**Appendix for article: Mortality in Adults with MDR-TB and HIV-infection by ART and TB Drug Use: Individual Patient Data Meta-Analysis**

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**Search Strategy: MDR-TB Treatment Outcomes Studies**

**Medline search (through Ovid)­­­­**

**MDR or XDR**

1. exp multidrug resistant tuberculosis/ or exp extensively drug resistant tuberculosis/

2. (multidrug resistant tuberculosis or extensive\* drug resistant tuberculosis or MDR-TB or XDR-TB).ti,ab,kw.

3. (tuberc\* and (MDR or XDR or drug resistan\* or multidrug resistan\* or multi drug resistan\* or poly drug resistan\* or extensive\* drug resistan\*)).ti,ab,kw.

**Drugs**

4. exp Fluoroquinolones/ or exp Quinolones/ or exp Levofloxacin/ or (fluoroquin­­­­olone\* or quinolone\* or levofloxacin or Levaquin or moxifloxacin or Avelox).ti,ab,kw.

5. exp Kanamycin/ or exp Amikacin/ or exp Capreomycin/ or exp Aminoglycosides/ or (Kanamycin or Amikacin or Capreomycin or (tuberc\* and injectable\*)).ti,ab,kw.

6. exp Pyrazinamide/ or exp Ethambutol/ or exp Cycloserine/ or exp Ethionamide/ or exp Prothionamide/ or (Pyrazinamide or Ethambutol or para-aminosalicylic acid or Cycloserine or Ethionamide or Prothionamide).ti,ab,kw.

7. high dose.ti,ab,kw. and ((INH or isoniazid).ti,ab,kw. or exp isoniazid/)

**Efficacy**

8. exp Treatment Outcome/ or exp Prognosis/ or exp Death/ or exp Mortality/ or exp Treatment Failure/ or exp Survival/ or exp Recurrence/ or exp Patient Dropouts/ or exp Patient Compliance/

9. (Treatment Outcome\* or Prognosis or Death or Mortality or Treatment Failure or drug treatment failure or failure or Survival or Recurrence or relapse or Patient Dropout\* or dropout or non-compliance or compliance or efficacy or effective\* or cure or success\* or default or adheren\* or conversion\* or microbiologic conversion or smear conversion or culture conversion or sputum conversion).ti,ab,kw.

**Toxicity**

10. exp Treatment Outcome/ or exp Prognosis/ or exp Death/ or exp Mortality/ or exp Treatment Failure/ or exp Survival/ or exp Recurrence/ or exp Toxicity Tests/ or exp Drug Tolerance/ or exp "Drug-Related Side Effects and Adverse Reactions"/

11. (Treatment outcome\* or Prognosis or Death or Mortality or Treatment Failure or drug treatment failure or failure or Survival or Recurrence or relapse or Toxicity Test\* or toxicity or Drug Tolerance or toler\* or intolerance or Side Effect\* or Adverse Drug Reaction\* or adverse drug event\* or adverse event\* or adverse reaction\* or safe\* or drug safety).ti,ab,kw.

**New drugs**

12. (Bedaquiline or TMC-207 or delamanid or OPC-67683).ti,ab,kw.

**Final steps**

13. 1 or 2 or 3

14. 4 or 5 or 6 or 7

15. 8 or 9

16. 10 or 11­­

17. 13 and 14 and 15

18. 13 and 14 and 16

19. 12 and 13 and 15

20. 12 and 13 and 16

21. limit 17 to (humans and yr="2009 -Current")

22. limit 18 to (humans and yr="2009 -Current")

23. limit 19 to (humans and yr="2012 -Current")

24. limit 20 to (humans and yr="2012 -Current")

25. 21 or 22

26. 23 or 24

27. 25 or 26

(EmBase and the Cochrane Library were searched using the same strategy)

**Supplemental Figure 1: Flow diagram for studies included in the individual patient data meta-analysis**

82 potentially eligible studies identified

by investigators at McGill University,

Montreal, QC, Canada

74 included in previous systematic

review

4 describing delamanid

4 with >10% of patients with

extra-pulmonary disease†

23 potentially eligible studies from

10 other systematic reviews

3 linezolid systematic reviews

3 clofazimine systematic reviews

2 group 5 drug systematic reviews

1 bedaquiline systematic review

1 carbapenems systematic review

2 excluded

2 studies of

multidrug-resistant

tuberculosis in children

2 included

2 identified by

additional search

105 studies identified

7 additional cohorts identified

25 excluded

25 same or overlapping cohorts

87 eligible studies identified

37 studies excluded

14 no author response

7 investigator refused

1 data sent then agreement withdrawn

7 inadequate data about regimen or outcome

4 investigators no longer had access to data

2 emails for all authors unavailable or incorrect

2 datasets duplicate of previous meta-analysis

50 studies from the original IPD study (included in the 2018 Ahmad, Lancet paper)

(n=13,104 patients with multidrug-resistant tuberculosis)

7 studies excluded (N=3,156)

Drug susceptibility testing results for at least one fluoroquinolone and at least one second-line injectable reported in < 80% of the participants

9 additional datasets included

(N=4,064)

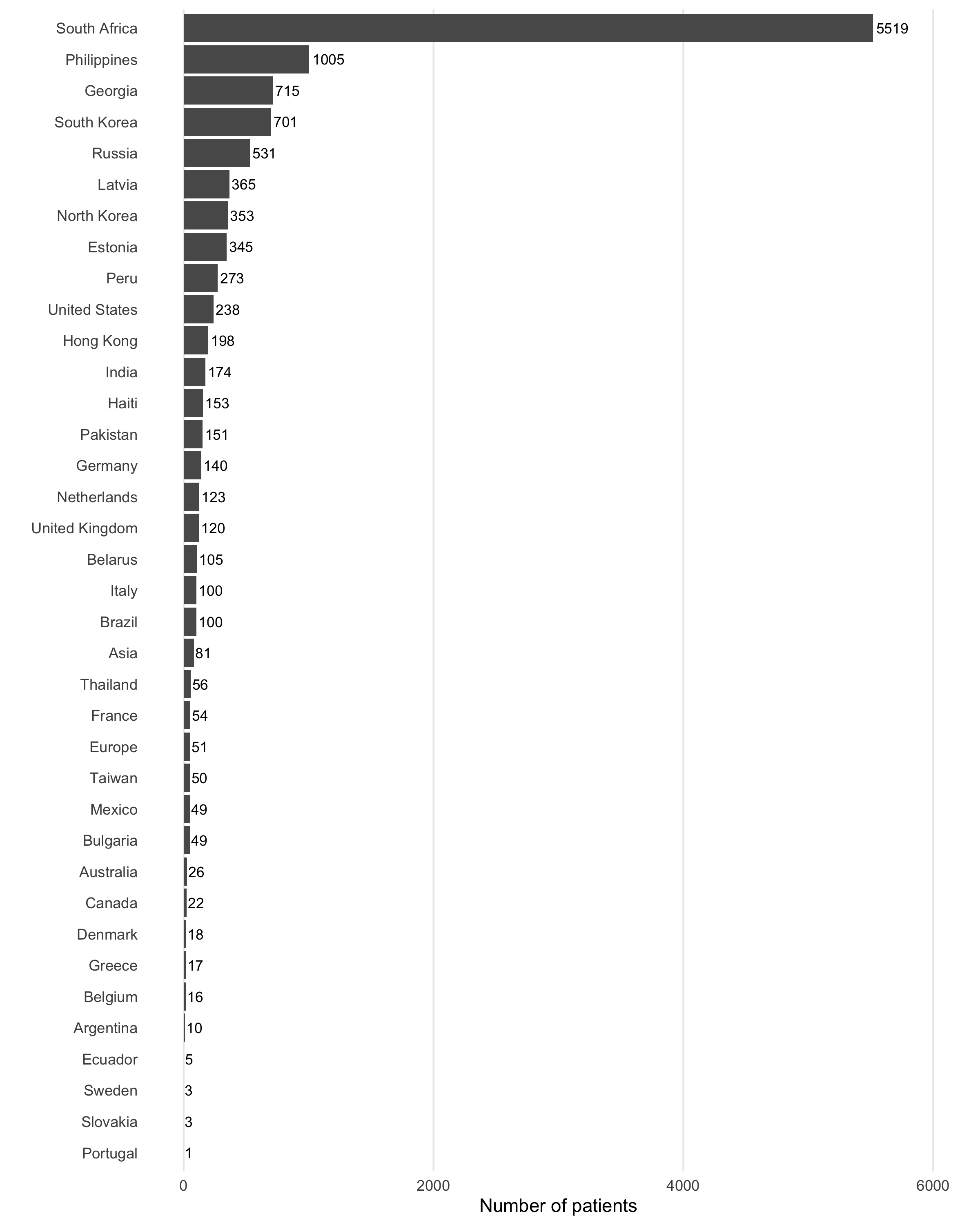
52 studies in the 2018 IPD, 12,938 multi-drug resistant tuberculosis patients

Excluded population

HIV unknown status: 670 patients

Age <18 years or unknown: 348 patients

52 studies, 11,920 multi-drug resistant tuberculosis patients



**Supplemental Figure 2. Bar graph showing number of patients contributing data by country/geographic location. Studies labeled as “Europe” and “Asia” were multi-site studies.**



