Treatment of INH Resistant-TB An aggregate data, and an Individual Patient Data (IPD) meta-analyses

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- All authors for sharing data and answering (many) questions
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- Tommy (Zhiyi) Lan – for constant collaboration
- Pei Zhi Li for advanced SAS help
- Andrea Benedetti- for statistical advice
- WHO for funding

Outline

- Aggregate data meta-analysis
- Individual Patient Data (IPD) Meta-analyis:
  - Methods – study selection, data gathering
  - Methods - analysis, and definitions of outcomes
  - Results - Analyzable populations
  - Results – for the four PICO questions:
    - Characteristics by regimen
    - aOR and RD for each outcome

Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis

Medea Gegia, Nicholas Winters, Andrea Benedetti, Dick van Soolingen, Dick Menzies

Summary

Background The results of some reports have suggested that treatment of isoniazid-resistant tuberculosis with the recommended regimens of first-line drugs might be suboptimal. We updated a previous systematic review of treatment outcomes associated with use of first-line drugs in patients with tuberculosis resistant to isoniazid but not rifampicin.

Methods In this systematic review, we updated the results of a previous review to include randomised trials and cohort studies published in English, French, or Spanish to March 31, 2015, containing results of standardised treatment of patients with bacteriologically confirmed isoniazid-resistant tuberculosis (but not multidrug-resistant

Lancet Infect Dis 2016

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Aggregate data meta-analysis of treatment of INHR – Gegia et al, Lancet Inf Dis; 2016

- The last RCT specifically for INH-R was published in 1997
- 19 cohorts and 33 RCTs
- 3744 patients with INHR and 19,022 with DS-TB
- 102 different regimens used
- Regimens analyzed by major components: RIF, PZA, SM
- Failure/relapse and acquired MDR were analyzed
  - All bacteriologically confirmed

Meta-analysis of treatment of INHR – Gegia et al, Lancet Inf Dis; 2016

Results with WHO Cat 1 (2HRZE/4HR)

OUTCOME DST	Arms (N)	Events	Subjects	Pooled Event Rate	(95% CI)
FAILURE					
INH-R	24	170	1239	11%	(6-17%)
DS-TB	19	241	9792	2%	(1-3%)
RELAPSE					
INH-R	17	59	482	10%	(5-15%)
DS-TB	15	269	4740	5%	(2-7%)
ACQUIRED MDR					
INH-R	18	89	701	8%	(3-13%)
DS-TB	15	102	5415	1%	(0-2%)

Meta-analysis of treatment of INHR – Gegia et al, Lancet Inf Dis; 2016

Results with WHO Cat 2 (2SHRZE/1HRZE/5HRE)

OUTCOME DST	Arms (N)	Events	Subjects	Pooled Event Rate	(95% CI)
FAILURE					
INH-R	24	41	505	6%	(2-10%)
DS-TB	21	40	2609	1%	(0-2%)
RELAPSE					
INH-R	20	13	277	5%	(2-8%)
DS-TB	18	115	2505	5%	(4-7%)
ACQUIRED MDR					
INH-R	17	7	284	3%	(0-6%)
DS-TB	16	7	2091	0.3%	(0-0.6%)

Meta-analysis of treatment of INHR – Gegia et al, Lancet Inf Dis; 2016

Results with 6-9RZE

OUTCOME DST	Arms (N)	Events	Subjects	Pooled Event Rate	(95% CI)
FAILURE					
INH-R	13	82	911	1%	(0-2%)
DS-TB	10	13	1098	1%	(0-2%)
RELAPSE					
INH-R	9	11	157	7%	(2-11%)
DS-TB	10	55	1010	6%	(3-8%)
ACQUIRED MDR					
INH-R	9	3	164	0.3%	(0-2%)
DS-TB	8	11	939	0.1%	(0-0.4%)

Meta-analysis of treatment of INHR – Gegia et al, Lancet Inf Dis; 2016

Results - Summary

- ***WHO Cat 1 (2HRZE/4HR):*** Substantially worse outcomes with INHR than DS-TB.
  - Failure and relapse rates: 11 & 10% vs 2 & 5% in DS-TB
  - Acquired MDR rates 8% vs 1% in DS-TB
- ***WHO Cat 2 (2SHRZE/1HRZE/5HRE)***: Somewhat worse outcomes than DS-TB
  - Failure rates: 6% vs 1% in DS-TB. Relapse rates same.
  - Acquired MDR: 3% vs <1%
- ***6-9 REZ:*** Almost identical results as in DS-TB.
  - Issue of toxicity raised. But few studies reported AE adequately

Individual Patient Data (IPD) Meta-analysis in INH Resistant TB

QUESTIONS

For the outcomes of Success v Fail/relapse, acquired MDR, and Mortality:

1. 6 months REZ vs 8-9 months REZ
    1. With or without INH
2. Adding a FQ – to 6+ months REZ
    1. With/without INH
    2. To 1-3 months Z, and 6+months RE
    3. Later gen FQ only
3. Adding Strep – to 6+ months REZ
    1. With/without INH

Individual Patient Data (IPD) Meta-analysis in INH Resistant TB

METHODS

What is an Individual patient data (IPD) meta-analysis?

