  - IGRAs should be performed and interpreted according to established protocols using FDA approved test formats, in compliance with Clinical Laboratory Improvement Amendment (CLIA) standards
  - Both standard qualitative interpretation and quantitative assay measurements should be reported
  - Arrangement for IGRA testing should be made prior to blood collection to assure that blood is collected in proper tubes and testing performed within the required timeframe on viable blood cells
- As with the TST, IGRAs should not be used for testing persons with low risk of infection and low risk of disease due to *M. tuberculosis* (noted exception for those likely to be at increased risk in the future)

- CDC, 2009

Provisional Recommendations - 2

- Selection of the most suitable test or combination of tests for detection of *M. tuberculosis* infection based on rationale and context for testing, test availability, and overall cost effectiveness of testing

- IGRAs may be used in place of (not in addition to) TST in all situations in which CDC recommends tuberculin skin testing as an aid to diagnose *M. tuberculosis* infection — with noted preferences and special considerations

- CDC, 2009
• IGRA is preferred for testing persons from groups that historically have poor rates of return for TST reading
• IGRA is preferred for testing persons who have received BCG (as a vaccine or for cancer therapy)
• TST is preferred for testing children younger than 5 years of age

- CDC, 2009

• IGRA’s may be used in place of TST (without preference) to test recent contacts of persons with infectious tuberculosis with special considerations for follow-up testing
  - Negative results prior to 8 wks typically should be confirmed by repeating the test 8–10 weeks after the end of exposure
  - Repeating same test minimizes misclassification due to test discordance

• IGRA’s may be used in place of TST (without preference) for periodic screening to address occupational exposure to TB with special considerations regarding conversions and reversions

- CDC, 2009

• Both TST & IGRA may be useful if the initial test is negative and:
  - risk of infection, risk of progression, and risk of poor outcomes are high (e.g., persons with HIV infection, children < 5 years exposed to persons with infectious TB)
  - clinical suspicion for active tuberculosis (persons with symptoms, signs, and/or radiographic evidence suggestive of active tuberculosis) and confirmation of M. tuberculosis infection is desired

- CDC, 2009
Both TST & IGRA may be useful if the initial test is positive and:
- additional evidence of infection is required to encourage compliance (such as in foreign-born healthcare workers who believe their positive TST is due to BCG)
- healthy persons who have a low risk of both infection and progression

Repeating an IGRA or performing a TST may be useful when the initial IGRA result is indeterminate, borderline, or invalid, and reason for testing persists

Each institution and TB control program should evaluate availability, overall cost effectiveness, and benefits of IGRAs in their setting
- CDC, 2009

Diagnosis of *M. tuberculosis* infection, and decisions about medical or public health management should include epidemiological, historical, and other clinical information when using IGRA or TST results

Persons with a positive TST or IGRA result should be evaluated for likelihood of *M. tuberculosis* infection, for risks of disease progression if infected, and for symptoms and signs of tuberculosis disease
- With these risks, symptoms, or signs, additional evaluation is indicated and should include a chest radiograph and possibly testing of sputum or other clinical samples for the presence of *M. tuberculosis*

Diagnosis of LTBI requires that tuberculosis disease be excluded by medical evaluation
- CDC, 2009

Persons with symptoms, signs, or radiographic evidence of TB disease, and in those at high risk of disease progression if infected, a positive result with either an IGRA or TST may be taken as evidence of *M. tuberculosis* infection
- However, negative IGRA or TST results are not sufficient to exclude infection in these persons

Healthy persons with low likelihood both of *M. tuberculosis* infection and of progression to TB disease if infected, a single positive IGRA or TST result should not be taken as reliable evidence of *M. tuberculosis* infection
- Reevaluation to confirm lack of risk and consider repeat testing on a case-by-case basis; or
- alternatively, assume, without additional testing, that the initial result is falsely positive
- CDC, 2009
**Provisional Recommendations - 9**

- Persons with discordant test results (one positive and the other negative) – decisions about medical or public health management requires individualized judgment to assess
  - quality of each test & magnitude of each result,
  - probability of infection,
  - risk of disease if infected, and
  - risk of a poor outcome if disease occurs

  - CDC, 2009

**Provisional Recommendations - 10**

- Further studies should focus on determining the value and limitations of IGRAs in situations critical to TB control
  - Are IGRAs better at predicting subsequent tuberculosis disease than TST?
  - Do IGRAs perform differently in children as compared to adults?
  - Why do simultaneously performed TST, QFT-GIT, QFT-G, and T-Spot results differ?

  - CDC, 2009

**General Advice**

- IGRAs are best utilized in:
  - Non-adherent populations (results with one visit)
  - BCG vaccinated populations (higher TB specificity)
  - Confirming positive TST results in individuals without risk for TB
  - Confirming questionable TST results
  - Other reasons: immediate hypersensitivity to PPD, convincing high risk patient with strongly positive TST to take LTBI treatment
IGRA Summary

- IGRA is a significant advance because of its high specificity and operational advantages to the TST.

