

SUPPLEMENTARY MATERIALS

Title: Group 5 drugs for the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis

Supplementary Table S1: Summary of eligibility criteria for studies included in the three included meta-analyses upon which this individual patient data meta-analysis was based

| Meta-analysis | Eligibility criteria |
|----------------------------|--|
| Johnston et al, 2010 [18] | <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Study reported outcomes for adult patients with culture confirmed MDR-TB • Reported outcomes allowed for comparison (treatment completed, cure, death, default, failed or transferred out) <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Studies with less than 10 participants • Language other than English • Series of surgery only • Exclusive use of first-line therapy |
| Orenstein et al, 2009 [33] | <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Patients had MDR-TB based on drug susceptibility testing on cultured <i>M. tuberculosis</i> • Treatment outcomes defined by microbacterial end-points • Clearly defined treatment protocols, including second line drugs • Outcomes reported according to the WHO categories of treatment success (cure or completion), failure, death or default <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Studies where patients only have XDR-TB |
| Akcakir, 2010 [1] | <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Reported outcomes for patients with microbiologically proven resistance to isoniazid and rifampicin • Reported at least one of treatment success, failure, relapse, death or default <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Studies where patients only had XDR-TB • Studies with less than 25 subjects • Languages other than English, French or Spanish • Published before 1970 |

MDR-TB: Multi-drug resistant tuberculosis. XDR-TB: Extensively drug resistant tuberculosis.

Supplementary Table S2: Overview of included studies in individual patient data meta-analysis.

| First Author [Reference] | Years of Study* | Location | Catchment Area | Source of MDR-TB cases | Type of Drug Regimen (with second line drugs unless marked) |
|---------------------------------------|------------------------|---------------------|--------------------------|--|--|
| Avendano [4] | 2000-2009 | Canada (Toronto) | Hospital | Referral centre | Individualized |
| Burgos [6] | 1983-2000 | USA (San Francisco) | City | TB Section of San Francisco Department of Public Health | Individualized |
| Chan [7, 17] | 1984-1998 | USA (Colorado) | Hospital | National Jewish Medical and Research Center | Individualized |
| Chiang (Enarson) [8] | 1992-1996 | Taiwan (Taipei) | City (network) | <i>Mycobacteriology</i> Laboratory of the Chronic Disease Control Bureau (linked with network of public health nurses in townships & villages) | Individualized |
| Cox [9] | 2003-2005 | Uzbekistan | Community (multi-center) | Nukus City hospital and outpatient clinics and DOTS clinics in Chimbay district | Individualized |
| <i>De Riemer (Garcia-Garcia) [10]</i> | 1994-2009 | Mexico (Veracruz) | Community (multi-center) | National TB Program | Standardized (43 patients received first-line drugs only) |
| Escudero [11] | 1998-2000 | Spain (Madrid) | Hospital | University Hospital | Individualized |
| Geerligs [13] | 1987-1988, 1998-2008 | The Netherlands | Community (multi-center) | Two specialized referral centers for TB | Individualized |

| First Author [Reference] | Years of Study* | Location | Catchment Area | Source of MDR-TB cases | Type of Drug Regimen (with second line drugs unless marked) |
|--|-----------------------------------|-------------------------------|---------------------------|--|--|
| <i>Granich/ Banerjee (Flood)</i> [5, 14] | 1994-2006 (paper goes to 2003) | USA (California) | State (California) | State TB Program data | Individualized |
| <i>Holtz (Van der Walt)</i> [15] | 2000-2004 | South Africa (All centres) | Country (multi-center) | National TB Program | Standardized |
| Kim/Shim [19] | 2000-2002 | South Korea (Seoul) | Country (multi-center) | National TB Hospitals, Korean National TB Association Chest Clinics & eight randomly selected university hospitals | Individualized |
| Kim/Yim [20] | 1980-2007 | South Korea (Seoul) | Hospital | University-affiliated tertiary care referral hospital (Seoul National University Hospital) | Individualized |
| Kwon [21] | 1995-2005 | South Korea (Seoul) | Hospital | University-affiliated Tertiary Care Hospital (Samsung Medical Center) | Individualized |
| Leimane [16, 22, 38] | 2000-2004 | Latvia (Stopinu Novads) | Clinic | National TB Control Program | Individualized |
| Lockman [24] | 2000-2002 | Estonia (All centres) | Country | National TB Program | Individualized |
| Masjedi [25] | 2002-2006 | Iran | Country (multi-center) | National Mycobacteriological Reference Laboratory | Standardized |

