THE LANCET
Respiratory Medicine

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Fregonese F, Ahuja S D, Akkerman O W, et al. Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis. *Lancet Respir Med* 2018; **6:** 265–75.

Supplemental Tables

Table S1a. Characteristics of the 23 studies included in current analysis

First author	Bang 2010[1]	Brazilian NTP[2]	Cattamanchi 2009[3]	Chien 2015[4]	Cox 2006[5]	Gegia 2012[6]	Huyen 2013[7]	Jacobson 2011[8]
Country	Denmark	Brazil	US (California)	Taiwan	Uzbekistan	Georgia	Vietnam	South Africa
Years of study	2002-07	2012-14	1992-2005	2004-12	2001-02	2007-09	2005-07	2001-09
Concentration used to define H resistance (μm/mL)	0·1	0·2	0·2	0·2	0·1	0·2	0·2	0·1
Regimen[a]	Indiv.	Stand.	Stand.	Indiv.	Stand.	Stand.	Stand.	Indiv.
Duration (known vs planned)	Known	Known	Known	Known	Known	Planned	Planned	Known
Age in years (median, IQR)	37 (27; 47)	41 (31; 52)	48 (30; 67)	63 (48; 76)	31 (25; 40)	35 (26; 48)	49 (39; 65)	40 (31; 46)
Sex female, %	35%	30%	38%	25%	30%	23%	25%	44%
HIV positive, % of tested[b]	27%	6%	7%	2%	0%	na	na	27%
Past TB treatment, %[b]	13%	na	36%	12%	53%	14%	16%	80%
Cavity on chest-x ray, %[b]	na	69%	21%	28%	na	na	na	na
Resistance to SM, %[b]	50%	4%	na	na	78%	69%	65%	0%
Total analyzable, N:	71	167	98	242	55	864	204	23
- Success, %	83%	67%	90%	86%	31%	70%	85%	65%
- Failure/relapse, %	4%	15%	1%	4%	49%	9%	9%	22%
- Deaths, %	3%	4%	1%	10%	5%	4%	5%	0
- Loss to follow-up, %	10%	14%	8%	0	15%	17%	1%	13%
N included in analysis:								
- Mortality	64	144	90	242	47	716	201	20
- Success	61	107	55	133	23	686	32	6
- Acquired R resistance	--	--	--	127	11	649	--	6

Notes: **a**) Regimens were classified as "standardized" if standard regimen was given to all patients; "individualized" if regimens were tailored to individual patients' characteristics such as prior therapy, or drug susceptibility testing (DST) results; " randomized" if standard regimens were given within a randomized clinical trial.

b) Percentages are of the total for who the information was available. In some sites this information was available for less than 50% of the population

Abbreviations: **H** isoniazid; **Individ**. Individualized; **IQR** Interquartile range; **na**: information in not available for that database or if it is available in less than 10% of the population; **R**: rifampin; **Random.** Randomized; **SM** streptomycin; **Stand**. Standardized.

Table S1a -continued. Characteristics of the 23 studies included in current analysis

First author	Jones-Lopez 2011[9]	Kim 2008[10]	Lee 2016[11]	Munang 2015[12]	Netherlands NTP[13]	New York city[14]	Ohkado 2006[15]	Park 2016[16]
Country	Uganda	Korea	Korea	UK	Netherlands	US	Philippines	Korea
Years	2005	2001-05	2005-12	1999-2010	1993-2015	1994-2014	2000	2005-13
Concentration used to define H resistance (μm/mL)	0·1	0·2	0·2	0·1	0·2	0·1; 0·2	0·2	0·2
Regimen[a]	Stand.	Stand.	Stand.	Indiv.	Indiv.	Indiv.	Stand.	Indiv.
Duration (known vs planned)	Planned	Planned	Known	Known	Known	Known	Known	Known
Age in years (median, IQR)	na	43 (31; 61)	54 (38; 67)	30 (25; 38)	30 (23; 40)	41 (30; 54)	43 (26; 57)	59 (49; 73)
Sex female, %	na	33%	34%	50%	42%	36%	30%	31%
HIV positive, % on tested[b]	44%	0%	0%	5%	na	24%	na	0%
Past TB treatment, %[b]	100%	36%	30%	na	7%	3%	3%	50%
Cavity on chest-x ray, %[b]	na	41%	24%	15%	na	25%	na	31%
Resistance to SM, %[b]	na	13%	14%	na	na	36%	40%	13%
Total analyzable, N:	34	39	115	41	509	824	33	6
- Success, %	68%	92%	90%	83%	87%	88%	82%	100%
- Failure/relapse, %	9%	8%	10%	5%	0	1%	6%	0
- Deaths, %	18%	0	0	0	2%	6%	3%	0
- Loss to follow-up, %	6%	0	0	12%	11%	5%	9%	0
N included in analysis:								
- Mortality	32	39	115	36	454	778	30	6
- Success	26	13	91	12	15	541	2	5
- Acquired R resistance	26	12	83	12	--	539	--	--

Notes:

a) Regimens were classified as "standardized" if standard regimen was given to all patients; "individualized" if regimens were tailored to individual patients' characteristics such as prior therapy, or drug susceptibility testing (DST) results; " randomized" if standard regimens were given within a randomized clinical trial.

Abbreviations: **H** isoniazid; **Individ**. Individualized; **IQR** Interquartile range; **na**: information in not available for that database or if it is available in less than 10% of the population; **R**: rifampin; **SM** streptomycin; **Stand**. Standardized.

Table S1a-continued. Characteristics of the 23 studies included in current analysis

First author	Quy 2003,2006[17,18]	Reves 2014[19]	Romanowski 2017[20]	Skrahina[21]	Swaminathan 2010[22]	Viiklepp[23]	Yoshiyama 2010[24]	Total
Country	Vietnam	US & Canada	Canada	Belarus	India	Estonia	Nepal	--
Years	1998-2000	1999-2004	2002-14	2012-15	2000-05	2008-15	2003-05	1992-2015
Concentration used to define H resistance (μm/mL)	0·2	0·2 or 1·0	0·1	0·1	1·0	0·1	0·25	--
Regimen [a]	Stand.	Stand.	Indiv.	Indiv.	Random.	Indiv.	Stand.	--
Duration (known vs planned)	Planned	Known	Known	Known	Planned	Known	Planned	--
Age in years (median, IQR)	38 (30; 46)	45 (33; 56)	49 (37; 65)	43 (33; 53)	35 (29; 37)	49 (39; 56)	30 (25; 41)	35 (25; 50)
Sex female, %	30%	30%	32%	39%	26%	22%	41%	31%
HIV positive, % of tested[b]	2%	0%	3%	0%	100%	12%	na	13%
Past TB treatment, %[b]	27%	17%	18%	12%	na	7%	100%	16%
Cavity on chest-x ray, %[b]	na	45%	42%	0%	9%	54%	na	32%
Resistance to SM, %[b]	72%	25%	28%	67%[b]	43%	74%	65%	47%
Total analyzable, N:	315	60	121	15	25	42	20	3923
- Success, %	81%	75%	80%	60%	36%	79%	75%	80%
- Failure/relapse, %	9%	3%	1%	20%	48%	2%	10%	6%
- Deaths, %	3%	0	4%	0	8%	14%	0	4%
- Loss to follow-up, %	7%	22%	15%	20%	8%	5%	15%	10%
N included in analysis:								
- Mortality	294	47	103	12	23	40	17	3,550
- Success	101	45	44	11	4	14	17	2,044
- Acquired R resistance	--	--	44	10	3	14	16	1,552

Notes:

a) Regimens were classified as "standardized" if standard regimen was given to all patients; "individualized" if regimens were tailored to individual patients' characteristics such as prior therapy, or drug susceptibility testing (DST) results; " randomized" if standard regimens were given within a randomized clinical trial.

Abbreviations: **H** isoniazid; **Individ**. Individualized; **IQR** Interquartile range; **na**: information in not available for that database or if it is available in less than 10% of the population; **R**: rifampin; **SM** streptomycin; **Stand**. Standardized.