**Supplemental Figure 3. Geographic distribution of patients included in the analysis**

**Supplemental Table 1: Missing data by HIV and antiretroviral therapy status in the individual patient data analysis of HIV and MDR-TB**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Characteristic** | **HIV-negative**  **n=8037** | **HIV-positive, all**  **n=3883** | **HIV-positive, on ART**  **n=2997** | **HIV-positive, not on ART n=703** | **HIV-positive, ART unknown**  **n=183** |
| **Age, n (%)** | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Sex, n (%)** | 1 (0%) | 1 (0%) | 1 (0%) | 0 (0%) | 0 (0%) |
| **Body mass index, n (%)** | 3122 (39%) | 3091 (80%) | 2500 (83%) | 431 (61%) | 161 (88%) |
| **Diabetes, n (%)** | 2681 (33%) | 3111 (80%) | 2575 (86%) | 419 (60%) | 117 (64%) |
| **Site of TB disease, n (%)** | 16 (0%) | 59 (0%) | 57 (2%) | 0 (0%) | 2 (0%) |
| **Past TB treatment, n (%)** | 127 (2%) | 84 (2%) | 67 (2%) | 13 (2%) | 4 (0%) |
| **Acid fast bacilli smear status, n (%)** | 1684 (21%) | 412 (11%) | 31 (1%) | 377 (54%) | 4 (0%) |
| **Cavitation on chest X-ray, n (%)** | 2460 (31%) | 3186 (82%) | 2630 (88%) | 418 (59%) | 138 (75%) |
| **Bilateral disease on chest X-ray, n (%)** | 3253 (40%) | 3319 (85%) | 2700 (90%) | 456 (65%) | 163 (89%) |
| **Year of MDR-TB treatment initiation, n (%)** | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **World Bank income level, n (%)** | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Drug susceptibility testing, n (%)** |  |  |  |  |  |
| Isoniazid | 254 (3%) | 557 (14%) | 517 (17%) | 0 (0%) | 40 (22%) |
| Rifampin | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Ethambutol | 1432 (18%) | 2765 (71%) | 2540 (85%) | 87 (12%) | 138 (75%) |
| Pyrazinamide | 3099 (39%) | 3546 (91%) | 2785 (93%) | 624 (89%) | 137 (75%) |
| Streptomycin | 1591 (20%) | 2440 (63%) | 2189 (73%) | 109 (16%) | 142 (78%) |
| Rifabutin | 5969(75%) | 3667 (94%) | 2893 (97%) | 601 (85%) | 173 (95%) |
| Amikacin | 3834 (48%) | 2989 (77%) | 2337 (78%) | 533 (76%) | 119 (65%) |
| Capreomycin | 1694 (21%) | 994 (26%) | 417 (14%) | 547 (78%) | 30 (16%) |
| Kanamycin | 1844 (23%) | 2532 (65%) | 2309 (77%) | 93 (13%) | 130 (71%) |
| Ofloxacin | 1750 (22%) | 2336 (60%) | 2104 (70%) | 122 (17%) | 110 (60%) |
| Ciprofloxacin | 5660 (70%) | 3075 (79%) | 2765 (92%) | 163 (23%) | 147 (80%) |
| Moxifloxacin | 6755 (84%) | 3633 (94%) | 2805 (94%) | 676 (96%) | 152 (83%) |
| Levofloxacin | 7071 (88%) | 3861 (99%) | 2284 (96%) | 701 (99%) | 176 (96%) |
| Ethionamide | 3406 (42%) | 2974 (77%) | 2662(89%) | 172 (24%) | 140 (77%) |
| Prothionamide | 6695 (83%) | 3799 (98%) | 2953 (99%) | 693 (99%) | 153 (84%) |
| Cycloserine | 4493 (56%) | 3352 (86%) | 2895 (97%) | 317 (45%) | 140 (77%) |
| Para-aminosalicylic acid | 3593 (45%) | 3433 (88%) | 2742 (91%) | 547 (78%) | 144 (79%) |
| Linezolid | 7285 (91%) | 3840 (99%) | 2955 (99%) | 690 (98%) | 176 (96%) |
| Clofazimine | 7843 (98%) | 3834 (99%) | 2951 (99%) | 701 (99%) | 182 (99%) |
| Clarithromycin | 7966 (99%) | 3874 (99%) | 2989 (99%) | 703 (100%) | 182 (99%) |
| High-dose isoniazid | 7820 (97%) | 3866 (99%) | 2997 (100%) | 686 (98%) | 183 (100%) |
| **Patient on directly observed therapy, n (%)** | 429 (5%) | 196 (5%) | 119 (4%) | 40 (6%) | 37 (20%) |
| **Second line injectable resistance, n (%)** | 319 (4%) | 88 (2%) | 45 (2%) | 42 (6%) | 1 (1%) |
| **Fluoroquinolone resistance, n (%)** | 330 (4%) | 87 (2%) | 43 (1%) | 43 (6%) | 1 (1%) |
| **Hospitalization, n (%)** | 1971 (25%) | 2558 (66%) | 2394 (80%) | 19 (3%) | 145 (79%) |
| N and %’s are for the number of patients included in the analysis who have missing data on that factor  ART=antiretroviral therapy; MDR-TB=multi-drug resistant TB | | | | | |

**Supplemental Table 2: Detailed characteristics of adult MDR-TB patients included in the individual patient data meta-analysis, stratified by HIV status and use of antiretroviral therapy**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Characteristic** | **HIV-negative**  **n=8037** | **HIV-positive, all**  **n=3883** | **P value** | **HIV-positive, on ART**  **n=2997** | **P value**  **(vs HIV-negative)** | **HIV-positive, not on ART n=703** | **P value**  **(vs HIV-negative)** | **HIV-positive, ART unknown n=183** | **P value**  **(vs HIV-negative)** |
| **Age, mean (range)** | 39 (18, 94) | 36 (18, 76) | <0.001 | 37 (18,94) | <0.001 | 34 (18, 65) | <0.001 | 36 (19, 73) | 0.001 |
| **Sex, n (%**) |  |  | <0.001 |  | <0.001 |  | <0.001 |  | <0.001 |
| Male | 5314 (66%) | 2020 (52%) |  | 1564 (52%) |  | 336 (48%) |  | 94 (51%) |  |
| Female | 2722 (34%) | 1862 (48%) |  | 1432 (48%) |  | 367 (52%) |  | 89 (49%) |  |
| Unknown | 1 (0%) | 1 (0%) |  | 1 (0%) |  | 0 (0%) |  | 0 (0%) |  |
| **Body mass index, mean (range)1** | 20.16  (10.2, 55.1) | 20.00  (10.0, 50.5) | 0.484 | 20.13  (10.0, 55.0) | 0.934 | 19.82  (11.9, 55.1) | 0.222 | 19.5  (15.1, 25.3) | 0.301 |
| **Site of disease, n (%**) |  |  | <0.001 |  | <0.001 |  | 0.160 |  | <0.001 |
| Pulmonary | 7763 (97%) | 3674 (95%) |  | 2839 (95%) |  | 676 (96%) |  | 159 (87%) |  |
| Pulmonary & extrapulmonary | 258 (3%) | 150 (4%) |  | 101 (3%) |  | 27 (4%) |  | 22 (12%) |  |
| Unknown | 16 (0%) | 59 (2%) |  | 57 (2%) |  | 0 (0%) |  | 2 (1%) |  |
| **Diabetes, n (%)** |  |  | <0.001 |  | <0.001 |  | <0.001 |  | <0.001 |
| Yes | 705 (9%) | 22 (1%) |  | 9 (0%) |  | 12 (2%) |  | 1 (1%) |  |
| No | 4651 (58%) | 750 (19%) |  | 413 (14%) |  | 272 (39%) |  | 65 (36%) |  |
| Unknown | 2681 (33%) | 3111 (80%) |  | 2575 (86%) |  | 419 (60%) |  | 117 (64%) |  |
| **Past TB treatment, n (%)** |  |  | <0.001 |  | <0.001 |  | <0.001 |  | <0.001 |
| Yes | 5809 (72%) | 2479 (64%) |  | 1795 (60%) |  | 586 (83%) |  | 98 (54%) |  |
| No | 2101 (26%) | 1320 (34%) |  | 1135 (38%) |  | 104 (15%) |  | 81 (44%) |  |
| Unknown | 127 (2%) | 84 (2%) |  | 67 (2%) |  | 13 (2%) |  | 4 (2%) |  |
| **Acid-fast bacilli smear status, n (%)** |  |  | <0.001 |  | <0.001 |  | <0.001 |  | <0.001 |
| Positive | 4770 (59%) | 2303 (59%) |  | 1950 (65%) |  | 245 (35%) |  | 108 (59%) |  |
| Negative | 1583 (20%) | 1168 (30%) |  | 1016 (34%) |  | 81 (12%) |  | 71 (39%) |  |
| Unknown | 1684 (21%) | 412 (11%) |  | 31 (1%) |  | 377 (54%) |  | 4 (2%) |  |
| **Cavitation on chest X-ray, n (%)** |  |  | <0.001 |  | <0.001 |  | <0.001 |  | <0.001 |
| Present | 3506 (44%) | 379 (10%) |  | 182 (6%) |  | 178 (25%) |  | 19 (10%) |  |
| Absent | 2071 (26%) | 318 (8%) |  | 185 (6%) |  | 107 (15%) |  | 26 (14%) |  |
| Unknown | 2460 (31%) | 3186 (82%) |  | 2630 (88%) |  | 418 (59%) |  | 138 (75%) |  |
| **Bilateral disease on chest X-ray, n (%)** |  |  | <0.001 |  | <0.001 |  | <0.001 |  | <0.001 |
| Present | 3253 (40%) | 443 (11%) |  | 240 (8%) |  | 195 (28%) |  | 8 (4%) |  |
| Absent | 1507 (19%) | 121 (3%) |  | 57 (2%) |  | 52 (7%) |  | 12 (7%) |  |
| Unknown | 3277(41%) | 3319 (85%) |  | 2700 (90%) |  | 456 (65%) |  | 163 (89%) |  |
| **Year of MDR-TB treatment initiation, median (IQR)** | 2008  (2006, 2012) | 2015  (2008, 2016) | <0.001 | 2015  (2015, 2016) | <0.001 | 2003  (2002, 2007) | <0.001 | 2015 (2007, 2016) | <0.001 |

**Supplemental Table 2 (continued)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Characteristic** | **HIV-negative**  **n=8037** | **HIV-positive, all**  **n=3883** | **P value** | **HIV-positive, on ART**  **n=2997** | **P value**  **(vs HIV-negative)** | **HIV-positive, not on ART n=703** | **P value**  **(vs HIV-negative)** | **HIV-positive, ART unknown n=183** | **P value**  **(vs HIV-negative)** |
| **World Bank income level, n (%)** |  |  | <0.001 |  | <0.001 |  | <0.001 |  | <0.001 |
| Low and low-middle | 2421 (30%) | 130 (3%) |  | 115 (4%) |  | 15 (2%) |  | 0 (0%) |  |
| Upper-middle | 3244 (40%) | 3585 (92%) |  | 2786 (93%) |  | 660 (94%) |  | 139 (76%) |  |
| High | 2372 (30%) | 168 (4%) |  | 96 (3%) |  | 28 (4%) |  | 44 (24%) |  |
| **Drug resistance profile of TB, n (%)** |  |  | <0.001 |  | <0.001 |  | 0.021 |  | 0.02 |
| Rifampicin-resistant TB | 9 (0%) | 7 (0%) |  | 6 (0%) |  | 1 (0%) |  | 0 (0%) |  |
| MDR-TB | 6997 (87%) | 3158 (81%) |  | 2427 (81%) |  | 584 (83%) |  | 147 (80%) |  |
| XDR-TB | 1031 (13%) | 718 (18%) |  | 564 (19%) |  | 118 (17%) |  | 36 (20%) |  |
| **Second-line injectable resistance, n (%)** |  |  |  |  |  |  |  |  |  |
| Yes | 2026 (25%) | 1020 (26%) | <0.001 | 820 (27%) | <0.001 | 156 (22%) | 0.004 | 44 (24%) | 0.049 |
| No | 5692 (71%) | 2775 (71%) |  | 2132 (71%) |  | 505 (72%) |  | 138 (75%) |  |
| Unknown | 319 (4%) | 88 (2%) |  | 45 (2%) |  | 42 (6%) |  | 1 (1%) |  |
| **Fluoroquinolone resistance, n (%)** |  |  | <0.001 |  | <0.001 |  | <0.001 |  | 0.048 |
| Yes | 1846 (23%) | 952 (25%) |  | 777 (26%) |  | 129 (18%) |  | 46 (24%) |  |
| No | 5861 (73%) | 2844 (73%) |  | 2177 (73%) |  | 531 (76%) |  | 136 (75%) |  |
| Unknown | 330 (4%) | 87 (2%) |  | 43 (2%) |  | 43 (6%) |  | 1 (1%) |  |
| **Patient on directly observed therapy, n (%)** |  |  | 0.07 |  | <0.001 |  | <0.001 |  | <0.001 |
| Yes | 6734 (84%) | 3320 (86%) |  | 2875 (96%) |  | 299 (43%) |  | 146 (80%) |  |
| No | 874 (11%) | 367 (9%) |  | 3 (0%) |  | 364 (52%) |  | 0 (0%) |  |
| Unknown | 429 (5%) | 196 (5%) |  | 119 (4%) |  | 40 (6%) |  | 37 (20%) |  |
| **Use of Group A drugs, n (%)** |  |  | <0.001 |  | <0.001 |  | <0.001 |  | <0.001 |
| Yes | 5708 (71%) | 2885 (74%) |  | 2648 (88%) |  | 83 (12%) |  | 154 (84%) |  |
| No | 2329 (29%) | 998 (26%) |  | 349 (12%) |  | 620 (88%) |  | 29 (16%) |  |
| **Number of Group A drugs used, n (%)** |  |  | <0.001 |  | <0.001 |  | <0.001 |  | <0.001 |
| 0 | 2329 (29%) | 998 (26%) |  | 349 (12%) |  | 620 (88%) |  | 29 (16%) |  |
| 1 | 4194 (52%) | 1885 (49%) |  | 1682 (56%) |  | 66 (9%) |  | 137 (75%) |  |
| 2 or more | 1514 (19%) | 1000 (26%) |  | 966 (32%) |  | 17 (2%) |  | 17 (9%) |  |
| **Use of Group B drugs, n (%)** |  |  | 0.07 |  | <0.001 |  | <0.001 |  | <0.001 |
| Yes | 6913 (86%) | 3297 (85%) |  | 2764 (92%) |  | 396 (56%) |  | 137 (75%) |  |
| No | 1124(14%) | 586 (15%) |  | 233 (8%) |  | 307 (44%) |  | 46 (25%) |  |