| First Author [Reference] | Years of Study* | Location | Catchment Area | Source of MDR-TB cases | Type of Drug Regimen (with second line drugs unless marked) |
|------------------------------------|------------------------|--------------------------|------------------------|--|--|
| Migliori [26, 27] | 2001-2004 | Italy | Country (multi-centre) | TB Clinical Reference Centers in Italy | Individualized |
| Mitnick [28, 29] | 1996-2002 | Peru (Lima) | City (multi-centre) | Peruvian National TB Programme | Individualized |
| Munsiff [23, 30] | 1992-1997 | USA (New York) | City and State | Local and State TB Program | Individualized |
| Narita [31] | 1993-1997 | USA (Florida) | State | Florida State TB Laboratory | Individualized |
| ORiordan / Pasvol [32] | 1982-2004 | UK (London) | Hospital | Northwick Park Hospital (local population, Health Care Unit at London's Heathrow & Gatwick Airport, and tertiary referrals from other hospitals) | Individualized |
| Palmero [34] | 1996-1999 | Argentina (Buenos Aires) | Hospital | National Reference Hospital for Infectious Diseases (Hospital Muñiz) | Individualized |
| Park (Seung) [35] | 1998-2002 | South Korea (Masan) | Hospital | National TB Hospital (National Masan Tuberculosis Hospital) | Standardized |
| Perez-Guzman (Vargas) [36] | 1994-1995 | Mexico | Hospital | Pulmonary TB Clinics of the Instituto Nacional de Enfermedades Respiratorias | Individualized |

| First Author [Reference] | Years of Study* | Location | Catchment Area | Source of MDR-TB cases | Type of Drug Regimen (with second line drugs unless marked) |
|------------------------------------|------------------------|--|----------------------------------|---|--|
| <i>Quy (Dang/Cobelens)</i> [37] | 1998-2000 | Vietnam (Ho Chi Minh City) | City (multi-center) | National TB Control Program | Standardized (First-line drugs only) |
| Schaaf [39] | 1998-2002 | South Africa (Western Cape, Capetown Metropole, West Coast) | Multi-regional (multi-center) | MDR-TB clinics & Local hospitals | Individualized |
| Shin [40] | 2000-2004 | Russian Federation (Tomsk) | Oblast (multi-center) | Tomsk Oblast TB Services, Tomsk Penitentiary Services and Tomsk TB Hospital | Individualized |
| Shiraishi [41] | 2000-2007 | Japan (Tokyo) | Hospital | Fukujuji Hospital | Individualized |
| Tupasi (Quelapio) [42, 43] | 1999-2003 | Philippines | Clinic | Makati Medical Center Dots Clinic | Individualized |
| <i>Uffredi (Robert)</i> [44] | 1998-1999 | France (Paris) | Multi-regional | National Reference Center | Individualized |
| <i>Yew (Leung)</i> [47, 48] | 1990-1997 | Hong Kong | Hospital | Tertiary Referral Hospital for TB (Grantham Hospital) | Individualized |

* Defined by start date of MDR-TB treatment. Table modified from Supplementary Table in Ahuja et al [2].

Supplementary Table S3: Patients in 31 studies included in the meta-analyses, according to treatment with amoxicillin/clavulanic acid, clofazamine, macrolides or thioacetazone

| Number* | Study | Amoxicillin + clavulanic acid | | No amoxicillin / clavulanic acid | | Clofazamine | | No clofazamine | | Macrolides ⁺ | | No macrolides | | Thio- acetazone | | No thio- acetazone | | Any Group 5 Drug** | | No Group 5 Drug, or not reported | | Total patients |
|---------|---|-------------------------------------|---------|---|---------|-------------|---------|----------------|---------|-------------------------|---------|---------------|---------|--------------------|------|-----------------------|--------|-----------------------|---------|--|---------|-------------------|
| | | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | | |
| 1 | Avendano [4] | 10 | (13.9%) | 62 | (86.1%) | 72 | (100%) | 0 | (0%) | 8 | (11.1%) | 64 | (88.9%) | 0 | (0%) | 72 | (100%) | 72 | (100%) | 0 | (0%) | 72 |
| 2 | Burgos [6] | 3 | (6.7%) | 42 | (93.3%) | 2 | (4.4%) | 43 | (95.6%) | NR | | NR | | NR | | NR | | 4 | (8.9%) | 41 | (91.1%) | 45 |
| 3 | Chan [7, 17] | 1 | (0.5%) | 202 | (99.5%) | 51 | (25.1%) | 152 | (74.9%) | 12 | (5.9%) | 191 | (94.1%) | 4 | (2%) | 199 | (98%) | 61 | (30%) | 142 | (70%) | 203 |
| 4 | Chiang (Enarson) [8] | NR | | NR | | NR | | NR | | NR | | NR | | NR | | NR | | 0 | (0%) | 125 | (100%) | 125 |
| 5 | Cox [9] | 48 | (62.3%) | 29 | (37.7%) | 14 | (18.2%) | 63 | (81.8%) | 0 | (0%) | 77 | (100%) | 0 | (0%) | 77 | (100%) | 48 | (62.3%) | 29 | (37.7%) | 77 |
| 6 | De Riemer (Garcia- Garcia) [10] | NR | | NR | | NR | | NR | | NR | | NR | | NR | | NR | | 0 | (0%) | 47 | (100%) | 47 |
| 7 | Escudero [11] | 4 | (19%) | 17 | (81%) | 7 | (33.3%) | 14 | (66.7%) | 0 | (0%) | 21 | (100%) | 0 | (0%) | 21 | (100%) | 7 | (33.3%) | 14 | (66.7%) | 21 |
| 8 | Geerligs [13] | 0 | (0%) | 43 | (100%) | 34 | (79.1%) | 9 | (20.9%) | 1 | (2.3%) | 42 | (97.7%) | 3 | (7%) | 40 | (93%) | 34 | (79.1%) | 9 | (20.9%) | 43 |

