Challenges to the Elimination of Tuberculosis (TB) in the United States

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Director, Division of Tuberculosis Elimination
Overview

- **Background (“TB 101”)**
  - Historic snapshot
  - Transmission, pathophysiology
  - Management and drug resistance

- **Epidemiology of TB in the U.S. and Globe**
  - Resurgence 1985-1992
  - Recovery 1992-2012

- **Challenges, threats, and opportunities**
  - Bridging three gaps for elimination
Years 1700 – 1900, global TB deaths estimated at 1 billion (1882 TB deaths ~7 million)

1882
Dr. Koch discovers TB bacteria

1936
TB culture: the gold standard in diagnosis

1943
First anti-TB drug (Streptomycin)

1960-70s
Last new anti-TB drug & the rise of drug resistance

1980s
Emergence of HIV and the TB/HIV co-epidemic

A Short TB Timeline
Ancient Scourge, Modern-day Killer

TB in skulls & vertebrae of mummies from 2000 BCE; Hippocrates Phthisis (consumption)
**Mycobacterium tuberculosis**

**Transmission and Pathophysiology**

- **TNFα-blockers**
- **Diabetes mellitus**
- **Other immunosuppressive Rx**
- **Disseminated, lymphatic, meningeal**

Airborne droplet nuclei generated by persons with respiratory/vocal cord disease due to *M. tuberculosis*.

- **Newborn BCG vaccine**
- **Treatment of LTBI**
- **Treatment of TB disease**
- **Infection control**

Haematogenous spread: *M. tuberculosis* DNA detected in tissues by *in situ* PCR.

Reactivation of TB: for example, after immunosuppression, HIV infection or smoking.

Progression to cavitary TB.
Pre-antibiotic Management of Pulmonary TB

March 2013 issue of EID with cover art “T.B. Harlem,” 1940, by Alice Neel. It depicts Carlos Negrón consumed by TB, following radical chest surgery with removal of several ribs to allow collapse of the damaged lung. The painting depicts the patient’s suffering and deformed chest, and is a historical record of TB treatment before antibiotics.
Introduction of Anti-TB Drugs

- Streptomycin: 1944
- Para-aminosalicylic acid (PAS): 1946
- Isoniazid: 1952
- Pyrazinamide: 1956
- Rifampin: 1965
- Ethambutol: 1968
Goals of Modern-day Management of TB with Multidrug Regimens

- **Individual benefits**
  - Prevent suffering, disability, and deaths
    - Kill bacteria rapidly (initial phase)
    - Prevent relapse due to persistent bacilli (continuation phase)
    - Prevent selection of drug resistance

- **Public health benefits**
  - Prevent transmission (identify contacts in need of treatment for LTBI or TB disease)
  - Protect effective drug regimens

Reliance on DOT to improve adherence and successful completion of therapy
ATS/CDC/IDSA Recommendations for Treatment of Tuberculosis

### TABLE 2. Drug regimens for culture-positive pulmonary tuberculosis caused by drug-susceptible organisms

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs</th>
<th>Initial and doses† (minimal duration)</th>
<th>Continuation phase</th>
<th>Range of total doses (minimal duration)</th>
<th>Rating* (evidence)†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td>INH</td>
<td>Seven days per week for 56 doses</td>
<td>1a INH/RIF</td>
<td>182–130 (26 wk)</td>
<td>A (I)</td>
</tr>
<tr>
<td></td>
<td>RIF</td>
<td>(8 wk) or 5 d/wk for 40 doses</td>
<td></td>
<td></td>
<td>A (II)</td>
</tr>
<tr>
<td></td>
<td>PZA</td>
<td>(8 wk)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EMB</td>
<td></td>
<td>1b INH/RIF</td>
<td>92–76 (26 wk)</td>
<td>A (I)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B (II)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1c** INH/RIF</td>
<td>74–58 (26 wk)</td>
<td>B (I)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E (I)</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>INH</td>
<td>Seven days per week for 14 doses</td>
<td>2a INH/RIF</td>
<td>62–58 (26 wk)</td>
<td>A (II)</td>
</tr>
<tr>
<td></td>
<td>RIF</td>
<td>(2 wk), then twice weekly for 12</td>
<td></td>
<td></td>
<td>B (I)</td>
</tr>
<tr>
<td></td>
<td>PZA</td>
<td>doses (6 wk) or 5 d/wk for 10 doses</td>
<td>2b** INH/RIF</td>
<td>44–40 (26 wk)</td>
<td>A (II)</td>
</tr>
<tr>
<td></td>
<td>EMB</td>
<td>(2 wk), then twice weekly for 12</td>
<td></td>
<td></td>
<td>B (I)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>doses (6 wk)</td>
<td></td>
<td></td>
<td>E (I)</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>INH</td>
<td>Three times weekly for 24 doses</td>
<td>3a INH/RIF</td>
<td>78 (26 wk)</td>
<td>B (I)</td>
</tr>
<tr>
<td></td>
<td>RIF</td>
<td>(8 wk)</td>
<td></td>
<td></td>
<td>B (II)</td>
</tr>
<tr>
<td></td>
<td>PZA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EMB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>INH</td>
<td>Seven days per week for 56 doses</td>
<td>4a INH/RIF</td>
<td>273–195 (39 wk)</td>
<td>C (I)</td>
</tr>
<tr>
<td></td>
<td>RIF</td>
<td>(8 wk) or 5 d/wk for 40 doses</td>
<td></td>
<td></td>
<td>C (II)</td>
</tr>
<tr>
<td></td>
<td>EMB</td>
<td>(8 wk)‡</td>
<td>4b INH/RIF</td>
<td>118–102 (39 wk)</td>
<td>C (I)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C (II)</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** EMB = Ethambutol; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; RPT = rifapentine.

