

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 ($\mu\text{m/mL}$) | 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 ($\mu\text{m}/\text{mL}$) | 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 | Skrachina 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 ($\mu\text{m}/\text{mL}$) | 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 doses 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-aminosalicylic acid (PAS)

b) Group C or D3 drugs used were Clofazimine, Linezolid, p-aminosalicylic 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 |
| Bang¹ | 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 NTB² | 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 | According to weight ^b |
| Cattamanchi³ | 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 |
| Chien⁴ | 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 |
| Cox⁵ | 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 |
| Gegia⁶ | 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 |
| Huyen⁷ | 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 |
| Jacobson⁸ | 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-Lopez⁹ | 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). |
| Bang¹ | Same | Same | Same | Patient who is sputum smear positive or culture positive at five months or later during treatment | Same |
| Brazilian NTB² | Same | Same | Treatment interruption for 30 days or more | Same | Same |
| Cattamanchi³ | 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 |
| Chien⁴ | Same | Same | Same | Same | Same |
| Cox⁵ | Same | Same | Same | Same | Same |
| Gegia⁶ | Same | Same | Same | Same | Same |
| Huyen⁷ | 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" |
| Jacobson⁸ | Same | Same | Same | Same | Not measured |
| Jones-Lopez⁹ | 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 |
| Kim¹⁰ | Same | Same | Same | Same | Same |
| Lee¹¹ | Same | Same | Same | Same | Same |
| Munang¹² | 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 NTB¹³ | Negative sputum culture result after initial positive culture test. | Same | Same | Same | Not collected |
| NYC TB¹⁴ | 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 |
| Ohkado¹⁵ | 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)

IPD of INHR-TB - Supplemental Tables

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 ($\mu\text{m/mL}$) | 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” 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 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 |
|--|------------|
| <i>Total patients in the 10 studies</i> | 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) | |
|---|------------------------------|-------------------|---|------------------|
| | 6(H)REZ | >6 (H)REZ | 6(H)REZ | >6 (H)REZ |
| Regimens compared | | | | |
| 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 | 6.1 (6.0; 6.5) | 9.0 (9.0; 9.0) | 6.1 (6.0; 6.5) | 9.0 (9.0; 9.0) |
| - Pyrazinamide | 6.1 (6.0; 6.4) | 9.0 (9.0; 9.0) | 6.1 (6.0; 6.5) | 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 ^b (n=2698) | | Analyses of Success (n=1601) | | Analyses of Acquired Rifampin resistance (n=1381) | |
|---|--|-------------------|---------------------------------|-------------------|---|-------------------|
| | ≥ 6 (H)REZ FQ | ≥ 6 (H)REZ | ≥ 6 (H)REZ FQ | ≥ 6 (H)REZ | ≥ 6 (H)REZ FQ | ≥ 6 (H)REZ |
| Regimens compared | | | | | | |
| 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 | 9.0 (6.2; 11.0) | 9.0 (6.0; 9.0) | 9.0 (7.2; 11.2) | 9.0(8.3; 9.0) | 9.0 (7.7; 11.1) | 9.0 (9.0; 9.0) |
| - Fluoroquinolones | 6.6 (3.9; 9.0) ^f | -- | 6.1 (3.5; 8.4) ^g | -- | 5.7 (3.3; 8.1) | -- |
| - Pyrazinamide | 7.4 (4.1; 9.5) | 8.0 (2.1; 9.0) | 8.9 (6.8; 10.7) | 9.0 (8.1; 9.0) | 9.0 (7.0; 10.6) | 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 ≥ 6 m; 10 took FQ ≥ 1 m (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) | |
|---|---------------------------------|-------------------|--|-------------------|
| | ≥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

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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 | 6.0 (2.0; 8.0) | 9.0 (6.0; 9.0) | 8.0 (6.0; 8.0) | 9.0 (8.3; 9.0) | 8.0 (8.0; 8.0) | 9.0. (9.0; 9.0) |
| - Pyrazinamide | 2.0 (2.0; 3.0) | 7.4 (2.0; 9.0) | 3.0 (2.0; 3.0) | 9.0 (8.1; 9.0) | 3.0 (3.0; 3.0) | 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 >6(H)REZ | 12 | 252/260 387/397 | 260 | 0.7 (0.3; 2.2) 1.0 (reference) | No difference (from 30 fewer to 30 more) reference |
| Acquired rifampin resistance | 6(H)REZ >6(H)REZ | 7 | 1/166 1/338 | 166 | not estimable 1.0 (reference) | No difference (from 120 fewer to 130 more) reference |
| >=6(H)REZ+FQ vs >=6(H)REZ | | | | | | |
| Mortality | REZ FQ REZ | 12 | 25/531 67/1449 | 513 | 0.7 (0.4; 1.1) 1.0 (reference) | No difference (from 30 fewer to 30 more) reference |
| Success | >=6(H)REZ FQ >=6(H)REZ | 12 | 237/241 639/657 | 238 | 2.3 (0.7; 7.6) 1.0 (reference) | 20 more (from 10 fewer to 50 more) reference |
| Acquired rifampin resistance | >=6(H)REZ FQ >=6(H)REZ | 7 | 0/212 2/504 | 210 | not estimable 1.0 (reference) | -- reference |
| >=6(H)RE 1-3Z FQ vs >=6(H)REZ | | | | | | |
| Success | >=6(h)RE 1-3Z FQ >=6(H)REZ | 12 | 117/118 639/657 | 110 | 4.1 (0.4; 38.6) 1.0 (reference) | 30 more (from 30 fewer to 90 more) reference |
| Acquired rifampin resistance | >=6(h)RE 1-3Z FQ >=6(H)REZ | 7 | 0/113 2/504 | 105 | not estimable 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 low and middle-income countries only - 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: 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.