| Number* | Study | Amoxicillin + clavulanic acid | | No amoxicillin / clavulanic acid | | Clofazamine | | No clofazamine | | Macrolides ⁺ | | No macrolides | | Thio- acetazone | | No thio- acetazone | | Any Group 5 Drug** | | No Group 5 Drug, or not reported | Total patients | |
|---------|--|-------------------------------------|---------|---|---------|-------------|---------|----------------|---------|-------------------------|---------|---------------|---------|--------------------|---------|-----------------------|---------|-----------------------|---------|--|-------------------|------|
| | | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | | |
| 9 | Granich/ Banerjee (Flood) [5, 14] | NR | | NR | | NR | | NR | | NR | | NR | | NR | | NR | | 0 | (0%) | 101 | (100%) | 101 |
| 10 | Holtz (Van der Walt) [15] | 0 | (0%) | 2204 | (100%) | 0 | (0%) | 2204 | (100%) | 0 | (0%) | 2204 | (100%) | 0 | (0%) | 2204 | (100%) | 0 | (0%) | 2204 | (100%) | 2204 |
| 11 | Kim/Shim [19] | 23 | (1.7%) | 1331 | (98.3%) | 0 | (0%) | 1354 | (100%) | 28 | (2.1%) | 1326 | (97.9%) | 0 | (0%) | 1354 | (100%) | 43 | (3.2%) | 1311 | (96.8%) | 1354 |
| 12 | Kim/Yim [20] | 88 | (41.9%) | 122 | (58.1%) | 0 | (0%) | 210 | (100%) | 58 | (27.6%) | 152 | (72.4%) | 0 | (0%) | 210 | (100%) | 97 | (46.2%) | 113 | (53.8%) | 210 |
| 13 | Kwon [21] | 77 | (49.7%) | 78 | (50.3%) | NR | | NR | | 42 | (27.1%) | 113 | (72.9%) | NR | | NR | | 90 | (58.1%) | 65 | (41.9%) | 155 |
| 14 | Leimane [16, 22, 38] | 0 | (0%) | 992 | (100%) | 0 | (0%) | 992 | (100%) | 93 | (9.4%) | 899 | (90.6%) | 671 | (67.6%) | 321 | (32.4%) | 692 | (69.8%) | 300 | (30.2%) | 992 |
| 15 | Lockman [24] | 65 | (23%) | 218 | (77%) | 0 | (0%) | 283 | (100%) | 57 | (20.1%) | 226 | (79.9%) | 0 | (0%) | 283 | (100%) | 84 | (29.7%) | 199 | (70.3%) | 283 |
| 16 | Masjedi [25] | 12 | (27.9%) | 31 | (72.1%) | 21 | (48.8%) | 22 | (51.2%) | 0 | (0%) | 43 | (100%) | 0 | (0%) | 43 | (100%) | 26 | (60.5%) | 17 | (39.5%) | 43 |
| 17 | Migliori [26, 27] | 9 | (9.5%) | 86 | (90.5%) | 19 | (20%) | 76 | (80%) | 15 | (15.8%) | 80 | (84.2%) | 0 | (0%) | 95 | (100%) | 39 | (41.1%) | 56 | (58.9%) | 95 |
| 18 | Mitnick [28, 29] | 519 | (78.6%) | 141 | (21.4%) | 453 | (68.6%) | 207 | (31.4%) | 105 | (15.9%) | 555 | (84.1%) | 0 | (0%) | 660 | (100%) | 579 | (87.7%) | 81 | (12.3%) | 660 |
| 19 | Munsiff [23, 30] | 3 | (0.4%) | 668 | (99.6%) | 75 | (11.2%) | 596 | (88.8%) | 0 | (0%) | 671 | (100%) | 0 | (0%) | 671 | (100%) | 78 | (11.6%) | 593 | (88.4%) | 671 |

