Research priorities in DR-TB

Dr. Dick Menzies
TB Research Methods course
July 14-18, 2014
Overview

• Definitions:

• Importance of DR-TB globally.
  – How we got here - Case studies in 5 countries

• Research needs - how DR develops – from bacilli to populations

• Research needs in DR-TB Diagnosis – briefly

• Research needs in DR-TB Treatment –
  – What has been done?
  – What needs to be done
Definitions

- Primary DR: Resistance in person treated < 1 month or not at all
- Acquired DR: Resistance in person treated ≥ 1 month
- Mono-drug resistance: Resistance to 1 drug
- Poly-drug resistance: Resistance to > 1 drug, but not MDR.
- MDR: resistant to isoniazid and rifampin
- XDR: MDR & resistance to Quinolones & Injectable
Epidemiology of DR-TB - summary

- Global total in new cases: 17%
  - 3% MDR and 0.5% XDR
  - 14% other forms (INH most common)

- Highest in Former Soviet Union
  - And certain Latin American countries
  - Increasing in China, India, S Africa

- Low in Canada, US and Western Europe – mostly seen in immigrants from these high risk regions
Global TB Estimates

Estimated number of cases
9.23 million

Estimated number of deaths
1.7 million

All forms of TB
Greatest number of cases in Asia; greatest rates per capita in Africa

Multidrug-resistant TB (MDR-TB)
489,000 (5.3%)

Extensively drug-resistant TB (XDR-TB)
40,000 (0.5%)

20,000

Adapted from a slide provided by Dr. Paul Nunn, WHO Geneva
Estimated global MDR-TB cases

Prevalent ~1,000,000
Incident 489,000
Notified 23,000 (2,000 from GLC)
Not notified 466,000

Research priority # 1
How did we get to this?

• Observational data from 5 countries
Emergence of DR – Korea

- Very poor economic situation up to 1960
  - Rapid improvement in economy since
- Weak NTP with high rates of default
- Drugs prescribed and sold in private sector
- NTP strengthened in 1984-85

Prevalence Any Drug resistance
Cure rates
Emergence of DR – Peru

• Massive internal migration to Lima in 1970’s
  – Severe deprivation, shantytowns in Lima
• Pre 1990 - Treatment success low in NTP
• TB drugs widely available and uncontrolled
  – Large private sector
• DOTS strengthened beginning 1990
  – Coincident with economic improvements
• No HIV
TB notification rate per 100,000 and % MDR-TB in new cases, Peru, 1996 – 2005
PERU - Trend in default rate following country wide implementation of DOTs in 1990-91

All patients treated with 2RHZE/4 R$_2$H$_2$

From: JID 2001; 184
Emergence of DR – New York City
## New York City: Funding, Resources and TB

<table>
<thead>
<tr>
<th>Year</th>
<th>Resources</th>
<th>Incidence of TB / 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Harlem</td>
</tr>
<tr>
<td>1968</td>
<td>$40 million total</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>1000 TB Beds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22 Chest Clinics</td>
<td></td>
</tr>
<tr>
<td>1978</td>
<td>$23-$25 million total</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>$1.6 million – TB control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No TB beds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 Chest clinics</td>
<td></td>
</tr>
<tr>
<td>1988</td>
<td>$4 million TB control</td>
<td>160</td>
</tr>
<tr>
<td></td>
<td>Total unknown (but less than 1978)</td>
<td></td>
</tr>
</tbody>
</table>
Resurgent TB in New York City: HIV, homelessness, and the decline of TB control programs
(Brudney and Dobkin. ARRD, 1991;144:745-49)

- 224 patients admitted to Harlem hospital with TB
  - 53% alcoholic
  - 68% homeless or unstable housing
- 46 died. 178 improved and discharged
  - 19 of 178 (11%): cured, or still on treatment,
  - 11 died other causes
  - 148 (83%): < 3 months treatment completed
- 48 of 148 readmitted within 12 months with active TB
  - 40 improved and discharged
  - 35 (88%) lost again
- 8 of 35 admitted a third time with active TB
New York City – What really turned the tide

