Systematic Reviews in TB
Treatment - How and why?

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Overview

- A few general comments on methods
- Example 1: Treatment of New cases
  - Duration of Rifampin, and Intermittent regimens
  - RCT – head to head vs pooling across trials
- Example 2: Treatment of HIV-TB
  - Including cohort studies – pro’s and con’s
- Example 3: Treatment of DR-TB and Retreatment
  - Limited review (Time)
- Example 4: Treatment of MDR-TB
  - Individual Patient Data (IPD) meta-analysis
Methods of SR – a few points

- Essential elements:
  - Clear questions at start.
  - Pragmatic answers at end
  - Reproducible search and selection
  - Study selection based on biology
  - Read methods only when selecting studies!
  - Be open to other data / and analyses
  - Accept lower quality evidence if none better
    - Low quality better than none at all

Example 1

- Example 1: Treatment of New cases
  - Duration of Rifampin, and Intermittent regimens
  - RCT – head to head vs pooling across trials
WHO standard TB regimens for new patients – up to 2008: 2 Regimens

2 HRZE / 4 HR = 2 months of 4 drugs:
isoniazid (H), rifampin (R), pyrazinamide (Z) and ethambutol (E), Then 4 months of 2 drugs: H and R

OR

2 HRZE / 6 HE = 2 months of same 4 drugs:
Then 6 months of 2 drugs: H and E

WHO committee: Questions for SR

1. What is the optimal duration of RIF?
Considering Failure/relapse/Acquired Drug resistance

2. What is the optimal schedule of administration?
Considering the same treatment outcomes
Rates of failure, relapse, and ADR with 2RIF vs. 6RIF

**Search strategy**

- OVID Medline (1950-April 2008), EMBASE (1988-2008) and the Cochrane Central Database of Clinical trials searched for original articles and reviews
- Treatment of active TB/disease

**Studies included if:**

- **Randomized clinical trials**
  - Published in English, French, Spanish in peer-reviewed literature.
  - Active pulmonary TB that was microbiologically confirmed.
  - NEW cases only (or reported results by history of treatment)
  - Standardized regimens. Results reported by regimen
  - Rifampin containing regimens.
    - (Excluded if RBT or RPT)
  - Reported microbiologically confirmed outcomes of failure, or relapse.
  - Acquired drug resistance – if DST done initially plus with fail/relapse
Study selection

Identified from PubMed, EMBASE, Cochrane Database

literature search: (after eliminating duplicates) 2215 titles

1978 titles excluded

Titles retained for review of abstracts: 237

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

135 additional full texts identified from references and reviews

Full text reviewed: 301

226 Texts excluded after review
12 Reviews
25 In new cases
27 RCT in new cases No Rifampin
47 Previously treated cases
4 other designs (case-control or cross sectional design, program report)
8 Regimens not reported
16 Outcomes not by Regimen
30 Rifampin regimes not reported
13 Individualized treatment
1 Latent TB/Non M.TB/Non pulmonary TB
1 MDR TB
9 Not drug therapy
2 Mono-therapy
19 Other

75 Reports included (57 Trials)

Summary of literature search, and study selection – New cases

- Search in PubMed, Embase, Cochrane
  - Identified 2215 Titles
  - 1978 excluded
- 237 abstracts reviewed
- 301 Full text reviewed
  - 226 excluded
- 75 full text retained for meta-analysis
  - 57 RCT with 19,000 subjects
Head-to-head comparisons

Summary estimate from comparison of 2 treatments within each RCT. Pool these summary estimates across trials.

- Possible if two or more studies had same comparison.
- Maintains original randomization – so all other factors should be balanced between arms.
- Best control of confounding between studies.