| Number* | Study | Amoxicillin + clavulanic acid | | No amoxicillin / clavulanic acid | | Clofazamine | | No clofazamine | | Macrolides* | | No macrolides | | Thio- acetazone | | No thio- acetazone | | Any Group 5 Drug** | | No Group 5 Drug, or not reported | Total patients | |
|---------|--------------------------------------|-------------------------------------|---------|---|---------|-------------|---------|----------------|---------|-------------|---------|---------------|---------|--------------------|---------|-----------------------|---------|-----------------------|---------|--|-------------------|-----|
| | | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | | |
| 20 | Narita [31] | 5 | (7.5%) | 62 | (92.5%) | 20 | (29.9%) | 47 | (70.1%) | 2 | (3%) | 65 | (97%) | NR | | NR | | 23 | (34.3%) | 44 | (65.7%) | 67 |
| 21 | ORiordan / Pasvol [32] | NR | | NR | | NR | | N | | 9 | (32.1%) | 19 | (67.9%) | 1 | (3.6%) | 27 | (96.4%) | 11 | (39.3%) | 17 | (60.7%) | 28 |
| 22 | Palmero [34] | 0 | (0%) | 112 | (100%) | 22 | (19.6%) | 90 | (80.4%) | 0 | (0%) | 112 | (100%) | 0 | (0%) | 112 | (100%) | 31 | (27.7%) | 81 | (72.3%) | 112 |
| 23 | Park (Seung) [35] | 0 | (0%) | 142 | (100%) | 0 | (0%) | 142 | (100%) | 0 | (0%) | 142 | (100%) | 0 | (0%) | 142 | (100%) | 0 | (0%) | 142 | (100%) | 142 |
| 24 | Perez- Guzman (Vargas) [36] | 7 | (21.2%) | 26 | (78.8%) | 15 | (45.5%) | 18 | (54.5%) | 19 | (57.6%) | 14 | (42.4%) | 14 | (42.4%) | 19 | (57.6%) | 31 | (93.9%) | 2 | (6.1%) | 33 |
| 25 | Quy (Dang/Co belens) [37] | 0 | (0%) | 157 | (100%) | 0 | (0%) | 157 | (100%) | 0 | (0%) | 157 | (100%) | 0 | (0%) | 157 | (100%) | 0 | (0%) | 157 | (100%) | 157 |
| 26 | Schaaf [39] | 0 | (0%) | 36 | (100%) | 1 | (2.8%) | 35 | (97.2%) | 0 | (0%) | 36 | (100%) | 0 | (0%) | 36 | (100%) | 1 | (2.8%) | 35 | (97.2%) | 36 |
| 27 | Shin [40] | 45 | (7.4%) | 563 | (92.6%) | 0 | (0%) | 608 | (100%) | 0 | (0%) | 608 | (100%) | 0 | (0%) | 608 | (100%) | 45 | (7.4%) | 563 | (92.6%) | 608 |
| 28 | Shiraishi [41] | 0 | (0%) | 56 | (100%) | 0 | (0%) | 56 | (100%) | 0 | (0%) | 56 | (100%) | 11 | (19.6%) | 45 | (80.4%) | 11 | (19.6%) | 45 | (80.4%) | 56 |
| 29 | Tupasi (Quelapio) [42, 43] | 0 | (0%) | 163 | (100%) | 0 | (0%) | 163 | (100%) | 79 | (48.5%) | 84 | (51.5%) | 0 | (0%) | 163 | (100%) | 79 | (48.5%) | 84 | (51.5%) | 163 |

| Number* | Study | Amoxicillin + clavulanic acid | | No amoxicillin / clavulanic acid | | Clofazamine | | No clofazamine | | Macrolides ⁺ | | No macrolides | | Thio- acetazone | | No thio- acetazone | | Any Group 5 Drug** | | No Group 5 Drug, or not reported | Total patients |
|--------------|--------------------------------------|-------------------------------------|-----|---|-----|-----------------|-----|----------------------|-----|-------------------------|-----|----------------------|-----|--------------------|-----|-----------------------|-----|-----------------------|-----|--|-------------------|
| | | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | |
| 30 | <i>Uffredi (Robert) [44]</i> | NR | | NR | | NR | | NR | | 4 (9.5%) | | 38 (90.5%) | | 1 (2.4%) | | 41 (97.6%) | | 5 (11.9%) | | 37 (88.1%) | 42 |
| 31 | <i>Yew (Leung) [47, 48]</i> | NR | | NR | | NR | | NR | | NR | | NR | | NR | | NR | | 0 (0%) | | 99 (100%) | 99 |
| Total | | 919 (10.3%) | | 7,583 (84.8%) | | 806 (9%) | | 7,541 (84.3%) | | 532 (5.9%) | | 7,995 (89.4%) | | 705 (7.9%) | | 7,600 (85%) | | 2,191 (24.5%) | | 6,753 (75.5%) | 8,944 |