(From: Frieden et al., NEJM, 1995: 333; 229-233)
Emergence of DR – Russia
Trends in TB cases - Russia

Trends in case notification 1970-1990 and projections to 2005

Trends in the reported TB death rate
## Trends in Global Drug Resistance in New Cases

*(AZIZ, Lancet 2006)*

<table>
<thead>
<tr>
<th>Middle Income</th>
<th>1994 - 96</th>
<th>2001 – 02</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latvia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Resistance</td>
<td>34%</td>
<td>32%</td>
</tr>
<tr>
<td>MDR</td>
<td>14%</td>
<td>12%</td>
</tr>
<tr>
<td>Russia (Tomsk)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Resistance</td>
<td>29%</td>
<td>37%</td>
</tr>
<tr>
<td>MDR</td>
<td><strong>7%</strong></td>
<td><strong>14%</strong></td>
</tr>
</tbody>
</table>
Emergence of DR – South Africa
## Tripling of MDR cases in S Africa – in 6 years

*(Streicher et al, Infection, Genetics and Evolution, 2011)*

<table>
<thead>
<tr>
<th>Province</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern Cape</td>
<td>379</td>
<td>545</td>
<td>836</td>
<td>1092</td>
<td>1501</td>
<td>1858</td>
<td>6211</td>
</tr>
<tr>
<td>Free state</td>
<td>116</td>
<td>151</td>
<td>198</td>
<td>179</td>
<td>381</td>
<td>253</td>
<td>1278</td>
</tr>
<tr>
<td>Gauteng</td>
<td>537</td>
<td>676</td>
<td>732</td>
<td>986</td>
<td>1028</td>
<td>1307</td>
<td>5266</td>
</tr>
<tr>
<td>Kwazulu-Natal</td>
<td>583</td>
<td>1024</td>
<td>2200</td>
<td>2208</td>
<td>1573</td>
<td>1773</td>
<td>9361</td>
</tr>
<tr>
<td>Western Cape</td>
<td>1085</td>
<td>1192</td>
<td>1179</td>
<td>1771</td>
<td>2220</td>
<td>2078</td>
<td>9525</td>
</tr>
<tr>
<td>All S. Africa</td>
<td><strong>3219</strong></td>
<td><strong>4120</strong></td>
<td><strong>5774</strong></td>
<td><strong>7429</strong></td>
<td><strong>8198</strong></td>
<td><strong>9070</strong></td>
<td><strong>37810</strong></td>
</tr>
</tbody>
</table>
7-fold increase in XDR cases in S Africa – in 6 years  
*(Streicher et al, Infection, Genetics and Evolution, 2011)*

<table>
<thead>
<tr>
<th>Province</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern Cape</td>
<td>3</td>
<td>18</td>
<td>61</td>
<td>108</td>
<td>175</td>
<td>123</td>
<td>488</td>
</tr>
<tr>
<td>Free state</td>
<td>1</td>
<td>6</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Gauteng</td>
<td>5</td>
<td>14</td>
<td>19</td>
<td>38</td>
<td>30</td>
<td>65</td>
<td>171</td>
</tr>
<tr>
<td>Kwazulu-Natal</td>
<td>59</td>
<td>227</td>
<td>336</td>
<td>241</td>
<td>181</td>
<td>254</td>
<td>1298</td>
</tr>
<tr>
<td>Western Cape</td>
<td>12</td>
<td>16</td>
<td>28</td>
<td>42</td>
<td>60</td>
<td>73</td>
<td>230</td>
</tr>
<tr>
<td>All S. Africa</td>
<td>85</td>
<td>298</td>
<td>464</td>
<td>458</td>
<td>488</td>
<td>594</td>
<td>2387</td>
</tr>
</tbody>
</table>
Emergence of DR – South Africa

- HIV epidemic fueling massive TB epidemic
- Health facilities - focal points of transmission
  \[Calver 2010, \textit{Gandhi} 2006\]
  - ? Role of gold mines in transmission
- TB completion rates:
  - Nationally less than 50\% \[NTP data\]
  - 18\% in Kwazulu Natal recently \[Loveday 2008\]
- TB Drugs controlled by NTP.
  - But poor quality Rifampin documented \[McIlleron \textit{et al}\]
Summary - What we know about how drug resistance develops