- Direct collection of the original data for each patient from all the relevant studies
- Meta-analyses based on individual level data rather than aggregated study level data. Allows adjustment for confounders, or stratified analyses (eg by HIV, or added resistance)
- Improved quality of both the data and the analyses
- Considered to be a ‘gold standard’ of systematic reviews
- More work. Much more. Relies on extensive collaboration between researchers

Cochrane Handbook for Systematic Reviews of Interventions, 2011

IPD in INHR Inclusion Criteria - Studies

- Identifying eligible studies:
  - Included in the systematic review (Gegia et al. 2016)
  - Plus studies available through contacted authors
  - Plus update literature search (Mar 2015 to Feb 2016)
  - Plus 3 surveillance databases – European meeting
- Studies included if:
  - Authors contacted successfully; willing and able to share data
  - Data available on treatment regimen, and outcomes
  - INH-R and RIF-S before TB treatment start
- Minimum number of 20 patients with INHR TB for cohorts, any number for RCT

IPD in INHR Inclusion Criteria - Patients

- Treatment known (including duration) – and applicable to study questions
- End-of-treatment outcomes known
- Pulmonary TB (could have Ex-pulm as well)
- Confirmed INH Resistant, and RIF sensitive

Data Sharing

- IRB approval at Montreal Chest Institute
- Local IRB approval when necessary (no patients contacted, no need for new data)

- Letters of agreement signed with authors
  - Authors continue to own data
  - All results shared as available
  - Results kept confidential until collective publication
  - All contributors listed on any publications

- Electronic transfer of non-nominal data to Montreal Chest Institute, McGill

Data Management

- Mapped and renamed original variables to common set of variables for IPD analysis
- Authors contacted for missing data and to clarify/verify variables
- Summary tables of clinical characteristics of the study population compiled. These were compared with equivalent table in each study's original publication

Patient-level information

- Clinical factors
  - Age at time of diagnosis
  - Sex, BMI, Diabetes
  - Smoking, Alcohol use
  - HIV infection, ART use
  - Past TB treatment
  - Site of disease
  - AFB smear results
  - Chest X-ray (cavity, bilateral)
- Outcomes
  - End of treatment & relapse
  - 2-month sputum conversion
  - Acquired drug resistance
- Drug sensitivity testing (DST)
  - Initial & With Failure or relapse
- Treatment
  - Drugs and duration

Site-level information

- Laboratory methods (Culture, DST)
- Type of follow up (DOT vs SAT)
- Drug doses
- Outcome definitions