* Number of studies: The first published IPD meta-analysis of MDR-TB treatment using these data included 32 datasets. [3]. In this study, the authors of one study included in the initial meta-analysis withdrew [45, 46]. Hence, only 31 studies are included in the present meta-analyses. Patient selection: In the present study, individuals were included if they had extensively drug resistant TB (XDR-TB). In contrast, these individuals were excluded from the original study. In both the present meta-analysis and the initial meta-analysis, individuals were excluded if they had only extrapulmonary disease without pulmonary disease.

+ Clarithromycin: In a previous meta-analysis of patients taking macrolides, those with XDR-TB had been excluded. In the present individuals with XDR-TB were included, explaining a slight difference in the total patients included between the two papers.

**Group 5 drugs: Individuals were classified as having at least one Group 5 drug if they were given one or more of: amoxycillin/clavulanic acid, clofazamine, a macrolide antibiotic, thioacetazone, linezolid, imipenem or teridizone. In total, 40 individuals took linezolid, 12 individuals took teridizone and 8 individuals took imipenem. The number of individuals taking linezolid, imipenem or teridizone in each study are not shown, as a meta-analyses were not performed, since there were less than 50 individuals included across all studies.

NR = Use of the drug not reported in original dataset.

Supplementary Table S4: Proportion of variables with missing values, grouped by individual study.

| First Author [Reference] | Gender n / total (%) | Age n / total (%) | Extent of disease n / total (%) | Prior TB history n / total (%) | Prior MDR-TB history n / total (%) | Number of intensive phase drugs n / total (%) | Total duration of therapy n / total (%) | HIV status n / total (%) | Proportion lost to follow-up n / total (%) |
|--|--------------------------------|-----------------------------|---|--|--|---|---|------------------------------------|--|
| <i>Avendano [4]</i> | 72/72 (100%) | 72/72 (100%) | 72/72 (100%) | 72/72 (100%) | 72/72 (100%) | 72/72 (100%) | 70/72 (97.2%) | 72/72 (100%) | 6/72 (8.3%) |
| <i>Burgos [6]</i> | 45/45 (100%) | 45/45 (100%) | 45/45 (100%) | 45/45 (100%) | 0/45 (0%) | 45/45 (100%) | 42/45 (93.3%) | 45/45 (100%) | 4/45 (8.9%) |
| <i>Chan [7, 17]</i> | 203/203 (100%) | 203/203 (100%) | 203/203 (100%) | 202/203 (99.5%) | 202/203 (99.5%) | 0/203 (0%) | 0/203 (0%) | 203/203 (100%) | 23/203 (11.3%) |
| <i>Chiang (Enarson) [8]</i> | 125/125 (100%) | 125/125 (100%) | 117/125 (93.6%) | 125/125 (100%) | 125/125 (100%) | 125/125 (100%) | 125/125 (100%) | 125/125 (100%) | 34/125 (27.2%) |
| <i>Cox [9]</i> | 77/77 (100%) | 77/77 (100%) | 77/77 (100%) | 77/77 (100%) | 77/77 (100%) | 77/77 (100%) | 77/77 (100%) | 77/77 (100%) | 6/77 (7.8%) |
| <i>De Riemer (Garcia-Garcia) [10]</i> | 47/47 (100%) | 47/47 (100%) | 47/47 (100%) | 47/47 (100%) | 47/47 (100%) | 47/47 (100%) | 47/47 (100%) | 47/47 (100%) | 17/47 (36.2%) |
| <i>Escudero [11]</i> | 21/21 (100%) | 21/21 (100%) | 21/21 (100%) | 21/21 (100%) | 21/21 (100%) | 21/21 (100%) | 21/21 (100%) | 21/21 (100%) | 4/21 (19%) |
| <i>Geerligs [13]</i> | 43/43 (100%) | 42/43 (97.7%) | 0/43 (0%) | 0/43 (0%) | 0/43 (0%) | 43/43 (100%) | 43/43 (100%) | 43/43 (100%) | 1/43 (2.3%) |
| <i>Granich/ Banerjee (Flood) [5, 14]</i> | 101/101 (100%) | 101/101 (100%) | 98/101 (97%) | 101/101 (100%) | 101/101 (100%) | 101/101 (100%) | 0/101 (0%) | 101/101 (100%) | 18/101 (17.8%) |
| <i>Holtz (Van der Walt) [15]</i> | 2201/2204 (99.9%) | 2180/2204 (98.9%) | 2125/2204 (96.4%) | 2124/2204 (96.4%) | 2124/2204 (96.4%) | 2204/2204 (100%) | 2204/2204 (100%) | 2204/2204 (100%) | 520/2204 (23.6%) |
| <i>Kim/Shim [19]</i> | 1354/1354 (100%) | 1354/1354 (100%) | 1354/1354 (100%) | 1350/1354 (99.7%) | 1350/1354 (99.7%) | 1354/1354 (100%) | 0/1354 (0%) | 1354/1354 (100%) | 670/1354 (49.5%) |
| <i>Kim/Yim [20]</i> | 210/210 (100%) | 210/210 (100%) | 208/210 (99%) | 210/210 (100%) | 0/210 (0%) | 210/210 (100%) | 210/210 (100%) | 210/210 (100%) | 14/210 (6.7%) |
| <i>Kwon [21]</i> | 155/155 (100%) | 155/155 (100%) | 155/155 (100%) | 155/155 (100%) | 155/155 (100%) | 155/155 (100%) | 155/155 (100%) | 155/155 (100%) | 21/155 (13.5%) |
| <i>Leimane [16, 22, 38]</i> | 992/992 (100%) | 992/992 (100%) | 992/992 (100%) | 992/992 (100%) | 992/992 (100%) | 992/992 (100%) | 992/992 (100%) | 992/992 (100%) | 130/992 (13.1%) |
| <i>Lockman [24]</i> | 283/283 (100%) | 283/283 (100%) | 283/283 (100%) | 0/283 (0%) | 0/283 (0%) | 283/283 (100%) | 283/283 (100%) | 283/283 (100%) | 68/283 (24%) |
| <i>Masjedi [25]</i> | 43/43 (100%) | 43/43 (100%) | 43/43 (100%) | 43/43 (100%) | 43/43 (100%) | 43/43 (100%) | 43/43 (100%) | 43/43 (100%) | 0/43 (0%) |