* Definitions of evidence ratings: A = preferred; B = acceptable alternative; C = offer when A and B cannot be given; E = should never be given.
† Definition of evidence ratings: I = randomized clinical trial; II = data from clinical trials that were not randomized or were conducted in other populations; III = expert opinion.
‡ When DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.
§ Patients with cavitary on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31 week; either 217 doses daily or 62 doses [twice weekly]) continuation phase.
¶ Five-day-a-week administration is always given by DOT. Rating for 5-day/week regimen is All.
** Not recommended for HIV-infected patients with CD4+ cell counts <100 cells/μL.
** Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitary on initial chest radiograph (see text). For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

MMWR 2003;52(RR-11). Reliance on DOT to improve adherence and successful completion of therapy.
## Multi- and Extensively-drug Resistant TB

### 1st-line drugs

<table>
<thead>
<tr>
<th>“2 most important”</th>
<th>MDR</th>
<th>XDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>isoniazid</td>
<td><strong>X</strong></td>
<td><strong>X</strong></td>
</tr>
<tr>
<td>rifampicin</td>
<td><strong>X</strong></td>
<td><strong>X</strong></td>
</tr>
<tr>
<td>pyrazinamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ethambutol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 2nd-line drugs

<table>
<thead>
<tr>
<th>“2 most important”</th>
<th>“injectables”</th>
<th>“injectables”</th>
</tr>
</thead>
<tbody>
<tr>
<td>quinolones</td>
<td><strong>X</strong></td>
<td><strong>X</strong></td>
</tr>
<tr>
<td>ethionamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cycloserine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2nd line drugs are less effective than 1st LDs, more toxic and much more expensive.

= resistance by definition
Causes and Consequences of MDR TB

- Requires treatment with less potent, more toxic drugs that include ≥ 4 second-line drugs likely to be effective (based on results of DST)*
  - PZA, a fluoroquinolone, a second-line injectable, ethionamide (or prothionamide), and either cycloserine or PAS
  - Consider clofazimine, linezolid, amoxicillin/clavulanate, imipenem, clarithromycin, thioacetazone
  - Initial phase 8 months; total duration ≥ 20 months

- Requires specialty care, monitoring of response, management of side effects, and possible hospitalization
- May require surgical resection of affected lung lobe
- Cost of treatment 100-fold (vs. susceptible TB)

Treatment Outcomes for MDRTB Systematic Review & Meta–Analysis

- 34 studies, mean of 250 patients/study
- Treatment success, pooled 64% (95%CI 59–68)
  - Individualized vs. standardized regimens 64% vs. 54%
  - >18 months, DOT vs. shorter, no DOT 71% vs. 58%
- Failure 6% (95%CI 3–9)
- Default 12% (95%CI 8–16)
- Death 11% (95%CI 7–15)

