Barriers to Global TB Control

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TB Cases & Deaths: 2011

- 12.0 million people living with active TB
  - 8.7 million new cases in 2011
- 1.4 million TB deaths in 2011
- Twenty-two countries are considered “high-burden countries (HBCs)”, accounting for approximately 82% of new TB cases each year.


http://gamapserver.who.int/mapLibrary/Files/Maps/Global_TB_incidence_2011.png
TB: Global Impact

TB is one of 3 top infectious disease killers world wide

- TB; HIV/AIDS; malaria
- TB is often the final “nail in the coffin”
  - Employment lost
  - Stable housing lost
  - Families torn apart
  - Poverty to extreme poverty
  - Most vulnerable: Babies and children, pregnant women, poorly educated/skilled men, elderly

TB in Pregnant Women

- 10-fold increase of miscarriage
- 2-fold increase in low birth weight and premature births (both risk factors for childhood death) and a six-fold increase of perinatal death (within the first 28 days of life).
- Studies from sub-Saharan Africa and India have shown that TB was a direct cause of an estimated 6-15% of all maternal deaths and an indirect cause of another 15-34%
TB Cases & Deaths: 2011

- **TB & HIV**
  - Dual-epidemics due to high rate of co-infection
  - TB is the leading cause of death among people with HIV in developing countries
  - In 2011, ~ 12% of new TB cases were also HIV+
  - Of the 1.4 million people who died from TB, 30% were HIV+


http://gamapserver.who.int/mapLibrary/Files/Maps/Global_TB_incidence_2011.png
TB Cases & Deaths: 2011

- **Drug-Resistant TB**
  - Isoniazid resistance becoming very common, can sabotage successful first-line regimen
  - Multidrug-resistant TB (MDR-TB) (resistant to INH and Rifampin), making standard first line regimen obsolete
  - Extensively drug-resistant TB (XDR-TB), fails to respond to both first and second line drugs

- Among the 12.0 million prevalent cases of TB in **2011**
  - Estimated **630,000** cases of MDR-TB and XDR-TB had been reported in 84 countries and territories

Number of MDR-TB* cases estimated to occur among notified pulmonary tuberculosis cases, 2011

* MDR-TB: multidrug-resistant tuberculosis (resistance to, at least, isoniazid and rifampicin)

The boundaries and names shown and the designations used 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 and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

What Are the Barriers to TB Control Globally? Your experience tells you...

**Individual**
- **Access** to health care
  - Distance, transportation
  - Time off work
  - Money for diagnostic tests (even if TB treatment is “free”)
- **Stigma/Consequences** – willingness to be diagnosed with TB and/or HIV
- **Confidence**
  - Qualified HCW to diagnose?
  - Have medicines available (for free)
  - Testing and treating efficiently

**Structural/systems**
- # Health care facilities per sq mile/pop
- # trained HCW/facility to diagnose
- # trained microscopists/x-ray/diagnostics
  - QA systems, ongoing training, turnover staff
- Supply chain management – drugs and diagnostic reagents, equipment
- Knowledgeable HCW to manage treatment

$$$

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THE SCIENCE OF IMPROVING LIVES
What Are the Barriers to TB Control Globally? Your experience tells you...

Disease-specific

- **TB diagnostics**
  - No culture - smear microscopy only
  - Lengthy process
  - Presence of drug-resistance?

- **TB treatment**
  - Requires 6 months treatment
  - Multiple drugs, side effects
  - Emergence of drug resistance
  - Many countries require hospitalization for first 8 weeks
  - Food with treatment – often an issue

- **TB prevention**
  - Lack of infection control knowledge, practice
  - Low uptake of INH prevention (TLTBI/IPT)

- **Structural/systems**

NATIONAL PRIORITIES: TB is **NOT** the only problem!
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<thead>
<tr>
<th>Country 1</th>
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<td>Zimbabwe</td>
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**Countries with high burden of TB are usually those with other deadly diseases (HIV/AIDS, malaria), high infant and childhood mortality and widespread, extreme poverty.**

Shaded boxes indicate countries “most-affected” in at least 3 conditions.

http://kff.org/global-indicator/
Where to Start!?