| First Author [Reference] | Gender n / total (%) | Age n / total (%) | Extent of disease n / total (%) | Prior TB history n / total (%) | Prior MDR-TB history n / total (%) | Number of intensive phase drugs n / total (%) | Total duration of therapy n / total (%) | HIV status n / total (%) | Proportion lost to follow-up n / total (%) |
|---|-----------------------------|------------------------------|---------------------------------------|--------------------------------------|--|--|--|-----------------------------|---|
| <i>Migliori [26, 27]</i> | 95/95 (100%) | 95/95 (100%) | 95/95 (100%) | 95/95 (100%) | 95/95 (100%) | 95/95 (100%) | 95/95 (100%) | 95/95 (100%) | 64/95 (67.4%) |
| <i>Mitnick [28, 29]</i> | 660/660 (100%) | 660/660 (100%) | 658/660 (99.7%) | 660/660 (100%) | 660/660 (100%) | 660/660 (100%) | 660/660 (100%) | 660/660 (100%) | 87/660 (13.2%) |
| <i>Munsiff [23, 30]</i> | 671/671 (100%) | 671/671 (100%) | 633/671 (94.3%) | 671/671 (100%) | 671/671 (100%) | 671/671 (100%) | 671/671 (100%) | 671/671 (100%) | 80/671 (11.9%) |
| <i>Narita [31]</i> | 67/67 (100%) | 67/67 (100%) | 67/67 (100%) | 61/67 (91%) | 0/67 (0%) | 0/67 (0%) | 0/67 (0%) | 67/67 (100%) | 23/67 (34.3%) |
| <i>ORiordan / Pasvol [32]</i> | 28/28 (100%) | 28/28 (100%) | 28/28 (100%) | 28/28 (100%) | 0/28 (0%) | 0/28 (0%) | 24/28 (85.7%) | 28/28 (100%) | 8/28 (28.6%) |
| <i>Palmero [34]</i> | 112/112 (100%) | 112/112 (100%) | 112/112 (100%) | 112/112 (100%) | 112/112 (100%) | 112/112 (100%) | 112/112 (100%) | 112/112 (100%) | 28/112 (25%) |
| <i>Park (Seung) [35]</i> | 142/142 (100%) | 142/142 (100%) | 142/142 (100%) | 142/142 (100%) | 142/142 (100%) | 142/142 (100%) | 134/142 (94.4%) | 142/142 (100%) | 56/142 (39.4%) |
| <i>Perez-Guzman (Vargas) [36]</i> | 33/33 (100%) | 33/33 (100%) | 33/33 (100%) | 33/33 (100%) | 33/33 (100%) | 33/33 (100%) | 33/33 (100%) | 33/33 (100%) | 11/33 (33.3%) |
| <i>Quy (Dang/Cobelens) [37]</i> | 157/157 (100%) | 157/157 (100%) | 157/157 (100%) | 157/157 (100%) | 157/157 (100%) | 157/157 (100%) | 157/157 (100%) | 157/157 (100%) | 20/157 (12.7%) |
| <i>Schaaf [39]</i> | 36/36 (100%) | 36/36 (100%) | 36/36 (100%) | 36/36 (100%) | 36/36 (100%) | 36/36 (100%) | 36/36 (100%) | 36/36 (100%) | 9/36 (25%) |
| <i>Shin [40]</i> | 608/608 (100%) | 608/608 (100%) | 608/608 (100%) | 595/608 (97.9%) | 595/608 (97.9%) | 608/608 (100%) | 608/608 (100%) | 608/608 (100%) | 123/608 (20.2%) |
| <i>Shiraishi [41]</i> | 56/56 (100%) | 56/56 (100%) | 56/56 (100%) | 0/56 (0%) | 0/56 (0%) | 56/56 (100%) | 56/56 (100%) | 56/56 (100%) | 0/56 (0%) |
| <i>Tupasi (Quelapio) [42, 43]</i> | 163/163 (100%) | 163/163 (100%) | 163/163 (100%) | 163/163 (100%) | 163/163 (100%) | 163/163 (100%) | 163/163 (100%) | 163/163 (100%) | 26/163 (16%) |
| <i>Uffredi (Robert) [44]</i> | 42/42 (100%) | 42/42 (100%) | 42/42 (100%) | 23/42 (54.8%) | 23/42 (54.8%) | 42/42 (100%) | 42/42 (100%) | 42/42 (100%) | 7/42 (16.7%) |
| <i>Yew (Leung) [47, 48]</i> | 99/99 (100%) | 99/99 (100%) | 99/99 (100%) | 99/99 (100%) | 99/99 (100%) | 99/99 (100%) | 99/99 (100%) | 99/99 (100%) | 2/99 (2%) |
| TOTAL | 8941/8944 (100%) | 8919/8944 (99.7%) | 8769/8944 (98%) | 8439/8944 (94.4%) | 8095/8944 (90.5%) | 8646/8944 (96.7%) | 7202/8944 (80.5%) | 8944/8944 (100%) | 2080/8944 (23.3%) |