XDR TB Treatment Outcomes
Systematic Review & Meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Proportion Favorable Outcomes (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banerjee et al [18]</td>
<td>0.41 (0.18, 0.65)</td>
</tr>
<tr>
<td>Blaas et al [19]</td>
<td>0.50 (0.01, 0.99)</td>
</tr>
<tr>
<td>Chan et al [20]</td>
<td>0.20 (-0.05, 0.45)</td>
</tr>
<tr>
<td>Condos et al [21]</td>
<td>0.50 (0.11, 0.89)</td>
</tr>
<tr>
<td>Eker et al [22]</td>
<td>0.57 (0.20, 0.94)</td>
</tr>
<tr>
<td>Jeon et al [23]</td>
<td>0.18 (0.12, 0.24)</td>
</tr>
<tr>
<td>Keshavjee et al [9]</td>
<td>0.48 (0.30, 0.67)</td>
</tr>
<tr>
<td>Kim H et al [5]</td>
<td>0.54 (0.39, 0.68)</td>
</tr>
<tr>
<td>Kim D et al [24]</td>
<td>0.29 (0.19, 0.40)</td>
</tr>
<tr>
<td>Kliiman et al [25]</td>
<td>0.43 (0.29, 0.56)</td>
</tr>
<tr>
<td>Kwon et al [26]</td>
<td>0.67 (0.49, 0.85)</td>
</tr>
<tr>
<td>Mitnik et al [27]</td>
<td>0.62 (0.48, 0.76)</td>
</tr>
<tr>
<td>Shah et al [28]</td>
<td>0.44 (0.33, 0.55)</td>
</tr>
<tr>
<td>Overall (I² = 84.3%)</td>
<td>0.44 (0.33, 0.55)</td>
</tr>
</tbody>
</table>

Note: Weights are from random effects analysis.
And Now “Totally Drug Resistant TB”?

  
  *Totally Drug-Resistant Tuberculosis in India*

  
  *Emergence of New Forms of Totally Drug-Resistant Tuberculosis Bacilli*
Epidemiology and Trends in U.S. and Globe
Resurgent TB in U.S.
Trends reversal, excess morbidity, 1985-1992


Associated Conditions
- Eroded infrastructure
- HIV epidemic
- Institutional transmission
- MDR-TB
- Immigration
Problems Unveiled During MDRTB Outbreaks in U.S., 1985-1992

- Difficulties in diagnosing TB among persons with HIV
- Lack of real-time diagnostic results (persons died before knowing of their MDRTB)
- Absence of infection control precautions
  - Death of healthcare workers and prison guard
- Cost of recovery inordinate
  - “Pay now or pay later”
Challenges in HIV-associated TB

- Atypical clinical presentation
  - Anergy with advanced immunosuppression
  - Extrapulmonary, disseminated TB
  - Paucibacillary disease

- Drug-drug interactions (rifamycins–protease inhibitors)
  - Optimal timing of treatment

- Immune reconstitution inflammatory syndrome
  - Worsening symptoms and clinical presentation

- Risk of relapse with highly intermittent regimens
Evidence of institutional MDRTB transmission

<table>
<thead>
<tr>
<th>Location, date [reference]</th>
<th>Patients with MDR-TB</th>
<th>Time to death, median, weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total, no.</td>
<td>HIV infected, %</td>
</tr>
<tr>
<td>Hospital (Florida), 1988–1990 [25]</td>
<td>65</td>
<td>93</td>
</tr>
<tr>
<td>Hospital (New York City), 1989–1990 [26, 27]</td>
<td>51</td>
<td>100</td>
</tr>
<tr>
<td>Hospital (New York City), 1990–1991 [27, 28]</td>
<td>70</td>
<td>95</td>
</tr>
<tr>
<td>Hospital (New York City), 1991–1992 [27, 29]</td>
<td>32</td>
<td>91</td>
</tr>
<tr>
<td>Hospital (Madrid, Spain), 1991–1995 [31]</td>
<td>48</td>
<td>100</td>
</tr>
<tr>
<td>Hospital (Buenos Aires, Argentina), 1994–1995 [32]</td>
<td>68</td>
<td>100</td>
</tr>
<tr>
<td>Prison system (New York State), 1990–1991 [33]</td>
<td>42</td>
<td>98</td>
</tr>
</tbody>
</table>

Hospital KZN, South Africa, 2006 (Gandhi N, et al) 53 100 98 2

NY State Correctional Guard Dies of MDRTB, 1991

Peter Petrosino  
**Rank:** Correctional Officer  
**Department:** NY State Department of Correctional Services  
**Institution:** Auburn Correctional Facility, NY  
**EOW:** 10/24/1991  

On 10/24/1991 Correctional Officer Petrosino contracted multi drug resistant tuberculosis while keeping guard over four inmates with AIDS and the same strain of tuberculosis at the hospital. His duties required him to sit outside the patient's rooms and to enter the room whenever any health care worker had reason to enter the room. Because the illness progressed in the inmate patients, the rooms became progressively more infectious during the course of treatment spreading the bacteria outside to the hallways when the doors were opened or closed. Fifty health care workers also tested positive for the same drug resistant strain after the outbreak. Source: Correctional Peace Officers Foundation

[http://www.cpoft.org/fallen_officers/?officer=peter_petrosino&id=48](http://www.cpoft.org/fallen_officers/?officer=peter_petrosino&id=48)
Healthcare Worker Union and ACT-UP Demonstrations, Circa 1991
U.S. Response to TB Resurgence

