Eliminating Tuberculosis: Advances, Residual Challenges, and Opportunities

C PTR Annual Workshop
Washington, DC
24 September 2014

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Disclosure and Disclaimer

I have no conflicts of interest to disclose.

This presentation was prepared in my personal capacity. The opinions expressed in it are my own, and do not reflect the view of the Centers for Disease Control and Prevention, the Department of Health and Human Services, or the United States government.
Brief Overview

- Painful and powerful lessons from the resurgence of TB in the U.S. and globe
- Response and subsequent trends
- Bridging 3 remaining gaps to achieve elimination
- Recent advances in diagnostics and drug treatment
- Improving our situational awareness and work to leverage political will and opportunities
Resurgent TB in U.S.
Trends reversal, excess morbidity, 1985-1992

Associated Conditions
- Eroded infrastructure
- HIV epidemic
- Institutional transmission
- MDR-TB
- Immigration

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.”

Challenges in HIV-associated TB

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

With introduction of ARTs:

- **Drug-drug interactions (rifamycins – protease inhibitors)**
  - Optimal timing of treatment for TB vs. HIV

- **Imune reconstitution inflammatory syndrome**
  - Worsening symptoms and clinical presentation

Evidence of institutional MDR TB transmission

<table>
<thead>
<tr>
<th>Location, date [reference]</th>
<th>Patients with MDR-TB</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total, no.</td>
<td>HIV infected, %</td>
<td>Died, %</td>
<td>Time to death, median, weeks</td>
</tr>
<tr>
<td>Hospital (Florida), 1988–1990 [25]</td>
<td>65</td>
<td>93</td>
<td>72</td>
<td>7</td>
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<tr>
<td>Hospital (New York City), 1989–1990 [26, 27]</td>
<td>51</td>
<td>100</td>
<td>89</td>
<td>16</td>
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<tr>
<td>Hospital (New York City), 1990–1991 [27, 28]</td>
<td>70</td>
<td>95</td>
<td>77</td>
<td>4</td>
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<tr>
<td>Hospital (New York City), 1991–1992 [27, 29]</td>
<td>32</td>
<td>91</td>
<td>83</td>
<td>4</td>
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<tr>
<td>Hospital (Madrid, Spain), 1991–1995 [31]</td>
<td>48</td>
<td>100</td>
<td>98</td>
<td>7</td>
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<tr>
<td>Hospital (Buenos Aires, Argentina), 1994–1995 [32]</td>
<td>68</td>
<td>100</td>
<td>93</td>
<td>5</td>
</tr>
<tr>
<td>Prison system (New York State), 1990–1991 [33]</td>
<td>42</td>
<td>98</td>
<td>79</td>
<td>4</td>
</tr>
<tr>
<td>Hospital KZN, South Africa, 2006 (Gandhi N, et al)</td>
<td>53</td>
<td>100</td>
<td>98</td>
<td>2</td>
</tr>
</tbody>
</table>

Problems Unveiled During MDR TB 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 MDR TB)
- Limited treatment options
- Absence of infection control precautions
  - Death of healthcare workers and prison guard
- Cost of recovery inordinate
  - “Pay now or pay later”

Patient observed ambulating past nurse while on “respiratory isolation”
NY State Correctional Guard Dies of MDR TB, 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.cpotf.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

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

Treatment of Tuberculosis and Tuberculosis Infection in Adults and Children

Reported TB Cases in U.S., 1982–2013

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

No. of Cases


Year

26 new diagnoses/day

9,588 TB Cases in 2013 (Rate 3.0/100,000)
### Annual CDC TB Budget, FY 1990–FY 2013*

> 50% drop in purchasing power in FY 2013 vs. FY 1994

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>U.S. Dollars (Million)</th>
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<tbody>
<tr>
<td>1990</td>
<td>180</td>
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<tr>
<td>1991</td>
<td>160</td>
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<tr>
<td>2012</td>
<td>260</td>
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<tr>
<td>2013</td>
<td>280</td>
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</table>

*Includes appropriation and TB/HIV dollars. Actual adjusted by 1990 dollars for Consumer Price Index (CPI) for Medical Care.

“It is unfortunate that we have been so effective in our work, but relatively ineffective in convincing the healthcare system of this value.” Bartlett JG. *Clin Infect Dis* 2014;59(Suppl 2):S88-92

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*Actual $* and CPI-Adjusted
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
Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946–1986, with relevant subsequent publications

Wallace Fox,* Gordon A. Ellard,† Denis A. Mitchison†
Redefine and Protect Core Public Health Functions in Prevention Through Healthcare

- 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

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)
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 2-4 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. (1)

Projections for treatment levels of active TB

Cutting transmission

Hill AN, Becerra JE, Castro KG. Epidemiology and Infection 2011 Jan: 1-11
Modeling Impact of Interventions and TB Elimination in U.S. (2)

Hill AN, Becerra JE, Castro KG. *Epidemiology and Infection* 2011 Jan: 1-11
Interventions to Reduce TB Burden in SE Asia

- Drug regimens that shorten treatment duration and are efficacious against drug-resistant strains reduce incidence by 10–27%.
- A triple combination of a portfolio vaccine, drug regimen, and diagnostics reduces incidence by 71%.