*Missing values were imputed using multiple imputation.

Supplementary Table S5: Treatment outcomes for thioacetazone in Leimane et al [22]

| Group | Events | Total | (%) | (95% CI) |
|------------------------------|---------------|--------------|------------|-----------------|
| Treatment success | 467 | 671 | (70%) | (66-73%) |
| Treatment failure or relapse | 92 | 671 | (14%) | (11-16%) |
| Loss to follow-up | 89 | 671 | (13%) | (11-16%) |
| Death | 23 | 671 | (3%) | (2-5%) |

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Supplementary Table S6: Study characteristics assessing the quality of the included studies

| First author | Allocation conceal-ment | Incomplete outcome data addressed | Blinding of participants, personnel and outcome assessors to primary outcome | Free of selective reporting | Risk of bias** |
|---------------------------|--------------------------------|--|---|------------------------------------|-----------------------|
| Burgos (Burgos) | No | Yes | No | Yes | Serious |
| Chan (Strand) | No | Yes | No | Yes | Serious |
| Chiang (Enarson) | No | Yes | No | Yes | Serious |
| Cox (Cox) | No | Yes | No | Yes | Serious |
| De Riemer (Garcia-Garcia) | No | Yes | No | Yes | Serious |
| Escudero (Pena) | No | Yes | No | Yes | Serious |
| Geerligs (van der Werf) | No | Yes | No | Yes | Serious |
| Holtz (Van der Walt) | No | Yes | No | Yes | Serious |
| DH Kim (Shim) | No | Yes | No | Yes | Serious |
| HR Kim (Yim) | No | Yes | No | Yes | Serious |
| Kwon (Koh) | No | Yes | No | Yes | Serious |
| Masjedi (Tabarsi) | No | Yes | No | Yes | Serious |
| Migliori (Centis) | No | Yes | No | Yes | Serious |
| Mitnick (Mitnick) | No | Yes | No | Yes | Serious |
| Munsiff/Li (Ahuja) | No | Yes | No | Yes | Serious |
| Narita (Narita) | No | Yes | No | Yes | Serious |
| O'Riordan (Pasvol) | No | Yes | No | Yes | Serious |
| Palmero (Palmero) | No | Yes | No | Yes | Serious |
| Perez-Guzman (Vargas) | No | Yes | No | Yes | Serious |