National MDR-TB Action Plan, Political Will & New Resources

Rebuilt Infrastructure & Training to Improve Case Identification

Focus on DOT, Outreach, Improved Rx Completion

Updated Diagnostic Labs, Real-time DST & Fingerprinting

Updated Infection Control & Treatment Recommendations

Rebuilt Research Capacity

MMWR Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Facilities, 1994

American Thoracic Society
Treatment of Tuberculosis and Tuberculosis Infection in Adults and Children

This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, March 1993. This is a joint statement of the American Thoracic Society and the Centers for Disease Control and Prevention. This statement was endorsed by the American Academy of Pediatrics, April 1993.
Reported TB Cases in U.S., 1982–2012

9,951 TB Cases in 2012
(Rate 3.2/100,000)
~27 new diagnoses/day

No. of Cases


0 5,000 10,000 15,000 20,000 25,000 30,000

0 5,000 10,000 15,000 20,000 25,000 30,000

9,951 TB Cases in 2012
(Rate 3.2/100,000)
~27 new diagnoses/day

Reported TB Cases in U.S., 1982–2012

No. of Cases

Estimated HIV Coinfection* in Persons with HIV Test Results, United States, 1993–2012

* Includes persons with positive, negative, or indeterminate HIV test results.

Data are updated as of 2/22/13 and are provisional.
2012 TB Cases Reported by State

- All states and the District of Columbia (DC) reported at least 1 TB case in 2012

- Range of state-specific rates/100,000
  - 0.4 (West Virginia) – 9.0 (Alaska)

- 33 states and DC had lower rates in 2012 than 2011

- California, Texas, New York, and Florida each reported more than 500 cases
  - Accounted for 4,967 (49.9%) of all TB cases in the United States
  - Among the 441 counties in these four states, 136 (30.8%) did not report a new TB case from 2010–2012
Rate* of Tuberculosis Cases, by State/area — United States, 2012

* Per 100,000 population.
Data are updated as of 2/22/13 and are provisional
Persons identified as white, black, Asian, or of other race are all non-Hispanic. Persons identified as Hispanic might be of any race.

* Persons included in this category are American Indian/Alaska Native, Native Hawaiian or other Pacific Islander, or multiple race.

Data are updated as of 2/22/13 and are provisional.
### Rate* of TB Cases by Race/Ethnicity — United States, 2012

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic</td>
<td>5.2</td>
</tr>
<tr>
<td>Asian</td>
<td>19.8</td>
</tr>
<tr>
<td>Black</td>
<td>5.7</td>
</tr>
<tr>
<td>White</td>
<td>0.8</td>
</tr>
</tbody>
</table>

* Per 100,000 population

Data are updated as of 2/22/13 and are provisional.
Other Risk Factors Reported for TB Cases, Ages ≥15 Years (N=9396), 2012

<table>
<thead>
<tr>
<th>Risk</th>
<th>No.</th>
<th>Percent*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homeless</td>
<td>510</td>
<td>5.6</td>
</tr>
<tr>
<td>Excess alcohol use</td>
<td>1,086</td>
<td>12.1</td>
</tr>
<tr>
<td>Resident of a correctional facility</td>
<td>386</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Rate of TB in homeless persons in 2011 was 88.8/100,000 (= 565/636,107 x 100,000) Compared to the TB rate of 3.4/100,000 for the overall U.S. population, for a rate ratio in homeless 26.1 times higher.

* Percent calculated excludes those with unknown risk factor data

Data are updated as of 2/22/13 and are provisional.

No. of TB cases among U.S.-born persons
No. of TB cases among foreign-born persons
TB rate among U.S.-born persons
TB rate among foreign-born persons

* Per 100,000 population
Data are updated as of 2/22/13 and are provisional.
Drug Resistance in Reported TB Cases, United States

- In 2011, 1.6% (127 of 7,817) of culture-confirmed cases with susceptibility test results for isoniazid and rifampin had evidence of multidrug-resistant (MDR) TB.

- 85.8% of MDRTB cases among foreign-born persons.

- One case of extensively drug-resistant (XDR) TB in 2012.