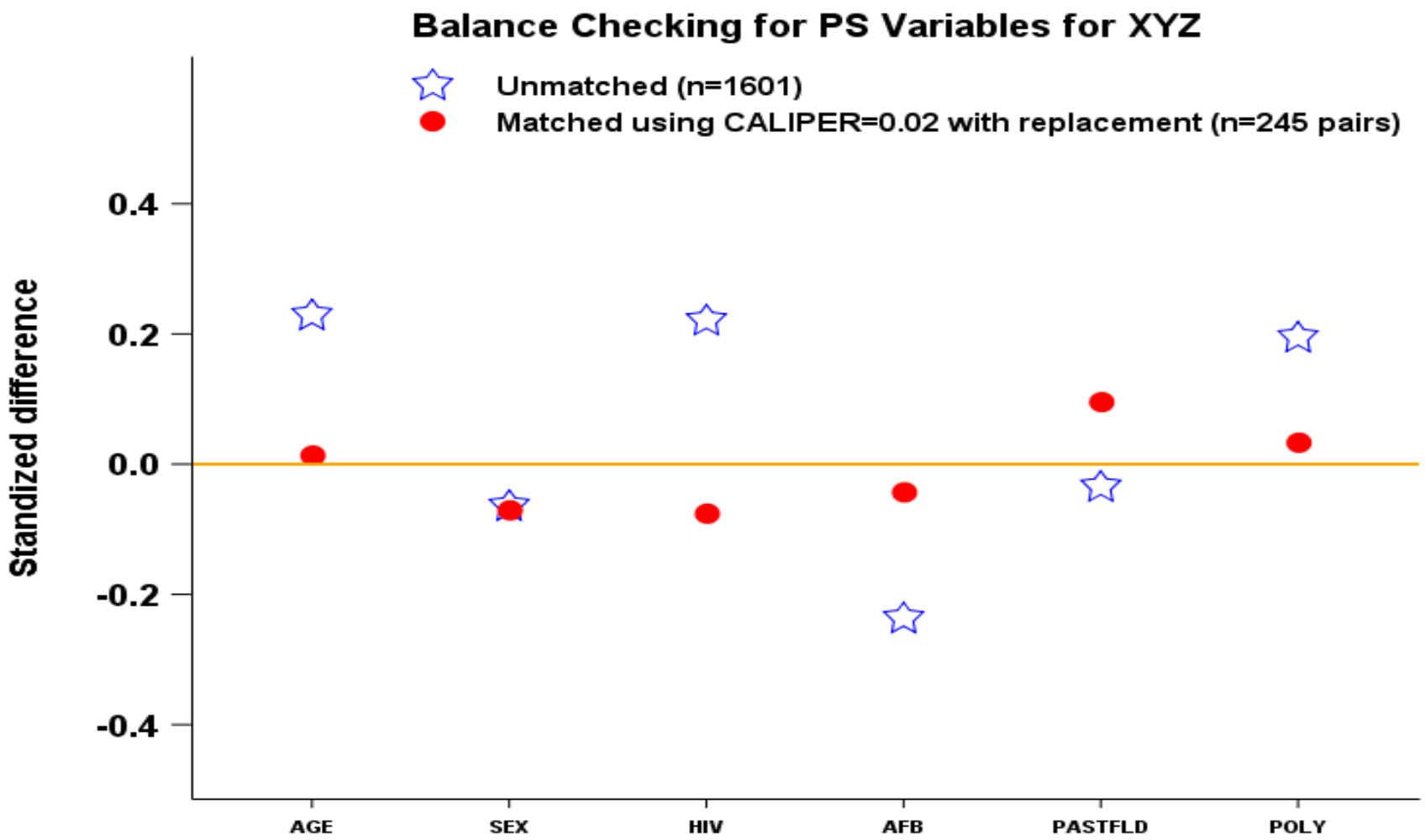
Definition: Outcomes

- Outcomes:
  - Cure/complete; Lost (Drop-out, Default, Transfer out, Unknown); Died; Failure
  - Relapse (19/23 included studies- 56% of patients in analysis- had info on relapse).
- Outcome comparisons:
  - Success vs. fail/relapse (Treatment efficacy)
  - Death vs. success/fail/relapse
  - Acquired RIF resistance (among fail/relapse) vs success

Analysis Methods

- Descriptive statistics
  - Patients' characteristics in each regimen of interest
- Assessment of potential confounding
  - Association of patient demographic and clinical characteristics with outcomes, and with different regimens
- Drug efficacy – adjusted for confounding
  - Odd ratios calculated with random effects multivariable logistic regression
  - Used propensity score matching (caliper 0.02, with replacement). Matching was based on sex, age, HIV, past TB treatment, AFB smear, poly resistance (to EMB,PZA,SM if used).
  - Propensity score matching method considered best method to adjust for measured confounding in observational studies.

Method of matching for propensity score. Example: 6(H)REZ-FQ vs >6(H)REZ.



Analysis of Outcomes

- For Success vs Fail/relapse:
  - Used precise duration of regimen (actual, or standardized)
  - Hence questions addressed were about very specific regimens
- For acquired RIF resistance (MDR):
  - Examined acquired RIF resistance among Failure/Relapse
  - Did not examine other acquired resistance
  - Also used precise regimens
- For Mortality:
  - Death truncated duration – hence could not analyze re specific durations
  - Assessed ***Use of FQ*** or ***Use of Strep***
- Adverse events – not analyzed
  - Not enough info, not standardized, not defined…..