IPD of INHR-TB - Supplemental Tables

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 | 108 | --- ^d | --- ^d |
| | (H)REZ | | 10/260 | | 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 | 55 | --- ^d | --- ^d |
| | ≥6(H)REZ | | 160/169 | | 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 ≥6(H)REZ | 15 | 117/118 1253/1350 | 108 | 5.2 (0.6 to 46.7) 1.0 (reference) | 40 more per 1,000 (from 20 fewer to 90 more) (reference) |
| Success (all FQ) in subsample with CXR info | ≥(H)6RE 1-3Z FQ ≥6(H)REZ | 11 | 114/115 586/603 | 108 | 4.1 (0.4 to 38.7) ^c 1.0 (reference) | 30 more per 1,000 (from 40 fewer to 10 more) (reference) |
| Success (all FQ) in subsample with cavity | ≥(H)6RE 1-3Z FQ ≥6(H)REZ | 11 | 28/28 160/169 | 25 | --- ^d 1.0 (reference) | --- ^d (reference) |
| Use of Streptomycin - all patients (with or without isoniazid) | | | | | | |
| Mortality (all durations) | 6(H)REZ + SM 6(H)REZ | 23 | 40/763 103/2263 | 756 | 0.9 (0.6 to 1.3) 1.0 (reference) | 10 fewer per 1,000 (from 30 fewer to 20 more) (reference) |
| Mortality (in subsample with CXR info) | 6(H)REZ + SM 6(H)REZ | 13 | 11/172 54/994 | 172 | 1.0 (0.4 to 2.4) ^c 1.0 (reference) | 0 difference per 1,000 (from 50 fewer to 60 more) (reference) |
| Mortality (in subsample with cavity) | 6(H)REZ + SM 6(H)REZ | 13 | 5/107 12/272 | 106 | 1.3 (0.3, 6.3) 1.0 (reference) | 10 more per 1,000 (from 40 fewer to 60 more) (reference) |
| Success | ≥6(H)RE 1-3Z 2SM ≥6(H)REZ | 23 | 271/325 1253/1350 | 296 | 0.4 (0.2 to 0.7) 1.0 (reference) | 120 fewer per 1,000 (from 190 fewer to 60 fewer) (reference) |
| Success (in subsample with CXR info) | ≥6(H)RE 1-3Z 2SM ≥6(H)REZ | 13 | 94/113 586/603 | 113 | 0.1 (0.0 to 0.5)^c 1.0 (reference) | 140 fewer per 1,000 (from 220 fewer to 70 fewer) (reference) |
| Success (in subsample with cavity) | ≥6(H)RE 1-3Z 2SM ≥6(H)REZ | 13 | 63/76 160/169 | 76 | 0.3 (0.1 to 0.9) 1.0 (reference) | 120 fewer per 1,000 (from 230 fewer to 10 fewer) (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:

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 ≥6(H)REZ | 15 | 245/251 1253/1350 | 248 | 2.8 (1.1 to 7.3) 1.0 (reference) | 50 more per 1,000 (from 0 difference to 90 more) (reference) |
| Success: in subsample FQ 1- 5months | ≥6(H)REZ 1-5FQ ≥6(H)REZ | 15 | 106/108 1253/1350 | 108 | 4.2 (0.9 to 20.9) 1.0 (reference) | 70 more per 1,000 (from 10 fewer to 150 more) (reference) |
| Success: in subsample FQ ≥6months | ≥6(H)REZ ≥6FQ ≥6(H)REZ | 15 | 129/133 1253/1350 | 131 | 2.1 (0.6 to 7.1) 1.0 (reference) | 30 more per 1,000 (from 20 fewer to 90 more) (reference) |
| Acquired rifampin resistance | ≥6(H)REZ FQ ≥6(H)REZ | 10 | 1/221 ^b 44/1160 ^b | 220 | 0.1 (0.0 to 1.2) 1.0 (reference) | 30 fewer per 1,000 (from 60 fewer to 0 difference) (reference) |
| Acquired rifampin resistance: in subsample FQ 1-5months | ≥6(H)REZ 1-5FQ ≥6(H)REZ | 15 | 0/106 44/1160 | -- | not estimable 1.0 (reference) | not estimable (reference) |
| Acquired rifampin resistance: in subsample FQ ≥6months | ≥6(H)REZ ≥6FQ ≥6(H)REZ | 15 | 1/107 1253/1350 | 107 | 0.2 (0.0 to 2.3) 1.0 (reference) | 30 fewer per 1,000 (from 10 fewer to 30 more) (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.

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