Table S1b. Regimens excluded from present analysis –in the 23 included studies. Note: regimens were excluded if they did not correspond to the three study questions.

Regimen	N data sets	N
Regimens excluded from present analysis		**817**
Any regimens with high-dose isoniazid		**139**
- High dose H plus R, E, Z		63
- High dose H plus R, E, Z, SM		22
- Containing both FQ and high dose H (+/- SM)		31
- Containing high does H, group C or D3 drugs[a] +/- FQ +/- any injectables		17
- Other combinations with high dose H		6
Containing WHO Group C or D3 drugs (+/-SM, +/- FQ) (without high dose H)		**141**
- Ethionamide/prothionamide		69
- Cycloserine/terizidone		36
- Both Ethionamide/prothionamide and Cycloserine/terizidone		19
- Other group C or D3 drugs[b]		17
(H)REZ-Second line injectables (+/- SM)		**19**
(H)REZ- FQ- Second line injectables (+/- SM)		**73**
Other regimens containing FQ		**240**
- (H)RE + FQ (+/- SM)		74
- (H)RZ + FQ (+/-SM)		65
- (H)REZ-SM-FQ		56
- Other combinations		45
Other regimens (RZ, RE, EZ) without FQ or injectables		**205**
- H, 6R 2Z, SM		108
- H, 6RZ		39
- H, 9RE		37
- Others		21

Notes:

a) Group C or D3 drugs used were Ethionamide/prothionamide or Cycloserine/terizidone or p-amynosalicidic acid (PAS)

b) Group C or D3 drugs used were Clofazimine, Linezolid, p-amynosalicidic acid (PAS), Macrolides, Thioacetazone

Abbreviations: **E**: Ethambutol; **FQ**: fluoroquinolones; **(H)**= isoniazid used in some, but not all regimens. **R** : rifampin (when patients used rifabutin in place of rifampin is specified in the notes); **SM**: Streptomycin; **Z**= pyrazinamide

Table 1Sc: Dosages of drugs used at sites of studies included in the individual patient data meta-analysis on isoniazid-resistant TB.

Author	Drug								
	First line drugs				Fluoroquinolones				Injectable
	H	R	E	Z	Ofloxacin	Levofloxacin	Moxifloxacin	Ciprofloxacin	SM
Bang[1]	4-6 mg/kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	600 mg/day	not used	400 mg/day	500 mg twice a day	12-18 mg/kg/day
Brazilian NTB[2]	4-6 mg/kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	400mg/kg	According to weight[a]	400 mg/day	Note used	Accoding to weight[b]
Cattamanchi[3]	4-6 mg/kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	not used	750-1000 mg/day	400 mg/day	not used	not used
Chien[4]	4-6 mg/kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	not used	750-1000 mg/day	400 mg/day	not used	not used
Cox[5]	4-6 mg/kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	not used	not used	not used	not used	12-18 mg/kg/day
Gegia[6]	4-6 mg/kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	not used	750-1000 mg/day	400 mg/day	not used	not used
Huyen[7]	4-6 mg/kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	not used	not used	not used	not used	12-18 mg/kg/day
Jacobson[8]	4-6 mg/kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	not used	not used	not used	not used	12-18 mg/kg/day
Jones-Lopez[9]	4-6 mg/kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	not used	not used	not used	not used	12-18 mg/kg/day

Notes:

a) According to weight: 20 kg: 10/mg/kg/day ; 21-35 kg: 250 mg-500 mg/day; 35-50 kg:500-750 mg/day;>50 kg: 750 mg/day.

b) 20 kg: 20 mg/kg/day; 21-35 kg: 500 mg/day ; 36-50 kg: 750-1000 mg /day; >50 kg:1000 mg /day

Table 1Sc (continued): Dosages of drugs used at sites of studies included in the individual patient data meta-analysis on isoniazid-resistant TB.

Author	Drug								
	first line drugs				Fluoroquinolones				Injectable
	H	R	E	Z	Ofloxacin	Levofloxacin	Moxifloxacin	Ciprofloxacin	SM
Kim[10]	4-6 mg/kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	400mg bid	750-1000 mg/day	400 mg/day	not used	12-18 mg/kg/day
Lee[11]	4-6 mg/kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	not used	750-1000 mg/day	400 mg/day	not used	12-18 mg/kg/day
Munang[12]	4-6 mg/kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	not used	not used	400 mg/day	500 -750 mg bid	12-18 mg/kg/day
Netherlands NTB[13]	4-6 mg/kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	not used	not used	400 mg/day	not used	not used
NYC TB[14]	4-6 mg/kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	800 mg/day	500-1000 mg/day	400 mg/day	1000-1500 mg/day	12-18 mg/kg/day
Ohkado[15]	4-6 mg/kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	not used	not used	not used	not used	12-18 mg/kg/day
Park[16]	4-6 mg/kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	not used	750-1000 mg/day	400 mg/day	not used	12-18 mg/kg/day
Quy[17,18]	4-6 mg/kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	not used	not used	not used	not used	12-18 mg/kg/day
Reves[19]	not used	600 mg, daily for at least 2 weeks then mostly bi-weekly, some thrice weekly	daily for at least 2 weeks then biweekly EMB 40–50 mg/kg and 25–35 mg/kg thrice weekly	daily for at least 2 weeks then biweekly PZA 40–70 mg/kg and 30–40 mg/kg thrice weekly	not used	not used	not used	not used	not used
Romanowski[20]	4-6 mg/kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	not used	750-1000 mg/day	not used	not used	12-18 mg/kg/day
Skrahina[21]	4-6 mg/kg/day	8-12 mg/kg/day	max 1600 mg/kg/day	30-30 mg/kg/day	800 mg/day	750-1000 mg/day	400 mg/day	not used	not used

Table 1Sc (continued): Dosages of drugs used at sites of studies included in the individual patient data meta-analysis on isoniazid-resistant TB.

Author	Drug								
	First line drugs				Fluoroquinolones				Injectable
	H	R	E	Z	Ofloxacin	Levofloxacin	Moxifloxacin	Ciprofloxacin	SM
Swaminathan[22]	10 mg/Kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	not used	not used	not used	not used	not used
Viiklepp[23]	4-6 mg/kg/day	8-12 mg/kg/day	5-25 mg/kg/day	20-30 mg/kg/day	not used	750-1000 mg/day	400 mg/day	not used	12-18 mg/kg
Yoshiyama[24]	4-6 mg/kg/day	8-12 mg/kg/day	15-25 mg/kg/day	20-30 mg/kg/day	not used	not used	not used	not used	12-18 mg/kg

Table 1Sd: Summary of treatment outcome definitions used in studies included in individual patient data meta-analysis.

Study	Outcome definition				
	Cure	**Treatment Completed**	**Lost to follow-up**	**Treatment Failure**	**Treatment Relapse**
WHO (Reference Standard)	A patient whose sputum smear or culture was positive at the beginning of the treatment but who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.	A patient who completed treatment but who does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion	A patient whose treatment was interrupted for 2 consecutive months or more.	A patient whose sputum smear or culture is positive at 5 months or later during treatment. Also included in this definition are patients found to harbour a multidrug-resistant (MDR) strain at any point of time during the treatment, whether they are smear-negative or -positive.	Recurrence of bacteriologically confirmed tuberculosis after treatment success (cure or treatment complete).
Bang[1]	Same	Same	Same	Patient who is sputum smear positive or culture positive at five months or later during treatment	Same
Brazilian NTB[2]	Same	Same	Treatment interruption for 30 days or more	Same	Same
Cattamanchi[3]	Same	Same		Same	Same

Note: "Same" means : as WHO reference definition.

Table 1Sd (continued): Summary of treatment outcome definitions used in studies included in individual patient data meta-analysis.