Data are updated as of 2/22/13 and are provisional.
## The Global Burden of TB, 2011

<table>
<thead>
<tr>
<th><strong>Type of TB</strong></th>
<th><strong>Estimated number of cases</strong></th>
<th><strong>Estimated number of deaths</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>All forms of TB</td>
<td>8.7 million (8.3–9.0 million)</td>
<td>1.4 million* (1.3–1.6 million)</td>
</tr>
<tr>
<td>HIV-associated TB</td>
<td>1.1 million (13%) (1.0–1.2 million)</td>
<td>430,000 (400,000–460,000)</td>
</tr>
<tr>
<td>Multidrug-resistant TB</td>
<td>Prevalence: 630,000 (460,000-790,000) out of ~12 million prevalent TB cases</td>
<td>Unknown, but probably &gt; 150,000</td>
</tr>
</tbody>
</table>

Source: WHO Global Tuberculosis Report 2012

* Including deaths attributed to HIV/TB
Global TB Incidence Rates, 2011

Highest rates in Africa
~80% of HIV+ TB cases in Africa

Source: WHO Global Tuberculosis Report 2012
Global New TB Cases, by Region, 2011

- South-East Asia: 40%
- Africa: 26%
- Western Pacific: 19%
- E. Mediterranean: 7%
- Europe: 5%
- Americas: 5%

Source: WHO Global Tuberculosis Report 2012
Estimated Number of MDR-TB Cases, 2011

>60% of cases in 5 countries: Russia, India, China, South Africa, Pakistan

The boundaries and names shown on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2012. All rights reserved.
Outcomes and Impact of Global TB Control Programs, 1995–2011

✓ 51 million patients treated
✓ 20 million lives saved
✓ 48% of HIV-infected TB on ARVs
✓ Reversed general epidemic and MDG TB mortality targets on track globally

However,

- TB incidence declining far too slowly
- 1/3 of TB cases not in the system
- Lagging behind on MDR-TB response
  - 19% of MDRTB reported/notified
- Off track for mortality decline in Africa & Europe

Source: WHO Global Tuberculosis Report 2012
Challenges, Threats, and Opportunities
A Paradox: As TB Declines in U.S.

- Loss of medical proficiency and expertise
  - Missed and delayed diagnoses
- Return of complacency (“problem solved”)
- Disease concentration in vulnerable populations
  - Homeless
  - Foreign-born
- Ongoing outbreaks of TB, associated with
  - Delays in diagnosis → transmission
  - Limited support to monitor therapy → relapse, resistance, transmission
  - Lack of thorough investigations to find/treat all contacts
- Unprecedented drug shortages
Latest Challenge to TB Elimination

- MMWR 2012;61(50):1029

**Notes from the Field**

**National Shortage of Isoniazid 300 mg Tablets**

On November 16, 2012, the Illinois State tuberculosis (TB) program notified CDC’s Division of Tuberculosis Elimination of a national shortage of 300 mg tablets of the antituberculosis medication isoniazid (INH). Subsequently, other state TB programs (e.g., California, Indiana, Maryland, New York, Virginia, and Wisconsin) reported difficulty obtaining INH 300 mg tablets. Other programs (e.g., San Diego) have experienced difficulties obtaining at least one of the commercially available anti-TB preparations containing the combination of rifampin and INH (IsonaRif [VersaPharm]).

- MMWR 2013;62(2):23-26

**Interruptions in Supplies of Second-Line Antituberculosis Drugs — United States, 2005–2012**

Second-line drugs (SLDs) are essential for treating multidrug-resistant and extensively drug-resistant tuberculosis (MDR TB* and XDR TB†). Drug shortages, in which supplies fail to trickle down in a timely manner, for true FDA-approved drugs like isoniazid, suspected TB disease, isoniazid, rifampin, pyrazinamide, and ethambutol are the four first-line drugs used worldwide as a 6-month standard regimen. In contrast, MDR TB generally requires 18–24 months of combination therapy involving
### 80% of USTB Programs that Treat MDRTB Experience Interruptions in Supply of 2nd line Drugs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n/N, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>Faced any challenges obtaining MDR-TB medications</em> in the past 5 years</em>*</td>
<td>21/26 (81)</td>
</tr>
<tr>
<td>If yes, which ones?</td>
<td></td>
</tr>
<tr>
<td>Nationwide shortage</td>
<td>21/21 (100)</td>
</tr>
<tr>
<td>Shipping delays</td>
<td>15/21 (71)</td>
</tr>
<tr>
<td>Medications too expensive for their program</td>
<td>13/21 (62)</td>
</tr>
<tr>
<td>Medications too expensive for insured patients</td>
<td>8/20 (40)</td>
</tr>
<tr>
<td>Medications too expensive for uninsured patients</td>
<td>10/20 (50)</td>
</tr>
<tr>
<td>Delays caused by the IND/IRB process</td>
<td>10/21 (48)</td>
</tr>
<tr>
<td>Payor bureaucracy</td>
<td>7/19 (37)</td>
</tr>
</tbody>
</table>

