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

5

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

6

Rates of failure, relapse, and ADR with 2RIF vs. 6RIF

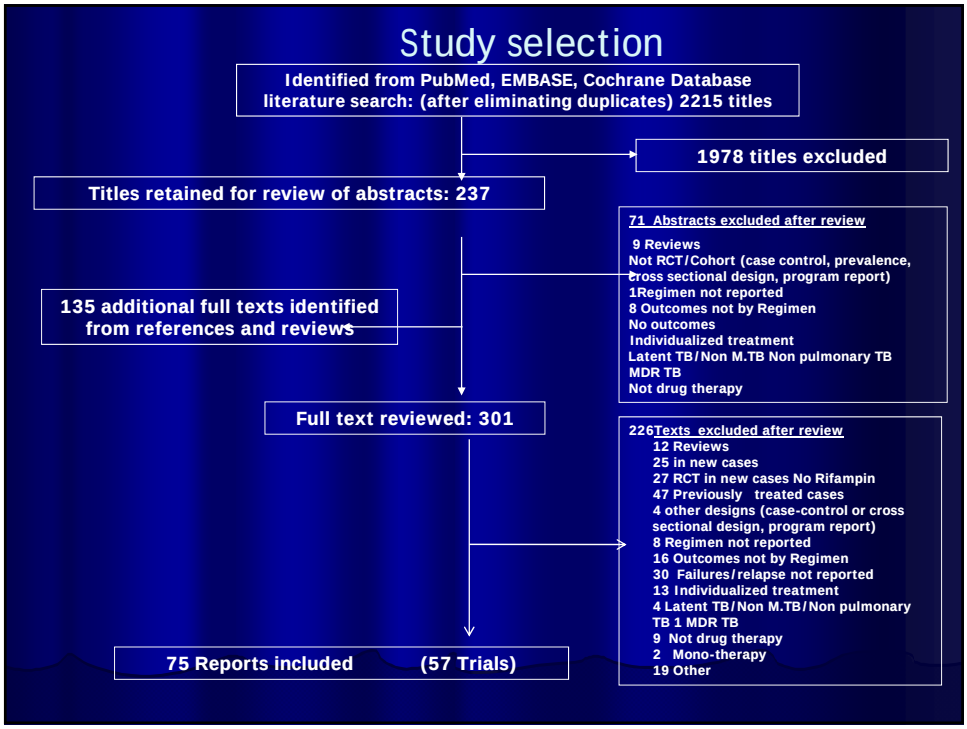
Search strategy

- 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

Rates of failure, relapse, and ADR with 2RIF vs. 6RIF

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



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

2 vs 3-4 Months	2 Months		3-4 Months		Risk Difference
Regimens †	Relapse	Non	Relapse	Non	
2SHRZ/2HZ 2SHRZ/2HRZ	38	78	30	200	19.7%
2SHRZ 3SHRZ	20	64	8	73	13.9%
Pooled risk difference (95% CI)					17.7% (10.3, 25
Overall I squared (95%CI)					0 (-,-)

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

	2 Months		6 Months		Risk Difference
Regimens †	Relapse	Non	Relapse	Non	
2SHRZ/4HZ 2SHRZ/4HR	13	168	6	171	3.8%
2EHRZ/6HE 2EHRZ/4HR	57	344	6	236	11.7%
$2HRZE/4[HRZ]_2$ $2HRZE/4[HZE]_2$	20	21	6	45	37%
Pooled risk difference (95% CI)					11.2% (8.1, 14.3)
Overall I squared (95% CI)					.9 (.66, .96)

Duration of Rifampin and Failure New cases

Rifampin duration	Arms (N)	Events/ Subjects	Event rate	(95% CI)
1-2 months	72	94/4133	**1.8%**	**(0.2, 3.3)**
3-5 months	42	16/2508	**0.3%**	**(0.0, 0.6)**
6-7 months	178	150/10060	**0.4%**	**(0.1, 0.7)**
8+ months	20	12/1607	0.3%	(0, 0.6)

Duration of Rifampin and Relapse New cases

Rifampin duration	Arms (N)	Events/ Subjects	Event rate	(95% CI)
1-2 months	70	637/3349	**16.0%**	**(11.1, 20.9)**
3-5 months	42	185/2389	**7.1%**	**(4.5, 9.7)**
6-7 months	171	364/9639	**3.8%**	**(2.9, 4.7)**
8+ months	18	14/1181	1.0%	(0.2 1.7)