Pooling across studies

- Pooling across studies: Each arm is considered like a cohort. Pooling is made across studies.
  - Advantage – can include (a lot) more studies
  - Disadvantage – Does not take advantage of randomization. Differences between arms is more than just treatment.
  - May be significant confounding.
### Head-to-head comparisons 2 vs 3-4 Months Rifampin and Relapse

<table>
<thead>
<tr>
<th>Regimens †</th>
<th>2 Months</th>
<th>3-4 Months</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relapse</td>
<td>Non</td>
<td>Relapse</td>
</tr>
<tr>
<td>2SHRZ/2HZ</td>
<td>38</td>
<td>78</td>
<td>30</td>
</tr>
<tr>
<td>2SHRZ/2HRZ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2SHRZ</td>
<td>20</td>
<td>64</td>
<td>8</td>
</tr>
<tr>
<td>3SHRZ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled risk difference (95% CI)</td>
<td></td>
<td></td>
<td>17.7%</td>
</tr>
<tr>
<td>Overall I squared (95% CI)</td>
<td></td>
<td></td>
<td>0 (-,-)</td>
</tr>
</tbody>
</table>

### Head-to-head comparisons 2 vs 6 Months Rifampin and Relapse

<table>
<thead>
<tr>
<th>Regimens †</th>
<th>2 Months</th>
<th>6 Months</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relapse</td>
<td>Non</td>
<td>Relapse</td>
</tr>
<tr>
<td>2SHRZ/4HZ</td>
<td>13</td>
<td>168</td>
<td>6</td>
</tr>
<tr>
<td>2SHRZ/4HR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2EHRZ/6HE</td>
<td>57</td>
<td>344</td>
<td>6</td>
</tr>
<tr>
<td>2EHRZ/4HR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2HRZE/4[HRE]</td>
<td>20</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>2HRZE/4[HZE]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled risk difference (95% CI)</td>
<td></td>
<td></td>
<td>11.2%</td>
</tr>
<tr>
<td>Overall I squared (95% CI)</td>
<td></td>
<td></td>
<td>.9 (.66, .96)</td>
</tr>
</tbody>
</table>
### Duration of Rifampin and Failure
#### New cases

<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>72</td>
<td>94/4133</td>
<td>1.8%</td>
<td>(0.2, 3.3)</td>
</tr>
<tr>
<td>3-5 months</td>
<td>42</td>
<td>16/2508</td>
<td>0.3%</td>
<td>(0.0, 0.6)</td>
</tr>
<tr>
<td>6-7 months</td>
<td>178</td>
<td>150/10060</td>
<td>0.4%</td>
<td>(0.1, 0.7)</td>
</tr>
<tr>
<td>8+ months</td>
<td>20</td>
<td>12/1607</td>
<td>0.3%</td>
<td>(0, 0.6)</td>
</tr>
</tbody>
</table>

### Duration of Rifampin and Relapse
#### New cases

<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>70</td>
<td>637/3349</td>
<td>16.0%</td>
<td>(11.1, 20.9)</td>
</tr>
<tr>
<td>3-5 months</td>
<td>42</td>
<td>185/2389</td>
<td>7.1%</td>
<td>(4.5, 9.7)</td>
</tr>
<tr>
<td>6-7 months</td>
<td>171</td>
<td>364/9639</td>
<td>3.8%</td>
<td>(2.9, 4.7)</td>
</tr>
<tr>
<td>8+ months</td>
<td>18</td>
<td>14/1181</td>
<td>1.0%</td>
<td>(0.2, 1.7)</td>
</tr>
</tbody>
</table>
## Duration of Rifampin and treatment outcomes in new cases

(Results of Meta-regression)

<table>
<thead>
<tr>
<th>Rifampin duration</th>
<th>Failure IRR (95% CI)</th>
<th>Relapse IRR (95% CI)</th>
<th>ADR IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 months</td>
<td>5.8 (2.9, 11.0)</td>
<td>3.6 (2.5, 5.3)</td>
<td>4.6 (2.0, 0.4)</td>
</tr>
<tr>
<td>3-5 months</td>
<td>1.3 (0.6, 3.0)</td>
<td>2.6 (1.6, 4.0)</td>
<td>1.2 (0.4, 3.1)</td>
</tr>
<tr>
<td>6-7 months</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>8+ months</td>
<td>2.0 (0.8, 4.9)</td>
<td>0.4 (0.2, 0.7)</td>
<td>2.1 (0.8, 5.3)</td>
</tr>
</tbody>
</table>