**Supplemental Table 2 (continued)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Characteristic** | **HIV-negative**  **n=8037** | **HIV-positive, all**  **n=3883** | **P value** | **HIV-positive, on ART**  **n=2997** | **P value**  **(vs HIV-negative)** | **HIV-positive, not on ART n=703** | **P value**  **(vs HIV-negative)** | **HIV-positive, ART unknown n=183** | **P value**  **(vs HIV uninfected)** |
| **Number of Group B drugs used, n (%)** |  |  | <0.001 |  | <0.001 |  | <0.001 |  | <0.001 |
| 0 | 1124 (14%) | 586 (15%) |  | 233 (8%) |  | 307 (44%) |  | 46 (25%) |  |
| 1 | 6194 (77%) | 2758 (71%) |  | 2241 (75%) |  | 385 (55%) |  | 132 (72%) |  |
| 2 or more | 719 (9%) | 539 (14%) |  | 523 (17%) |  | 11 (2%) |  | 5 (3%) |  |
| **Use of Group C drugs, n (%)** |  |  | <0.001 |  | <0.001 |  | <0.001 |  | 0.18 |
| Yes | 7949 (99%) | 3872 (100%) |  | 2986 (100%) |  | 703 (100%) |  | 183 (100%) |  |
| No | 88 (1%) | 11 (0%) |  | 11 (0%) |  | 0 (0%) |  | 0 (0%) |  |
| **Number of Group C drugs used, n (%)** |  |  | <0.001 |  | <0.001 |  | <0.001 |  | <0.001 |
| 0-1 | 686 (9%) | 214 (6%) |  | 203 (7%) |  | 4 (1%) |  | 7 (4%) |  |
| **2** | 2241 (28%) | 1320 (34%) |  | 1011 (34%) |  | 232 (33%) |  | 77 (42%) |  |
| 3 | 3454 (43%) | 1581 (41%) |  | 1292 (43%) |  | 222 (32%) |  | 67 (37%) |  |
| 4 or more | 1656 (21%) | 768 (20%) |  | 491 (16%) |  | 245 (35%) |  | 32(17%) |  |
| **Fluoroquinolone used, n (%)** |  |  | <0.0001 |  | <0.001 |  | <0.001 |  | <0.001 |
| Yes | 5343 (66%) | 2831 (73%) |  | 2607 (87%) |  | 72 (10%) |  | 152 (83%) |  |
| No | 2694 (34%) | 1052 (27%) |  | 390 (13%) |  | 631 90%) |  | 31 (17%) |  |
| **Bedaquiline used, n (%)** |  |  |  |  |  |  |  |  |  |
| Yes | 1108 (14%) | 955 (25%) | <0.0001 | 916 (31%) | <0.001 | 27 (4%) | <0.001 | 12 (7%) | 0.01 |
| No | 6929 (86%) | 2928 (75%) |  | 2081 (69%) |  | 676 (96%) |  | 171 (93%) |  |
| **Linezolid used, n (%)** |  |  | 0.901 |  | <0.001 |  | <0.001 |  | <0.001 |
| Yes | 1289 (16%) | 664 (17%) |  | 638 (21%) |  | 14 (2%) |  | 12 (7%) |  |
| No | 6748 (84%) | 3219 (83%) |  | 2359 (79%) |  | 689 (98%) |  | 171 (93%) |  |
| **Clofazimine used, n (%)** |  |  | <0.0001 |  | <0.001 |  | <0.001 |  | 0.01 |
| Yes | 916 (11%) | 589 (15%) |  | 568 (19%) |  | 12 (2%) |  | 9 (5%) |  |
| No | 7121 (89%) | 3294 (85%) |  | 2429 (81%) |  | 691 (98%) |  | 174 (95%) |  |
| **Delamanid used, n (%)** |  |  | <0.001 |  | <0.001 |  | 0.021 |  | 0.002 |
| Yes | 63 (1%) | 9 (0%) |  | 3 (0%) |  | 0 (0%) |  | 6 (3%) |  |
| No | 7974 (99%) | 3874 (100%) |  | 2994 (100%) |  | 703 (100%) |  | 177 (97%) |  |
| **Surgery, n (%)** |  |  | <0.001 |  | <0.001 |  | <0.001 |  | <0.001 |
| Yes | 367 (5%) | 6 (0%) |  | 5 (0%) |  | 1 (0%) |  | 0 (0%) |  |
| No | 4841 (60%) | 622 (16%) |  | 367 (12%) |  | 234 (33%) |  | 21 (11%) |  |
| Unknown | 2829 (35%) | 3255 (84%) |  | 2625 (88%) |  | 468 (67%) |  | 162 (89%) |  |
| **Hospitalization, n (%)** |  |  | <0.001 |  | <0.001 |  | <0.001 |  | <0.001 |
| Yes | 3783 (47%) | 1186 (31%) |  | 490 (16%) |  | 661 (94%) |  | 35 (19%) |  |
| No | 2283 (28%) | 139 (4%) |  | 113 (4%) |  | 23 (3%) |  | 3 (1%) |  |
| Unknown | 1971 (25%) | 2558 (66%) |  | 2394 (80%) |  | 19 (3%) |  | 145 (79%) |  |
| 1-Unknown body mass index: HIV-negative=3,122 (39%), HIV-positive =3,091 (80%)  Abbreviations: ART=antiretroviral therapy; MDR-TB = multi-drug resistant TB; XDR-TB = extensively drug resistant TB; ART=antiretroviral therapy  WHO classification of antitubercular agents  Group A drugs are bedaquiline, moxifloxacin, levofloxacin, and linezolid.  Group B drugs are clofazimine, cycloserine and terizidone.  Group C drugs are ethambutol, pyrazinamide, delamanid, carbapenems, amikacin, streptomycin, ethionamide and prothionamide, and para-aminosalicylic acid.  Percentages may not add to 100% due to rounding. | | | | | | | | | |

**Supplemental Table 3: Characteristics of adult MDR-TB patients lost to follow-up vs not lost to follow-up**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **Not lost to follow-up**  **(N=9,905)** | **Lost to follow-up**  **(N=2,015)** | **P value** |
| **Age, mean (range)** | 38 (18-94) | 37 (18-81) | <0.001 |
| **Sex, n (%)1** |  |  |  |
| **Male** | 5955 (60%) | 1379 (68%) | <0.001 |
| **Female** | 3948 (40%) | 636 (32%) |  |
| **HIV status** |  |  |  |
| HIV-negative | 6709 (68%) | 1328 (66%) | 0.006 |
| HIV-positive on ART | 2494 (25%) | 503 (25%) |  |
| HIV-positive not on ART OR not known on ART | 702 (7%) | 184 (9%) |  |
| **Past TB treatment, n (%)** |  |  |  |
| No or unknown | 3924 (40%) | 779 (39%) | 0.172 |
| Prior 1st-line TB drugs | 4202 (42%) | 898 (44%) |  |
| Prior 2nd-line TB drugs | 1779 (18%) | 338 (17%) |  |
| **Directly-observed TB therapy, n (%)** |  |  |  |
| Yes | 8357 (85%) | 1697 (84%) | 0.529 |
| No | 1021 (10%) | 220 (11%) |  |
| Unknown | 527 (5%) | 98 (5%) |  |
| **Acid-fast bacilli smear status, n (%)** |  |  | 0.410 |
| Positive | 5853 (59%) | 1220 (61%) |  |
| Negative | 2307 (23%) | 444 (22%) |  |
| Unknown | 1745 (18%) | 351 (17%) |  |
| **Cavitation on chest X-ray, n (%)** |  |  | 0.003 |
| Present | 3265 (33%) | 620 (31%) |  |
| Absent | 2016 (20%) | 373 (18%) |  |
| Unknown | 4624 (47%) | 1022 (51%) |  |
| **Year of MDR-TB treatment initiation, median (IQR)** | 2010 (2007, 2015) | 2009 (2006, 2015) | 0.014 |
| **World Bank Income classification level, n (%)** |  |  | <0.001 |
| Low and low-middle | 2138 (22%) | 413 (20%) |  |
| Upper-middle | 5585 (56%) | 1244 (62%) |  |
| High | 2182 (22%) | 358 (18%) |  |
| **Drug resistance profile of TB, n (%)**2 |  |  | <0.001 |
| MDR, without fluoroquinolone or second-line injectable resistance | 6056 (64%) | 1349 (69%) |  |
| MDR, fluoroquinolone susceptible but with any second-line injectable resistance | 1047 (11%) | 239 (12%) |  |
| MDR, fluoroquinolone resistant but without any second-line injectable resistance | 873 (9%) | 166 (8%) |  |
| XDR, with both fluoroquinolone and any second-line injectable resistance | 1547 (16%) | 202 (10%) |  |
| **Number of effective Group A drugs used, n (%)3** |  |  | <0.001 |
| 0 | 3427 (35%) | 786 (39%) |  |
| 1 | 4750 (48%) | 979 (49%) |  |
| 2 or more | 1728 (17%) | 250 (12%) |  |
| **Number of effective Group B and C drugs used, n (%)4** |  |  | 0.18 |
| 0-1 | 1152 (12%) | 208 (10%) |  |
| 2-3 | 5572 (56%) | 1132 (56%) |  |
| 4 or more | 3181 (32%) | 675 (34%) |  |
| **Fluoroquinolone use, n (%)** |  |  | <0.001 |
| Used ofloxacin or ciprofloxacin | 2652 (27%) | 663 (33%) |  |
| Used moxifloxacin or levofloxacin | 6554 (66%) | 1250 (62%) |  |
| No fluoroquinolone used | 699 (7%) | 102 (5%) |  |
| **Bedaquiline & linezolid use, n (%)** |  |  | <0.001 |
| Neither used | 7488 (76%) | 1639 (81%) |  |
| Used linezolid but not bedaquiline | 641 (6%) | 89 (5%) |  |
| Used bedaquiline but not linezolid | 674 (7%) | 166 (8%) |  |
| Used both linezolid and bedaquiline | 1102 (11%) | 121 (6%) |  |
| 1 Missing information in two patients who where not lost to follow-up  2Missing drug susceptibility testing in 382 and 59 in the not lost to follow-up group and lost to follow-up group, respectively. Percentages refers to those that had drug susceptibility testing results known.  3. WHO classification: Group A drugs are bedaquiline, moxifloxacin, levofloxacin and linezolid. Efficacy was estimated based on imputed drug susceptibility testing results.  4. WHO classification: Group B drugs are clofazimine, cycloserine or terizidone. Group C drugs are ethambutol, pyrazinamide, delamanid, amikacin/streptomycin, ethionamide/protionamide, para-aminosalicylic acid. Use of ofloxacin, ciprofloxacin, and gatifloxacin were included in Group B and C. | | | |