Study	Outcome definition				
	Cure	**Treatment Completed**	**Lost to follow-up**	**Treatment Failure**	**Treatment Relapse**
Chien[4]	Same	Same	Same	Same	Same
Cox[5]	Same	Same	Same	Same	Same
Gegia[6]	Same	Same	Same	Same	Same
Huyen[7]	Same	Same	Same	Any positive sputum or culture at 5 months or later during treatment	Recurrent TB with initial and follow-up M. tuberculosis isolates had identical spoligotypes and VNTR patterns, or if the VNTR patterns differed by "1 locus, and as reinfection if otherwise"
Jacobson[8]	Same	Same	Same	Same	Not measured
Jones-Lopez[9]	Treatment completed and one negative culture on solid medium at the end of treatment	Completed 8 months of treatment and free of Tb symptoms at the first post-treatment follow-up visit		Patients culture positive at month 8 OR patients with no culture positive at month 5 and with no culture at month 8 and no confirmation that they were free of TB after the end of treatment	

Note: “Same” means same as WHO reference definition.

Table 1Sd (continued): Summary of treatment outcome definitions used in studies included in individual patient data meta-analysis.

Study	Outcome definition				
	Cure	**Treatment Completed**	**Lost to follow-up**	**Treatment Failure**	**Treatment Relapse**
Kim[10]	Same	Same	Same	Same	Same
Lee [11]	Same	Same	Same	Same	Same
Munang[12]	Combined with complete (see)	Patients were considered successfully treated if they completed a full course of prescribed treatment and had documented sputum culture conversion (for sputum culture-positive cases) or were discharged by their attending physician.	Same	Treatment failed if a case was smear- or culture- positive at month 5 or later during treatment.	Suspected OR bacteriologically confirmed tuberculosis after treatment success (cure or complete).
Netherlands NTB [13]	Negative sputum culture result after initial positive culture test.	Same	Same	Same	Not collected
NYC TB[14]	Same	Same	Lost to follow-up, adverse reaction that resulted in the discontinuation of treatment, or refusal of treatment	Positive culture after culture conversion	Treatment was restarted after treatment completion
Ohkado[15]	A sputum smear positive patient who has been completed treatment and is sputum smear negative in the last month of treatment and on at least one previous occasion.	Same	Same	A patient who is sputum smear-positive at five months or later during the treatment OR a sputum smear-negative patient who becomes smear-positive during the treatment.	Same

Note: “Same” means : as WHO reference definition.

Table 1Sd (continued): Summary of treatment outcome definitions used in studies included in individual patient data meta-analysis.

Study	Outcome definition				
	Cure	**Treatment Completed**	**Lost to follow-up**	**Treatment Failure**	**Treatment Relapse**
Park[16]	Same	Same	Same	Same	Same
Quy[17,18]	Same	Same	Same	Positive smear at 5 months of later during treatment	Same
Reves[19]	Same	Same	Same	Treatment failure was suspected for a positive TB culture following 16 calendar weeks of treatment, and relapse was suspected for a positive TB culture within 2 years of treatment completion.	Relapse was suspected for a positive TB culture within 2 years of treatment completion.
Romanowski[20]	Same	Same	Same	Same	Same
Skrahina[21]	Same	same	Same	Same	Same
Swaminathan[22]	All cultures negative in the last 2 months of treatment	Clinical resolution with regression of nodes or radiographic clearance	Same	Same	Same
Viiklepp[23]	Same	Same	Same	Same	Same
Yoshiyama[24]	Same	Same	Same	Same	Same

Note: "Same" means : as WHO reference definition

Table S1E: Assessment of Quality of the Included studies

Study	1. Sampling method	2. Outcome measures		3. Participation rate (%)	4. Lost to follow-up rate (%)	5.-8. Completeness of information (%)				Overall Study Quality
		Post-treatment Follow-up >=12mo (%)	Culture confirmed cure			5. Age	6. HIV	7. Cavity	8. AFB	
Bang[1]	census	100	Yes	100	9·0	100	21·6[a]	6·3	100	High
Brazilian NTP[2]	census	0	Yes	100	15·2	100	77·0[b]	98·4	82.7	High
Cattamanchi[3]	census	62	Yes	100	9·5	100	100	97.1	100	High
Chien[4]	census	21	Yes	100	7·0	99·7	92·1	100	100	High
Cox[5]	census	100	No	68	14·3	100	100	0	100	Moderate
Gegia[6]	census	0	No	100	18·6	100	0[a]	0	96·6	Moderate
Huyen[7]	census	100	Yes	97·5	1·5	99·5	0[a]	0	100	High
Jacobson[8]	census	0	Yes	100	33·8	100	83·8	0	96·0	High
Jones-Lopez[9]	census	100	Yes	100	5·9	0	100	0	100	High
Kim[10]	census	31	Yes	100	13·0	100	71·8[a]	100	100	High
Lee[11]	census	55	Yes	100	5·9	100	100	100	100	High
Munang[12]	census	7	Yes	100	10·1	100	100	100	79·8	High
Netherland NTP[13]	census	0	No	100	10·9	100	9·6[a]	0	52·2	Low
NYC[14]	census	0	Yes	100	6·2	100	74·6[b]	84·7	99·4	High
Ohkado[15]	census	0	No	83·3	18·9	100	0[a]	0	100	Moderate
Park[16]	census	100	Yes	100	0	100	100	100	100	High
Quy[17,18]	census	0	No	95·8	6·7	100	100	0	100	Moderate
Reves[19]	RCT	81	Yes	100	4·2	100	100	94·4	88·7	High
Romanowski[20]	census	43	Yes	100	8·0	99·5	99·5	96·5	100	High
Skrahina[21]	census	0	Yes	100	10·3	100	100	100	100	High
Swaminathan[22]	RCT	100	Yes	57·8	7·4	100	100	100	100	High
Viklepp[23]	census	0	Yes	100	7·8	100	97·4	98·3	100	High
Yoshiyama[24]	census	100	Yes	100	15·0	100	0[a]	0	100	High

Notes: a) HIV prevalence is reported to be less than 10% in TB cases in the Country of the study, therefore the reporting on HIV was considered of high quality.
b) HIV prevalence is reported to be less than 1% in the general population in the Country of the study (i.e., low HIV prevalence), therefore the reporting on HIV was considered of high quality.

Definitions used for quality assessment:

Critical criteria:

1. What is the sampling method in the study: census (all patients), random sampling, or convenience sampling? (Must be census or random)

2. Was end of treatment outcome "cure" confirmed with culture, or were at least 80% of patients with cure/complete outcome followed for at least 1 year for recurrence? (Must be yes to either).

Important criteria

1. Was the participation rate in the study >80%
2. Lost to follow-up rate - defined as : LFU + transferred out (if in DOT or surveillance program, not counted if in tertiary hospital) + unknown outcome. LFU rate must be <=10%.
3. Was age reported in at least 90% of the participants?
4. Was HIV status reported in at least 80% of the participants? (If HIV prevalence is known to be less than 10% in TB cases, or less than 1% in the general population in the country (i.e., low HIV prevalence), this item will be considered acceptable even if HIV status for individuals is not reported)
5. Was cavity reported in at least 80% of the participants?
6. Was AFB reported in at least 80% of the participants?

High quality: Both critical criteria and at least 4 of the 6 important criteria.
Moderate quality: Both critical criteria and 3 of the 6 important criteria OR 1 critical criteria and at least 4 of the 6 important criteria.
Low quality: all remaining.

Table S2a. Characteristics of 10 studies excluded from current IPD analyses. Note: studies were excluded, after the data was received, if no patients received any of the specific regimens of interest for the three research questions.