### Direct head-to-head comparisons vs Pooling across trials:

- Head-to-head was a sub-group of 11 studies with comparable Regimens
- Shorter RIF significantly associated with higher Relapse (2>4>6>8+)
  - Same in head-to-head and pooled across
- Shorter RIF somewhat associated with higher Failure
  - Again same magnitude and significance with both strategies
Stratified analyses:

- Method to account for major potential confounders
- If there is substantial heterogeneity, and this is reduced through stratified analyses, then factor of interest may explain substantial proportion of heterogeneity
- Possible if studies report outcomes stratified by this factor

Stratified analyses: Impact of drug resistance on treatment outcomes in new cases, and interaction with duration of Rifampicin

Original studies performed DST, but randomized patients to regimens regardless.

Analyzed and reported data by initial drug resistance.

Unexpected finding of pooled analyses was impact of mono- or poly-drug resistance on outcomes (Note – cases with MDR Excluded)

Lead to a series of additional stratified analyses
### Initial Drug Resistance and Treatment outcomes

*(Results of Meta-regression)*

<table>
<thead>
<tr>
<th>Initial Drug resistance</th>
<th>Failure IRR (95% CI)</th>
<th>Relapse IRR (95% CI)</th>
<th>Acquired drug resistance IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan-Sensitive</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>INH resistant</td>
<td>10.9 (5.9, 20)</td>
<td>1.8 (1.2, 2.6)</td>
<td>5.1 (2.3, 11.0)</td>
</tr>
<tr>
<td>Streptomycin Resistant</td>
<td>3.9 (1.4, 11.0)</td>
<td>1.4 (0.9, 2.2)</td>
<td>4.1 (1.6, 10.0)</td>
</tr>
<tr>
<td>Poly-drug resistance</td>
<td>33 (16, 62)</td>
<td>1.8 (1.1, 2.9)</td>
<td>10.0 (4.5, 22)</td>
</tr>
</tbody>
</table>

### Interaction of Duration of RIF with underlying type of drug resistance: FAILURE

<table>
<thead>
<tr>
<th>Underlying drug resistance pattern</th>
<th>2 month RIF</th>
<th>6 month RIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan-sensitive</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Single - INH</td>
<td>12.9%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Single - Strep</td>
<td>2.5%</td>
<td>1.6%</td>
</tr>
<tr>
<td>All Single</td>
<td>10.4%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Poly-Drug (2+)</td>
<td>34.8%</td>
<td>4.5%</td>
</tr>
</tbody>
</table>
Interaction of Duration of RIF with underlying type of drug resistance: RELAPSE

<table>
<thead>
<tr>
<th>Underlying drug resistance pattern</th>
<th>2 months RIF</th>
<th>6 months RIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan-sensitive</td>
<td>8.2%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Single - INH</td>
<td>28.3%</td>
<td>8.6%</td>
</tr>
<tr>
<td>Single - Strep</td>
<td>21.5%</td>
<td>6.6%</td>
</tr>
<tr>
<td>All Single</td>
<td>28.2%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Poly-Drug (2+)</td>
<td>26.9%</td>
<td>6.7%</td>
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</table>

Duration of Rifampin – WHO recommendations

- 2HRZE/4HR – the 6-month RIF regimen – *Considered the regimen of first choice for all new cases*
- 2HRZE/6HE – the 2-month RIF regimen – *Should be phased out as rapidly as possible*
Example 2

- Treatment of HIV-TB
- Including cohort studies – pro’s and con’s

Evidence base for HIV-TB - RCT
Number by decade when they started enrolment

![Bar chart showing number of studies by decade for HIV-TB RCTs]
Using lower quality evidence – Cohort studies - Pro