**Supplemental Table 4.** **Characteristics of patients, stratified by outcomes during MDR-TB treatment in the individual patient data analysis of HIV and MDR-TB1**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **Died**  **n=1853** | **Survived**  **n=8052** | **P value (survived vs died)** |
| **Age, mean (range)** | 39 (18, 84) | 38 (18, 94) | <0.001 |
| **HIV status, n (%)** |  |  | <0.001 |
| HIV-negative | 882 (48%) | 5827 (72%) |  |
| HIV-positive (all) | 971 (52%) | 2225 (28%) |  |
| **HIV ART use, n (%)** |  |  | <0.001 |
| HIV-positive on ART | 672 (36%) | 1822 (23%) |  |
| HIV-positive no ART | 216 (12%) | 336 (4%) |  |
| HIV-positive unknown ART | 83 (4%) | 67 (1%) |  |
| HIV-negative | 882 (47%) | 5827 (72%) |  |
| **Sex, n (%)** |  |  | 0.142 |
| Male | 1083 (58%) | 4872 (61%) |  |
| Female | 769 (42%) | 3179 (39%) |  |
| Unknown | 1 (0%) | 1 (0%) |  |
| **Body mass index, median (IQR)** | 18.0 (16.0, 20.7) | 19.9 (17.9,22.4) | <0.001 |
| **Diabetes, n (%)** |  |  | <0.001 |
| Yes | 73 (4%%) | 541 (7%) |  |
| No | 752 (41%) | 3732 (46%) |  |
| Unknown | 1028 (55%) | 3779 (47%) |  |
| **Past TB treatment, n (%)** |  |  | <0.001 |
| Yes | 1397 (75%) | 5461 (68%) |  |
| No | 421 (23%) | 2448 (30%) |  |
| Unknown | 35 (2%) | 143 (2%) |  |
| **Acid-fast bacilli smear status, n (%)** |  |  | 0.326 |
| Positive | 1119 (60%) | 4734 (59%) |  |
| Negative | 408 (22%) | 1899 (24%) |  |
| Unknown | 326 (18%) | 1419 (18%) |  |
| **Cavitation on chest X-ray, n (%)** |  |  | <0.001 |
| Present | 534 (29%) | 2731 (34%) |  |
| Absent | 255 (14%) | 1761 (22%) |  |
| Unknown | 1064 (57%) | 3560 (44%) |  |
| **Bilateral disease on chest X-ray, n (%)** |  |  | <0.001 |
| Present | 535 (29%) | 2538 (32%) |  |
| Absent | 106 (6%) | 1236 (15%) |  |
| Unknown | 1212 (65%) | 4278 (53%) |  |
| **Year of MDR-TB treatment initiation, median (IQR)** | 2009 (2007, 2015) | 2010 (2007,2015) | 0.704 |
| **World Bank income Level, n (%)** |  |  | <0.001 |
| Low and low-middle | 324 (17%) | 1814 (23%) |  |
| Middle | 1379 (74%) | 4206 (52%) |  |
| High | 150 (8%) | 2032 (25%) |  |
| **Drug resistance profile of TB** |  |  | <0.001 |
| Rifampin mono-resistant TB | 3 (0%) | 12 (0%) |  |
| MDR-TB | 1311 (71%) | 7032 (87%) |  |
| XDR-TB | 539 (29%) | 1008 (13%) |  |
| **Second-line injectable resistance, n (%)** |  |  | <0.001 |
| Yes | 720 (39%) | 1885 (23%) |  |
| No | 1080 (58%) | 5872 (73%) |  |
| Unknown | 53 (3%) | 295 (4%) |  |
| **Fluoroquinolone resistance, n (%)** |  |  | <0.001 |
| Yes | 679 (37%) | 1751 (22%) |  |
| No | 1115 (60%) | 6000 (75%) |  |
| Unknown | 59 (3%) | 301 (4%) |  |

**Supplemental Table 4 (continued)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **Died (n=1853)** | **Survived (n=8052)** | **P value (survived vs died)** |
| **Patient on directly observed TB therapy, n (%)** |  |  | <0.001 |
| Yes | 1622 (88%) | 6735 (84%) |  |
| No | 126 (7%) | 895 (11%) |  |
| Unknown | 105 (6%) | 422 (5%) |  |
| **Use of Group A drugs, n (%)** |  |  |  |
| Yes | 1174 (63%) | 6052 (75%) | <0.001 |
| No | 679 (37%) | 2000 (25%) |  |
| **Number of Group A drug used, n (%)** |  |  | <0.001 |
| 0 | 679 (37%) | 2000 (25%) |  |
| 1 | 889 (48%) | 4146 (51%) |  |
| 2 or more | 285 (15%) | 1906 (24%) |  |
| **Use of Group B drugs, n (%)** |  |  | <0.001 |
| Yes | 1492 (81%) | 7013 (87%) |  |
| No | 361 (19%) | 1039 (13%) |  |
| **Number of Group B drugs used, n (%)** |  |  | <0.001 |
| 0 | 361 (19%) | 1039 (13%) |  |
| 1 | 1287 (69%) | 6123 (76%) |  |
| 2 | 205 (11%) | 890 (11%) |  |
| **Use of Group C drugs, n (%)** |  |  | 0.341 |
| Yes | 1840 (99%) | 7977 (99%) |  |
| No | 13 (1%) | 75 (1%) |  |
| **Number of Group C drugs used, n (%)** |  |  | <0.001 |
| 0-1 | 109 (6%) | 665 (8%) |  |
| 2 | 504 (27%) | 2486 (31%) |  |
| 3 | 709 (38%) | 3396 (42%) |  |
| 4 or more | 531 (29%) | 1505 (19%) |  |
| **Levofloxacin or moxifloxacin used, n (%)** |  |  | <0.001 |
| Yes | 1135 (61%) | 5734 (71%) |  |
| No | 718 (39%) | 2318 (29%) |  |
| **Bedaquiline used, n (%)** |  |  | <0.001 |
| Yes | 246 (13%) | 1530 (19%) |  |
| No | 1607 (87%) | 6522 (81%) |  |
| **Linezolid used, n (%)** |  |  | <0.001 |
| Yes | 210 (11%) | 1533 (19%) |  |
| No | 1643 (89%) | 6519 (81%) |  |
| **Clofazimine used, n (%)** |  |  | 0.372 |
| Yes | 235 (13%) | 1084 (13%) |  |
| No | 1618 (87%) | 6968 (87%) |  |
| **Use of delamanid, n (%)** |  |  | 0.003 |
| Yes | 3 (0%) | 61 (1%) |  |
| No | 1850 (100%) | 7991 (99%) |  |
| **Surgery, n (%)** |  |  | <0.001 |
| Yes | 26 (1%) | 313 (4%) |  |
| No | 706 (38%) | 3900 (48%) |  |
| Unknown | 1121 (60%) | 3839 (48%) |  |
| **Hospitalization, n (%)** |  |  | <0.001 |
| Yes | 870 (47%) | 3244 (40%) |  |
| No | 242 (13%) | 1788 (22%) |  |
| Unknown | 741 (40%) | 3020 (38%) |  |
| Abbreviations: MDR-TB = multi-drug resistant TB; ART=antiretroviral therapy  WHO classification of antitubercular agents  Group A drugs are bedaquiline, moxifloxacin, levofloxacin, and linezolid.  Group B drugs are clofazimine, cycloserine and terizidone.  Group C drugs are ethambutol, pyrazinamide, delamanid, carbapenems, amikacin, streptomycin, ethionamide and prothionamide, and para-aminosalicylic acid.  Percentages may not add to 100% due to rounding.  1-Survived includes: Success/Failure/Relapse. Loss to follow-up excluded=2015 | | | |