Individual Patient Data (IPD) Meta-analysis in INH Resistant TB

RESULTS

The Collaborative Group for Meta-Analysis of Individual Patient Data in INHR-TB

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- Seung K
- Schaaf HS
- Skrahina A
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- Trieu L
- Viiklepp P
- Nguyen VN
- Wang J-Y
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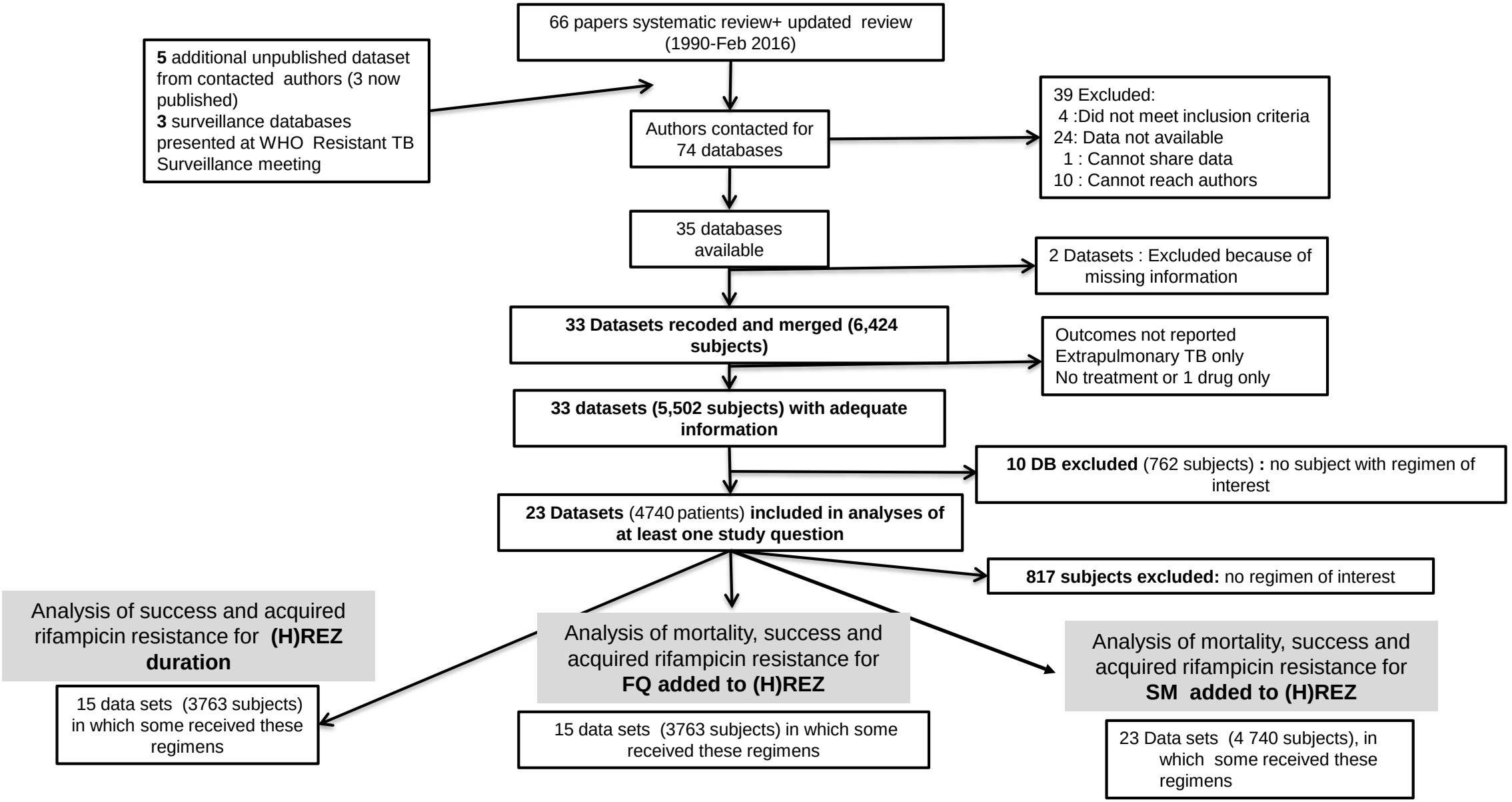

66 papers systematic review+ updated review (1990-Feb 2016)
5 additional unpublished dataset from contacted authors (3 now published)
3 surveillance databases presented at WHO Resistant TB Surveillance meeting
Authors contacted for 74 databases
39 Excluded:
4 :Did not meet inclusion criteria
24: Data not available
1 : Cannot share data
10 : Cannot reach authors
35 databases available
2 Datasets : Excluded because of missing information
33 Datasets recoded and merged (6,424 subjects)
Outcomes not reported
Extrapulmonary TB only
No treatment or 1 drug only
33 datasets (5,502 subjects) with adequate information
10 DB excluded (762 subjects) : no subject with regimen of interest
23 Datasets (4740 patients) included in analyses of at least one study question
817 subjects excluded: no regimen of interest
Analysis of success and acquired rifampicin resistance for (H)REZ duration
15 data sets (3763 subjects) in which some received these regimens
Analysis of mortality, success and acquired rifampicin resistance for FQ added to (H)REZ
15 data sets (3763 subjects) in which some received these regimens
Analysis of mortality, success and acquired rifampicin resistance for SM added to (H)REZ
23 Data sets (4 740 subjects), in which some received these regimens