- Better than no evidence at all
- More ‘real-life’ so more generalizable
  - Selection of patients (sicker, older)
  - Follow-up under routine conditions
- BUT – therapy must be standardized

Using lower quality evidence – Cohort studies - Con

- May be mis-leading from bias – so in fact actually worse than no evidence at all
  - Selection bias (surgical series)
  - Drop-outs not accounted for
  - Information missing
- More chance of publication bias
  - Better centres – more likely to publish
  - Better results = more likely to publish
  - So, an overestimate of treatment success
Summary of literature search, and study selection – HIV-TB

- Search in PubMed, Embase, Cochrane
  - Identified 5158 Titles
  - Excluded 4916 from title/abstract
- 245 Full text reviewed
  - 214 excluded
- 36 full text retained for meta-analysis
  - 6 RCT and 23 cohort

HIV-TB Systematic review and meta-analysis

Results: Duration of Rifampin

<table>
<thead>
<tr>
<th>Duration of Rifampin</th>
<th>Studies</th>
<th>Event/Subjects (N)</th>
<th>Pooled event rate</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months</td>
<td>6</td>
<td>40/258</td>
<td><strong>10.0%</strong></td>
<td>(0, 24.8)</td>
</tr>
<tr>
<td>6 months</td>
<td>13</td>
<td>110/863</td>
<td><strong>9.7%</strong></td>
<td>(0.6, 18.7)</td>
</tr>
<tr>
<td>9 months</td>
<td>6</td>
<td>20/314</td>
<td><strong>3.3%</strong></td>
<td>(0, 9.0)</td>
</tr>
</tbody>
</table>
### HIV-TB Systematic review and meta-analysis

**Effect of Intermittent regimens**

#### FAILURE

<table>
<thead>
<tr>
<th>Intermittent therapy</th>
<th>Studies</th>
<th>Event/Subjects (N)</th>
<th>Pooled event rate</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent through-out</td>
<td>6</td>
<td>17/343</td>
<td>4.9%</td>
<td>(0.1, 8.9)</td>
</tr>
<tr>
<td>Daily Initially</td>
<td>35</td>
<td>74/2532</td>
<td>2.5%</td>
<td>(1.5, 3.5)</td>
</tr>
</tbody>
</table>

#### RELAPSE

<table>
<thead>
<tr>
<th>Intermittent therapy</th>
<th>Studies</th>
<th>Event/Subjects (N)</th>
<th>Pooled event rate</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent through-out</td>
<td>5</td>
<td>28/193</td>
<td>20.4%</td>
<td>(0, 48.9)</td>
</tr>
<tr>
<td>Daily Initially</td>
<td>20</td>
<td>142/1242</td>
<td>6.6%</td>
<td>(1.0, 12.1)</td>
</tr>
</tbody>
</table>
HIV-TB treatment – WHO recommendations

- Do NOT use Intermittent therapy in the first 2 months for HIV-TB
- Length of therapy – not changed
- Evidence needed

Treatment of Drug resistance
Example 3:
- Treatment of DR-TB and Retreatment
  - What to do - when there is no evidence

Re-Treatment & INH resistance
Questions:
- What is the evidence supporting use of the currently recommended WHO retreatment regimen in retreatment cases?
- What is the optimal regimen for treatment of INH resistant active TB.
  - Considering Failure/Relapse/ADR
Evidence base - all Randomized trials in TB
Number by decade when they started enrolment

Evidence base for TB treatment – RCT
Number of Randomized trials of treatment in New cases by decade when they started enrolment

Note: all but 2 of the RCT were publicly funded
RCT in Drug resistance / Re-treatment
Number by decade when they started enrolment

Note: To date No published RCT in MDR-TB

Example 4:

- Treatment of MDR-TB
  - Problems with systematic reviews
  - Individual Patient Data (IPD) meta-analysis
Treatment of MDR-TB

Problems of usual systematic reviews

- No RCT in MDR-TB
- Cohorts from specialized centres
- Therapy individualized
- Patients very different
  - History of prior treatment
  - Drug resistance patterns
  - Severity of illness and co-morbidities (HIV)
- Analysis of % Patients with Km resistance, or % receiving a Quinolone!