What are you doing to save time?

http://www.timdumas.com/
WHO developed DOTS and the STOP TB Strategy

1. **Political commitment with increased and sustained financing**
2. **Case detection through quality-assured bacteriology**
3. **Standardized treatment, with supervision and patient support**
4. **An effective drug supply and management system**
5. **Monitoring and evaluation system, and impact measurement**

*Direct observation treatment, short course*
DOTS: What IS it? A Good start...

- Making the political case that treating TB in-country is important
- Create a National TB Program with corresponding local units
- Have a consistent National and/or Provincial budget that supports TB drugs and TB Control

DOTS*

Political commitment with increased and sustained financing

http://www.who.int/topics/tuberculosis/en/
DOTS: What IS it? A Good start...

Case detection through quality-assured bacteriology

- Remember, culture is rarely available
- Microscopes have to be maintained and work properly
- Electricity reliably available (generators as needed)
- Reagents to do AFB staining available
- Techs trained
- Routine QA
- Routine supervision
- Reporting

*Direct observation treatment, short course
DOTS: What IS it? A Good start...

- The “DOT” part is not the main emphasis
- Every person gets standard RIF-based 6-month regimen
- Every person with TB gets treated, even if poor
- Nursing staff and community supporters
- Financial and food aid as needed

*http://www.who.int/topics/tuberculosis/en/
DOTS: What IS it? A Good start...

• Budget and staff to effectively manage
• Training and systems to reduce or eliminate drug stock-outs
• Temperature-regulated spaces to store drugs, diagnostics and reagents
• WHO-qualified vendors to supply TB drugs

*Direct observation treatment, short course

An effective drug supply and management system
Global Health | Interpol Seizes $6.65M in Counterfeit HIV/AIDS, Malaria, TB Drugs in Southeast Asia
[November 17, 2008]

The International Criminal Police Organization recently confiscated $6.65 million worth of counterfeit HIV/AIDS, malaria and tuberculosis drugs in Southeast Asia and made 27 arrests as part of a five-month investigation involving nearly 200 raids, Aline Plancon, an officer involved in the operation, said on Monday, Bloomberg reports. During the investigation, called Operation Storm, authorities seized more than 16 million pills between April 15 and Sept. 15 in Cambodia, China, Laos, Myanmar, Singapore, Thailand and Vietnam. The operation was a joint effort between Interpol, the World Health Organization and the World Customs Organization. It was the first time customs officials, drug regulators, health authorities and police from different countries have collaborated to prevent the distribution of counterfeit medicines, Plancon said.
DOTS*: What IS it? A Good start...

- Policies and procedures, definitions for cure, completion
- Quarterly and annual reports of numbers of cases, treatment outcomes
- Smear+ only at this time
- Kids and other smear negative estimated more often than “counted”

Monitoring and evaluation system, and impact measurement

*Direct observation treatment, short course
WHO STOP TB Strategy, another good step

- Builds on the successes of DOTS
- Addresses key challenges facing TB
- Goal is to dramatically reduce the global burden of tuberculosis by 2015
- Focus on inclusiveness
  - Don’t ignore children, smear-negatives, MDR TB
- Supports development of new and effective tools
DOTS and the STOP TB Strategy: WHO and the world community

**STOP TB Strategy**

1. Pursue DOTS expansion
2. Address HIV/AIDS, MDR TB, TB in prisoners, others vulnerable
3. Health systems strengthening
4. Engage all health care providers
5. Empower people with TB to expect quality diagnosis, care, treatment
6. Promote research

http://www.who.int/topics/tuberculosis/en/
Stop TB Strategy: High Quality DOTS Expansion