Duration of REZ (6 vs 8-9 months)
Success versus failure/relapse *(mortality not analyzable)*

Comparison	N Success/N on regimen	Propensity score	
		Odds ratio aOR (95% CI)	Risk Difference aRD (95% CI)
All Patients			
6REZ (±INH)	254/262	**2.4 (1.0 – 5.5)**	+4% (0 to +8%)
>6REZ (±INH)	999/1088	1.0 (reference)	Reference
Only if no INH			
6REZ	136/142	2.5 (0.9; 7.5)	+5% (-1% to +8%)
>6REZ	701/785	1.0 (reference)	Reference

Acquired RIF resistance: Non-significant – but **lower** with 6REZ than 8-9REZ

Adding a FQ to ≥6(H)REZ. **Success** versus failure/relapse

Comparison	N Success/ N on regimen	Propensity score	
		Odds ratio aOR (95% CI)	Risk Difference aRD (95% CI)
All Patients			
≥6(H)REZ **&FQ ***	245/251	**2.8 (1.1; 7.3)**	+5% (0 to +9%)
≥6 (H)REZ	1253/1350	1.0 (reference)	Reference
FQ are only moxifloxacin/levofloxacin/gatifloxacin			
≥6(H)REZ &**FQ**	161/165	2.9 (0.9; 9.3)	+6% (-2% to +14%)
≥6 (H)REZ	1253/1350	1.0 (reference)	Reference

Median duration of FQ: 6 months
Acquired RIF resistance: **Significantly lower if received a FQ**
Findings virtually identical in patients who did not receive any INH

Adding a FQ to (H)REZ. **Only 1-3 months Z. Success** versus failure/relapse

Comparison	N Success/ N on regimen	Propensity score	
		Odds ratio aOR (95% CI)	Risk Difference aRD (95% CI)
All Patients			
≥6RE **1-3Z & FQ** (±INH)	117/118	5.2 (0.6; 46.7)	+4% (-2% to +9%)
≥6REZ (±INH)	1253/1350	1.0 (reference)	reference
FQ are only moxifloxacin/levofloxacin/gatifloxacin			
≥6RE **1-3Z & FQ** (+INH)	104/105	5.2 (0.6, 47.2)	+5% (-3% to +12%)
≥6REZ (+INH)	1253/1350	1.0 (reference)	reference
Acquired RIF resistance: **No patient who received a FQ developed MDR** Median Duration of FQ: 7 months			

Adding a FQ to (H)REZ **Mortality** (all durations)

Comparison	N Success/ N on regimen	Propensity score	
		Odds ratio aOR (95% CI)	Risk Difference aRD (95% CI)
All Patients			
(H)REZ **&FQ ***	25/524	0.7 (0.4; 1.1)	-2% (-5% to 0)
(H)REZ	97/2174	1.0 (reference)	reference
Only if no INH			
REZ &**FQ**	8/219	0.4 (0.2; 1.1)	-2% (-6% to +2%)
REZ	41/1054	1.0 (reference)	reference

*Median duration FQ 6.6 months

Adding Streptomycin (SM) to (H)REZ. **Success** versus failure/relapse

Comparison	N Success/ N on regimen	Propensity score	
		Odds ratio aOR (95% CI)	Risk Difference aRD (95% CI)
All Patients			
≥6 RE 1-3Z 1-3**SM** (±INH)	271/325	**0.4 (0.2 to 0.7)**	**-12% (-19% to -6%)**
≥6REZ (±INH)	1253/1350	1.0 (reference)	reference
Subgroup analysis: No INH			
≥6 RE 1-3Z 1-3**SM**	89/107	0.5 (0.2 to 1.2)	-8% (-17% to +10%)
≥6REZ	837/927	1.0 (reference)	reference
Acquired RIF resistance: Could not be calculated			