Treatment of MDR-TB

Individual patient Data meta-analysis

- Collect data sets from published cohort studies
- Individual patient data re:
  - History of prior treatment
  - Drug resistance patterns
  - Severity of illness and co-morbidities (HIV)
- Analysis of each Patient according to resistance, and treatment received.
IPD Objectives

- WHO Question 5: “Which are the most (and least) effective drugs for MDR-TB treatment?”
- WHO Question 6: “What is the optimal number of drugs?”
  - Overall (total)
  - Intensive phase
- WHO Question 7: “What is the optimal duration of treatment?”
  - Initial intensive phase (duration of Injectable)
  - Total duration

IPD Study (data-set) Selection

- Study Eligible if:
  - Included in one of 3 systematic reviews of MDR treatment
    - Johnston (published 2009)
    - Orenstein (published 2009)
    - Akcakir (McGill MSc thesis, completed 2009)
- Inclusion criteria of these 3 reviews:
  - Report of original data, published since 1970
  - At least one reported treatment outcome that conformed with established definitions for success, failure, relapse, death, or default
  - All patients had bacteriological confirmation of TB, and confirmed INH and RIF resistance
  - Studies excluded if only XDR-TB patients
IPD study - Inclusion criteria

- Authors could be contacted successfully
- Investigators willing and able to share their data.
- Minimum of 25 patients treated for confirmed MDR-TB
- At least one standard treatment outcome reported

Data Sharing

- Letters describing the IPD meta-analysis were sent to all authors of eligible studies
- IRB approval at Montreal Chest Institute. Local IRB approval sought when necessary. No patients contacted.
- Letters of agreement signed with authors
  - Authors continue to own data
  - All results shared, as they are available
  - Results kept confidential.
  - All contributors listed on any publications
- Electronic data transferred to Montreal Chest Institute. Non-nominal
Data Collection

- Centre information
- Patient-level information
  - Patient factors
    - Treatment outcomes
    - Age at time of diagnosis
    - Sex
    - HIV infection
    - ART use
  - Clinical factors
    - Site of disease
    - AFB smear results
    - Culture results
    - Chest X-ray (cavitations)
- Drug Sensitivity Testing (DST) - Initial & repeat
  - First line DST results
  - Second line DST results
- Treatment Factors
  - Initial phase treatment regimen (drugs and duration)
  - Continuation phase treatment regimen (drugs and duration)
  - Modifications to treatment (in response to DST, or AE)
  - Adverse events
  - Surgical resection

Data Management

- Mapped and renamed original variables to common set of variables for pooled meta-analysis dataset
  - Individual data dictionaries
  - Completed variable extraction forms
- Authors contacted for missing data, clarify variables, verify certain results.
- Summary tables of clinical characteristics of the study population in each study compared with original publications
- Variables provided in few data sets were noted, but not analysed.
Meta-analysis

- Random effects logistic regression to obtain the odds of cure for each drug - in all patients and among patients with MTB that was sensitive to drug of interest
- Multivariate approach: Pooled estimates calculated using PROC GLIMMIX in SAS – a random effects logistic regression model using penalized quasi-likelihood estimation
  - standard group of covariates: Age, Gender, HIV, Extent of disease (AFB smear/CXR cavities), and Past TB treatment (none, previous TB treatment, previous MDR-TB treatment)
- Heterogeneity examined using Forest plots, $I^2$, and $\tau^2$ statistics

**Figure 1. Study Selection**

3 Systematic reviews identified – Orenstein, Johnston, Akcakir

94 studies identified from 3 systematic reviews.