- Every country and every country/district in country
  - Imagine TB control rules, funding, nursing support, culture and drug susceptibility diagnostics and free TB services were only available to those living in in Mecklenberg, Wake, Winston-Salem, Guilford and Durham counties
    - Others see private docs if they can afford it
    - This is how it is in countries without 100% “DOTS”
DOTS and the STOP TB Strategy: WHO and the world community

STOP TB Strategy

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http://www.who.int/topics/tuberculosis/en/
Stop TB Strategy: Address HIV/AIDS, MDR TB, TB in prisoners, others vulnerable

- Previously: “we just do ‘normal’ TB”
  - TB and HIV/AIDS – high mortality anyway...
- The “new” Strategy articulates that important, challenging populations MUST be prioritized
  - Facilitate Integration of activities between TB-HIV/AIDS services
### Key characteristics of trials of timing of ART during TB treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Arms (number enrolled)</th>
<th>Results</th>
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<tbody>
<tr>
<td>CAMELIA</td>
<td>Cambodia</td>
<td>Immediate ART vs 8 wks (n=660)</td>
<td>Reduction in mortality by 34%</td>
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<tr>
<td>STRIDE</td>
<td>Multicenter</td>
<td>Immediate ART vs 8-12 wks (n=806)</td>
<td>42% Reduction in AIDS and mortality in CD4 &lt;50</td>
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<tr>
<td>SAPIT</td>
<td>South Africa</td>
<td>“Early” ART vs after TB treatment (n=429)</td>
<td>68% Reduction in mortality</td>
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</tbody>
</table>

CAMELIA, NEJM 2011, 365: 1471-81  
STRIDE, NEJM 2011, 365: 1482-91  
SAPIT, NEJM 2011, 365: 1492-501
TB + ART therapy

• Within days of TB diagnosis/evaluation/treatment
  – Rapid HIV testing (PICT); obtain CD4 count
  – If CD4 < 100, consider starting ART within 2 weeks an EMERGENCY
  – If CD4 not available, ASSUME it is <100 and start ART

• Within 8 weeks of TB treatment
  – Every HIV positive patient should be on ART
  – Evaluate the initial effectiveness of therapy
    • Sputum smears; CXR; viral load; CD4
WHO policy on collaborative TB/HIV activities
Guidelines for national programmes and other stakeholders

TB/HIV
A CLINICAL MANUAL
second edition
2004

World Health Organization

TB/HIV
2012
Stop TB Strategy: Address HIV/AIDS, MDR TB, TB in prisoners, others vulnerable

• Previously: “we just do ‘normal’ TB”
  – MDR TB – only can afford 1\textsuperscript{st}-line drugs, so just keep treating with that till patient gives up, stops coming

• The “new” Strategy (and guidance past \textasciitilde10 years) articulates that important, challenging populations MUST be prioritized
  – Algorithms and Diagnostic capacities for DR TB
  – Affordable 2\textsuperscript{nd} line TB drugs
Why is MDR TB an “Emergency”?

• What’s the “big deal” about MDR TB?
  – 2\textsuperscript{nd}-line drugs required for >24 months
  – 2\textsuperscript{nd}-line drugs are more costly, toxic and less effective
  – Mortality rate high
    • Especially if in HIV/AIDS
  – The step after MDR is XDR and then TDR
    • Extensively and then totally drug resistant TB
TB is SPREAD by COUGH-PRODUCED AEROSOLS

Imagine: This is someone with tuberculosis… or even multi-drug-resistant [MDR] TB…
Paths to Drug Resistance

1. Start with pulmonary MDR TB (often not recognized) in a coughing patient

2. Lack of infection control practices

3. Respiratory spread of MDR TB
   a. Clinic & hospital stays
   b. Family and community

Primary DRUG RESISTANCE
1. Start with fully-susceptible TB

2. Erratic treatment – interruptions in drug supply, poor adherence by patient, wrong prescription

3. Susceptible M.Tb bacteria are killed quickly, but those with natural resistance have selective advantage, thrive

Secondary Drug Resistance
DOTS and the STOP TB Strategy: WHO and the world community