First author	BanuRekha 2012[25]	Bonnet 2011[26]	Cegielski[27]	Escalante 2001[28]	Garcia-Prats 2016[29]	Gillespie 2014[30]	Glynn 2015[31]	Merle 2014[32]	Swaminathan 2011[33]	Tabarsi 2009[34]	Total
Country	India	Georgia	US (Texas)	US (Texas)	South Africa	Multiple	Malawi	Multiple	India	Iran	--
Years	2004-06	2003-13	1984-2007	1990-97	2006-12	2013	1986-2015	2007	2006-08	2003-15	1984- 2015
Concentration used to define H resistance (μm/mL)	1·0	0·1	1·0	0·4	0·1	0·1	varied over time	0·2	1·0	0·2	--
Regimen [a]	Random.	Indiv.	Indiv.	Indiv.	Indiv.	Random.	Stand.	Random.	Random.	Indiv.	--
Duration (known vs planned)	Planned	Known	Known	Known	Known	Planned	Known	Planned	Planned	Known	--
Age in years (median, IQR)	32 (27; 39)	43 (32; 52)	46 (29; 60)	39 (25; 49)	4 (2;7)	30 (24; 45)	37 (30; 45)	26 (23; 36)	35 (32; 35)	47 (34; 60)	35 (25; 48)
Sex female, %	27%	18%	24%	22%	58%	34%	37%	27%	40%	32%	34%
HIV positive, % of tested[b]	0%	na	8%	9%	22%	9%	35%	8%	100%	11%	14%
Past TB treatment, %[b]	3%	42%	39%	24%	29%	0%	23%	na	0%	84%	34%
Cavity on chest-x ray, %[b]	na	44%	na	65%	23%	71%	na	45%	na	74%	58%
Resistance to SM,% [b]	na	79%	24%	37%	11%[b]	27%	23%	14%	0%	41%[c]	38%
Analyzable population, N	30	59	43	51	51	127	201	68	5	127	762

Notes:
a) Regimens were classified as "standardized" is standard regimen was given to all patients; "individualized" if regimens were tailored to individual patients' characteristics such as prior therapy, or drug susceptibility testing (DST) results; " randomized" if a standard regimens were given within a randomized clinical trial; **b)** percentage are on total available information. In some sites this information was available for less than 50% of the population
Abbreviations: **DST**: drug susceptibility test; **H** isoniazid; **Individ**. Individualized; **IQR** Interquartile range; **na**: information in not available for that database or if it is available in less than 10% of the population; **Random.** Randomized; **SM** streptomycin; **Stand**. Standardized.

Table S2b: Regimens used in the 10 excluded studies

Regimen	N
Total patients in the 10 studies	***762***
(H) REZ	**261**
- 6(H)R, 2E, 2Z	204
- unknown duration	57
REZ(H)-FQ	**105**
-4(H)R 2E, 2Z, FQ	46
-unknown duration	59
REZ(H)-SM	**30**
Other regimens	**366**
Included high dose isoniazid	35
Included Ethionamide/prothionamide or Cycloserine/Terizidone	66
Included Thioacetazone	63
Included Clofazimine	2
Other combinations of H, R, E, Z (other than HREZ)	11
Other combinations of H, R, E, Z, SM (other than HREZ-SM)	11
Used second line injectables	6
Used FQ and second line injectables	74
Used Other FQ-containing regimens	87
Used combinations of FQ and SM	11

Notes:
Abbreviations: **H**: Isoniazid, **E**: Ethambutol, **FQ**: fluoroquinolones; **SM**: Streptomycin; **R**: Rifampin; **Z**: pyrazinamide.

Table S3: Characteristics of the populations included in analyses of success and acquired rifampin resistance for 6(H)REZ versus >6(H)REZ[a]

Type of analysis	Analyses of Success (n=1350)		Analyses of Acquired Rifampin resistance (n=1160)	
Regimens compared	**6(H)REZ**	**>6 (H)REZ**	**6(H)REZ**	**>6 (H)REZ**
Total N[b]	262	1088[c]	168	992[c]
High Income Country, N(%)	260/262(99)*	397/1088 (36)	166/168 (99)*	338/992(34)
Age (median, IQR)	42 (29; 58)*	37 (27; 50)	43 (30; 61)*	36 (27; 50)
Sex, female, N /tot with info **(%)**	84/262 (32)	317/1088 (29)	53/168 (32)	286/992 (29)
HIV: positive, N/tot with info (%)	7/221 (3)*	23/295 (8)	5/142 (4)	20/257 (8)
on Antiretroviral therapy, N (% on HIV+)	1/7 (14)	1/23 (4)	0/5 (0)	1/20 (5)
Diabetes, N/tot with info (%)	16/113 (14)	19/99 (19)	5/66 (8)	14/86 (16)
Any Past TB treatment, N/tot with info (%)	44/260 (17)*	116/979 (12)	17/166 (10)	91/888 (11)
Sputum smear positive, N/tot with info (%)	127/252 (50)*	853/1071 (80)	81/166 (49)*	780/976 (80)
Cavity on chest X-ray, N/tot with info (%)	54/237 (23)*	115/366 (31)	27/164 (16)*	103/329 (31)
Poly resistance (resistance to E, Z or SM if used), N/tot with info, **%**	2/262(1)	3/1088(0)	2/168 (1)	3/992 (0)
Resistance to SM, N/total tested	63/209 (30)*	598/1053 (57)	51/165 (31)*	559/986 (57)
Resistance to E, N/total tested	1/261(0)	3/1086 (0)	1/167 (1)	3/990 (0)
Resistance to Z, N/total tested	1/224 (0.5)	0/325 (0)	1/138 (1)	0/273 (0)
On DOT, N/tot with info(%)	81/162 (50)*	760/842(90)	25/68 (37)*	707/747(95)
Duration in months, median (IQR): - Rifampin - Pyrazinamide	 6·1 (6·0; 6·5) 6·1 (6·0; 6·4)	 9·0 (9·0; 9·0) 9·0 (9·0; 9·0)	 6·1 (6·0; 6·5) 6·1 (6·0; 6·5)	 9·0 (9·0; 9·0) 9·0 (9·0; 9·0)

Notes: * p<0. ·05 for Chi Squared tests (or Fisher's exact test) for categorical variables, and from T Tests for continuous variables **;**

a) Treatment was administered daily for all but 1 study (n=45 subjects) included in this analysis

b) A total of 13 children under 14 years old were treated in population analyzed for success and 9 in analyzed for acquired rifampin resistance;

c) Two patients took rifabutin and rifampin.

Abbreviations: **DOT**: directly observed therapy; **IQR**: Inter Quartile Range; **E**: Ethambutol; **(H)**= Isoniazid used in some, but not all regimens **SM**: Streptomycin; **R**: Rifampin; **Z**: pyrazinamide.

Table S4: Characteristics of the population included in analyses of FQ added to ≥6(H)REZ.