**Supplemental Table 5. Unadjusted analysis of factors associated with death (versus any survival outcome including success, failure, and relapse) in the individual patient data analysis of HIV and MDR-TB.** Odds ratios with 95% CIs that do not include 1 were statistically significant (p<0.05) and are in bold text.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** | **HIV-negative**  **odds ratio (95% CI)** | **HIV-positive**  **odds ratio (95% CI)** | **HIV-positive on ART**  **odds ratio (95% CI)** | **HIV-positive not on ART or unknown ART**  **odds ratio (95% CI)** |
| **Age (per 1 year older)** | **1.03 (1.02, 1.03)** | 1.00 (0.99, 1.01) | 1.00 (0.99, 1.01) | 1.00 (0.99, 1.02) |
| **Sex (male)** | **1.34 (1.14, 1.57)** | 0.94 (0.80, 1.10) | 0.91 (0.76, 1.10) | 1.01 (0.72, 1.41) |
| **Body mass index (per unit increase)** | **0.84 (0.81, 0.86)** | 0.90 (0.87, 0.95) | 0.94 (0.89, 1.00) | **0.84 (0.77, 0.92)** |
| **Year (per one year)** | 0.97 (0.93,1.03) | **0.94 (0.93, 0.95)** | **0.92 (0.91, 0.92)** | **0.92 (0.91, 0.93)** |
| **Positive acid-fast bacilli smear** | **1.53 (1.22, 1.91)** | 1.11 (0.93, 1.33) | 1.13 (0.93,1.38) | 1.14 (0.67, 1.93) |
| **Presence of cavity on chest X-ray** | **1.75 (1.41, 2.17)** | **1.27 (1.06, 1.85)** | 1.56 (0.95,2.56) | 0.99 (0.55, 1.78) |
| **Bilateral disease on chest X-ray** | **2.27 (1.75, 2.95)** | **1.87 (1.05, 3.31)** | 2.24(0.98, 5.17) | 1.70 (0.75, 3.86) |
| **Diabetes (yes)** | 0.91 (0.68, 1.21) | 0.69 (0.25, 1.87) | 1.78 (0.39,8.06) | 0.23 (0.04, 1.14) |
| **Site of disease (only pulmonary)** | **0.63 (0.42, 0.96)** | 0.81 (0.53,1.25) | 1.04 (0.61, 1.78) | 0.66 (0.29, 1.48) |
| **On directly observed therapy** | 0.99 (0.29, 3.29) | 0.17 (0.03, 1.00) | *Did not converge* | 0.93 (0.08, 10.55) |
| **Any past history of TB** | **1.55 (1.26, 1.91)** | **1.30 (1.08, 1.56)** | **1.47 (1.20, 1.81)** | 0.91 (0.58, 1.42) |
| **Past history of first-line TB drug use** | **1.45 (1.14, 1.83)** | **1.29 (1.04, 1.59)** | **1.14 (1.13,1.76)** | 0.84 (0.44, 1.62) |
| **Past history of second-line TB drug use** | **2.22 (1.68, 2.94)** | **1.54 (1.16, 2.06)** | 1.24 (0.98,1.56) | **2.05 (0.82, 5.13)** |
| **World Bank income level of country** |  |  |  |  |
| Low | **Reference** | **Reference** | **Reference** | **Reference** |
| Lower/middle | **2.11 (1.47,3.03)** | 1.28 (0.37,4.40) | 1.32 (0.39, 4.39) | 3.92 (0.21, 70.08) |
| High | **0.56 (0.35, 0.87)** | 0.72 (0.19, 2.63) | 0.77 (0.20, 2.96) | 1.65 (0.08, 30.89) |
| **Resistant to fluoroquinolone** | **1.71 (1.41, 2.07)** | 1.19 (0.95, 1.49) | 1.15 (0.90, 1.45) | **2.90 (1.38, 6.07)** |
| **Resistant to second-line injectable agent** | **1.59 (1.32, 1.92)** | **1.29 (1.05, 1.59)** | 1.25 (0.98, 1.56) | **2.91 (1.63, 5.20)** |
| **Used Group A drugs** | **0.76 (0.60, 0.96)** | **0.58 (0.38, 0.87)** | **0.60 (0.37, 0.98)** | **0.42 (0.20, 0.90)** |
| **Number of drugs Group A used** |  |  |  |  |
| 0 | **Reference** | **Reference** | **Reference** | **Reference** |
| 1 | **0.76 (0.60, 0.96)** | **0.63 (0.42, 0.95)** | 0.66 (0.41,1.08) | **0.45 (0.21, 0.96)** |
| 2 or more | 0.76 (0.54, 1.07) | **0.32 (0.21, 0.50)** | **0.37 (0.22, 0.61)** | **0.16 (0.04, 0.69)** |
| **Used Group B drugs** | 0.82 (0.65, 1.05) | 1.06 (0.80, 1.40) | 0.95 (0.63, 1.44) | 1.14 (0.78, 1.67) |
| **Number of drugs Group B used** |  |  |  |  |
| 0 | **Reference** | **Reference** | **Reference** | **Reference** |
| 1 | 0.81 (0.64, 1.03) | 1.07 (0.81, 1.42) | 0.96 (0.63, 1.47) | 1.13 (0.77, 1.66) |
| 2 | 1.03 (0.72, 1.47) | 0.90 (0.62, 1.29) | 0.83 (0.53, 1.34) | 3.20 (0.55, 18.41) |
| **Used Group C drugs** | 0.59 (0.28, 1.26) | 0.68 (0.17, 2.81) | 0.69 (0.16, 2.91) | *Did not converge* |
| **Number of drugs Group C used** |  |  |  |  |
| 0-1 | **Reference** | **Reference** | **Reference** | **Reference** |
| 2 | 0.81 (0.58, 1.23) | 1.23 (0.82, 1.78) | 1.19 (0.81, 1.76) | 0.38 (0.06, 2.16) |
| 3 | 0.97 (0.70, 1.34) | 1.00 (0.69, 1.45) | 1.02 (0.69, 1.51) | 0.32 (0.05, 1.83) |
| 4 or more | 1.19 (0.84, 1.69) | 1.28 (0.83, 1.97) | 1.44 (0.92, 2.28) | 0.32 (0.05, 1.93) |
| Note: Used generalized linear mixed model random effect (binomial family)  Abbreviations: MDR-TB=multi-drug resistant TB; ART=antiretroviral therapy  WHO classification of antitubercular agents  Group A drugs are bedaquiline, moxifloxacin, levofloxacin, and linezolid.  Group B drugs are clofazimine, cycloserine and terizidone.  Group C drugs are ethambutol, pyrazinamide, delamanid, carbapenems, amikacin, streptomycin, ethionamide and prothionamide, and para-aminosalicylic acid. | | | | |

**Supplemental Table 6: Stratified analysis of the association between HIV and death among adult patients with MDR-TB1.** Odds ratios with 95% CIs that do not include 1 were statistically significant (p<0.05) and are in bold text.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Incidence of death among all HIV-negative**  (n/N) | **Incidence of death among HIV-positive on ART**  (n/N) | **Adjusted OR for death HIV-positive on ART vs HIV-negative (95% CI) 1** | **Incidence of death among HIV-positive not on ART or ART unknown** (n/N) | **Adjusted OR for death HIV-positive not on ART or unknown ART vs HIV-negative (95% CI) 1** |
| **All patients** | 882/6709 | 672/2494 | **1.8 (1.5, 2.2)** | 299/702 | **4.2 (3.0, 5.9)** |
| **MDR-TB excluding XDR-TB and pre-XDR-TB2** | 410/4011 | 364/1570 | **2.1 (1.7, 2.6)** | 159/475 | **5.4 (3.2, 9.3)** |
| **Pre-XDR (resistant to second-line injectable agent)2** | 105/798 | 58/210 | **2.0 (1.1,3.7)** | 18/39 | **-** |
| **Pre-XDR (resistant to fluoroquinolone)2** | 93/685 | 41/172 | 1.4 (0.7,3.1) | 5/16 | **-** |
| **XDR-TB only2** | 236/910 | 197/501 | 1.3 (0.9,2.6) | 106/136 | **3.9 (1.8, 8.3)** |
| **Number of Group A drugs used** |  |  |  |  |  |
| 0 | 317/1865 | 144/295 | 1.3 (0.9, 1.9) | 218/519 | **3.3 (2.1, 5.3)** |
| 1 | 428/3504 | 384/1370 | **1.9 (1.5, 2.4)** | 77/161 | **6.0 (2.7, 13.7)** |
| 2 or more | 137/1340 | 144/829 | 1.3 (0.9, 2.0) | 4/22 | - |
| **Used at least 5 effective drugs** |  |  |  |  |  |
| Yes | 192/2004 | 125/705 | **1.6 (1.1, 2.6)** | 22/93 | - |
| No | 690/4705 | 547/1789 | **2.0 (1.6, 2.4)** | 277/609 | **4.7 (3.1, 7.2)** |
| **Used moxifloxacin or levofloxacin** |  |  |  |  |  |
| Yes | 533/4524 | 520/2164 | **1.9 (1.6, 2.3)** | 80/173 | **7.6 (3.4, 17.0)** |
| No | 349/2185 | 152/330 | **1.5 (1.1, 2.2)** | 219/529 | **4.0 (2.6, 6.3)** |
| **Used**  **bedaquiline** |  |  |  |  |  |
| Yes | 109/965 | 132/785 | **1.4 (1.02, 2.0)** | 5/26 | - |
| No | 773/5744 | 540/1709 | **2.1 (1.7, 2.6)** | 294/676 | **4.0 (2.7, 5.8)** |
| **Used**  **linezolid** |  |  |  |  |  |
| Yes | 112/1158 | 95/567 | 1.4 (0.9, 2.0) | 3/18 | **-** |
| No | 770/5551 | 577/1927 | **2.2 (1.8, 2.7)** | 296/684 | **4.7 (3.2, 6.9)** |
| **Used**  **clofazimine** |  |  |  |  |  |
| Yes | 109/801 | 119/502 | **2.9 (1.8, 4.5)** | 7/16 | **-** |
| No | 773/5908 | 553/1992 | **1.9 (1.6, 2.3)** | 292/686 | **4.2 (2.9, 6.2)** |
| **Used any Group A drug AND used at least 5 effective drugs** |  |  |  |  |  |
| Yes | 153/1643 | 113/656 | 1.6 (0.99, 2.6) | 11/36 | - |
| No | 729/5066 | 559/1838 | **2.0 (1.6, 2.6)** | 288/666 | **4.7 (3.1, 7.0)** |
| **Bedaquiline and linezolid use** |  |  |  |  |  |
| None | 720/5166 | 522/1652 | **2.0 (1.6, 2.5)** | 294/670 | **4.2 (2.9, 6.0**) |
| Used only linezolid | 53/578 | 18/57 | 2.1 (0.8, 5.4) | 0/6 | - |
| Used only bedaquiline | 50/385 | 55/275 | 1.6 (0.9, 3.0) | 2/14 | - |
| Used both | 59/580 | 77/510 | 1.4 (0.9, 2.3) | 3/12 | - |
| Abbreviations: MDR-TB = multi-drug resistant TB; XDR-TB = extensively drug resistant TB; ART=antiretroviral therapy  Notes:  1-Model includes propensity score matching for age, sex, site, year, past treatment, DOT, AFB smear. Exact matching for World Bank Income classification, SLI resistance, FQ resistance  2- Model includes propensity score matching for age, sex, site, year, past treatment, DOT, AFB smear. Exact matching for World Bank Income classification | | | | | |