Duration of Rifampin and treatment outcomes in new cases

(Results of Meta-regression)

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

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 RIF

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)

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

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

Underlying drug resistance pattern	2 month RIF	6 month RIF
Pan-sensitive	0.2%	0.2%
Single – INH	12.9%	4.3%
Single – Strep	2.5%	1.6%
All Single	10.4%	1.7%
Poly-Drug (2+)	34.8%	4.5%

Interaction of Duration of RIF with underlying type of drug resistance: RELAPSE

Underlying drug resistance pattern	2 months RIF	6 months RIF
Pan-sensitive	**8.2%**	3.3%
Single – INH	**28.3%**	8.6%
Single – Strep	**21.5%**	6.6%
All Single	**28.2%**	6.1%
Poly-Drug (2+)	**26.9%**	6.7%

Duration of Rifampin – WHO recommendations

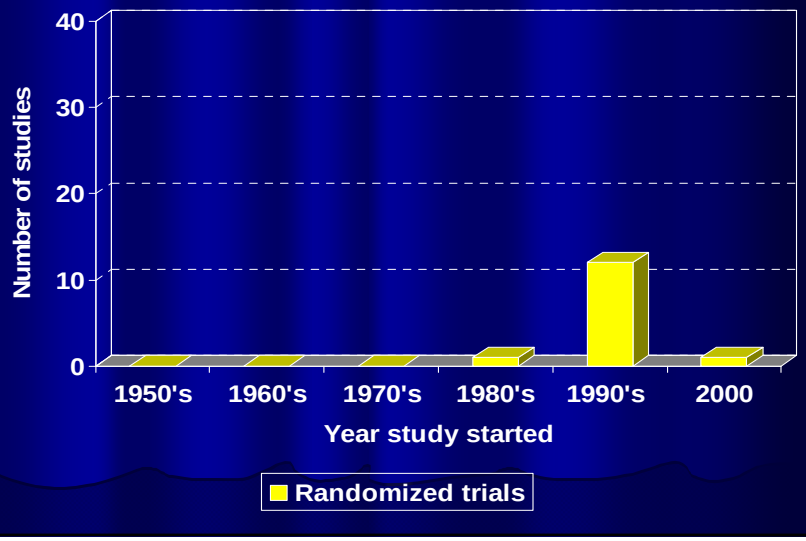
- 2HRZE/4HR – the 6-month RIF regimen – *Considered the regimen of first choice for all new cases*
- 2HRZE/6HE – the 2-month RIF regimen – *Should be phased out as rapidly as possible*

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



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

RELAPSE

Duration of Rifampin	Studies	Event / Subjects (N)	Pooled event rate	(95% CI)
2 months	6	40/258	10.0%	(0, 24.8)
6 months	13	110/863	9.7%	(0.6, 18.7)
9 months	6	20/314	3.3%	(0, 9.0)

HIV-TB Systematic review and meta-analysis

Effect of Intermittent regimens

FAILURE

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

HIV-TB Systematic review and meta-analysis

Effect of Intermittent regimens

RELAPSE

Intermittent therapy	Studies	Event / Subjects (N)	Pooled event rate	(95% CI)
Intermittent through-out	5	28/193	20.4%	(0, 48.9)
Daily Initially	20	142/1242	6.6%	(1.0, 12.1)

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:

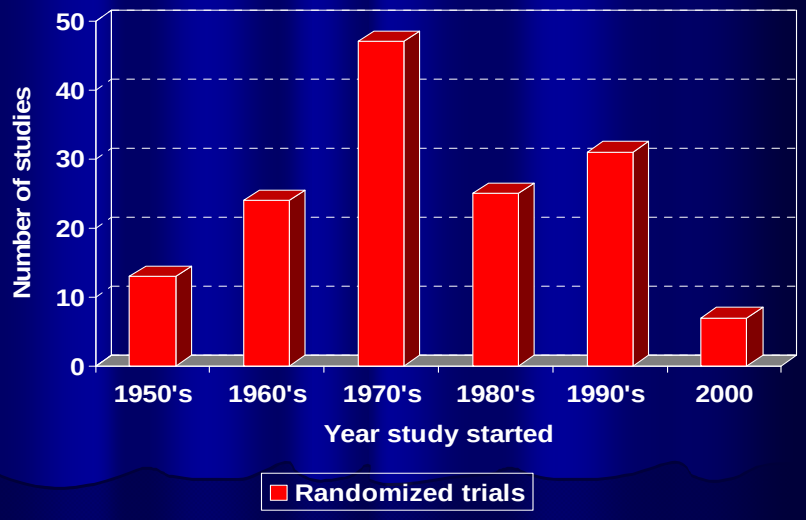
- Treatment of DR-TB and Retreatment
  - What to do - when there is no evidence

