Genesis of drug resistance in Tuberculosis in South Africa

Rob Warren
Spontaneous evolution of drug resistance

10⁹ bacteria

Rifampicin

Rifampicin

GCCGACTGTTGGCGCTGG
CGGCTGACAACCGCGACC

rpoB gene
Number of MDR-TB cases in 2013

MDR-TB = resistance to isoniazid and rifampicin

WHO Global Tuberculosis Report 2014
Number of Patients with confirmed XDR-TB 2013

XDR-TB = MDR-TB plus resistance aminoglycoside and fluoroquinolone

WHO Global Tuberculosis Report 2014
MDR-TB Treatment outcome in Africa

WHO Global Tuberculosis Report 2014
81% of people with DR-TB don’t get effective treatment.

Of the 19% that do, only half are cured.

We need better treatment now.
What is the Cost of Diagnosis and Management of Drug Resistant Tuberculosis in South Africa?

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Figure 2. The total number, national costs and cost breakdown of notified cases of drug sensitive (DS-TB), multi-drug resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) reported in 2010. Costs are expressed in $US and refer to the cost of diagnosis and treatment of confirmed cases. *Other indicates surgery, ADRs and death related costs.
doi:10.1371/journal.pone.0054587.g002
**Indiscriminate Treatment**

“The indiscriminate giving of streptomycin in South Africa has resulted in a large number of cases with completely resistant organisms.............”

**Bacterial Fitness**

“...only isoniazid-sensitive strains are generally virulent i.e. capable of setting up disease from a local focus to spread throughout the body of the host.”

**Susceptibility Testing**

“When using combinations of these 3 drugs, it is essential to request regular laboratory tests for the emergence of drug resistance in the organisms.”

**Patients at Risk**

**Primary resistance**
- streptomycin 5.29%
- isoniazid 14.9%

**Acquired resistance**
- streptomycin 21%
- isoniazid 39%
Treatment guidelines 2002

New Case
- Isoniazid
- Rifampicin
- Ethambutol
- Pyrazinamide

Retreatment Case
- Ofloxacin
- Kanamycin
- Ethambutol
- Pyrazinamide
- Ethionamide

DST

Treatment failure

Standardized MDR-TB treatment
Amplification of Resistance in MDR-TB

48 MDR-TB cases enrolled

Standardized MDR-TB treatment

Different strain during treatment
n=12 (25%)

9 (75%) gained additional resistance

Same strain during treatment
n=36 (75%)

13 (36%) gained additional resistance

46%

Mphahlele et al Unpublished data
Weakened standardized MDR-TB treatment

52% of MDR-TB isolates showed resistance to PZA

>50% of MDR-TB isolates showed mutations conferring EMB resistance


Cross-resistance between isoniazid and ethionamide via *inhA* mutations

Type 1: katG315 ACC, rrs513 CAC, inhA 17, embB306 ATA, pncA ins172G, rpoB 516GTC, rrs1401G

Type 2: katG315 ACC, rrs513 CAC, inhA 15, embB306 ATC, pncA14 GCG, rpoB 531 TTG, rrs1401G
# XDR-TB Treatment outcomes

<table>
<thead>
<tr>
<th></th>
<th>24 months</th>
<th>36 months</th>
<th>48 months</th>
<th>60 months</th>
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</thead>
<tbody>
<tr>
<td>Died</td>
<td>49 (46%)</td>
<td>61 (57%)</td>
<td>74 (69%)</td>
<td><strong>78 (73%)</strong></td>
</tr>
<tr>
<td>Treatment default*</td>
<td>7 (7%)</td>
<td>6 (6%)</td>
<td>5 (5%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Treatment cure</td>
<td>7 (7%)</td>
<td>6 (6%)</td>
<td>5 (5%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>25 (23%)</td>
<td>19 (18%)</td>
<td>14 (13%)</td>
<td>11 (10%)</td>
</tr>
<tr>
<td>Treatment completion</td>
<td>10 (9%)</td>
<td>10 (9%)</td>
<td>6 (6%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Insufficient information</td>
<td>9 (8%)</td>
<td>5 (5%)</td>
<td>3 (3%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

Data are n (%). *Interruption of treatment for at least 2 consecutive months for any reason; once patient classified as a default, the classification remained unless individual died; all other categories (except died) needed a minimum of 24 months’ treatment.