Adding Streptomycin (SM) to (H)REZ. Mortality

Comparison	N Success/ N on regimen	Propensity score	
		Odds ratio aOR (95% CI)	Risk Difference aRD (95% CI)
All Patients (23 data sets)			
(H)REZ+SM	40/763	0.9 (0.6; 1.3)	-1% (-3% to +2%)
(H)REZ	103/2263	1.0 (reference)	reference
Subgroup analysis: No INH			
REZ+SM	6/140	1.2 (0.4 to 4.1)	0 (-5% to +6%)
REZ	42/1090	1.0 (reference)	reference

Conclusions: Duration of REZ

- **Success: 6 months REZ as good as longer duration of REZ**
  - Overall Success actually better
  - Without INH – not significantly different
- Acquired MDR: **6 months REZ = 8-9 months REZ**
  - 6(H)REZ risk of aMDR <1%
  - 6REZ – risk of aMDR = 0

Conclusions: Adding a FQ

- Any FQ added to ≥6REZ – better outcomes
  - Significantly better success than 6(H)REZ
  - In the sub-group with no INH - also significantly better
  - Later gen FQ used - non-significantly better.
  - Acquired MDR <1%, lower than 6(H)REZ (but not significantly)
- Any FQ added to (H)RE 1-3Z: only 118 received this
  - Success rate very high. Better than 6(H)REZ (but not significantly - small number of patients)
  - Acquired MDR = 0
- Mortality: Lower if FQ added to (H)REZ (but not significantly).

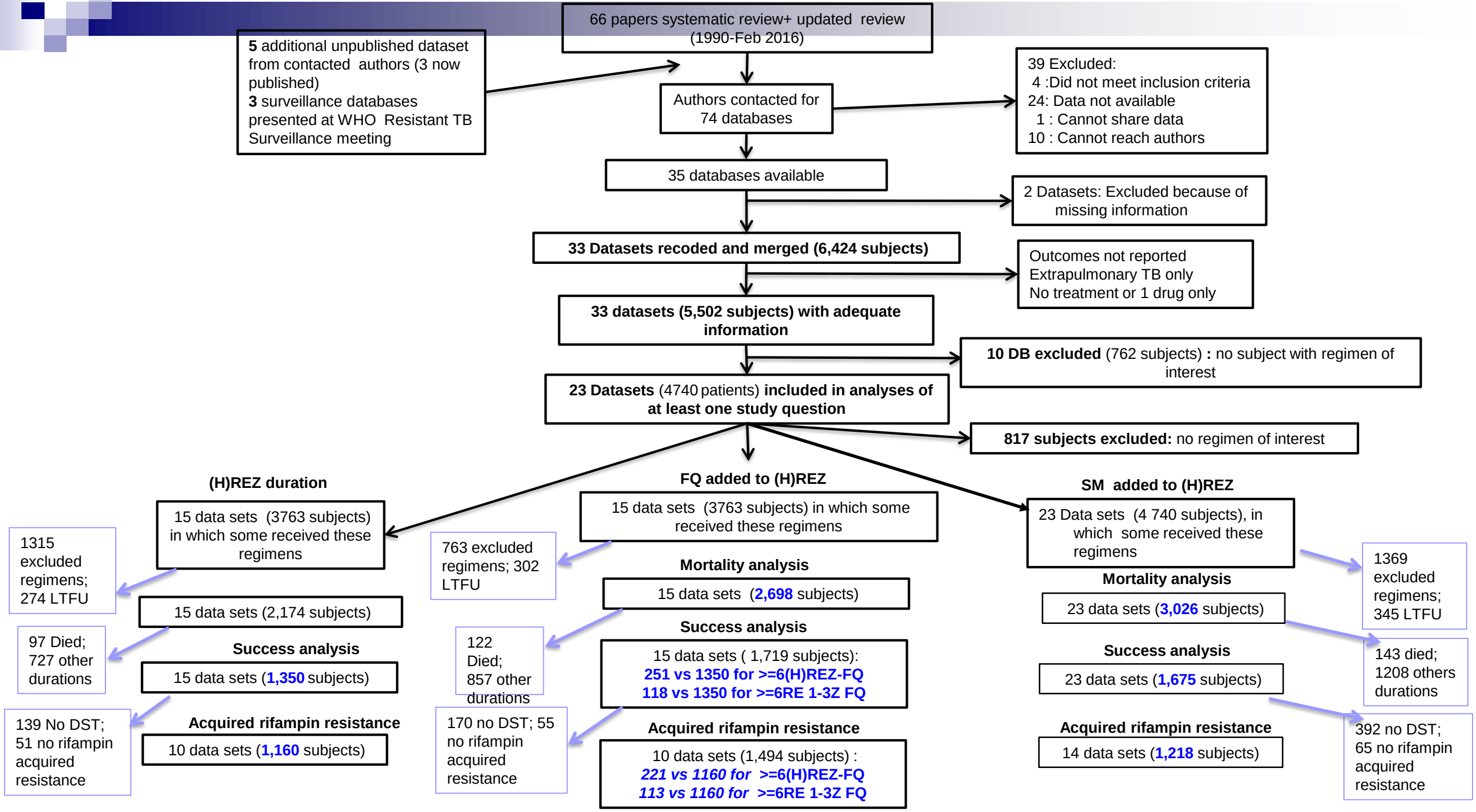
Conclusions – adding Strep (1-3 months)

