What you need to know about TB?

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Conflict of interest

- No financial or commercial disclosures
The German physician and scientist Robert Koch presented his discovery of *Mycobacterium tuberculosis* on March 24, 1882, noting:

"If the importance of a disease for mankind is measured by the number of fatalities it causes, then tuberculosis must be considered much more important than those most feared infectious diseases, plague, cholera and the like. One in seven of all human beings dies from tuberculosis. If one only considers the productive middle-age groups, tuberculosis carries away one-third, and often more."

More than 125 years later, tuberculosis (TB) is surging, leading to more deaths than any previous year. Damage from this disease continues to grow despite effective therapies for drug-susceptible TB that continues to keep the incidence of TB in Western countries at record lows.
## Global Burden of Tuberculosis
### 2009 WHO Estimates

<table>
<thead>
<tr>
<th>All forms of TB</th>
<th>Estimated number of cases</th>
<th>Estimated number of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9.4 million</td>
<td>1.8 million</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multidrug-resistant TB (MDR-TB)</th>
<th>440,000</th>
<th>150,000</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>eXtensively drug-resistant TB (XDR-TB)</th>
<th>27,000 (0.3%)</th>
<th>16,000 (1%)</th>
</tr>
</thead>
</table>

*Approximately 2 billion people have latent TB infection*

*TB is the leading cause of morbidity / mortality in HIV co-infected persons in the developing world*
Tuberculosis: Natural History

Exposure (close contacts)

No Infection (70%)

Primary Active ~10% of Active TB

Infection (30%)

Latent

Reactivation (10% per lifetime)

HIV Infection (5-10% per year)

Continued Latent TB ~90% of Active TB

Infection (asymptomatic)

Disease (symptomatic)

Parrish et al., Trends Microbiol., 1998
DEADLY AFRICAN XDR-TB STRAIN

COUGH!

COUGH!

COUGH!

OTHER COUNTRIES

!!!
Extensively drug-resistant (XDR) TB

- XDR strains are resistant to:
  - rifampicin and isoniazid (MDR)
  - any fluoroquinolone
  - and to at least one of three injectable second-line anti-TB drugs (capreomycin, kanamycin, and amikacin)

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**Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa**

Neel R Gandhi, Anthony Moll, A Willem Sturm, Robert Pawinski, Thiloshini Govender, Umesh Laloo, Kimberly Zeller, Jason Andrews, Gerald Friedland

- assessed the prevalence and consequences of MDR and XDR TB in a rural area in KwaZulu Natal, South Africa (Jan 2005-Mar 2006).
- of 544 patients who were culture-positive, 221 patients had MDR strains of which 53 were XDR. Of these 53 patients, all 44 tested for HIV were positive; 52 of 53 patients died, with a median survival of 16 days -- including those benefiting from antiretroviral drugs.

Gandhi NR et al., Lancet 2006;368:1575-80
TB Incidence and Rates
United States, 2000-08

2008 MDR TB: 103 cases (0.8% of all TB)

CDC - as of May 20, 2009
TB Case Rates by Ethnicity
United States, 2000-08

Cases per 100,000

- Hispanic / Latino
- American Indian / Alaska Native
- Asian
- African American
- White

CDC - as of May 20, 2009
TB Case Rates by Origin of Birth
United States, 2000-08

Cases per 100,000

CDC - as of May 20, 2009
Factors Associated with Transmission of TB Infection to Contacts of US-Born TB Cases in Maryland

<table>
<thead>
<tr>
<th>Source Case Variable</th>
<th>% Contacts TST+</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavitary CXR: No</td>
<td>26%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Yes</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>Sputum smear: –</td>
<td>15%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>+</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>Dx Delay: ≤ 60 days</td>
<td>25%</td>
<td>0.05</td>
</tr>
<tr>
<td>&gt; 60 days</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>Dx Delay: ≤ 90 days</td>
<td>24%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&gt; 90 days</td>
<td>40%</td>
<td></td>
</tr>
</tbody>
</table>

Golub et al, Int J TB Lung Dis, 2006
Delays in the Diagnosis of TB in Maryland, 2000 – 2001

- Median patient delay – 26 days
- Median health care delay – 32 days
- Median total delay – 89 days
- Patient factors
  - Language, education, insurance, race, national origin