#### Adverse effects due to challenges

<table>
<thead>
<tr>
<th>Adverse effects due to challenges</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay in starting treatment</td>
<td>11/19 (58)</td>
</tr>
<tr>
<td>Treatment lapse/interruption</td>
<td>6/19 (32)</td>
</tr>
<tr>
<td>Inadequate Regimen</td>
<td>6/19 (32)</td>
</tr>
<tr>
<td>Substantial staff time tied up with drug procurement</td>
<td>13/19 (68)</td>
</tr>
</tbody>
</table>

* MDR medications include Capreomycin, Amikacin, Kanamycin, Moxifloxacin, Levofloxacin, PAS, Cycloserine, Ethionamide, Linezolid, Clofazamine

NTCA Survey. MMWR 2013;62:23-26
TB Elimination Requires Bridging 3 Gaps (≤ 1 case/ million population)

Implementation  Knowledge  Ambition

Castro KG, LoBue P. *Emerg Infect Dis* 2011;17:337-342
Bridging the Implementation Gap in TB

- W. Fox, London (1963): “little attempt to adapt present knowledge to their specific problems”

- NR Fendall, New York (1972): refers to medicine in 20th century as “…superb in technological breakthroughs, but woefully inept in its application of knowledge to those most in need.” Further suggests “the ‘implementation gap’ must be closed”

Castro KG, LoBue P. Emerg Infect Dis 2011;17:337-342
Domestic Returns from Investment in the Control of Tuberculosis in Other Countries

Redefine and Protect Core Public Health Functions

- Update and articulate essential components and terms for engagement with other health sector providers

Tuberculosis Commentary

Tuberculosis Control in a Changing Health Care System: Model Contract Specifications for Managed Care Organizations

Bess Miller, Sara Rosenbaum, Paul V. Stange, Steven L. Solomon, and Kenneth G. Castro

Core TB Laboratory Services for Public Health Laboratories

by the APHL TB Steering Committee

# National TB Program Objectives and Performance Targets for 2015

<table>
<thead>
<tr>
<th>Objective Categories</th>
<th>Objectives and Performance Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completion of Treatment</td>
<td>For patients with newly diagnosed TB for whom 12 months or less of treatment is indicated, increase the proportion of patients who complete treatment within 12 months to 93.0%.</td>
</tr>
</tbody>
</table>
| TB Case Rates | Decrease the TB case rate in U.S.-born persons to less than 0.7 cases per 100,000.  
  |  |  
  |  |   - Increase the average yearly decline in TB case rate in U.S.-born persons to at least 11.0%.  
  |  |  
  | U.S.-born Persons | Decrease the TB case rate for foreign-born persons to less than 14.0 cases per 100,000.  
  |  |  
  |  |   - Increase the average yearly decline in TB case rate in foreign-born persons to at least 4.0%.  
  |  |  
  | Foreign-born Persons | Decrease the TB case rate in U.S.-born non-Hispanic blacks to less than 1.3 cases per 100,000.  
  |  |  
  | U.S.-born non-Hispanic Blacks | Decrease the TB case rate for children younger than 5 years of age to less than 0.4 cases per 100,000.  
  |  |  
  | Children Younger than 5 Years of Age |  

Areas of Coverage

Curry International Tuberculosis Center
Mayo Clinic Center for Tuberculosis
New Jersey Medical School Global Tuberculosis Institute
Heartland National Tuberculosis Center
Southeastern National Tuberculosis Center

Center Location
Federal/CDCTB Funding Formula, FY 2013–15

Adapt to changing environment, reductions in federal and state/local health department budgets, and the prospects of Affordable Care Act (ACA)

- Support TB core program basics: directly observed therapy; completion of therapy; laboratory capacity; training; contact investigations (~100,000 contacts/year); drug susceptibility testing; early warning
- Provide incentives for improving performance
- Provide safety net for persons who remain uninsured under ACA (foreign-born with limited documentation, homeless, marginalized)
- Support human resource development/training and access to medical consultation with subject-matter experts
- Add flexibility for response to outbreaks in areas with diminished capacity to address increasingly complex scenarios (homelessness/incarceration/M&XDR TB)
- Align domestic and global activities to reduce importation of TB (63% cases are foreign-born)
- Support research for innovation and program improvements
Bridging the Knowledge Gap in TB

Research, develop, and implement:

- Understanding local epidemiology and drivers
- Rapid (i.e., same-day) diagnosis of TB and drug resistance to guide optimal therapeutic regimen use
- Safe and effective new drugs, and short effective regimens. Aim for cure with 2-3 months of therapy
- Understanding of genetic markers of bacterial virulence to enable targeted interventions
- Understanding of host defense correlates of protection for effective vaccine, and surrogate markers of disease progression for targeted prevention efforts in people with latent TB

Castro KG, LoBue P. *Emerg Infect Dis* 2011;17:337-342
Modeling Impact of Interventions and TB Elimination in U.S. (2)