- Success:
  - Significantly lower success than ≥6(H)REZ
  - No INH subgroup: non-significantly lower success
- Acquired drug resistance – aMDR
  - Few studies and few patients
  - Crude rate 10% with SM added.
- Mortality:
  - Same as with (H)REZ

THANK YOU

ADDITIONAL SLIDES

Regimen in included studies	N	%
N analyzable	4740	100
Regimens considered in present analysis	3923	82.8
(H)REZ	**1645**	**34.7**
(H)REZ-FQ	**524**	**11.1**
(H)REZ- SM	**763**	**16.1**
Regimens excluded from present analysis	817	17.2
(H)REZ-SLI (+/-SM)	19	0.4
(H)REZ- FQ- SLI (+/-SM)	73	1.5
Containing any WHO Group C or D3 drugs	141	3.0
Other combinations:		
a) REZ, FQ and SM (+/- INH)	56	1.2
b) RE, FQ and SM (+/- INH)	74	1.6
c) RZ, FQ and SM (+/- INH)	65	1.4
d) RZ, RE or EZ (+/- INH)	205	4.3
e) other combinations FQ	45	0.9
Regimens with HIGH dose INH	139	2.9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33 datasets (5,502 subjects) with adequate information
10 DB excluded (762 subjects) : no subject with regimen of interest
23 Datasets (4740 patients) included in analyses of at least one study question
817 subjects excluded: no regimen of interest
(H)REZ duration
15 data sets (3763 subjects) in which some received these regimens
1315 excluded regimens; 274 LTFU
15 data sets (2,174 subjects)
97 Died; 727 other durations
Success analysis
15 data sets (1,350 subjects)
139 No DST; 51 no rifampin acquired resistance
Acquired rifampin resistance
10 data sets (1,160 subjects)
FQ added to (H)REZ
15 data sets (3763 subjects) in which some received these regimens
763 excluded regimens; 302 LTFU
Mortality analysis
15 data sets (2,698 subjects)
122 Died; 857 other durations
Success analysis
15 data sets (1,719 subjects):
251 vs 1350 for >=6(H)REZ-FQ
118 vs 1350 for >=6RE 1-3Z FQ
170 no DST; 55 no rifampin acquired resistance
Acquired rifampin resistance
10 data sets (1,494 subjects) :
221 vs 1160 for >=6(H)REZ-FQ
113 vs 1160 for >=6RE 1-3Z FQ
SM added to (H)REZ
23 Data sets (4 740 subjects), in which some received these regimens
1369 excluded regimens; 345 LTFU
Mortality analysis
23 data sets (3,026 subjects)
143 died; 1208 others durations
Success analysis
23 data sets (1,675 subjects)
392 no DST; 65 no rifampin acquired resistance
Acquired rifampin resistance
14 data sets (1,218 subjects)

6REZ (6 mos) vs >6REZ (8-9 mos): Characteristics of the population per each regimen

Regimen	6(H)REZ	>6m (H)REZ	6REZ	>6REZ
Total Number analyzable obs. for success	262	1088	142	785
AGE in years (median, IQR)	42 (29; 58)	37 (27; 50)	44 (30; 57)	35 (26; 48)
Sex, female, N(%)	84/262 (32%)	317/1088 (29)	46/142 (32)	201/785 (26)
HIV: positive, N(%)	7/221 (3%)*	23/295 (8)*	0/121*	5/75 (7)*
on ART, N (% on HIV+)	1/7(14%)	1/23 (4)	--	0/5
Diabetes, N(%)	16/113 (14%)	19/99 (19)	13/92 (14)	4/36 (11)
Any Past TB treatment, N (%)	**44/260 (17)***	**116/979 (12)***	**26/141 (18)**	**93/686 (14)**
Sputum smear positive, N (%)	127/252 (50)*	853/1071 (80)*	70/133 (53)*	652/788 (84)*
Cavity disease at chest X-ray, N (%)	54/237 (23)*	115/366 (31)*	36/128 (28)	25/87 (29)
Extensive disease (cavity or bilateral or AFB+), N(%)	167/261 (64)*	893/1085 (82)*	97/141 (69)*	666/782 (85)*
Poly resistance (resistance to EMB, PZA or SM), N(%)	**2/262(1)**	**3/1088(0)**	**0/142**	**0/785**

- P for Chi squared or t-test <0.05.