Type of analysis	Analyses of Mortality[h] (n=2698)		Analyses of Success (n=1601)		Analyses of Acquired Rifampin resistance (n=1381)	
Regimens compared	**≥6(H)REZ FQ**	**≥6 (H)REZ**	**≥6(H)REZ FQ**	**≥6 (H)REZ**	**≥6(H)REZ FQ**	**≥6 (H)REZ**
Total N	524[a]	2174[b]	251[c]	1350[d]	221[c]	1160[d]
High Income Country, N(%)	513 (98)*	1449 (67)	241 (96)*	657 (49)	212 (96)*	504 (43)
Age (median, IQR)[e]	48 (34; 63)*	37 (27; 52)	42 (32; 56)*	38 (27; 52)	43 (33; 58)*	37 (27; 51)
Sex, female, N /tot with info **(%)**	179 (34%)	711 (33%)	82 (33)	401 (30)	72 (33%)	339 (29%)
HIV: positive, N/tot with info (%)	62/428 (14)	106/884 (12)	17/203 (8)	30/516 (6)	14/191 (7%)	25/399 (6%)
on ART, N (% on HIV+)	6/62 (10)	3/106 (3)	0/17 (0)	2/30 (7)	0/14 (0%)	1/25 (4%)
Diabetes, N/tot with info (%)	27/185 (15)	67/385 (17)	8/82 (10)	35/212 (17)	8/80 (10%)	19/152 (13%)
Any Past TB treatment, N/tot with info (%)	57/508 (11)	237/1978 (12)	27/247 (11)	160/1239 (13)	21/217 (10%)	108/1054 (10%)
Sputum smear positive, N/tot with info (%)	286/482 (59)	1412/1997 (71)	154/245 (63)*	980/1323 (74)*	134/215 (62)*	861/1141 (75)
Cavity on chest X-ray, N/tot with info (%)	113/471 (24)	260/959(27)	56/220 (25)	169/603 (28)	54/215 (25%)	130/493 (26%)
Poly resistance (resistance to E, Z or SM if used), N/tot with info, **%**	38/524 (7)	26/2174 (1)	7/251 (3)*	5/1350 (0.4)*	5/221(2%)*	5/1160 (0%)
Resistance to SM, N/total tested (%)	166/482 (34)	754/1607 (47)	82/236 (35%)*	661/1262 (53%)	70/213 (33%)*	610/1151 (53%)
Resistance to FQ, N/total tested (%)	4/313 (1)	7/497 (1)	3/163 (2%)	3/346 (1%)	1/136 (1%)	3/306 (1%)
on DOT, N/total tested,%	84/246 (34)*	956/1689(57)	31/114 (27)*	841/1004(84)	28/85 (33)*	732/815(90)
Duration in months, median (IQR): - Rifampin - Fluoroquinolones - Pyrazinamide	 9·0 (6·2; 11·0) 6·6 (3·9; 9·0)[f] 7·4 (4·1; 9·5)	 9·0 (6·0; 9·0) -- 8·0 (2·1; 9·0)	 9·0 (7·2; 11·2) 6·1 (3·5; 8·4)[g] 8·9 (6·8; 10·7)	 9·0(8·3; 9·0) -- 9·0 (8·1; 9·0)	 9·0 (7·7; 11·1) 5·7 (3·3; 8·1) 9·0 (7·0; 10·6)	 9·0 (9·0; 9·0) -- 9·0 (8·9; 9·0)

Notes: * p<0·05 for Chi Squared tests (or Fisher's exact test) for categorical variables, and from T Tests for continuous variables**;**

a) 19 patients took rifabutin and 26 patients took both rifampin and rifabutin **b**) 13 patients took rifabutin and 17 patients took both rifampin and rifabutin

c) Four patients took both rifampin and rifabutin **d**) Two patients took both rifampin and rifabutin

e) A total of 46 children under 14 years old were included in population analyzed for mortality; 16 in analyzed for success and 11 in analyzed for acquired rifampin resistance;

f) Duration may have been truncated by mortality.

g) Duration of FQ: 104 took FQ for 1-5 months, 137 took FQ for ≥6m; 10 took FQ ≥1m (unknown duration, but at least one month).

Abbreviations: **DOT**: directly observed therapy; **IQR**: Inter Quartile Range; **E**: Ethambutol; **FQ**: fluoroquinolones; **(H)**= Isoniazid used in some, but not all regimens **; SM**: Streptomycin; **R**: Rifampin; **Z**: pyrazinamide.

Table S5: Characteristics of the population included in analyses of "FQ with short Z" question (i.e. Six months or more of RE plus 1-3 months of Z plus fluoroquinolone compared to 6 months or more of REZ - with or without isoniazid)

Type of analysis	**Analyses of Success (n=1468)**		**Analyses of Acquired rifampin resistance (n=1273)**	
Regimens compared	**≥6(H)RE 1-3Z FQ**	**≥6 (H)REZ**	**≥(H)6RE 1-3Z FQ**	**≥6 (H)REZ**
Total N	118[a]	1350[b]	113[a]	1160[b]
Age[c] (median, IQR)	56 (38; 69)*	38 (27; 52)	56 (38; 68)*	37 (27; 51)
High income countries (N,%)	118 (100)*	657 (49)	113 (100)*	504 (43)
Sex, female, N /tot with info **(%)**	39/118 (33)	401/1350 (30)	36 (32%)	339 (29%)
HIV: positive, N/tot with info (%)	7/97 (7)	30/516 (6)	7/92 (8%)	26/399 (6%)
On antiretroviral treatment, N (% on HIV+)	3/7 (43)*	2/30 (7)	3/7 (43%)*	1/25 (4%)
Diabetes, N/tot with info (%)	10/51 (20)	35/212 (17)	8/48 (17%)	19/152 (13%)
Any Past TB treatment, N/tot with info (%)	12/109 (11)	160/1239 (13)	10/104 (10%)	108/1054 (10%)
Sputum smear positive, N/tot with info (%)	47/96 (49)*	980/1323 (74)	47/91 (52%)*	861/1141 (75%)
Cavity on chest X-ray, N/tot with info (%)	28/115 (24)	169/603 (28)	27/110 (25%)	130/493 (26%)
Poly resistance (resistance to E, Z or SM if used), N/tot with info, **%**	15/118 (13)*	5/1350 (0.4)	15/113 (13%)*	5/1160 (0%)
Resistance to SM, N/total tested	37/113 (33%)*	661/1262 (52%)	37/110 (34%)*	610/1151 (53%)
Resistance to FQ, N/total tested	1/66(2%)	3/346 (1%)	1/64 (2%)	3/306 (1%)
on DOT, N/total tested,%	23/60 (38)*	841/1004(84)	21/55 (38%)*	732/815 (90%)
Duration in months, median (IQR):				
- Rifampin	9·6 (8·6; 11·9)	9·0 (8·3; 9·0)	9·5 (8·6; 11·8)	9·0 (9·0; 9·0)
- Fluoroquinolones	7·0 (5·0; 9·5)[d]	--	7·0 (5·0; 9·5)	--
- Pyrazinamide	2·5 (1·9; 3·8)	9·0 (8·1; 9·0)	2·5 (1·9; 3·8)	9·0 (8·9; 9·0)

Notes:

a) Three patients took both rifampin and rifabutin

b) Two patients took both rifampin and rifabutin

c) A total of 13 children under 14 years old were included in population analyzed for success; and 9 in population analyzed for acquired rifampin resistance.

d) Duration of FQ: 31 had 1-5m of FQ; 71 ≥6m and 16 ≥1m (unknown duration, but at least one month).

Abbreviations: **DOT**: directly observed therapy; **IQR**: Inter Quartile Range; **E** : ethambutol; **FQ**: fluoroquinolones; **(H)**= isoniazid used in some, but not all regimen; **SM**: Streptomycin; **R**:rifampin **Z**: pyrazinamide

Table S6. Characteristics of the populations included in Streptomycin-related analyses.