| First author | Allocation conceal-ment | Incomplete outcome data addressed | Blinding of participants, personnel and outcome assessors to primary outcome | Free of selective reporting | Risk of bias** |
|-----------------------|--------------------------------|--|---|------------------------------------|-----------------------|
| Park (Seung) | No | Yes | No | Yes | Serious |
| Quy (Dang/ Cobelens) | No | Yes | No | Yes | Serious |
| Schaaf (Schaaf) | No | Yes | No | Yes | Serious |
| Shin (Shin) | No | Yes | No | Yes | Serious |
| Shiraishi (Shiraishi) | No | Yes | No | Yes | Serious |
| Tupasi (Quelapio) | No | Yes | No | Yes | Serious |
| Uffredi (Robert) | No | Yes | No | Yes | Serious |

*Included studies were all observational cohort studies. Treatment allocation was determined according to the usual clinical practice in each setting. Bias in the selection of studies for inclusion in the individual patient data meta-analysis was unlikely, as patient outcomes in included studies was similar to that in studies that were not included. ** All studies were observational studies, therefore bias in the selection of patients for treatment (confounding by indication) cannot be excluded. Clinicians who assessed outcomes in the included studies were not blinded to treatment allocation. This table was based on an assessment of quality evaluation that has been reported [12].

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Supplementary Table 7: PRISMA-IPD checklist of items to include when reporting a systematic review and meta-analysis of individual patient data

| PRISMA-IPD Section/topic | Item No | Checklist item | Reported on page |
|-----------------------------|------------|---|---------------------|
| Title | | | |
| Title | 1 | Identify the report as a systematic review and meta-analysis of individual participant data. | p1 |
| Abstract | | | |
| Structured summary | 2 | Provide a structured summary including as applicable: | p4 |
| | | Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes. | |
| | | Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias. | |
| | | Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice. | |
| | | Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications. | |
| | | Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis. | |
| Introduction | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | p5-6 |
| Objectives | 4 | Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups. | p6 |
| Methods | | | |
| Protocol and registration | 5 | Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable. | n/a |
| Eligibility criteria | 6 | Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated. | p6-7 |
| Identifying studies - | 7 | Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers | |

| | | | |
|--|----|---|---------------------------|
| information sources | | and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation. | |
| Identifying studies - search | 8 | Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | n/a |
| Study selection processes | 9 | State the process for determining which studies were eligible for inclusion. | p6 |
| Data collection processes | 10 | Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study). | p6-7 Figure |
| | | If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators. | |
| Data items | 11 | Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies. | p7 |
| IPD integrity | A1 | Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done. | p7 |
| Risk of bias assessment in individual studies. | 12 | Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis. | p10-12 Supp Table 7 |
| Specification of outcomes and effect measures | 13 | State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome. | p6,8 |
| Synthesis methods | 14 | Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): <ul style="list-style-type: none"> • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analysed together (where applicable). • How missing data within the IPD were dealt with (where applicable). | p6-11 |

| | | | |
|-------------------------------------|----|---|-----------------------|
| Exploration of variation in effects | A2 | If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified. | n/a |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables. | Supp. Table 7 |
| Additional analyses | 16 | Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified. | n/a |
| Results | | | |
| Study selection and IPD obtained | 17 | Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram. | p12-13 |
| Study characteristics | 18 | For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD. | Supp. Tables 2-4 |
| IPD integrity | A3 | Report any important issues identified in checking IPD or state that there were none. | p12 |
| Risk of bias within studies | 19 | Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions. | n/a |
| Results of individual studies | 20 | For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot. | Supp. Table 4, Ref 3 |
| Results of syntheses | 21 | Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based. | pp13-14 Tables 4,5 |
| | | When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials. | |
| | | Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice. | |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the | Suppl Table 4 |

| | | | |
|---------------------------|----|---|-----|
| | | availability and representativeness of available studies, outcomes or other variables. | |
| Additional analyses | 23 | Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available. | n/a |
| Discussion | | | |
| Summary of evidence | 24 | Summarise the main findings, including the strength of evidence for each main outcome. | p15 |
| Strengths and limitations | 25 | Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available. | p18 |
| Conclusions | 26 | Provide a general interpretation of the findings in the context of other evidence. | p16 |
| Implications | A4 | Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research. | p19 |
| Funding | | | |
| Funding | 27 | Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support. | p19 |

A1 – A3 denote new items that are additional to standard PRISMA items. A4 has been created as a result of re-arranging content of the standard PRISMA statement to suit the way that systematic review IPD meta-analyses are reported.

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