Increase treatment of chronic LTBI

- **baseline**
- **2 x baseline**
- **4 x baseline**
- **reported**

**Incidence per million**

- **Foreign-born**
- **All**
- **U.S.-born**

**Year**

2000, 2020, 2040, 2060, 2080

Hill AN, Becerra JE, Castro KG. *Epidemiology and Infection* 2011 Jan: 1-11

<table>
<thead>
<tr>
<th>Population</th>
<th>% LTBI Prevalence (95% CI)</th>
<th>Estimated No. x Million (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>4.2 (3.3-5.2)</td>
<td>11.2 (8.9-14.0)</td>
</tr>
<tr>
<td>U.S.-born</td>
<td>1.8 (1.4-2.1)</td>
<td>4.1 (3.1-5.6)</td>
</tr>
<tr>
<td>Foreign-born</td>
<td>18.7 (13.5-25.2)</td>
<td>6.9 (5.0-9.3)</td>
</tr>
<tr>
<td>Poverty Index* ≥ 1</td>
<td>3.3 (2.5-4.4)</td>
<td>6.5 (4.9-8.6)</td>
</tr>
<tr>
<td>Poverty Index &lt; 1</td>
<td>6.1 (4.0-9.1)</td>
<td>2.8 (1.8-4.2)</td>
</tr>
<tr>
<td>Non-Hispanic whites</td>
<td>1.9 (1.3–2.9)</td>
<td>3.5 (2.4-5.3)</td>
</tr>
<tr>
<td>Non-Hispanic blacks</td>
<td>7.0 (5.3-9.1)</td>
<td>2.2 (1.7-2.9)</td>
</tr>
</tbody>
</table>

* Poverty Index = Family income / poverty threshold adjusted by family size. (Poverty defined as income/poverty threshold ratio < 1)

Recent Advances in TB Control: Diagnosis & Treatment

**GeneXpert MTB/RIF®**
- Endorsed by WHO in 2010
- **Returns results on TB and resistance to a primary drug (RIF) in < 2 hours**
- CDC/USAID/PEPFAR are part of the global rollout of this new tool

**Bedaquiline/Sirturo®**
- Approved by FDA in December 2012
- **First new anti-TB drug in 50 years**
- For use in MDR TB patients
- CDC is developing domestic, and contributing to international, guidelines on the use of this new drug
Molecular Detection of Drug Resistance (MDDR) Service for TB Offered by CDC

Conventional DST vs MDDR

Isolate Received

MGIT 960

Conventional Results: 42 day TAT

Agar Proportion

PCR

DNA Sequencing

Molecular Results: 2 day TAT

http://www.cdc.gov/tb/topic/laboratory/mddr.htm
Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection


Morbidity and Mortality Weekly Report
Dec 9, 2011;60(48):1650-1653

Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection
**Rational Vaccine Pipeline for TB**

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase IIb</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral-vectored</td>
<td></td>
<td></td>
<td>MVA85A</td>
</tr>
<tr>
<td>AdAg85A&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td>Modified vaccinia Ankara vector</td>
<td></td>
</tr>
<tr>
<td>Adenovirus 5</td>
<td></td>
<td>M. tuberculosis 85A</td>
<td></td>
</tr>
<tr>
<td>M. tuberculosis 85A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adjuvant</td>
<td>Hybrid-1 + CAF01&lt;sup&gt;4&lt;/sup&gt;</td>
<td>M72 + AS01&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Hybrid-1 + CAF01&lt;sup&gt;4&lt;/sup&gt;</td>
<td>M. tuberculosis 85B, ESAT-6</td>
<td>M. tuberculosis Rv1196, Rv0125</td>
<td></td>
</tr>
<tr>
<td>Hybrid 56 + IC31&lt;sup&gt;6&lt;/sup&gt;</td>
<td>M. tuberculosis 85B, ESAT-6, Rv2660</td>
<td>Hybrid-1 + IC31&lt;sup&gt;7&lt;/sup&gt;</td>
<td>M. tuberculosis 85B, ESAT-6</td>
</tr>
<tr>
<td>ID93 + GLA-SE&lt;sup&gt;9&lt;/sup&gt;</td>
<td>M. tuberculosis Rv1813, Rv2608, Rv3619, Rv3620</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recombinant BCG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Killed whole cell or extract</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bridging the Ambition Gap in TB

- Overcome impoverishment of will common to resource-limited settings
- Acknowledge that TB elimination and eradication are the ultimate goals (for present or future generation)
  - Mobilize political resolve and commitment
  - Develop solidarity of effort behind global elimination plan
  - Develop “status of intolerability” by authorities and public
- Bold ambition, expectations, and sustained actions (no room for premature declarations of victory or complacency)

Castro KG, LoBue P. Emerg Infect Dis 2011;17:337-342
Political Commitment

Public Law 110–392
110th Congress

(a) Short Title.—This Act may be cited as the “Comprehensive Tuberculosis Elimination Act of 2008”.