**Supplemental Table 7. Characteristics of patients, included and excluded in the survival analysis, due a missing outcome date in the individual patient data analysis of HIV and MDR-TB.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Included (N=8,432)** | **Excluded (N=3,488)** | **P-value** |
| **Age, mean (range)** | 38 (18, 94) | 37 (18, 81) | <0.001 |
| **HIV status, n (%)** |  |  |  |
| HIV-negative | 5584 (66%) | 2453(70%) | <0.001 |
| HIV-positive (all) | 2848 (34%) | 1035 (30%) |  |
| **HIV ART use, n (%)** |  |  | <0.001 |
| HIV-positive on ART | 2445 (29%) | 552 (16%) |  |
| HIV-positive not on ART or unknown ART | 403 (5%) | 483 (14%) |  |
| HIV-negative | 5584 (66%) | 2453 (70%) |  |
| **Outcome, n (%)** |  |  | <0.001 |
| Success | 6208 (74%) | 921 (26%) |  |
| Failure or relapse | 670 (8%) | 253 (7%) |  |
| Died | 1554 (18%) | 299 (9%) |  |
| Lost to follow-up | 0 (0%) | 2015 (58%) |  |
| **Sex, n (%)** |  |  |  |
| Male | 5035 (60%) | 1189 (34%) | 0.08 |
| Female | 3395 (40%) | 2299 (66%) |  |
| Unknown | 2 (0%) | 0 (0%) |  |
| **Body mass index, median (IQR)** | 19.8 (17.7, 21.9) | 19.8 (17.6, 22.3) |  |
| **Diabetes, n (%)** |  |  |  |
| Yes | 556 (7%) | 171 (5%) | <0.001 |
| No | 3990(47%) | 1411 (40%) |  |
| Unknown | 3886 (46%) | 1906 (55%) |  |
| **Past TB treatment, n (%)** |  |  | <0.001 |
| Yes | 5603 (66%) | 2685 (77%) |  |
| No | 2698 (32%) | 723 (21%) |  |
| Unknown | 131 (2%) | 80 (2%) |  |
| **Acid-fast bacilli smear status, n (%)** |  |  |  |
| Positive | 5617 (67%) | 1456 (42%) | <0.001 |
| Negative | 2251 (27%) | 500 (14%) |  |
| Unknown | 564 (7%) | 1532 (44%) |  |
| **Cavitation on chest X-ray, n (%)** |  |  |  |
| Present | 2928 (35%) | 957 (27%) | <0.001 |
| Absent | 1833 (22%) | 556 (16%) |  |
| Unknown | 3671 (44%) | 1975 (57%) |  |
| **Site of TB disease, n (%)** |  |  | <0.001 |
| Pulmonary | 8023 (95%) | 3414 (98%) |  |
| Pulmonary plus extrapulmonary | 347 (4%) | 61 (2%) |  |
| Unknown | 62 (1%) | 13 (0%) |  |
| **Bilateral disease on chest X-ray, n %** |  |  | 0.626 |
| Present | 2644 (31%) | 1076 (31%) |  |
| Absent | 1136 (13%) | 492 (14%) |  |
| Unknown | 4652 (55%) | 1920 (55%) |  |
| **Year of MDR-TB treatment start, median (IQR)** | 2010 (2007, 2015) | 2008 (2005, 2012) | <0.001 |
| **World Bank income level of country, n (%)** |  |  | <0.001 |
| Low and low-middle | 1338(16%) | 1213 (35%) |  |
| Middle | 4952 (59%) | 1877 (54%) |  |
| High | 2142 (25%) | 398 (11%) |  |

**Supplemental Table 7 (continued)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Included (N=8432)** | **Excluded (N=3488)** | **P-value** |
| **Second-line injectable resistance, n (%)** |  |  | <0.001 |
| Yes | 2343 (28%) | 703 (20%) |  |
| No | 5814 (69%) | 2653 (76%) |  |
| Unknown | 275 (3%) | 132 (4%) |  |
| **Fluoroquinolone resistance, n (%)** |  |  | <0.001 |
| Yes | 2145 (25%) | 653 (19%) |  |
| No | 5999 (71%) | 2706 (78%) |  |
| Unknown | 288 (3%) | 129 (4%) |  |
| **Patient on directly observed therapy, n (%)** |  |  |  |
| Yes | 7436 (88%) | 2618 (75%) | <0.001 |
| No | 483 (6%) | 758 (22%) |  |
| Unknown | 513 (6%) | 112 (3%) |  |
| **Use of Group A drugs, n (%)** |  |  |  |
| Yes | 6344 (75%) | 2249 (64%) | <0.001 |
| No | 2088 (25%) | 1239 (36%) |  |
| **Use of Group B drugs, n (%)** |  |  | <0.001 |
| Yes | 7307 (87%) | 2903 (83%) |  |
| No | 1125 (13%) | 585 (17%) |  |
| **Use of Group C drugs, n (%)** |  |  | <0.001 |
| Yes | 8349 (99%) | 3472 (100%) |  |
| No | 83 (1%) | 16 (0%) |  |
| **Levofloxacin or moxifloxacin used, n (%)** |  |  |  |
| Yes | 5998 (71%) | 2176 (62%) | <0.001 |
| No | 2434 (29%) | 1312 (38%) |  |
| **Bedaquiline used, n (%)** |  |  | **<0.001** |
| Yes | 6676 (79%) | 307 (9%) |  |
| No | 1756 (21%) | 3181 (91%) |  |
| **Linezolid used, n (%)** |  |  | **<0.001** |
| Yes | 1674 (20%) | 279 (8%) |  |
| No | 6758 (80%) | 3209 (92%) |  |
| **Clofazimine used, n (%)** |  |  | **<0.001** |
| Yes | 1135 (13%) | 370 (11%) |  |
| No | 7297 (87%) | 3118 (89%) |  |
| WHO classification of antitubercular agents  Group A drugs are bedaquiline, moxifloxacin, levofloxacin, and linezolid.  Group B drugs are clofazimine, cycloserine and terizidone.  Group C drugs are ethambutol, pyrazinamide, delamanid, carbapenems, amikacin, streptomycin, ethionamide and prothionamide, and para-aminosalicylic acid.  Percentages may not add to 100% due to rounding.  Abbreviations: MDR-TB=multi-drug resistant TB; ART=antiretroviral therapy | | | |

**Supplemental Table 8. Centre characteristics**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **No** | **Contact person (ref)** | **Study Location** | **Years** | **Catchment area** | **Type of Drug Regimen** |
| 1 | Ahmad1 | Peshawar, Pakistan | 2012-2013 | Hospital | Standardized and individualized |
| 2 | Ahuja2 | New York City, USA | 2000-2006 | State | Individualized |
| 3 | Anderson3 | UK | 2004-2007 | Country | Individualized |
| 4 | Bang4 | Denmark | 1992-2007 | Country | Individualized |
| 5 | Barkane5 | Riga, Latvia | 2014 | Hospital | Individualized |
| 6 | Barry (Korea)6,7 | Seoul and Changwon, South Korea | 2008-2011 | Hospital | Individualized |
| 7 | Barry/Flood (Calif)8 | California, USA | 2009-2015 | State | Individualized |
| 8 | Bonnet9 | Abkhazia | 2001-2014 | Region | Individualized |
| 9 | Brode10 | Toronto, Canada | 2010-2014 | Hospital | Individualized |
| 10 | Brust11 | KwaZulu-Natal, South Africa | 2000-2003 | Hospital | Standardized |
| 11 | Cegielski12,13 | Multination (Estonia, Latvia, Philippines, Peru, Russia, South Africa, South Korea, Taiwan, Thailand) | 2005-2010 | Clinical centres (multi-center) | Individualized |
| 12 | Chan (Denver)14 | Denver, USA | 1999-2015 | Hospital | Individualized |
| 13 | Dheda15-17 | Cape Town, Upington and Johannesburg in South Africa | 2002-2008 | Clinic (multi-center) | Individualized |
| 14 | Fox18 | Sydney, Australia | 2000-2018 | Clinic (multi-center) | Individualized |
| 15 | Gegia19 | Georgia | 2008 | Country | Standardized |
| 16 | Guglielmetti20,21 | Paris, France | 2010-2013 | Hospital | Individualized |
| 17 | Guglielmetti22 | Paris, France | 2014-2015 | Hospital | Individualized |
| 18 | Hughes23 | Khayelitsha, South Africa | 2011-2015 | Community | Individualized |
| 19 | Isaakidis23,24 | Mumbai, India | 2006-2016 | Clinic | Individualized |
| 20 | Jarlsberg25 | San Francisco, USA | 2001-2015 | City | Individualized |
| 21 | Kempker26 | Tbilisi, Georgia | 2009-2012 | Hospital | Individualized |
| 22 | Koenig27 | Port-au-Prince, Haiti | 2008-2015 | Clinic (multi-center) | Standardized and individualized |
| 23 | Koh28,29 | Seoul, South Korea | 2005-2011 | Hospital | Individualized |
| 24 | Kuksa30 | Riga, Latvia | 2014 | Hospital | Individualized |
| 25 | Kvasnovsky31,32 | Eastern Cape and KwaZulu-Natal, South Africa | 2006-2008 | Clinic (multi-center) | Individualized |
| 26 | Lange33 | Germany | 2004-2006 | Hospital (multi-center) | Individualized |
| 27 | Laniado-Laborin34 | Baja California, Mexico | 2006-2010 | Clinic (multi-center) | Individualized |
| 28 | Leung35,36 | Hong Kong | 1996-2009 | Territory | Individualized |
| 29 | Marks37 | California, New York City, and Texas in USA | 2005-2007 | State (multi-center) | Individualized |
| 30 | Migliori38,39 | Multination (Italy, Belgium, Ecuador, Belarus, Greece, Peru, Slovakia, Netherlands, UK) | 2003-2015 | Hospital (multi-center) | Individualized |
| 31 | Migliori (BDQ) 40 | Multination (Argentina, Australia, Belarus, Belgium, Greece, India, Italy, Netherlands, Peru, Portugal, Russia, South Africa, Spain, Sweden, UK) | 2010-2014 | Hospital (multi-center) | Individualized |
| 32 | Milanov41 | Gabrovo, Bulgaria | 2009-2010 | Hospital | Individualized |
| 33 | Ndjeka42 | South Africa | 2013-2015 | Hospital | Individualized |
| 34 | Ndjeka43 | South Africa |  |  |  |
| 35 | O’Donnell44 | KwaZulu-Natal, South Africa | 2006-2010 | Hospital | Individualized |
| 36 | Palmero45 | Buenos Aires, Argentina | 2012-2013 | Hospital | Individualized |
| 37 | Podewils46 | Makati, Phillipine | 1999-2006 | Clinic | Individualized |
| 38 | Riekstina/Leimane47 | Riga, Latvia | 2012-2013 | Country | Individualized |
| 39 | Rodrigues48 | Sao Paulo, Brazil | 2014-2016 | State | Standardized and individualized |
| 40 | Seo49 | South Korea |  |  |  |
| 41 | Seung50 | North Korea | 2012 | Sanatorium (multi-center) | Standardized |
| 42 | Shim29,51 | Seoul, South Korea | 2006-2012 | Hospital | Individualized |
| 43 | Singla52 | Delhi, India | 2006-2011 | Hospital | Individualized |
| 44 | Skrahina53 | Minsk, Belarus | 2015 | Hospital | Standardized and individualized |
| 45 | Smith54 | Arkhangelsk Oblast, Russia | 2005-2010 | Oblast (multi-center) | Individualized |
| 46 | TMC207-C20855,56 | Multination (Brazil, India, Latvia, Peru, Philippines, Russia, South Africa, Thailand) | 2008-2009 | Hospital (multi-center) | Individualized |
| 47 | TMC207-C20957 | Multination (China, South Korea, Philippines, Thailand, Estonia, Latvia, Russia, Turkey, Ukraine) | 2009-2010 | Hospital (multi-center) | Individualized |
| 48 | Udwadia58 | Mumbai, India | 2004-2007 | Hospital | Individualized |
| 49 | van der Werf59 | The Netherlands | 2000-2009 | Country | Individualized |
| 50 | Vasilyeva60 | Russia |  |  |  |
| 51 | Viiklepp61 | Estonia | 2008-2013 | Country | Individualized |
| 52 | Yim/Kwak62 | Seoul, South Korea | 2006-2010 | Hospital | Individualized |