- Like the TST, it is not a perfect test. Cases will be missed if relying exclusively on an IGRA result.

- IGRA is a powerful epidemiologic and clinical tool.

- Provider and patient misconceptions need to be met with widespread education and access to consultation.

- Training, Q/A and maintaining IGRA proficiency of laboratory are feasible, achievable, and preferable over maintaining TST proficiency of thousands of clinic personnel.

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"Is there still a role for the tuberculin skin test in this era of new science and new technological breakthroughs? Perhaps – just as there is still a role for the horse in our era of the modern car. Like horses, the tuberculin skin test has a long relationship with mankind. We feel comfortable with it. But also like horses, it is slower, less focused, its actions are often unpredictable, and occasionally it can leave a mess at the end – but – it is less expensive."

- John Sbarbaro: Second Global Symposium on Interferon Gamma Assays, Dubrovnik, 2009

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"In reality, the tuberculin test will always remain subject to variation in all of its phases: the test material, the individual response, and the application and reader interpretation. The tuberculin test can only serve as a "diagnostic aide."

- John Sbarbaro: Second Global Symposium on Interferon Gamma Assays, Dubrovnik, 2009
All testing activities should be accompanied by a plan for follow-up care

LTBI Treatment for TST (+) Contacts

• Isoniazid for 6-12 months has been the mainstay of treatment for LTBI in the United States for more than 30 years
• The application of isoniazid for LTBI has been limited because of poor adherence due to the relatively long duration of treatment required and because of concerns about toxicity
• There has been interest in the development of shorter, rifampin-based regimens as alternative to isoniazid for the treatment of LTBI
### Contacts to Smear Positive TB Cases - 2003

<table>
<thead>
<tr>
<th></th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact count</td>
<td>73,319</td>
</tr>
<tr>
<td>Contacts per case</td>
<td>14.0</td>
</tr>
<tr>
<td>Contacts evaluated for TB</td>
<td>80% 95%</td>
</tr>
<tr>
<td>Contacts with TB disease</td>
<td>1%</td>
</tr>
<tr>
<td>Contacts with LTBI</td>
<td>26%</td>
</tr>
<tr>
<td>Started treatment for LTBI</td>
<td>73%</td>
</tr>
<tr>
<td>Completed treatment for LTBI</td>
<td>59% 85%</td>
</tr>
</tbody>
</table>


### Treatment of Latent TB Infection – 2

- The isoniazid daily regimen for 9 months is recommended because prospective, randomized trials in HIV-negative persons indicate that 12 months of treatment is more effective than 6 months. However in subgroup analysis of several trials the maximal beneficial effect of isoniazid is likely achieved by 9 months, and minimal additional benefit is gained by extending therapy to 12 months
- Both the 9-month and 6-month isoniazid regimens may be given intermittently (only as directly observed therapy - DOT)

### Treatment of Latent TB Infection – 3

- Rifampin given daily for 4 months is recommended on the basis of the efficacy of a similar regimen in a prospective randomized trial of tuberculin-positive persons with silicosis and a non-randomized trial in persons exposed to persons with isoniazid-resistant TB
- In situations where rifampin cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted
- Before beginning treatment of LTBI, active TB must be ruled out by history, physical examination, chest radiography, and, when indicated, bacteriologic studies
We argue that 4R is an effective, relatively nontoxic, affordable strategy that clinicians and program managers should consider for more widespread use in selected populations and settings to effectively and efficiently treat LTBI, thereby accelerating the decline of TB in their communities.

AJRCCM 170; 832-835, 2004

- Study in County Chest Clinic
- 474 Patients
- 2000 Predominately 9 months Isoniazid (9H)
- 2003 Predominately 4 months Rifampin (4R)
- Treatment completion
  - 9H 53%
  - 4R 80.5%
  \( P < 0.0001 \)
- Treatment completion predicted by regimen (OR 5.1; 95% CI 3.3, 8.1)


Comparison of Regimen Features: 9H and 4R

<table>
<thead>
<tr>
<th>Regimen Feature</th>
<th>9H</th>
<th>4R</th>
</tr>
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<tbody>
<tr>
<td>High efficacy</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Lower hepatotoxicity</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Lower overall cost</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Higher adherence</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>More effective against INH-resistant strains</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>(e.g., among foreign-born persons)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Shorter duration</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fewer drug-drug interactions</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

* Good evidence that 3R is at least as efficacious as 6H. Inferential reasoning from other evidence suggests that efficacy of 4R may approach that of 9H.

AJRCCM 170; 832-835, 2004