STOP TB Strategy

1. Pursue DOTS expansion
2. Address HIV/AIDS, MDR TB, TB in prisoners, others vulnerable
3. Health systems strengthening
4. Engage all health care providers
5. **Empower people with TB to expect quality diagnosis, care, treatment**
6. Promote research

http://www.who.int/topics/tuberculosis/en/
Diagnostics for Active TB

• Ideal tests
  – Highly sensitive (including for sputum smear negative; in both HIV-infected and not)
  – Identifies DR
  – Accessible at point-of-care
  – Rapid (same day)
  – Affordable
Smear microscopy

- Problems with quality assurance
  - Training, re-training, supervision, re-training
- At best, several shortcomings
  - Does not detect drug resistance (DR)
  - Misses 50% of cases (especially HIV+)
- LED fluorescent microscopy more sensitive, but still lacking
TB Diagnostics: Improvements

• Solid or Liquid culture with DST
  – Increasing number of labs with MGIT/DST capacity
  – Referral level access
  – Expensive to equip and maintain lab
  – Sophisticated, ongoing training/HR

• MODS (microscopic-observation drug-susceptibility assay)
  – Innovation based on liquid culture techniques
  – Care required to prevent lab accidental spread
  – Requires thorough & ongoing training
State of the art culture and drug susceptibility testing lab

MGIT and lab needed to support
TB Diagnostics: New Molecular Tools!

- Automated nucleic acid amplification
  - Cartridge-based technology**
    - Very little training required; safe
  - High sensitivity in smear-negative and SM+
  - Detects RIF resistance
  - Currently machine ~$15,000 USD + cartridges $11 each
    - Price to go down with more use
  - Secondary, maybe primary level?

**based on Cepheid Xpert® MTB/RIF
State of the art culture and drug susceptibility testing lab

GeneXpert
Lessons Learned

- How did we get from ...

  <1930
  
  No drug options
  TB Sans
  50% mortality
  
  >1970
  
  95% cured 1st time
  Outpatient therapy
  low mortality

- How did we get from....

  1981
  
  No drug options
  100% mortality
  Expanding US & global
  
  >1998
  
  Chronic disease management
  >20 effective drugs
  Near-normal life expectancy
We bought it

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NIH funding for TB is < 7% of that for HIV/AIDS

Slide from R Reves, Denver Public Health
US Funding for Global TB Work

- **USAID (State Department)**
  - Money to support implementation of DOTS most high-burden countries
    - TB CARE – helps TB programs implement DOTS
      - FHI 360, WHO, the Union, ATS, KNCV, MSH, JATA
    - STREAM TB – research – testing the Bangladesh regimen for MDR TB

- **CDC**
  - International efforts mostly through PEPFAR

- **PEPFAR**
  - TB-HIV funding
8 Technical Areas

- Universal Access
- Laboratories
- Infection Control
- PMDT = MDR
- TB/HIV
- Health Systems Strengthening
- M&E, Surveillance and OR
- Drugs Supply and Management

**Sustain or exceed 84% case detection rate and 87% treatment success rate**

- Treat successfully 2.6 million new sputum-positive TB cases
- Diagnose and treat 57,200 new cases of MDR-TB
Four Strategies of our Global Program

Strengthen Health Systems

- Use innovations
- Strengthen partnerships
- Build on foundations
- Strengthen Health Systems

- Capacity building, Sustainable, and integrated approach
- Use developed tools, country offices, networks
- GIS, GXpert TB RIF Mobile telephone

TB CARE II, local NGOs, GF, NTPs Community of Practice
TB CARE Partners in 22 Countries
Conclusion

- There are MANY barriers to TB Control
- Many of the same barriers had to be overcome by us
- Many are new, more challenging
  - HIV/AIDS
  - Drug-resistance
- Many tools available now that were not earlier
  - New diagnostics being rolled out
  - Roadmaps, global support (comparatively small)
- Closing window of opportunity?
  - MDR and XDR TB