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

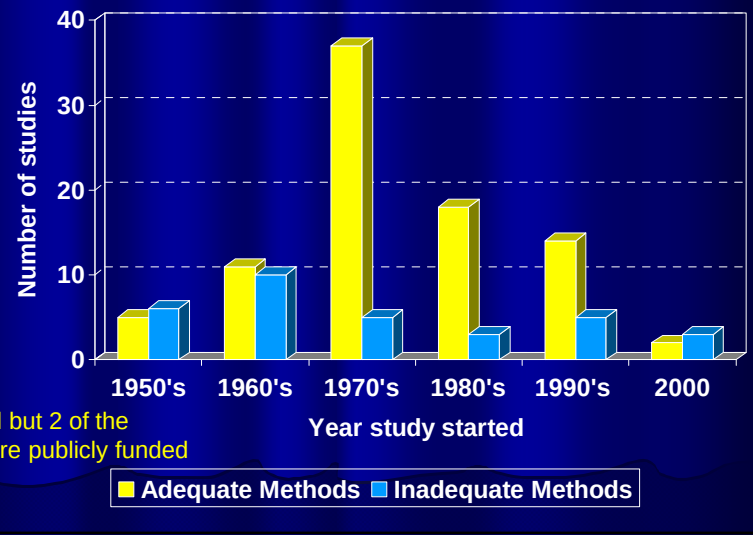
Evidence base - all Randomized trials in TB

Number by decade when they started enrolment



Evidence base for TB treatment – RCT

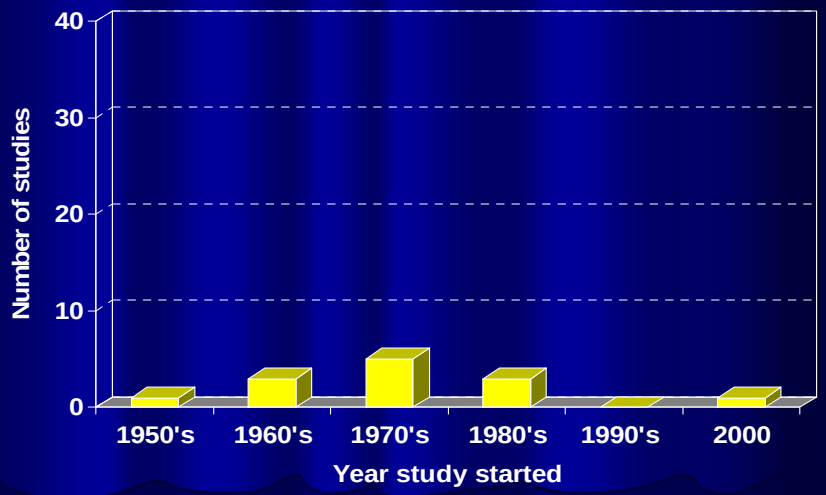
Number of Randomized trials of treatment in New cases by decade when they started enrolment