Golub et al, Int J TB Lung Dis, 2006
Tuberculosis: Diagnosis

• Depends upon the site of involvement
• Clinical signs & symptoms
• Risk factors
• *Tuberculin testing*
• Chest X-ray
• *Staining and cultures*
Tuberculin Skin Testing

Interpretation

• determines whether an individual has been infected by M. tuberculosis

• a positive test does not necessarily mean that the patient has active disease

• a negative test does not rule out active disease

• 5 TU of purified protein derivative (PPD) injected intradermally on the volar surface of the forearm to raise a wheal of 6-10 mm in size

Pediatric Tuberculosis Collaborative Group, Pediatrics 2004
Tuberculin Skin Testing

• The test should be read by a trained health care provider at 48-72 hours.
• Diameter of induration (not erythema) is measured.
• Results should be documented in millimeters of induration NOT 'positive' or 'negative'.

CORRECT: Only the induration is being measured.
INCORRECT: The erythema is being measured
### Tuberculin Skin Test

Factors associated with false negative and false positive test

<table>
<thead>
<tr>
<th>Factors</th>
<th>False-Negative Reactions</th>
<th>False-Positive Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>Viral illnesses (HIV, measles, varicella)</td>
<td>Exposure to NTM (e.g., <em>M. marinum</em>, <em>M. kansasii</em>)</td>
</tr>
<tr>
<td></td>
<td>Bacterial (typhoid fever, brucellosis, typhus, leprosy)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Early TB infection (&lt;12 wk)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TB disease (meningitis, miliary, pleural)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fungal (<em>Blastomycosis</em>)</td>
<td></td>
</tr>
<tr>
<td>Live virus vaccines</td>
<td>Measles</td>
<td>BCG vaccine</td>
</tr>
<tr>
<td></td>
<td>Polio</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smallpox</td>
<td></td>
</tr>
<tr>
<td>Concomitant medical conditions</td>
<td>Metabolic abnormalities (chronic renal failure)</td>
<td>Transfusion with whole blood from donors with known positive TST&lt;sup&gt;152&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Malignancies (Hodgkin’s disease, lymphoma, leukemia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor nutrition</td>
<td></td>
</tr>
<tr>
<td>Drugs and technical factors</td>
<td>Corticosteroids, chemotherapy</td>
<td>Inexperienced or biased reader</td>
</tr>
<tr>
<td></td>
<td>Newborns and &lt;2 y of age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Material: poor quality; inadequate dose (1 TU); improper storage (exposure to heat/light); expired</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Administration: not injected intradermally; too long in syringe</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reading: inexperienced or biased reader; recording error; read too early/late</td>
<td></td>
</tr>
<tr>
<td>Interpretative</td>
<td>Decreasing mm of induration</td>
<td>Increasing mm induration</td>
</tr>
</tbody>
</table>

Booster effect: An increase in TST size caused by repetitive TSTs in a previously sensitized individual

Pediatric Tuberculosis Collaborative Group, Pediatrics 2004
Previous BCG immunization

- Children born in countries with high case rates of TB are likely to have received BCG; WHO estimates that 79% of the world’s population has received BCG
- Data on effect of BCG on TST is confusing and sometimes conflicting
- In general children who have received BCG after infancy or those who receive >1 dose have increased rates of positive TST

- However, children from countries with high case rates of TB are more likely to TST positive due to latent TB that due to BCG

<table>
<thead>
<tr>
<th>Factors</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at immunization</td>
<td>Least effect if vaccinated at birth</td>
</tr>
<tr>
<td>Time since immunization</td>
<td>Most effect soon after immunization</td>
</tr>
<tr>
<td>Exposure to NTM</td>
<td>More effect with increased exposure</td>
</tr>
<tr>
<td>Prevalence of TB infection</td>
<td>Positive predictive value of TST increases with increasing prevalence of LTBI</td>
</tr>
<tr>
<td>Type of BCG vaccine used</td>
<td>Increased effect with increased number of viable bacilli</td>
</tr>
</tbody>
</table>

Pediatric Tuberculosis Collaborative Group, Pediatrics 2004
Tuberculosis: Staining and culture

- 3 single specimens are collected on 3 consecutive days; sputum / induced sputum collected in those who can produce it; early morning gastric contents should be aspirated after 8-10 hrs of fasting

- Acid fast staining (AFB), positive <10-15% of children with probable TB, does not distinguish TB from NTB and provides no information on drug susceptibility

- Conventional mycobacterial culture sensitivity with 2-3 consecutive gastric aspirate samples, used in lieu of sputa, is ~30-40% and takes several weeks

If patient’s isolate is not available, therapy can be guided based on the susceptibility of the organism from the source.