**Supplemental Table 9. Outcomes definitions**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **No** | **Contact person (ref)** | **Cure** | **Treatment Completed** | **Treatment Failure** | **Death** | **Lost to follow-up (default)** | **Relapse** |
| 1 | Ahmad1 | Laserson | Laserson | Laserson | Laserson | Laserson |  |
| 2 | Ahuja2 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 3 | Anderson3 | Not reported | Complete a full course of therapy within 12/24 months of starting treatment | Patient found to have stopped treatment (by choice) or for any other reason not mentioned below. | Laserson | Unable to contact patient before end of treatment. Treatment outcome unknown. | Laserson |
| 4 | Bang4 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 5 | Barkane5 | Laserson | Laserson | Laserson | Laserson | Laserson | WHO |
| 6 | Barry (Korea)6,7 | Laserson | Laserson | No culture conversion after 6 months of treatment | Laserson | Laserson | Laserson |
| 7 | Barry/Flood (Calif)8 | See footnote: A | Laserson | See footnote: B | Laserson | Laserson | Not used as an outcome. |
| 8 | Bonnet9 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 9 | Brode10 | Laserson | Laserson | 2013 WHO | Laserson | Laserson | Laserson |
| 10 | Brust11 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 11 | Cegielski12,13 | Laserson | Laserson | Laserson | Laserson | Laserson | Not assessed |
| 12 | Chan (Denver) 14 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 13 | Dheda15-17 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 14 | Fox18 | Laserson | Laserson | Laswerson | Laserson | Laserson | N/A |
| 15 | Gegia19 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 16 | Guglielmetti20,21 | See footnote: A | Laserson | See footnote: B | Laserson | Laserson | Laserson |
| 17 | Guglielmetti22 | See footnote: A | Laserson | See footnote: B | Laserson | Laserson | Laserson |
| 18 | Hughes23 | Laserson | Laserson | Sputum cultures do NOT convert to negative within 6–8 months. Two consecutive positive cultures (1 month apart) after 8 months. | Laserson | Laserson | Not assessed |
| 19 | Isaakidis23,24 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 20 | Jarlsberg25 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 21 | Kempker26 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 22 | Koenig27 | 2008-2013, Laserson;  2013-2015:  >3 consecutive negative results at the end of Rx | Laserson | Positive cultures after 6 months OR 2 consecutive positive cultures after culture conversion. | Laserson | Laserson | Laserson |
| 23 | Koh28,29 | See footnote: A | Laserson | See footnote: B | Laserson | Laserson | Laserson |
| 24 | Kuksa | Laserson | Laserson | Laserson | Laserson | Laserson | WHO |
| 25 | Kvasnovsky31,32 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 26 | Lange33 | Laserson | Laserson | Laserson | Laserson | Laserson |  |
| 27 | Laniado-Laborin34 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 28 | Leung35,36 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 29 | Marks37 | Not reported | Laserson | If >=2 positive cultures in final months of treatment; OR, treatment stopped due to AE | Laserson | Laserson |  |
| 30 | Migliori38,39 | See footnote: A | Laserson | See footnote: B | Laserson | Laserson | Laserson |
| 31 | Migliori (BDQ) 40 | WHO 2013 | WHO 2013 | WHO 2013 | WHO 2013 | WHO 2013 |  |
| 32 | Milanov41 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 33 | Ndjeka42 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 34 | Ndjeka43 |  |  |  |  |  |  |
| 35 | O’Donnell44 | Laserson | Laserson | Laserson | Laserson | Laserson |  |
|  |  |  |  |  |  |  |  |
| 36 | Palmero45 | 2013 WHO criteria | 2013 WHO criteria | See footnote: B | 2013 WHO criteria | Laserson | Laserson |
| 37 | Podewils46 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |

**Supplemental Table 9 (continued)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **No** | **Contact person (ref)** | **Cure** | **Treatment Completed** | **Treatment Failure** | **Death** | **Lost to follow-up (default)** | **Relapse** |
| 38 | Riekstina/Leimane47 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 39 | Rodrigues48 | 3 cultures negative at months 12,15 and18; or culture negative at month 15, 18, 21 and 24 | Laserson | Laserson | Laserson | Patient did not return to healthy facility > 30 consecutive days or > 30 consecutive days with no DOTS | Laserson |
| 40 | Seo49 |  |  |  |  |  |  |
| 41 | Seung50 |  |  |  |  |  |  |
| 42 | Shim29,51 | WHO 2013 | WHO 2013 | WHO 2013 | WHO 2013 | WHO 2013 | WHO 2013 |
| 43 | Singla52 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 44 | Skrahina53 | WHO 2013 | WHO 2013 | WHO 2013 | WHO 2013 | WHO 2013 | WHO 2013 |
| 45 | Smith54 | Laserson | Laserson | Laserson | Laserson | Laserson | Not assessed |
| 46 | TMC207-C20855,56 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 47 | TMC207-C20957 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 48 | Udwadia58 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 49 | van der Werf59 | Negative cultures, after initial positive culture. | Laserson |  | Laserson | Laserson | No relapses in the study |
| 50 | Vasilyeva60 |  |  |  |  |  |  |
| 51 | Viiklepp61 | Laserson | Laserson | Laserson | Laserson | Laserson | Laserson |
| 52 | Yim/Kwak62 | See footnote: A | Laserson | See footnote: B | Laserson | Laserson | Laserson |

*Laserson outcome definition:*

*Cure = An MDR-TB patient who has completed treatment according to country protocol and has been consistently culture-negative (with at least ﬁve results) for the ﬁnal 12 months of treatment. If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures, taken at least 30 days apart.*

*Treatment completed An MDR-TB patient who has completed treatment according to country protocol but does not meet the deﬁnition for cure or treatment failure due to lack of reported bacteriologic results (i.e., fewer than ﬁve cultures were performed in the ﬁnal 12 months of therapy).*

*Death An MDR-TB patient who dies for any reason during the course of MDR-TB treatment.​*

*Treatment default An MDR-TB patient whose MDR-TB treatment was interrupted for 2 or more consecutive months for any reason.​*

*Treatment failure\* Treatment will be considered to have failed if two or more of the ﬁve cultures recorded in the ﬁnal 12 months are positive, or if any one of the ﬁnal three cultures is positive. Treatment will also be considered to have failed if a clinical decision has been made to terminate treatment early due to poor response or adverse events*

*Commonly used alternative outcome definitions:*

*A: For Cure: Treatment completed as planned, or as per national guidelines, AND at least 3 consecutive negative cultures (at least one month apart) after the end of the intensive phase   
B: For Failure: Treatment terminated or permanent change of >2 anti-TB drugs because of: lack of conversion by the end of the intensive phase; OR, bacteriological reversion after conversion; OR, acquired resistance to fluoroquinolones or second-line injectables; OR, AE.*

**Supplemental Table 10. Drug susceptibility testing methods for 1st line drugs**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **No** | **Contact person (ref)** | **Type of culture media** | **Name of culture media (Culture method)** | **Critical Concentrations of Drug Susceptibility Testing for First-Line Drugs (if available)** | | | | |
| Isoniazid | Rifampin | Ethambutol | Streptomycin | Pyrazinamide |
| 1 | Ahmad1 | Solid | Middlebrook 7H10 | 0.2 μg/mL | 1.0 μg/mL | 5.0 μg/mL | 2.0 μg/mL | 100 μg/mL |
| 2 | Ahuja2 | Solid and Liquid | BACTEC/MIGIT | 0.1-0.2 μg/mL | 1.0 μg/mL | 5.0 μg/mL | 1.0 or 4.0 μg/mL | 100 μg/mL |
| 3 | Anderson3 | Solid | NA | NA | NA | NA | NA | NA |
| 4 | Bang4 | Solid | Lowenstein-Jensen (LJ) |  |  |  |  |  |
|  |  | Liquid | BACTEC | 0.1 μg/mL | 2.0 μg/mL | 2.5 μg/mL | 2.0 μg/mL | 100 μg/mL |
| 5 | Barkane5 | Solid | Lowenstein-Jensen (LJ) | 0.1&0.2 μg/mL | 40.0 μg/mL | 2.0 μg/mL | - | - |
|  |  | Liquid | Middlebrook | 0.1 μg/mL | 1.0 μg/mL | 5.0 μg/mL | - | 100.0 μg/mL |
| 6 | Barry (Korea)6,7 | Solid | Lowenstein-Jensen (LJ)/Middlebrook | 0.2 μg/mL | 40 μg/mL | 2.0 μg/mL | 10 μg/mL |  |
|  |  | Liquid | BACTECT/MIGIT |  |  |  |  |  |
| 7 | Barry/Flood (Calif)8 | Liquid | BACTEC/MGIT | 0.1 μg/mL 0.4 μg/mL | 1 μg/mL | 5 μg/mL | 1.0 and 2.0 μg/mL | 100 μg/mL |
| 8 | Bonnet9 | Liquid | MGIT | 0.1 μg/mL | 1.0 μg/mL | 5.0 μg/mL | 1.0 μg/mL |  |
| 9 | Brode10 | Liquid | BACTEC MGIT 960 | 0.1 μg/mL 0.4 μg/mL | 1.0 μg/mL | 5.0 μg/mL |  | 100 μg/mL |
|  |  | Solid | Lowenstein-Jensen (LJ) |  |  |  |  |  |
| 10 | Brust11 | Solid | Lowenstein-Jensen (LJ) | 0.2 μg/mL 1 μg/mL | 40 μg/mL | 2.0 μg/mL | 4.0 μg/mL |  |
| 11 | Cegielski12,13 | Solid | Middlebrook 7H10 | 0.2 μg/mL | 1.0 μg/mL | 5.0 μg/mL | 2.0 μg/mL |  |
| 12 | Chan (Denver)14 | Liquid | BACTEC MGIT 960 | 0.1 µg/mL | 1.0 μg/mL | 5.0 µg/mL | 1.0 and 4.0 µg/mL | 100 µg/mL |
| 13 | Dheda 15-17 | Solid | Middlebrooks 7H10 | 0.2 µg/mL | 1.0 µg/mL | 7.5 µg/mL | 2.0 µg/mL |  |
| 14 | Fox18 | Liquid | BACTEC MGIT 960 | 0.2ug/mL | 1.0 ug/mL | 5.0 ug/mL | 1.0 ug/mL | 100 ug/mL |
| 15 | Gegia19 | Solid | Lowenstein-Jensen (LJ) | 0.2 μg/mL | 40 μg/mL | 2.0 μg/mL |  | 100 μg/mL |
| 16 | Guglielmetti20,21 | Solid | Lowenstein-Jensen (LJ) | 0.2 μg/mL | 40 μg/mL | 2.0 μg/mL | 4.0 μg/mL | 300 μg/mL |
| 17 | Guglielmetti22 | Solid | Lowenstein-Jensen (LJ) | 0.2 μg/mL | 40 μg/mL | 2.0 μg/mL | 4.0 μg/mL | 300 μg/mL |
| 18 | Hughes23 | Solid | Lowenstein-Jensen (LJ)/Middlebrook | Line probe assay | Line probe assay |  |  |  |
|  |  | Other |  |  |  |  |  |  |
| 19 | Isaakidis23,24 | Liquid | BACTEC MGIT 960 | 0.1 μg/mL | 1.0 μg/mL | 5.0 μg/mL | 1.0 μg/mL | 100 μg/mL |
| 20 | Jarlsberg25 | Solid | Lowenstein-Jensen (LJ)/Middlebrook |  |  |  |  |  |
|  |  | Liquid | BACTEC/MGIT | 0.1 and 0.4 μg/mL | 1 μg/mL | 5 μg/mL |  | 100 μg/mL |
|  |  | Other | Nucleic acid amplification testing |  |  |  |  |  |
| 21 | Kempker26 | Solid | Lowenstein-Jensen solid medium | 0.2 μg/mL | 40 μg/mL | 5 μg/mL |  |  |
|  |  | Liquid | MGIT | 0.1 μg/mL | 1 μg/mL |  |  |  |
| 22 | Koenig27 | Liquid | MGIT | 0.1 μg/mL | 1.0 μg/mL | 5.0 μg/mL | 1.0 μg/mL | 100 μg/mL |
|  |  | Solid |  |  |  |  |  |  |
| 23 | Koh28,29 | Solid | Lowenstein-Jensen (LJ) | 0.2 μg/mL | 40 μg/mL | 2.0 μg/mL | 10 μg/mL | Pyrazinamidase test |
|  |  | Liquid | BACTEC/MGIT |  |  |  |  |  |
| 24 | Kuksa30 | Solid | Lowenstein-Jensen (LJ) | 0.1&0.2 μg/mL | 40.0 μg/mL | 2.0 μg/mL | - | - |
|  |  | Liquid | Middlebrook | 0.1 μg/mL | 1.0 μg/mL | 5.0 μg/mL | - | 100.0 μg/mL |
| 25 | Kvasnovsky31,32 | Solid | Middlebrook 7H10 | NA | NA | NA | NA | NA |
| 26 | Lange33 | Solid | BACTEC/MIGIT | NA | NA | NA | NA | NA |
|  |  | Liquid | Lowenstein-Jensen (LJ)/Middlebrook | 0.1 µg/mL | 1.0 μg/mL | 5.0 µg/mL | 1.0 and 4.0 µg/mL | 100 µg/mL |
| 27 | Laniado-Laborin34 | Liquid | MGIT | 0.1 μg/mL | 1.0 μg/mL | 5.0 μg/mL | 1.0 μg/mL | 100 μg/mL |
|  |  | Other | Xpert MTB/RIF |  |  |  |  |  |
| 28 | Leung35,36 | Solid | Lowenstein-Jensen (LJ) | 0.2 μg/mL | 32 μg/mL | 2.8 μg/mL | 16 μg/mL | 50 μg/mL |
|  |  | Other | Xpert, MTBDRplus and MTBDRsl |  |  |  |  |  |
| 29 | Marks37 | Solid or Liquid | Agar or BACTEC/MIGIT |  |  |  |  |  |
| 30 | Migliori38,39 | Liquid | BACTEC MGIT 960 |  |  |  |  |  |
|  |  | Other | Molecular LPA |  |  |  |  |  |