In bacilli
and individual patients
Rate of spontaneous mutations of M Tuberculosis to anti-TB drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin</td>
<td>$10^{-6}$</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>$10^{-6} - 10^{-7}$</td>
</tr>
<tr>
<td>Rifampin</td>
<td>$10^{-8} - 10^{-9}$</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>$10^{-7} - 10^{-8}$</td>
</tr>
<tr>
<td>INH &amp; Rifampin</td>
<td>$10^{-14}$</td>
</tr>
</tbody>
</table>
Treatment with Streptomycin alone, or PAS alone
% Patients with resistance - Days after Tx started

Source: Rieder, Interventions for TB control, IUATLD.
Summary - What we know about how drug resistance develops

In Populations
Research needed: What causes DR epidemics?

- Don’t believe the Dogma – Examples:
  - “Default causes resistance”
  - “INH resistance does not matter”
  - “DR strains are less transmissible”
  - “DOT prevents drug resistance”

- Possible study methods:
  - Modeling
  - Surveillance – with detailed clinical data
  - Case-control and cross-sectional DR-TB vs DS-TB
  - Mol Epi – large scale with complete population coverage
Diagnosis of drug resistance

(Research needs - very briefly)
Cepheid GeneXpert MTB/RIF
Boehme et al. 2010 NEJM

- Automated RT-PCR
- Simple 1-step specimen preparation
- Minimal biohazard risks
- Results in 2 HOURS!!
- Demonstration studies (6673 patients, 6 sites):
  - Sensitivity for diagnosis
    - 99% in smear +
    - 80% in smear - / culture +
  - Rifampicin resistance
    - 95% sensitive
    - 98% specific
Current status of diagnostic research - DR-TB?

- GX, Line probe assays, MODS – all have well established and high diagnostic accuracy
- Randomized trials of GX and LPA have also been conducted
  - Individual and cluster randomized
  - Surprisingly little impact
- Needed - Large scale trials/other designs – population impact of new diagnostics on DR-TB epidemiology.
Treatment of DR-TB

MDR-TB
XDR-TB
INH Mono-resistance and other forms
How good is the published evidence for treatment of DR-TB?
Evidence base – Phase 3 RCT in TB
Number of Randomized trials of treatment in New cases by decade when they started enrolment

Note: all but two of the RCT were publicly funded
Evidence base: Phase 3 RCT in Drug resistance / Re-treatment

Number by decade when they started enrolment

To date no published RCT in MDR-TB
Published randomized trials: DR-TB treatment

- Trials of retreatment
  - $N = 4$, all published before 1980
- Trials of INH resistant patients
  - $N = 5$, also older studies
- Trials of current standardized retreatment
  - NONE
- Phase 3 Trials of MDR treatment
  - NONE
  - Two Phase 2 trials – Bedaquiline and Delamanid
Recent research completed: treatment of DR-TB

- **MDR-TB** – Many observational studies
  - Several aggregate data meta-analyses (traditional)
  - One Individual patient data meta-analysis
  - Two Phase 2 trials

- **XDR-TB** – Several observational studies
  - Two aggregate data meta-analyses (traditional)
  - One Individual patient data meta-analysis
  - One Phase 2 trial
93 studies identified from 3 systematic reviews

Excluded: 26 publications representing the same or overlapping cohorts

Excluded - 35 cohorts
13 – No author response
8 – No longer have access to data
5 – Inadequate outcome data
2 – Refusals
2 – No response following initial contact
2 – No data on drug sensitivity testing
2 – Data never sent
1 – Cohort with less than 25 patients

32 data sets included, with 9898 patients

Excluded Patients
410 - XDR TB
127 - Extra-pulmonary TB
208 - No treatment info

9153 patients analyzed
The Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB
(members in alphabetic order)

Recent research completed: treatment of DR-TB

- MDR-TB – Many observational studies
  - Several aggregate data meta-analyses (traditional)
  - One Individual patient data meta-analysis
  - Two Phase 2 trials
- XDR-TB – Several observational studies
  - Two aggregate data meta-analyses (traditional)
  - One Individual patient data meta-analysis
  - One Phase 2 trial
- What more is needed?
What research is needed: DR-TB treatment?