“(h) Authorization of Appropriations.—
   “(1) General Program.—
      “(A) In general.—For the purpose of carrying out this section, there are authorized to be appropriated $200,000,000 for fiscal year 2009, $210,000,000 for fiscal year 2010, $220,500,000 for fiscal year 2011, $231,525,000 for fiscal year 2012, and $243,101,250 for fiscal year 2013.
≤ 1 TB case per million by 2035 would yield

- 253,000 fewer TB cases
- 15,200 fewer TB-related deaths
- $1.3 billion less in treatment costs (in 2006 dollars)
Tuberculosis Financing and Funding Gaps*

118 Countries Eligible for Global Fund Support

Total international funding required $4.8 billion each year to prevent & control TB

Gap: $1.6 billion funding/year

Anticipated yield:

17 million people treated,
6 million lives saved

* Analysis done by WHO in collaboration with The Global Fund to Fight AIDS, TB and Malaria
Lessons from Smallpox Eradication

- “Thousands of people participated in the smallpox global eradication effort...they were optimists...they were risk takers; there was no shortage of people telling them that the effort was futile...”

- “It wasn't science that threatened to stop us. It wasn't even nature per se. Rather, it was human nature: the human factors that involve strikes, job security, political concerns, turf.”

Foege WH. *House on Fire*. University of California Press. 2011
Summary

- U.S. 20-year recovery from devastating impact of resurgence and HIV-associated MDRTB must be sustained; global situation remains a health security threat

- Achieving TB elimination in U.S. requires
  - Sustaining recent gains, addressing health disparities
  - Marked improvements in global TB prevention and control
  - New tools and novel approaches: molecular detection of TB and drug resistance; safe and effective shorter regimens for both active TB and latent TB infection; ideally post-exposure vaccine(s) to replace BCG

- Commitment to the goal of TB elimination requires bridging three gaps
  - Implementation
  - Knowledge
  - Ambition
…the issue now confronting the nation is whether we will allow another cycle of neglect to begin or, instead, whether we will take decisive action to eliminate tuberculosis.

The Elimination of Tuberculosis in the United States
CAN YOU IMAGINE A WORLD WITHOUT TB?
WE CAN.

Stop TB Partnership
Acknowledgements

- Partners in state and local TB programs, RTMCCs, TBETN, TBPEN, TBGIMS, NTCA, Stop TB USA
- Collaborators in research consortia (TBTC, TBESC)
- Academic collaborators, ATS, IDSA, AAP, APHL
- Professionals staff in CDC/DTBE, other CDC partners
- Federal TB Task Force (FDA, HRSA, NIH, OGAC, USAID)

Thank You

The findings and conclusions presented here do not necessarily represent the official position of the Centers for Disease Control and Prevention
TB preys on the poor, but can affect anyone
Essential Components of a TB Prevention and Control Program

- Overall planning and policy, supportive laws, and funds
- Managing persons with disease or suspected to have TB
  - Clinical services, coordination of care, safety monitoring
  - Directly-observed therapy, infection control
- Identifying persons with clinically active TB
  - Diagnostic laboratory, chest radiograph, HIV C&T
  - Case finding, contact investigation
- Data collection and analysis
  - Case registry, confidentiality protection
  - Drug resistance surveillance
  - Program evaluation
- Training and education (human resource development)
Modeling Impact of Interventions and TB Elimination in U.S. (1)

Projections for treatment levels of active TB

Cutting transmission

Hill AN, Becerra JE, Castro KG. *Epidemiology and Infection* 2011 Jan: 1-11
Categorical TB Grants Ceased
1972-1982*

* Categorical funding reappeared via emergency grants in 1980, but amounted to only $3.6M in 1980 and $3.7M in 1981. “It was not until 1989 that funding reached the level at which it had peaked in 1969, before the institution of block grants.”

Annual CDCTB Budget, FY 1990–FY 2013*

50% drop in purchasing power in FY 2012 vs. FY 1994

U.S. Dollars (Million)

Fiscal Year

*Includes appropriation and TB/HIV dollars. Actual adjusted by 1990 dollars for Consumer Price Index (CPI) for Medical Care. Updated Dec 2012
Xpert MTB/RIF Roll-Out Progress
Rapid Diagnostic Access

Dec 2010
WHO policy announced

99 GeneXpert machines in the public sector in 23 countries

Q1 2011

966 GeneXperts machines in the public sector in 77 countries

Q4 2012

Data: Foundation for Innovative New Diagnostics