70 individual cohorts

Excluded: 1 Editorial and 26 publications representing the same or overlapping cohorts

33 individual cohort datasets received and included in analysis

32 data sets included in this analysis, with 9868 patients

9280 Patients analyzed

Excluded Patients
- 416 with XDR
- 208 No treatment info

Excluded - 37 cohorts
16 – No author response
5 – No longer have access to data
3 – Could not submit data
2 – Refusals
1 – Cohort with less than 20 patients
2 – No response following initial contact
2 – Inadequate outcome data
2 – No data on drug sensitivity testing
2 – Agreed to forward data - data not sent by Sept 8, 2010

Excluded - 1 Data-set. Still being prepared (Correspondence with author)
Overall Treatment Outcomes

- **Cure** - 4434 (45%)
- **Failure** - 746 (7%)
- **Relapse** - 90 (1%)
  - 11/32 (34%) studies reported
- **Death** - 1614 (16%)
- **Default** - 2181 (22%)

Association of Clinical Characteristics with Outcomes

- Cure rates **lower** with:
  - prior TB treatment
  - prior MDR-TB treatment
  - positive AFB smear
  - cavitations indicated on a chest x-ray
- Death rates **higher** with:
  - HIV
  - Older age
  - Positive smear or cavitory CXR
  - Prior treatment esp MDR treatment
- Default rates **higher** with:
  - Older age
  - HIV
### One injectable (any) vs. Two or more injectables

<table>
<thead>
<tr>
<th></th>
<th>One injectable (any)</th>
<th>Two or more injectables</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Cured</strong></td>
<td>4016</td>
<td>406</td>
</tr>
<tr>
<td><strong>Success vs. Fail/Relapse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>4569</td>
<td>492</td>
</tr>
<tr>
<td>Unadjusted Odds</td>
<td>1.0 (reference)</td>
<td>0.5 (0.3, 0.6)</td>
</tr>
<tr>
<td>Adjusted Odds</td>
<td>1.0 (reference)</td>
<td>0.5 (0.4, 0.7)</td>
</tr>
<tr>
<td><strong>Success vs. Fail/Relapse/Death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>5514</td>
<td>659</td>
</tr>
<tr>
<td>Unadjusted Odds</td>
<td>1.0 (reference)</td>
<td>0.7 (0.5, 0.8)</td>
</tr>
<tr>
<td>Adjusted Odds</td>
<td>1.0 (reference)</td>
<td>0.7 (0.6, 0.8)</td>
</tr>
<tr>
<td><strong>Success vs. Fail/Relapse/Death/Default</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>7065</td>
<td>750</td>
</tr>
<tr>
<td>Unadjusted Odds</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Adjusted Odds</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

### Kanamycin only vs. Capreomycin only

<table>
<thead>
<tr>
<th></th>
<th>Kanamycin only</th>
<th>Capreomycin only</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Cured</strong></td>
<td>2572</td>
<td>733</td>
</tr>
<tr>
<td><strong>Success vs. Fail/Relapse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>2884</td>
<td>841</td>
</tr>
<tr>
<td>Unadjusted Odds</td>
<td>1.0 (reference)</td>
<td>0.5 (0.3, 0.7)</td>
</tr>
<tr>
<td>Adjusted Odds</td>
<td>1.0 (reference)</td>
<td>0.5 (0.3, 0.7)</td>
</tr>
<tr>
<td><strong>Success vs. Fail/Relapse/Death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>3467</td>
<td>1018</td>
</tr>
<tr>
<td>Unadjusted Odds</td>
<td>1.0 (reference)</td>
<td>0.5 (0.4, 0.7)</td>
</tr>
<tr>
<td>Adjusted Odds</td>
<td>1.0 (reference)</td>
<td>0.6 (0.4, 0.8)</td>
</tr>
<tr>
<td><strong>Success vs. Fail/Relapse/Death/Default</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>4495</td>
<td>1211</td>
</tr>
<tr>
<td>Unadjusted Odds</td>
<td>1.0 (reference)</td>
<td>0.7 (0.6, 0.8)</td>
</tr>
<tr>
<td>Adjusted Odds</td>
<td>1.0 (reference)</td>
<td>0.8 (0.6, 0.9)</td>
</tr>
</tbody>
</table>
### Kanamycin only vs. Capreomycin only
In Kanamycin Sensitive* strains only