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

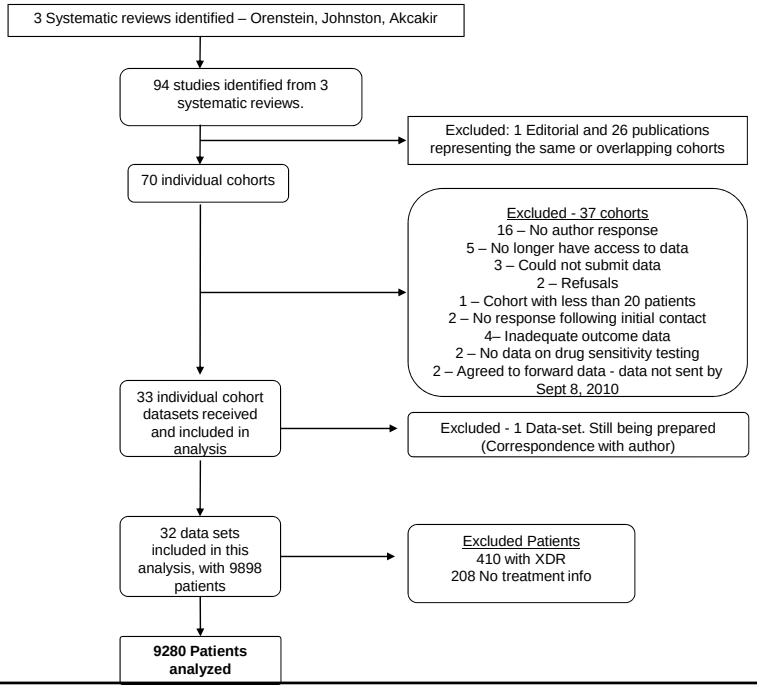
Data Management

- 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 τ^2 statistics

Figure 1. Study Selection



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 cavitary CXR
  - Prior treatment esp MDR treatment
- Default rates ***higher*** with:
  - Older age
  - HIV

One injectable (any) vs. Two or more injectables

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

Kanamycin only vs. Capreomycin only

	Kanamycin only	Capreomycin only
Total Cured	2572	733
Success vs. Fail/Relapse		
N	2884	841
Unadjusted Odds	1.0 (reference)	**0.5 (0.3, 0.7)**
Adjusted Odds	1.0 (reference)	**0.5 (0.3, 0.7)**
Success vs. Fail/Relapse/Death		
N	3467	1018
Unadjusted Odds	1.0 (reference)	**0.5 (0.4, 0.7)**
Adjusted Odds	1.0 (reference)	**0.6 (0.4, 0.8)**
Success vs. Fail/Relapse/Death/Default		
N	4495	1211
Unadjusted Odds	1.0 (reference)	**0.7 (0.6, 0.8)**
Adjusted Odds	1.0 (reference)	**0.8 (0.6, 0.9)**

Kanamycin only vs. Capreomycin only
In Kanamycin Sensitive* strains only

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

*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

	Kanamycin only	Capreomycin only
Total Cured	48	405
Success vs. Fail/Relapse		
N	74	485
Unadjusted Odds	1.0 (reference)	**2.7 (1.6. 4.7)**
Adjusted Odds	1.0 (reference)	**2.3 (1.2. 4.3)**
Success vs. Fail/Relapse/Death		
N	87	578
Unadjusted Odds	--	1.5 (0.8, 3.0)
Adjusted Odds	--	1.5 (0.8, 3.2)
Success vs. Fail/Relapse/Death/Default		
N	114	678
Unadjusted Odds	1.0 (reference)	1.6 (0.9, 2.8)
Adjusted Odds	1.0 (reference)	1.6 (0.9, 2.9)

Duration of Initial Phase

	1-3 months	4-5 months	6-7 months	8 or more months
Total Cured	1437	495	400	806
Success vs. Fail/Relapse				
N	1721	526	435	880
Unadjusted	--	**2.4 (1.5, 3.7)**	**2.8 (1.6, 4.8)**	**1.7 (1.1, 2.7)**
Adjusted	--	**2.4 (1.5, 3.8)**	**2.9 (1.7, 5.0)**	**1.9 (1.2, 3.1)**
Success vs. Fail/Relapse/Death				
N	2234	664	515	997
Unadjusted	--	1.1 (0.9, 1.4)	**1.8 (1.3, 2.6)**	**2.7 (2.0, 3.6)**
Adjusted	--	1.1 (0.9, 1.5)	**1.9 (1.3, 2.7)**	**2.8 (2.1, 3.8)**
Success vs. Fail/Relapse/Death/Default				
N	2867	867	657	1111
Unadjusted	--	1.0 (0.8, 1.2)	**2.0 (1.5, 2.6)**	**3.2 (2.5, 4.0)**
Adjusted	--	1.0 (0.8, 1.2)	**2.1 (1.6, 2.7)**	**3.5 (2.6, 4.3)**

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

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

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!

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