Zar HJ et al. Lancet 2005; Starke JR. Tuberculosis (Edinb) 2003
T-cell-based IFN-γ-release assays

- measure the response of patient’s lymphocytes *in vitro* to TB antigens
- two commercial assays available; both measure the lymphocyte response to ESAT-6 and CFP-10, which are secreted antigen produced by *M. tuberculosis* but not by *M. bovis* BCG and most NTM

**Pros**
- reported to be more sensitive and specific than PPD testing for *active disease*
- less effect of prior BCG immunization or NTM infection
- do not lead to boosting

**Cons**
- not approved for children in the US
- limited data in children
- expensive
- may be limited in distinguishing effect of prior BCG vaccination for *latent TB infection*
T-cell-based IFN-γ-release assays

T-SPOT.TB
- more cumbersome
- ? more sensitive

QuantiFERON ® -TB GOLD
- easier to perform
Standard Therapy for Active TB Disease

- 4 drugs → 2 drugs
- minimum of 6 months

*If culture positive at 2 mos and cavitation, extend therapy to 9 mos

IRZE
• 4 drugs
• minimum of 6 months

IR
• 2 drugs

All treatment should be directly observed therapy, DOT

I isoniazid, R rifampin, Z pyrazinamide, E ethambutol
Why so much drug? Why so long?

Uncomplicated TB:
- INH 47 g
- RIF 37 g
- PZA 32 g
- ETB 32 g

Cost:
- Pills < $1000
- DOT ~ $15,000 (60 visits)

Current model of short-course treatment for TB showing the intensive (bactericidal) phase in the first 2 months during which rapid killing is observed. The continuation (sterilizing) phase in the remaining 4 months is shown in which the rate of killing is lower thought due to “persister” bacteria which are slowly or sporadically multiplying. Adapted from Iseman 2000, Mitchison 1985, and Grosset 1980.

Jain SK et al. Microbe 2008
# Treatment of Drug Resistant TB

**“Seek Expert Advice”**

*Principle of treatment*: use 3-4 drugs active against the isolate

<table>
<thead>
<tr>
<th>Resistance Pattern</th>
<th>Duration of Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>6 months</td>
</tr>
<tr>
<td>RIF only</td>
<td>9-12 months</td>
</tr>
<tr>
<td>INH + RIF</td>
<td>18-24 months</td>
</tr>
<tr>
<td>XDR</td>
<td>24-? months</td>
</tr>
</tbody>
</table>
Anti-TB drug development

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>1945</td>
<td>Streptomycin</td>
</tr>
<tr>
<td>1946</td>
<td>PAS</td>
</tr>
<tr>
<td>1952</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>1955</td>
<td>Cycloserine</td>
</tr>
<tr>
<td>1958</td>
<td>Ethionamide</td>
</tr>
<tr>
<td>1960</td>
<td>Capreomycin</td>
</tr>
<tr>
<td>1963</td>
<td>Ethambutol</td>
</tr>
<tr>
<td>1967</td>
<td>Rifampin</td>
</tr>
</tbody>
</table>
How might new drugs improve the current situation?