Adding a FQ to >6(H)REZ.

Characteristics of the population receiving each regimen

Regimen	≥6(H)R(E)Z FQ	≥6m (H)REZ
Total analyzable observations for success v F/R	251	1350
AGE (median, IQR)	42 (32; 56)*	38 (27; 52)
Sex, female, N /tot with info (%)	82/251 (33)	401/1350 (30)
HIV: positive, N/tot with info (%)	17/203 (8)	30/516 (6)
on ART, N (% on HIV+)	**0/17 (0)**	**2/30 (7)**
Any Past TB treatment, N (%)	**27/247 (11)**	**160/1239 (13)**
Sputum smear positive, N (%)	154/245 (63)*	980/1323 (74)*
Cavity disease at chest X-ray, N/tot with info (%)	56/220 (25)	169/603 (28)
Extensive disease (cavity or bilateral or AFB+), N/tot with info (%)	171/251 (68)*	1060/1346 (79)*
Poly resistance (resistance to EMB, PZA or SM), N/tot with info (%)	**7/251 (3)***	**5/1350 (0.4)***
Resistance to FQ, N/total tested	3/163	3/346
Later generation FQ (Moxi/levo/gatifloxacin)	165	--

* P value from for Chi squared or t-test: <0.05.

Adding a FQ to (H)REZ. **Only 1-3 months Z.**
Characteristics of the population receiving each regimen

Regimen	≥6(H)R(E) 1-3Z FQ[a]	≥6m (H)REZ
Total analyzable obs. for success	118	1350
AGE (median, IQR)	56 (38; 69)*	38 (27; 52)*
Sex, female, N/tot with info (%)	39/118 (33)	401/1350 (30)
HIV: positive, N/tot with info (%)	7/97 (7)	30/516 (6)
on ART, N/tot with info (% on HIV+)	3/7 (43)*	2/30 (7)*
Any Past TB treatment, N/tot with info (%)	**12/109 (11)**	**160/1239 (13)**
Sputum smear positive, N/tot with info (%)	47/96 (49)*	980/1323 (74)*
Cavity disease at chest X-ray, N/tot with info (%)	28/115 (24)	169/603 (28)
Extensive disease (cavity or bilateral or AFB+), N/tot with info (%)	79/118 (67)*	1060/1346 (79)*
Poly resistance (resistance to EMB, PZA or SM), N/tot with info (%)	**15/118 (13)***	**5/1350 (0.4)***
Resistance to FQ, N/total tested	1/66	3/346
Later generation FQ (Moxi/Levo/Gatofloxacin), N(%)	105 (89%)	--

Notes: **a)** Median (IQR) fluoroquinolones duration: 7.0 (5.0; 9.5) months.
***** $p<0.05$ for Chi-square test of differences of this characteristic in the two regimens

Adding Streptomycin (SM) to (H)REZ
Characteristics of the population receiving each regimen

Characteristics	≥6 (H)RE 1-3Z 1-3SM	≥6REZ (±INH)
Total analyzable observations for success vs F/R	325	1350
AGE (median, IQR)	42 (31; 51)	38 (27; 52)
Sex, female, N/tot with info (%)	84/300 (28)	401/1350 (30)
HIV: positive, N(%)	17/238 (7)	30/516 (6)*
on ART, N (% on HIV+)	0/17 (0)	2/30 (7)*
Any Past TB treatment, N/tot with info (%)	**204/214 (95)***	**160/1239 (13)***
Sputum smear positive, N/tot with info (%)	289/312 (93)*	980/1323 (74)*
Cavity disease at chest X-ray, N/tot with info (%)	76/113 (67)*	169/603 (28)*
Extensive disease (cavity or bilateral or AFB+), N/tot with info (%)	314/323 (97)*	1060/1346 (79)*
Poly resistance (resistance to EMB, PZA or SM), N/tot with info (%)	**131/281 (47)***	**5/1350 (0.4)***

* P value from for Chi squared or t-test: <0.05.