<table>
<thead>
<tr>
<th></th>
<th>Kanamycin only</th>
<th>Capreomycin only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cured</td>
<td>2434</td>
<td>271</td>
</tr>
<tr>
<td><strong>Success vs. Fail/Relapse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>2712</td>
<td>297</td>
</tr>
<tr>
<td>Unadjusted Odds</td>
<td>1.0 (reference)</td>
<td>0.6 (0.4, 1.1)</td>
</tr>
<tr>
<td>Adjusted Odds</td>
<td>1.0 (reference)</td>
<td>0.6 (0.3, 1.1)</td>
</tr>
<tr>
<td><strong>Success vs. Fail/Relapse/Death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>3267</td>
<td>349</td>
</tr>
<tr>
<td>Unadjusted Odds</td>
<td>1.0 (reference)</td>
<td><strong>0.7 (0.5, 0.96)</strong></td>
</tr>
<tr>
<td>Adjusted Odds</td>
<td>1.0 (reference)</td>
<td>0.8 (0.5, 1.1)</td>
</tr>
<tr>
<td><strong>Success vs. Fail/Relapse/Death/Default</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>4247</td>
<td>425</td>
</tr>
<tr>
<td>Unadjusted Odds</td>
<td>1.0 (reference)</td>
<td><strong>0.7 (0.5, 0.9)</strong></td>
</tr>
<tr>
<td>Adjusted Odds</td>
<td>1.0 (reference)</td>
<td>0.8 (0.6, 1.05)</td>
</tr>
</tbody>
</table>

**if patient missing Kanamycin DST result and < 10% fellow cohort members resistant, then imputed that patient was sensitive to Kanamycin**

### Kanamycin only vs. Capreomycin only, among only Kanamycin resistant patients

<table>
<thead>
<tr>
<th></th>
<th>Kanamycin only</th>
<th>Capreomycin only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cured</td>
<td>48</td>
<td>405</td>
</tr>
<tr>
<td><strong>Success vs. Fail/Relapse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>74</td>
<td>485</td>
</tr>
<tr>
<td>Unadjusted Odds</td>
<td>1.0 (reference)</td>
<td><strong>2.7 (1.6, 4.7)</strong></td>
</tr>
<tr>
<td>Adjusted Odds</td>
<td>1.0 (reference)</td>
<td><strong>2.3 (1.2, 4.3)</strong></td>
</tr>
<tr>
<td><strong>Success vs. Fail/Relapse/Death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>87</td>
<td>578</td>
</tr>
<tr>
<td>Unadjusted Odds</td>
<td>--</td>
<td><strong>1.5 (0.8, 3.0)</strong></td>
</tr>
<tr>
<td>Adjusted Odds</td>
<td>--</td>
<td><strong>1.5 (0.8, 3.2)</strong></td>
</tr>
<tr>
<td><strong>Success vs. Fail/Relapse/Death/Default</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>114</td>
<td>678</td>
</tr>
<tr>
<td>Unadjusted Odds</td>
<td>1.0 (reference)</td>
<td><strong>1.6 (0.9, 2.8)</strong></td>
</tr>
<tr>
<td>Adjusted Odds</td>
<td>1.0 (reference)</td>
<td><strong>1.6 (0.9, 2.9)</strong></td>
</tr>
</tbody>
</table>
### Duration of Initial Phase

<table>
<thead>
<tr>
<th></th>
<th>1-3 months</th>
<th>4-5 months</th>
<th>6-7 months</th>
<th>8 or more months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Cured</strong></td>
<td>1437</td>
<td>495</td>
<td>400</td>
<td>806</td>
</tr>
</tbody>
</table>