**Table 3: Outcomes of 107 patients with extensively drug-resistant tuberculosis after treatment, by duration of follow-up**

Discharge into the Community

Figure 1: Kaplan-Meier for probability of survival since discharge from hospital. Crosses indicate censoring.

New TB diagnosis algorithm

ALL PEOPLE WITH SYMPTOMS OF TB

Collect one spot specimen (sputum, gastric washing/lavage, lymph node fine needle aspirate, pleural biopsy, cerebro spinal fluid). Sputum collection must be under supervision.

Xpert positive

Rifampicin susceptible

Treat as Drug Susceptible TB
Start on Regimen 1

If patient has Pulmonary TB
Collect one spot sputum specimen for microscopy

Follow up the microscopy results and record them in the patient’s treatment record

If smear positive
Conduct contact screening/source investigation

Xpert positive

Rifampicin unsuccessful

Treat as Drug susceptible TB
Start on Regimen 1

Collect one spot specimen for microscopy, LPA, or culture and DST

Follow up the laboratory results and record them in patient’s treatment record

If drug susceptible TB and smear positive
Record results
Continue treatment
Conduct contact screening/source investigation

Xpert positive

Rifampicin resistant

Refer to MDR-TB treatment initiation site
Conduct contact screening/source investigation

RR-TB patients must be started on treatment within 5 days

MDR-TB regimen for 18 – 24 months

On confirmation of MDR-TB the laboratory should conduct second-line DST routinely.
Impact of New TB diagnosis algorithm

904 samples with RIF resistant MTB on Xpert, November 2011 - June 2013

69 repeat test on the same patient
135 patients no additional testing found

700 patients had 2nd sample received

58 no MTB culture grew (includes initially contaminated samples)

642 cultures grew for second-line DST

71 second-line DST not done
56 additional samples contaminated
45 lost viability
4 incomplete second-line DST results

466 (55.8%) had second-line DST results
Time to second-line resistance test result

54 days (IQ range 27-259)
Second-line resistance profiles associated with rifampicin resistance

<table>
<thead>
<tr>
<th>Drug resistant</th>
<th>Patients with second-line results (%)</th>
<th>N=451</th>
</tr>
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<tbody>
<tr>
<td>Kanamycin(^a) only</td>
<td>3 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Ethionamide only</td>
<td>206 (45.7)</td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolone(^b) only</td>
<td>13 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Kanamycin + Ethionamide</td>
<td>25 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Kanamycin + Fluoroquinolone</td>
<td>4 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Ethionamide + Fluoroquinolone</td>
<td>14 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Kanamycin + Ethionamide + Fluoroquinolone</td>
<td>28 (6.2)</td>
<td></td>
</tr>
<tr>
<td>Any additional resistance</td>
<td>293 (65.0)</td>
<td></td>
</tr>
<tr>
<td>Pre-XDR</td>
<td>55 (12.2)</td>
<td></td>
</tr>
<tr>
<td>XDR</td>
<td>32 (7.1)</td>
<td></td>
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</table>
Proportion of patients with resistance to greater than 2 second-line drugs

47%
TAKE HOME MESSAGE

• Treating blindly leads to amplification of resistance
• Surveillance is essential to guide policy
• Treatment outcomes for M(X)DR-TB are poor
• Nearly half of patients diagnosed with RIF resistant MTB by Xpert also have resistance to at least two additional MDRTB drugs
• Culture based diagnostic delay treatment decisions by up to 8 weeks possible promoting amplification of resistance
• Rapid molecular based diagnostic methods are desperately needed
Thank You

Karen Jacobson  Marinus Barnard

Borna Muller  Violet Chihota

Gail Louw  Kim Hoek

Matsie Mphahlele  Elize Pietersen