Type of analysis	Analysis of Mortality (n=3,026)		Analysis of Success (n=1,675)		Analysis of Acquired rifampin resistance (n=1,218)	
Regimens compared	**(H)REZ SM**	**(H)REZ**	**≥6(H)R(E) 1-3Z 1-3SM**	**≥6 (H)REZ**	**≥6(H)R(E) 1-3Z 1-3SM**	**≥6 (H)REZ**
Total N	763	2263[a]	325	1350[b]	58	1160[b]
Age[c] (median, IQR)	42 (32; 52)*	37 (27; 51)	42 (31; 51)	38 (27; 52)	35 (25; 40)*	37 (27; 51)
High Income Countries, N(%)	52/763 (7)	1449/2263 (64)	13 (4)*	657 (49)	2 (3)*	504 (43)
Sex, female, N /tot with info **(%)**	197/731 (27)*	739 (33)	84/300 (28%)	401/1350 (30)	10/32 (31%)	339 (29%)
HIV: positive, N/tot with info (%)	33/495 (7)*	131/943 (14)	17/238 (7%)	30/516 (6)	12/42 (29%)*	25/399 (6%)
On Antiretroviral treatment, N (% on HIV+)	3/33 (9)	3/131(2)	0/17 (0%)	2/30 (7)	0/12 (0%)	1/25 (4%)
Diabetes, N/tot with info (%)	18/166 (11)	69/413 (17)	13/112 (12%)	35/212 (17)	0/4(0%)	19/152 (13%)
Any Past TB treatment, N/tot with info (%)	235/627 (37)*	238/2033(12)	204/214 (95%)*	160/1239 (13)	55/56 (98%)*	108/1054 (10%)
Sputum smear positive, N/tot with info (%)	705/744 (95)*	1486/2077 (72)	289/312 (93%)*	980/1323 (74)*	56/58 (97%)*	861/1141 (75%)
Cavity disease at chest X-ray, N/tot with info (%)	107/172 (62)*	272/994(27)	76/113 (67%)*	169/603 (28)	2/5 (40%)	130/493 (26%)
Poly resistance (resistance to E, Z or SM if used), N/tot with info, **%**	378/700 (54)*	36/2263(2)	131/281 (47)*	5/1350 (0.4)*	21/32 (66%)*	5/1160 (0%)
Resistance to SM, N/total tested	375/700 (54)	799/1694 (47)	129/280 (46%)	661/1262 (53%)	20/32 (63%)	610/1151 (53%)
Resistance to E, N/total tested	18/753 (2)*	23/2257 (1)	8/321 (2)*	4/1347 (0)	2/58 (3)*	4/1157 (0)
on DOT, N/tot with info, %	286/346(83)	873/1037(84)	267/325(82)	841/1004(84)	58 (100%)*	732/815 (90%)
Duration in months, median (IQR): - Rifampin - Pyrazinamide	 6·0 (2·0; 8·0) 2·0 (2·0; 3·0)	 9·0 (6·0; 9·0) 7·4 (2·0; 9·0)	 8·0 (6·0; 8·0) 3·0 (2·0; 3·0)	 9·0 (8·3; 9·0) 9·0 (8·1; 9·0)	 8·0 (8·0; 8·0) 3·0 (3·0; 3·0)	 9·0. (9·0; 9·0) 9·0 (8·9; 9·0)

Notes: * p<0·05 for Chi-square test for differences of this characteristic in the two regimens;

a) Thirteen patients took rifabutin, 17 took both rifabutin and rifampin **b**) Two patients took both rifampin and rifabutin

c) A total of 37 children under 14 years old were included in population analyzed for mortality; 13 in analyzed for success and 9 in analyzed for acquired rifampin resistance.

Abbreviations: **DOT**: directly observed therapy; **IQR**: Inter Quartile Range; **E** : Ethambutol; **FQ**: fluoroquinolones; **SM**: Streptomycin; **R**: Rifampin; **Z**: pyrazinamide.

Table S7. Results for analyses restricted to high income countries only – success, mortality and acquired rifampin resistance. Note: this analysis is not possible for SM-REZ regimens, because very few patients received this regimen in high-income countries

Outcome and comparison	Regimens:	N datasets included	N of events/N on treatment	N pairs used[a]	from Propensity Score matched Analysis[b]	
					aOR (95% CI)	Risk Difference (per 1,000 treated with 95%CI)
6 (H)REZ vs >6(H)REZ						
Success	**6(H)REZ**	12	252/260	260	0·7 (0·3; 2·2)	No difference (from 30 fewer to 30 more)
	>6(H)REZ		387/397		1·0 (reference)	reference
Acquired rifampin resistance	**6(H)REZ**	7	1/166	166	not estimable	No difference (from 120 fewer to 130 more)
	>6(H)REZ		1/338		1·0 (reference)	reference
>=6(H)REZ+FQ vs >=6(H)REZ						
Mortality	**REZ FQ**	12	25/531		0·7 (0·4; 1·1)	No difference (from 30 fewer to 30 more)
	REZ		67/1449	513	1·0 (reference)	reference
Success	**>=6(H)REZ FQ**	12	237/241		2·3 (0·7; 7·6)	20 more (from 10 fewer to 50 more)
	>=6(H)REZ		639/657	238	1 .0 (reference)	reference
Acquired rifampin resistance	**>=6(H)REZ FQ**	7	0/212	210	not estimable	--
	>=6(H)REZ		2/504		1·0 (reference)	reference
>=6(H)RE 1-3Z FQ vs >=6(H)REZ						
Success	**>=6(h)RE 1-3Z FQ**	12	117/118		4·1 (0·4; 38·6)	30 more (from 30 fewer to 90 more)
	>=6(H)REZ		639/657	110	1.0 (reference)	reference
Acquired rifampin resistance	**>=6(h)RE 1-3Z FQ**	7	0/113	105	not estimable	--
	>=6(H)REZ		2/504		1.0 (reference)	reference

Notes:
a) Number of pairs used in propensity score matched analysis.
b) Estimates based on pairs matched for age, sex, HIV, past TB treatment, sputum AFB smear (positive vs negative) and resistance to other drugs besides isoniazid, if used.
Abbreviations: **aOR**: adjusted odds ratio; **CI** Confidence interval **E**: ethambutol; **FQ**: fluoroquinolones; **(H)**= isoniazid used in some, but not all regimens. **SM**: streptomycin; **R**: rifampin; **Z**: pyrazinamide.

Table S8. Results for analyses of Streptomycin restricted to <u>low and middle-income countries only</u> - success, mortality and acquired rifampin resistance.
Note**:** This analysis is possible only for SM-REZ based regimens, as other regimens are taken mostly in high-income countries

Outcome and comparison	Regimens:	N datasets included	N of events/N on treatment	N pairs used[a]	from Propensity Score matched Analysis[b]	
					aOR (95% CI)	Risk Difference (per 1,000 treated with 95%CI)
>=6(H) RE 1-3 Z 2SM vs >=6(H)REZ						
Mortality	**(H)REZ SM**	11	34/711	703	**1·8 (1·0; 3·2)**	**40 more (from 20 more to 60 more)**
	(H) REZ		36/814		1·0 (reference)	reference
Success	**>-6(H) RE 1-3 Z 2SM**	11	258/312	161	0·7 (0·4; 1·3)	50 fewer (from 120 fewer to 30 more)
	>=6(H)REZ		614/693		1·0 (reference)	reference
Acquired rifampin resistance	**>-6(H) RE 1-3 Z 2SM**	3	6/56	23	not estimable	--
	>=6(H)REZ		42/656		1·0 (reference)	reference

Notes:
a) Number of pairs used in propensity score matched analysis.
b) Estimates based on pairs matched for age, sex, HIV, past TB treatment, sputum AFB smear (positive vs negative) and resistance to other drugs besides isoniazid, if used.
Abbreviations: a**OR**: adjusted odds ratio; **CI** Confidence interval **E**: ethambutol; **FQ**: fluoroquinolones; **(H)**= isoniazid used in some, but not all regimens. **SM**: streptomycin; **R**: rifampin; **Z**: pyrazinamide.

TABLE S9: Comparison of Outcomes in sub-group with cavitation status known, and with cavitation - vs all patients. (Notes: Analysis of patients who did not receive INH not shown because too few patients in sub-sample and the models did not converge; Analysis of acquired drug resistance not shown, because there was zero acquired resistance in one, or both groups in each analysis).