### Success vs. Fail/Relapse

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>1721</td>
<td>526</td>
</tr>
<tr>
<td><strong>Unadjusted</strong></td>
<td>2.4 (1.5, 3.7)</td>
<td>2.4 (1.5, 3.8)</td>
</tr>
<tr>
<td><strong>Adjusted</strong></td>
<td>2.4 (1.5, 3.7)</td>
<td>2.4 (1.5, 3.8)</td>
</tr>
</tbody>
</table>

### Success vs. Fail/Relapse/Death

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>2234</td>
<td>664</td>
</tr>
<tr>
<td><strong>Unadjusted</strong></td>
<td>1.1 (0.9, 1.4)</td>
<td>1.1 (0.9, 1.5)</td>
</tr>
<tr>
<td><strong>Adjusted</strong></td>
<td>1.1 (0.9, 1.4)</td>
<td>1.1 (0.9, 1.5)</td>
</tr>
</tbody>
</table>

### Success vs. Fail/Relapse/Death/Default

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>2867</td>
<td>867</td>
</tr>
<tr>
<td><strong>Unadjusted</strong></td>
<td>1.0 (0.8, 1.2)</td>
<td>1.0 (0.8, 1.2)</td>
</tr>
<tr>
<td><strong>Adjusted</strong></td>
<td>1.0 (0.8, 1.2)</td>
<td>1.0 (0.8, 1.2)</td>
</tr>
</tbody>
</table>

### Duration of Initial Phase and Success vs. Fail/Relapse (excluding patients with 2 or more injectables)

<table>
<thead>
<tr>
<th>Months</th>
<th>N</th>
<th>Cured</th>
<th>Unadjusted Odds</th>
<th>Adjusted Odds</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0-2.5</td>
<td>333</td>
<td>247</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>2.6-3.9</td>
<td>1353</td>
<td>1163</td>
<td>1.1 (0.7, 1.7)</td>
<td>1.1 (0.7, 1.7)</td>
</tr>
<tr>
<td>4.0-5.5</td>
<td>470</td>
<td>443</td>
<td>2.5 (1.4, 4.4)</td>
<td><strong>2.5 (1.4, 4.5)</strong></td>
</tr>
<tr>
<td>5.6-6.9</td>
<td>351</td>
<td>322</td>
<td>3.4 (1.8, 6.6)</td>
<td><strong>3.7 (1.9, 7.2)</strong></td>
</tr>
<tr>
<td>7.0-8.5</td>
<td>156</td>
<td>150</td>
<td>4.6 (1.8, 11.9)</td>
<td><strong>5.0 (1.9, 13)</strong></td>
</tr>
<tr>
<td>8.6-10.0</td>
<td>650</td>
<td>592</td>
<td>1.9 (1.04, 3.3)</td>
<td><strong>2.2 (1.2, 3.9)</strong></td>
</tr>
</tbody>
</table>
IPD - conclusions

- A lot of work!
- Able to account for specific DR pattern, and specific treatment given
- Can identify and adjust for important confounders. Or restrict to certain sub-groups.
- Much more sensitive method to detect relationships
- Assumes independent effect of meds

Final conclusions

- A lot of evidence is still missing
- Very few publicly funded RCTs in past 10 years
  - Expectation of Pharma?
  - Lack of Interest?
- Evidence base very weak for HIV-TB, and DR-TB, especially MDR-TB
Thank you!
Merci!
Gracias!!

“The Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB”,
Members (in alphabetic order):


Corresponding Author: Dr. Dick Menzies
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- Actual reviews:
  - Woojin Lew, Faiz Khan, Jessi Minion, Dan Martin, Anita Paydar, Ian Martin
- Data analysis:
  - Andrea Benedetti, Madhu Pai
- Secretarial (tables, tables and more tables)
  - Anita Paydar and Ria Choe