- Trials, trials and more trials
- In MDR-TB & XDR-TB
  - How to use the new drugs (DMD, BDQ)
  - Optimal use of existing drugs (FQN, LZD, CFZ)
  - Duration, number of drugs, schedule

- How many trials will be needed?
  - Trials needed for current First line therapy
Summary of study review and selection

Identified from PubMed, EMBASE, Cochrane Database literature search: (after eliminating duplicates) 2215 titles

1978 titles excluded

Titles retained for review of abstracts: 237

78 abstracts excluded after review 9 Reviews
25 Not RCT/Cohort (case control, prevalence, cross sectional design, program report)
1 Regimen not reported 8
Outcomes not by Regimen 17 No outcomes
Individualized treatment 4
Latent TB/Non M.TB/Non pulmonary TB 3
MDR TB 2
Not drug therapy

135 additional full texts identified from references and reviews

Full text reviewed: 301

109 were excluded
4 Reviews
4 Not RCT/Cohort (case control, prevalence, cross sectional design, program report)
8 Regimen not reported
16 Outcomes not by Regimen
30 No Outcomes
12 Individualized treatment
4 Latent TB/Non M.TB/Non pulmonary TB
1 MDR TB, 9 Not drug therapy
2 Mono-therapy, 19 other

192 Reports included (Trials +Cohort studies)
How many RCT are needed - example

RCT to address Duration of RIF to prevent Relapse:
57 trials with 16377 subjects

<table>
<thead>
<tr>
<th>Rifampin duration</th>
<th>Arms (N)</th>
<th>Events/Subjects</th>
<th>Event rate</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 months</td>
<td>67</td>
<td>373/3545</td>
<td>10.8%</td>
<td>(6.5, 15.1)</td>
</tr>
<tr>
<td>3-5 months</td>
<td>40</td>
<td>198/2732</td>
<td>6.4%</td>
<td>(3.6, 9.3)</td>
</tr>
<tr>
<td>6-7 months</td>
<td>167</td>
<td>364/8611</td>
<td>3.5%</td>
<td>(2.6, 4.4)</td>
</tr>
<tr>
<td>8+ months</td>
<td>20</td>
<td>15/1489</td>
<td>1.0%</td>
<td>(0.3, 1.7)</td>
</tr>
</tbody>
</table>
What research is needed: DR-TB treatment?

- Trials, trials and more trials
- In MDR-TB & XDR-TB
  - How to use the new drugs (DMD, BDQ)
  - Optimal use of existing drugs (FQN, LZD, CFZ)
  - Duration, number of drugs, schedule

- What else is needed?
  - What has been largely ignored in past 20 years?
The ignored DR-TB
INH resistance (and other non-MDR)

Global weighted mean, 1994-2007*

• 7.4% in new cases
• 12.4% in previously treated cases

Treatment

• Dogma: “INH-R is of no importance. Treat with standard therapy”
• Evidence – from two systematic reviews
  – Much higher risk of failure (10 times higher)
  – Much higher rate of relapse (8-10%)
  – High risk of acquiring MDR-TB if fail or relapse
Research needs: DR-TB treatment

- Trials, trials and more trials
- In MDR-TB & XDR-TB
  - New drugs, old drugs
  - Duration, number of drugs, schedule
- But also trials are needed for non-MDR-TB
  - INH resistance and poly drug resistance
  - “old drugs” (FQN, LZD)
  - Duration, combinations, Schedule
  - Enhancing cure, avoiding drug resistance
Thank you!

Merci!

Gracias!!
Acknowledgements

• Systematic Reviews – Woojin Lew, Olivia Oxlade, Madhu Pai, Faiz Khan
• Ecologic studies: Anita Paydar, Anton Mak
• IPD meta-analysis: Melissa Bauer, Maria Holmes-Delgado, Sandra Ramoutar, Lena Shah,
• Slides (with some edits) from:
  – Kitty Lambregts, Fuad Myrzayev, Matteo Zignol, Sarah Royce, Jessica Minion, Madhu Pai,