• New regimens may make treatment easier to deliver
  – by shortening the duration to ≤ 3 months
  – by improving intermittent treatment
  – by not interacting with anti-retrovirals

• New regimens may be capable of curing MDR- & XDR-TB in ≤ 6 months
Obstacles to TB drug development

- Complacency with current regimen
- Financial disincentives
- Difficult pathogen to study
- Limited understanding of “persistence”
### Global TB Drug Portfolio

<table>
<thead>
<tr>
<th><strong>Discovery</strong></th>
<th><strong>Preclinical</strong></th>
<th><strong>Clinical Testing</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxylates</td>
<td>Dipiperidine SQ609</td>
<td>Fluoroquinolone Gatifloxacin</td>
</tr>
<tr>
<td>DBA</td>
<td>Nitrofuranylamides</td>
<td>OFLOTUB Consortium, Lupin, NIAID TBRU, Tuberculosis Research Centre, WHO TDR</td>
</tr>
<tr>
<td>TB Alliance, Wellesley College</td>
<td>NIAID, University of Tennessee</td>
<td></td>
</tr>
<tr>
<td>Cell Wall Inhibitors</td>
<td>Protein kinase inhibitors</td>
<td>Fluoroquinolone Moxifloxacin</td>
</tr>
<tr>
<td>Colorado State University, NIAID</td>
<td>Vertex</td>
<td>Bayer Pharmaceuticals, CDC TBTC, Johns Hopkins University, NIAID TBRU, TB Alliance</td>
</tr>
<tr>
<td>Dihydrolipoamide Acyltransferase Inhibitors</td>
<td>Novel Antibiotic Class</td>
<td>Diarylquinoline TMC207</td>
</tr>
<tr>
<td>Cornell University, NIAID</td>
<td>GlaxoSmithKline, TB Alliance</td>
<td>Tibotec</td>
</tr>
<tr>
<td>InhA Inhibitors</td>
<td>Picolinamide Imidazoles</td>
<td>Nitroimidazole PA-824</td>
</tr>
<tr>
<td>GlaxoSmithKline, TB Alliance</td>
<td>NIAID, TAACF</td>
<td>Chiron Corporation, TB Alliance</td>
</tr>
<tr>
<td>Isocitrate Lyase Inhibitors (ICL)</td>
<td>Pleuromutilins</td>
<td>Nitroimidazo-oxazole OPC-67683</td>
</tr>
<tr>
<td>GlaxoSmithKline, TB Alliance</td>
<td>GlaxoSmithKline, TB Alliance</td>
<td>Otsuka, TB Alliance</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Riminophenazine derivatives</td>
<td>Diamine SQ-109</td>
</tr>
<tr>
<td>TB Alliance, Univ. of Illinois at Chicago</td>
<td>Institute of Materia Medica, TB Alliance</td>
<td>Sequella Inc.</td>
</tr>
<tr>
<td>Methyltransferase Inhibitors</td>
<td>Screening and Target Identification</td>
<td>Pyrrole LL-3858</td>
</tr>
<tr>
<td>Anacor Pharmaceuticals</td>
<td>AstraZeneca</td>
<td>Lupin Limited</td>
</tr>
<tr>
<td>Natural Products Exploration</td>
<td>Thiolactomycin Analogs</td>
<td>Osaxolidinones linezolid, PNU-100480</td>
</tr>
<tr>
<td>BIOTEC, California State Univ., ITR, NIAID, TAACF, University of Auckland</td>
<td>NIAID, NIH</td>
<td>Pfizer</td>
</tr>
</tbody>
</table>
Where “new” drugs are coming from?

1. Adoption of existing drug used for other infections
   Fluoroquinolones, linezolid

2. Improved use of existing TB drug
   Rifapentine

3. Development of new chemical entity
   PA-824 (Global Alliance for TB Drug Devpmt)
   OPC-67683 (Otsuka)
   TMC-207 (Tibotec)
   SQ-109 (Sequella)
   PNU-100480 (Pfizer)
Targeted Tuberculin Skin Testing

- "Routine" or "mandated" LTBI testing policies for pediatric patients without risk factors are strongly discouraged (eg, entry into day care, school, summer camp, or college).

- Children and adolescents should be screened for risk factors for TB and LTBI and tested with a TST only if ≥1 risk factors are present.

Questions

1. Was your child born outside the United States?
   If yes, this question would be followed by: Where was your child born? If the child was born in Africa, Asia, Latin America, or Eastern Europe, a TST should be placed.

2. Has your child traveled outside the United States?
   If yes, this question would be followed by: Where did the child travel, with whom did the child stay, and how long did the child travel? If the child stayed with friends or family members in Africa, Asia, Latin America, or Eastern Europe for ≥1 week cumulatively, a TST should be placed.