Outcome and comparison	Regimens:	N datasets included	N of events/N on treatment	N pairs used[a]	from Propensity Score matched Analysis[b]	
					aOR (95% CI)	Risk Difference (per 1,000 treated with 95%CI)
Duration of REZ - all patients (with or without isoniazid)						
Success (all patients)	**6(H)REZ**	15	254/262	262	2·4 (1·0; 5·5)	40 more per 1,000 (from 0 difference to 80 more)
	>6(H)REZ		999/1088		1·0 (reference)	(reference)
Success (in subsample with CXR info - ALL)	**6(H)REZ**	11	230/237	235	0·4 (0·1; 1·7) [c]	20 fewer per 1,000 (from 60 fewer to 10 more)
	>6(H)REZ		356/366		1·0 (reference)	(reference)
Success (in subsample with cavity)	**6(H)REZ**	11	49/54	49	0·2 (0, 2·3)	70 fewer per 1,000 (from 220 fewer to 80 more)
	>6(H)REZ		111/115		1·0 (reference)	(reference)
Use of Fluoroquinolones - all patients (with or without isoniazid)						
Mortality (all durations)	**(H)REZ FQ**	15	25/524	522	0·7 (0·4; 1·1)	20 fewer per 1,000 (from 50 fewer to 0 difference)
	(H)REZ		97/2174		1·0 (reference)	(reference)
Mortality (all durations, in subsample with CXR info ALL)	**(H)REZ FQ**	12	24/471	470	**0·6 (0·4; 1·0)** [c]	0 difference per 1,000 (from 30 fewer to 30 more)
	(H)REZ		51/959		1·0 (reference)	(reference)
Mortality (all durations, in subsample with cavity)	**(H)REZ FQ**	12	0/113		- - - [D]	- - - [D]
	(H)REZ		10/260	108	1·0 (reference)	(reference)
Success	**≥6(H)REZ FQ**	15	245/251	248	**2·8 (1·1 to 7·3)**	**50 more per 1,000 (from 0 difference to 90 more)**
	≥6(H)REZ		1253/1350		1·0 (reference)	(reference)
Success (in subsample with CXR info)	**≥6(H)REZ FQ**	11	216/220	220	2·0 (0·6 to 6·9) [c]	20 more per 1,000 (from 10 fewer to 50 more)
	≥6(H)REZ		586/603		1·0 (reference)	(reference)
Success (in subsample with cavity)	**≥6(H)REZ FQ**	11	56/56		- - - [D]	- - - [D]
	≥6(H)REZ		160/169	55	1·0 (reference)	(reference)

Notes at the end of the table (next page).

Table S9 continuation

Outcome and comparison	Regimens:	N datasets included	N of events/N on treatment	N pairs used[a]	from Propensity Score matched Analysis[b]	
					aOR (95% CI)	Risk Difference (per 1,000 treated with 95%CI)
Use of Fluoroquinolone with 1-3 months PZA - all patients (with or without isoniazid)						
Success (all FQ)	**≥(H)6RE 1-3Z FQ**	15	117/118	108	5·2 (0·6 to 46·7)	40 more per 1,000 (from 20 fewer to 90 more)
	≥6(H)REZ		1253/1350		1·0 (reference)	(reference)
Success (all FQ) in subsample with CXR info	**≥(H)6RE 1-3Z FQ**	11	114/115	108	4·1 (0·4 to 38·7)[c]	30 more per 1,000 (from 40 fewer to 10 more)
	≥6(H)REZ		586/603		1·0 (reference)	(reference)
Success (all FQ) in subsample with cavity	**≥(H)6RE 1-3Z FQ**	11	28/28		- - -[D]	- - -[D]
	≥6(H)REZ		160/169	25	1·0 (reference)	(reference)
Use of Streptomycin - all patients (with or without isoniazid)						
Mortality (all durations)	6(H)REZ + SM	23	40/763	756	0·9 (0·6 to 1·3)	10 fewer per 1,000 (from 30 fewer to 20 more)
	6(H)REZ		103/2263		1·0 (reference)	(reference)
Mortality (in subsample with CXR info)	6(H)REZ + SM	13	11/172	172	1·0 (0·4 to 2·4)[c]	0 difference per 1,000 (from 50 fewer to 60 more)
	6(H)REZ		54/994		1·0 (reference)	(reference)
Mortality (in subsample with cavity)	6(H)REZ + SM	13	5/107		1·3 (0·3, 6·3)	10 more per 1,000 (from 40 fewer to 60 more)
	6(H)REZ		12/272	106	1·0 (reference)	(reference)
Success	≥6(H)RE 1-3Z 2SM	23	271/325	296	**0·4 (0·2 to 0·7)**	120 fewer per 1,000 (from 190 fewer to 60 fewer)
	≥6(H)REZ		1253/1350		1·0 (reference)	(reference)
Success (in subsample with CXR info)	≥6(H)RE 1-3Z 2SM	13	94/113	113	**0·1 (0·0 to 0·5)[c]**	140 fewer per 1,000 (from 220 fewer to 70 fewer)
	≥6(H)REZ		586/603		1·0 (reference)	(reference)
Success (in subsample with cavity)	≥6(H)RE 1-3Z 2SM	13	63/76	76	**0·3 (0·1 to 0·9)**	120 fewer per 1,000 (from 230 fewer to 10 fewer)
	≥6(H)REZ		160/169		1·0 (reference)	(reference)

Notes:

a) Number of pairs used in propensity score matched analysis.

b) Estimates based on pairs matched for age, sex, HIV status, past TB treatment, sputum AFB smear (positive vs negative) and resistance to other drugs besides isoniazid, if used. Percentage of patents missing information for these variables: past TB treatment: 8%; AFB smear: 2%; HIV 8%, polyresistance, age and sex: 0%. HIV status was missing, but assumed to be negative in 3 studies (n =720 patients) in settings where the prevalence of HIV co-infection rate in patients with active TB was <5% based on WHO surveillance data.

c) Estimates in subsample with CXR info are based on pairs matched also for cavity, in addition to other covariates used (i.e. age, sex, HIV status, past TB treatment, sputum AFB smear (positive vs negative) and resistance to other drugs besides isoniazid, if used.

d) Models did not converge, and/or zero outcomes for one group in this analysis

Abbreviations: **aOR**: adjusted odds ratio; **CI** Confidence interval; **CXR**: Chest-x ray; **E**: ethambutol; **(H)**= isoniazid used in some, but not all regimens **SM**: streptomycin; **R**: rifampin; **Z**: pyrazinamide; **FQ:** fluoroquinolone.

TABLE S10. Duration of use of fluoroquinolones and treatment success, or acquired rifampin resistance.

Outcome and comparison	Regimens: FQ Comparator	N datasets included	N of events/N on treatment	N pairs used[c]	from Propensity Score matched Analysis[d]	
					aOR (95% CI)	Risk Difference (per 1,000 treated with 95%CI)
Analyses in all patients (with or without isoniazid)						
Success (All duration of FQ, REZ for ≥6months)	**≥6(H)REZ FQ**	15	245/251	248	**2·8 (1·1 to 7·3)**	**50 more per 1,000 (from 0 difference to 90 more)**
	≥6(H)REZ		1253/1350		1·0 (reference)	(reference)
Success: in subsample FQ 1-5months	**≥6(H)REZ 1-5FQ**	15	106/108	108	4·2 (0·9 to 20·9)	70 more per 1,000 (from 10 fewer to 150 more)
	≥6(H)REZ		1253/1350		1·0 (reference)	(reference)
Success: in subsample FQ ≥6months	**≥6(H)REZ ≥6FQ**	15	129/133	131	2·1 (0·6 to 7·1)	30 more per 1,000 (from 20 fewer to 90 more)
	≥6(H)REZ		1253/1350		1·0 (reference)	(reference)
Acquired rifampin resistance	**≥6(H)REZ FQ**	10	1/221[b]	220	0·1 (0·0 to 1·2)	30 fewer per 1,000 (from 60 fewer to 0 difference)
	≥6(H)REZ		44/1160[b]		1·0 (reference)	(reference)
Acquired rifampin resistance: in subsample FQ 1-5months	**≥6(H)REZ 1-5FQ**	15	0/ 106	--	not estimable	not estimable
	≥6(H)REZ		44/1160		1·0 (reference)	(reference)
Acquired rifampin resistance: in subsample FQ ≥6months	**≥6(H)REZ ≥6FQ**	15	1/107	107	0·2 (0·0 to 2·3)	30 fewer per 1,000 (from 10 fewer to 30 more)
	≥6(H)REZ		1253/1350		1·0 (reference)	(reference)

Notes:
a) Of the 165 treated, 67 received isoniazid for one month or more and 98 did not receive any Isoniazid;
b) Number treated is less than in success analysis because patients with fail/relapse but no acquired drug resistance or with non-rifampin acquired resistances were excluded from this analysis.
c) Number of pairs used in propensity score matched analysis.
d) Estimates based on pairs matched for age, sex, HIV status, past TB treatment, sputum AFB smear(positive vs negative) and resistance to other drugs besides ISONIAZID, if used. Percentage of patents missing information for these variables: past TB treatment: 8%; AFB smear: 8%; HIV 8%, polyresistance, age and sex: 0%. HIV was missing, but assumed to be negative in 3 studies (n=1164 patients) in settings where the prevalence of HIV coinfection rate in patients with active TB was <5%, based on WHO surveillance data.
Abbreviations: **aOR**: adjusted odds ratio; **CI** Confidence interval **E**: ethambutol; **(H)**= isoniazid used in some, but not all regimens; **SM**: streptomycin; **R**: rifampin; **Z**: pyrazinamide; **FQ:** fluoroquinolone.