Abu-Raddad LJ, et al., PNAS, 2009;106:13980-13985
Recent Advances in TB Diagnosis

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/GF/UNITAIDS part of global rollout of this new tool

Conventional DST

Isolate/Sediment Received

MGIT 960

Agar Proportion

Conventional Results: 42 day TAT

PCR

DNA Sequencing

MDDR

Conventional DST

MDDR

http://www.cdc.gov/tb/topic/laboratory/mddr.htm
Recent Advances in TB Treatment

**Delaminid** (Deltyba®)

- OBR vs OBR + Delaminid 100mg BID vs OBR + Delaminid 200mg BID
- 29.6% vs 45.4% vs 41.9% sputum conversion at 2 months
- QT prolongation associated with delaminid, but no clinical events
- Approved by EMA May 2014, for use in MDR TB patients

**Bedaquiline/Sirturo®**

- Approved by FDA in December 2012, for use in MDR TB patients
- First new anti-TB drug in 50 years
- CDC and WHO developed domestic, and international guidelines on the use of this new drug
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
Recent (Dubious) Advances

Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis

Stephen H. Gillespie, M.D., D.Sc., Angela M. Crook, Ph.D.,
Timothy D. McHugh, Ph.D., Carl M. Mendel, M.D., Sarah K. Meredith, M.B., B.S.,
Stephen R. Murray, M.D., Ph.D., Frances Pappas, M.A., Patrick P.J. Phillips, Ph.D.,
and Andrew J. Nunn, M.Sc., for the REMoxTB Consortium∗

ReMOX

- 8wk HRZE + 18wk HR (control) vs. 17wk HRZM + 9wk
  Placebo(H) vs. 17wk MRZE + 9wk Placebo(E)
- 92% vs 85% vs 80% favorable outcomes
- M-containing regimens associated with rapid initial decline bacterial load, but no effective shortening of Rx to 4 months

Gillespie SH, et al. NEJM 2014 (Sept 7) DOI: 10.1056/NEJMoa1407426
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
Smallpox Eradication Lessons*

- **Political commitment, coordination, and implementation**
  - Decision by 1959 WHA, ratified in 1966 WHA with new resources

- **Special program**
  - Specifically targeted and time-limited
  - Adapted to local epidemiology and different local conditions
  - Identify and address set-backs

- **Defined objectives and goals**
  - Complete disease reporting and nil incidence
  - Discover cases and contain outbreaks within 2 weeks

- **Quality control and program management**
  - Network of professional staff: “many thousands of health staff received training in the execution of vaccination programmes and in field epidemiology”

- **Research**
  - Better methods for quality vaccine production and targeted delivery

- **Certification, Costs**

A Call for Action on the Tuberculosis Elimination Plan for the United States

≤ 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)
Economics of TB Prevention and Control

- tuberculosis case finding & treatment: US$ 30
- heart attacks acute low-cost management: US$ 25
- expanded immunization: US$ 20
- malaria prevention & treatment: US$ 20
- HIV combination prevention: US$ 12
- local surgical capacity: US$ 10
- heart attacks: US$ 30

return on investment for every one dollar spent on the most cost-effective health interventions

Estimate of Global TB Funding Needs

Total funding needed: US$46.7 billion 2011–2015
Growing Awareness About Unmet Needs

The New York Times | http://nyti.ms/1nkg1x5

BUSINESS DAY

A Dearth in Innovation for Key Drugs

JULY 22, 2014

Eduardo Porter

“Antibiotic-resistant infections sicken more than two million Americans every year and kill at least 23,000. The World Health Organization has warned that a “post-antibiotic era” may be upon us…. No major new type of antibiotic has been developed since the late 1980s, according to the W.H.O.”

“…Research on new antibiotics could be encouraged by allowing shorter clinical trials for the promising molecules or guaranteeing minimum returns for ground-breaking drugs… the market isn’t delivering the innovation we need.”
Situational Awareness of Opportunities

The White House
Office of the Press Secretary

For Immediate Release

September 18, 2014

Executive Order -- Combating Antibiotic-Resistant Bacteria

GOAL 1: Slow the Development of Resistant Bacteria and Prevent the Spread of Resistant Infections ................................................................. 7

GOAL 2: Strengthen National One-Health Surveillance Efforts to Combat Resistance .......... 11

GOAL 3: Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria ......................................................... 15

GOAL 4: Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines ................................................................. 17

GOAL 5: Improve International Collaboration and Capacities for Antibiotic Resistance Prevention, Surveillance, Control, and Antibiotic Research and Development ........... 20

SERIOUS Threat Level Pathogens

Drug-Resistant Tuberculosis (Notifiable to CDC)

Tuberculosis (TB) is among the most common infectious diseases and cause of death worldwide.

Of 9,588 TB cases in the U.S. in 2013, it is estimated that 1-2% of these cases were resistant to antibiotics with direct costs for treatment of MDR-TB averaging $134,000 per case (in 2010 dollars)
Critical Path to TB Drug Regimens (CPTR)

- Initiative to speed the development of new and markedly improved drug regimens for TB

  Partnership brings together
  - the world’s leading pharmaceutical, other drug developers,
  - global regulatory agencies, and
  - civil society organizations

- Support advances in
  - regulatory science,
  - the development of infrastructure, and
  - other progress needed to facilitate the development and availability of new TB drug treatments.

- Work with stakeholders around the world to advance a new paradigm that dramatically speeds new TB drug regimens to patients

http://cptrinitiative.org/
Ending Neglect

“...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

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CAN YOU IMAGINE A WORLD WITHOUT TB? WE CAN.