3. Has your child been exposed to anyone with TB disease?
   If yes, this question should be followed by questions to determine if the person had TB disease or LTBI, when the exposure occurred, and what the nature of the contact was. If confirmed that the child has been exposed to someone with suspected or known TB disease, a TST should be placed.

   If it is determined that a child had contact with a person with TB disease, notify the local health department per local reporting guidelines.

4. Does your child have close contact with a person who has a positive TB skin test?
   If yes, see question 3 (above) for follow-up questions.

Risk-assessment questionnaires can include the following questions based on local epidemiology and priorities:

1. Does your child spend time with anyone who has been in jail (or prison) or a shelter, uses illegal drugs, or has HIV?
2. Has your child drank raw milk or eaten unpasteurized cheese?
3. Does your child have a household member who was born outside the United States?
4. Does your child have a household member who has traveled outside the United States?
Figure 1. Lifetime Risk of Active Tuberculosis among Persons with a Non-conversion Positive Tuberculin Skin Test.

Risks were calculated with the assumption of a decrease in risk of 10 percent per decade.
How long does one treat with INH?

- Longer duration of therapy corresponded to lower TB rates among those who took 0-9 months.
- No extra increase in protection among those who took >9 months.

Comstock GW, 1999.
**Latent TB infection**

**Treatment for Latent TB**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Duration, mo</th>
<th>Interval</th>
<th>Rating* (Evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>9</td>
<td>Daily</td>
<td>A(II)</td>
</tr>
<tr>
<td>INH</td>
<td>9</td>
<td>2 or 3 times per wk (DOT)</td>
<td>B(II)</td>
</tr>
<tr>
<td>Rifampin†</td>
<td>6</td>
<td>Daily</td>
<td>A(III)</td>
</tr>
<tr>
<td>Rifampin-pyrazinamide*</td>
<td>2</td>
<td>—</td>
<td>D(II)</td>
</tr>
</tbody>
</table>

Strength of the recommendation: A indicates preferred; B, acceptable alternative; C, offer when preferred or alternative regimens cannot be given and should not generally be given; D, should never be offered. Quality of evidence supporting the recommendation: I indicates at least 1 randomized trial with clinical endpoints; II, data from clinical trials that are not randomized or were conducted in other populations; III, expert opinion.

*USPHS rating system.²
†Rifampin preferred for LTBI caused by INH-resistant, rifampin-susceptible source.

Baseline liver functions tests not recommended for INH only regimen if no other risk factors for hepatotoxicity are present

*Rifampin-pyrazinamide regimen has been shown to have high risk of hepatotoxicity in adults and should be avoided

**ALWAYS PROVIDE THE PATIENT WITH INFORMATION ABOUT THE SIDE EFFECTS WITH THERAPY**

*Pediatric Tuberculosis Collaborative Group, Pediatrics 2004*
Mycobacterium tuberculosis infected C3HeB/FeJ mice develop well-defined caseous granulomas


Complete segmentation of healthy lungs, used as template shape.

Registration of the complete template shape onto the incomplete segmentation. Notice how the template fills in the holes of the lesions.

A controlled amount of lesions are generated in a lung shape. The recovered lung shape is compared to the original one after registration using different method. Using our method even when 50% of the lung is covered with lesion, 90% of the lung volume is recovered properly (p = 0.007).

TB granulomas: Inflammation is dynamic
$^{125}\text{I}}$FIAU-SPECT: Measuring bacterial burden

C3HeB/FeJ mice – low dose aerosol infection

*M. tuberculosis WT* Infected mouse
Summary

- TB is a major worldwide disease
  - MDR and XDR-TB incidence is an alarming problem
  - In USA:
    - rates are declining
    - more prevalent in foreign born / high risk groups
    - diagnostic delays

- TST (correct way of performing and interpreting)
  - intra-dermal, not subcutaneous
  - induration, not erythema
  - consider factors associated with false –ve and +ve test
  - IGRAs may be useful for diagnosis of active TB

- Children from countries with high case rates of TB are more likely to be TST positive due to latent TB than due to BCG

- New drugs to treat drug sensitive and resistant strains of TB are in the drug developmental pipeline

- "Routine / mandated" TST policies are strongly discouraged