References for Appendix tables

1 Bang D, Andersen PH, Andersen ÅB, Thomsen VØ. Isoniazid-resistant tuberculosis in Denmark: mutations, transmission and treatment outcome. *Journal of Infection* 2010; **60**: 452-7.

2 Trajman A, Lisboa Bastos M, Dockhorn Costa F, Barbosa Codenotti S, Pelissari D, Menzies D. Factors associated with treatment outcomes in Brazilian isoniazid-monoresistant tuberculosis cohort. 47th World Conference on Lung Health of the International Union Againt Tuberculosis and Lung Diseases (The Union). Liverpool, UK.; 2016.

3 Cattamanchi A, Dantes RB, Metcalfe JZ, et al. Clinical characteristics and treatment outcomes of patients with isoniazid-monoresistant tuberculosis. *Clinical Infectious Diseases* 2009; **48**: 179-85.

4 Chien JY, Chen YT, Wu SG, Lee JJ, Wang JY, Yu CJ. Treatment outcome of patients with isoniazid mono-resistant tuberculosis. *Clin Microbiol Infect* 2015; **21**: 59-68.

5 Cox H, Kebede Y, Allamuratova S, et al. Tuberculosis recurrence and mortality after successful treatment: impact of drug resistance. *PLOS Med* 2006; **3**: e384.

6 Gegia M, Cohen T, Kalandadze I, Vashakidze L, Furin J. Outcomes among tuberculosis patients with isoniazid resistance in Georgia, 2007–2009. *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease* 2012; **16**: 812.

7 Huyen MN, Cobelens FG, Buu TN, et al. Epidemiology of isoniazid resistance mutations and their effect on tuberculosis treatment outcomes. *Antimicrob Agents Chemother* 2013; **57**: 3620-7.

8 Jacobson KR, Theron D, Victor TC, Streicher EM, Warren RM, Murray MB. Treatment outcomes of isoniazid-resistant tuberculosis patients, Western Cape Province, South Africa. *Clinical Infectious Diseases* 2011; **53**: 369-72.

9 Jones-Lopez EC, Ayakaka I, Levin J, et al. Effectiveness of the standard WHO recommended retreatment regimen (category II) for tuberculosis in Kampala, Uganda: a prospective cohort study. *PLOS Med* 2011; **8**: e1000427.

10 Kim YH, Suh GY, Chung MP, et al. Treatment of isoniazid-resistant pulmonary tuberculosis. *BMC Infectious Diseases* 2008; **8**: 6.

11 Lee H, Jeong BH, Park HY, et al. Treatment Outcomes with Fluoroquinolone-Containing Regimens for Isoniazid-Resistant Pulmonary Tuberculosis. *Antimicrob Agents Chemother* 2015; **60**: 471-7.

12 Munang ML, Kariuki M, Dedicoat M. Isoniazid-resistant tuberculosis in Birmingham, United Kingdom, 1999-2010. *QJM* 2015; **108**: 19-25.

13 The Netherlands National TB Surveillance. Unpublished data.

14 New York Department of Health and Mental Hygiene. New York City TB Surveillance - Unpublished data.

15 Ohkado A, Aguiman L, Adlawan S, et al. Tuberculosis drug resistance and treatment outcomes under DOTS settings in large cities in the Philippines. *The International Journal of Tuberculosis and Lung Disease* 2006; **10**: 283-9.

16 Park JS, Lee JY, Lee YJ, et al. Serum Levels of Antituberculosis Drugs and Their Effect on Tuberculosis Treatment Outcome. *Antimicrob Agents Chemother* 2015; **60**: 92-8.

17 Quy H, Cobelens F, Lan N, Buu T, Lambregts C, Borgdorff M. Treatment outcomes by drug resistance and HIV status among tuberculosis patients in Ho Chi Minh City, Vietnam. *The International Journal of Tuberculosis and Lung Disease* 2006; **10**: 45-51.

18 Quy H, Lan N, Borgdorff M, et al. Drug resistance among failure and relapse cases of tuberculosis: is the standard re-treatment regimen adequate? *The International Journal of Tuberculosis and Lung Disease* 2003; **7**: 631-6.

19 Reves R, Heilig C, Tapy J, et al. Intermittent tuberculosis treatment for patients with isoniazid intolerance or drug resistance. *The International Journal of Tuberculosis and Lung Disease* 2014; **18**: 571-80.

20 Romanowski K, Chiang LY, Roth DZ, et al. Treatment outcomes for isoniazid-resistant tuberculosis under program conditions in British Columbia, Canada. *BMC Infect Dis* 2017; **17**: 604.

21 Skrahina A. Unpublished data (Belarus).

22 Swaminathan S, Narendran G, Venkatesan P, et al. Efficacy of a 6-month versus 9-month intermittent treatment regimen in HIV-infected patients with tuberculosis: a randomized clinical trial. *Am J Respir Crit Care Med* 2010; **181**: 743-51.

23 Viiklepp P. Unpublished data (Estonia).

24 Yoshiyama T, Shrestha B, Maharjan B. Risk of relapse and failure after retreatment with the Category II regimen in Nepal. *The International Journal of Tuberculosis and Lung Disease* 2010; **14**: 1418-23.

25 Banu Rekha VV, Rajaram K, Kripasankar AS, et al. Efficacy of the 6-month thrice-weekly regimen in the treatment of new sputum smear-positive pulmonary tuberculosis under clinical trial conditions. *Natl Med J India* 2012; **25**: 196-200.

26 Bonnet MP, Manuela; Meacci, Francesca; Orrù, Germano; Yesilkaya, Hasan; Jarosz, Thierry; Andrew, Peter W; Barer, Mike; Checchi, Francesco; Rinder, Heinz. Treatment of tuberculosis in a region with high drug resistance: outcomes, drug resistance amplification and re-infection. *Plos ONE* 2011; **6**: e23081-e.

27 Cegielski P, Griffith D (Personal communication). Unpublished data (Texas, USA).

28 Escalante PG, Edward A; Griffith, David E; Musser, James M; Awe, Robert J. Treatment of isoniazid-resistant tuberculosis in southeastern Texas. *CHEST Journal* 2001; **119**: 1730-6.

29 Garcia-Prats AJ, du Plessis L, Draper HR, et al. Outcome of culture-confirmed isoniazid-resistant rifampicin-susceptible tuberculosis in children. *Int J Tuberc Lung Dis* 2016; **20**: 1469-76.

30 Gillespie SH, Crook A, McHugh T, et al. Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis. *N Eng J Med* 2014; **371**: 1577-87.

31 Guerra-Assuncao JA, Houben RM, Crampin AC, et al. Recurrence due to relapse or reinfection with Mycobacterium tuberculosis: a whole-genome sequencing approach in a large, population-based cohort with a high HIV infection prevalence and active follow-up. *J Infect Dis* 2015; **211**: 1154-63.

32 Merle C, Fielding K, Sow OB, et al. A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis. *N Engl J Med* 2014; **371**: 1588-98.

33 Swaminathan S, Padmapriyadarsini C, Venkatesan P, et al. Efficacy and safety of once-daily nevirapine- or efavirenz-based antiretroviral therapy in HIV-associated tuberculosis: a randomized clinical trial. *Clin Infect Dis* 2011; **53**: 716-24.

34 Tabarsi P, Baghaei P, Hemmati N, et al. Comparison of the effectiveness of 2 treatment regimens in patients with isoniazid-resistant tuberculosis. 2009.