**Supplemental Table 10 (continued)**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **No** | **Contact person (ref)** | **Type of culture media** | **Name of culture media (Culture method)** | **Critical Concentrations of DST for First-Line Drugs (if available)** | | | | |
| Isoniazid | Rifampin | Ethambutol | Streptomycin | Pyrazinamide |
| 31 | Migliori (BDQ)40 | Liquid | BACTEC MGIT 960 |  |  |  |  |  |
| 32 | Milanov41 | Solid | Lowenstein-Jensen (LJ) solid media |  |  |  |  |  |
|  |  | Liquid | BACTEC MGIT 960 | 0.1 µg/mL | 1.0 µg/mL | 5.0 µg/mL | 1.0 µg/mL |  |
|  |  | Liquid | MGIT | 0.1 µg/mL | 1.0 µg/mL | 5.0 µg/mL | 1.0 µg/mL | 100 µg/mL |
| 33 | Ndjeka42 | Liquid | BACTEC MGIT 960 |  |  |  |  |  |
|  |  | Other | HAIN GenotypeMTBDR plus / Xpert MTB/RIF |  |  |  |  |  |
| 34 | Ndjeka43 |  |  |  |  |  |  |  |
| 35 | O'Donnell44 | Solid | 7H11 agar |  |  |  |  |  |
|  |  | Liquid | BACTEC MGIT 960 |  |  |  |  |  |
| 36 | Palmero45 | Solid | Lowenstein-Jensen (LJ)/Middlebrook | 0.1 and 1.0 µg/mL | 1.0 µg/mL | 2.0 µg/mL |  | Wayne test |
|  |  | Liquid | BACTEC/MGIT |  |  |  |  |  |
| 37 | Podewils46 | Solid | Lowenstein-Jensen (LJ)/Middlebrook | 0.2 and 1.0 µg/mL | 1.0 µg/mL | 5.0 µg/mL | 2.0 µg/mL | Wayne test |
|  |  | Liquid | MGIT | 0.1 µg/mL | 1.0 µg/mL | 5.0 µg/mL | 1.0 µg/mL | 100 µg/mL |
| 38 | Riekstina/Leimane47 | Solid | Lowenstein-Jensen (LJ) | 1.0 μg/mL | 40 μg/mL | 2.0 μg/mL |  |  |
|  |  | Liquid | MIGIT | 0.1 μg/mL | 1.0 μg/mL | 5.0 μg/mL |  | 100 μg/mL |
| 39 | Rodrigues48 | liquid | BACTEC/MGIT | 0.10 μg/mL | 1.0μg/mL | 5.0 μg/mL | 1.0 μg/mL | Not available |
| 40 | Seo49 |  |  |  |  |  |  |  |
| 41 | Seung50 | Xpert MTB/RIF |  |  |  |  |  |  |
|  |  | Solid |  |  |  |  |  |  |
| 42 | Shim29,51 | Solid | Lowenstein-Jensen (LJ) | 0.2 μg/mL | 40 ug/ml | 2.0 μg/mL | 10 μg/mL | Pyrazinamidase test |
| 43 | Singla52 | Solid | Lowenstein-Jensen medium | 0.2 µg/mL | 40 µg/mL | 2.0 µg/mL | 4.0 µg/mL |  |
| 44 | Skrahina53 | Solid | L J (absolute concentration method) | 0.2 µg/mL | 40 µg/mL | 2.0 µg/mL | NA | NA |
|  |  | Liquid | MGIT (proportion method) | 0.1 µg/mL | 1.0 µg/mL | 5.0 µg/mL | NA | 100 µg/mL |
| 45 | Smith54 | Solid | Middlebrook 7H10 | 0.2 μg/mL | 1.0 μg/mL | 5.0 μg/mL | 2.0 μg/mL |  |
| 46 | TMC207-C20855,56 | Liquid | MGIT for culture conversion |  |  |  |  |  |
|  |  | Solid | Middlebrook 7H10 | 0.2 μg/mL | 1.0 μg/mL | 7.5 μg/mL | 2.0 μg/mL | 100 μg/mL |
| 47 | TMC207-C20957 | Liquid | MGIT for culture conversion |  |  |  |  |  |
|  |  | Solid | Middlebrook 7H10 | 0.2 μg/mL | 1.0 μg/mL | 7.5 μg/mL | 2.0 μg/mL | 100 μg/mL |
| 48 | Udwadia58 | Liquid | MGIT | 0.1 μg/mL | 1.0 μg/mL | 5.0 μg/mL |  | 100 μg/mL |
| 49 | van der Werf59 | Liquid | MGIT | 0.2 μg/mL | 1.0 μg/mL | 5.0 μg/mL | 5.0 μg/mL |  |
| 50 | Vasilyeva60 |  |  |  |  |  |  |  |
| 51 | Viiklepp61 | Liquid | MIGIT | 0.1 μg/mL | 1.0 μg/mL | 5.0 μg/mL | 1.0 μg/mL | 100 μg/mL |
|  |  | Other | Genotype MTBDR Plus |  |  |  |  |  |
| 52 | Yim/Kwak62 | Solid | Lowenstein-Jensen (LJ) | 0.2 μg/mL | 40 μg/mL | 2.0 μg/mL | 10 μg/mL | Pyrazinamidase test |

**Supplemental Table 11. Drug susceptibility testing methods for 2nd line drugs**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **No** | **Contact person (ref)** | **Name of culture media (Culture method)** | **Critical Concentrations of DST for Second-Line Drugs (if available)** | | | | | | | | | | | |
| Kanamycin | Amikacin | Capreomycin | Ofloxacin | Ciprofloxacin | Moxifloxacin | Levofloxacin | Ethionamide | Prothionamide | Cycloserine | Para-aminosalicylic acid | Linezolid |
| 1 | Ahmad1 | Agar proportion method on Middlebrook 7H10 |  |  | 5.0 μg/mL |  |  |  |  |  |  | 5.0 μg/mL |  |  |
| 2 | Ahuja2 | Agar proportion method |  |  | x |  | x | x | x |  |  | x |  | x |
| 3 | Anderson3 | Proportion or resistance ratio method | NA |  | NA | NA | NA | NA |  | NA |  | NA | NA | NA |
| 4 | Bang4 | Lowenstein Jensen proportion method |  |  |  |  | 20/40/50 μg/mL |  |  |  |  |  |  | 20/40/50 μg/mL |
|  |  | BACTEC 460 TB |  |  | 2.5 μg/mL |  |  | 4.0 μg/mL |  |  |  | 2.5 μg/mL |  |  |
| 5 | Barkane5 | Lowenstein Jensen (LJ) | 30.0 μg/mL | 30.0 μg/mL | 40.0 μg/mL | 4.0 μg/mL | - | - | - | 40.0 μg/mL | - | 30.0 μg/mL | 1.0 μg/mL | - |
| 6 | Barry (Korea)6,7 | Absolute concentration method | x | x |  | x | x | x |  | x | x |  | x | x |
| 7 | Barry/Flood (Calif)8 | agar proportion: Sm, Cfx, Ofx, Cm, Km, PAS. MGIT 960 for: Mfx, Am, Eto, Rbt | x | x | x |  | x | x | x | x | x | x |  | x |
| 8 | Bonnet9 | proportion methods on 7H10 | x |  | x | x |  |  |  | x |  | x | x |  |
| 9 | Brode10 | Bactec MGIT 960 (prior Oct 1,2010, BACTEC 460) | x | x | x | x |  | x |  | x |  |  | x | x |
| 10 | Brust11 | Lowenstein Jensen (LJ) | 20 μg/mL |  |  | 2.5 μg/mL |  |  |  | 20 μg/mL |  |  |  |  |
| 11 | Cegielski12,13 | Indirect agar proportion method on Middlebrook 7h10 agar | 5.0 μg/mL | 4.0 μg/mL | 10 μg/mL | 2.0 μg/mL | 2.0 μg/mL |  |  | 10 μg/mL |  |  | 2.0 μg/mL |  |
| 12 | Chan (Denver) 14 | MGIT 960 | 2.5 µg/mL | 1.0 µg/mL | 2.5 µg/mL | 2.0 µg/mL |  | 0.25 µg/mL | 1.5 µg/mL | 5.0 µg/mL |  |  |  | 1.0 µg/mL |
| 13 | Dheda15-17 | Indirect method on Middlebrook 7H11 | x | x |  | x |  |  |  | x |  |  |  |  |
| 14 | Fox18 | BACTEC MGIT 960 | N/A | 1.0 ug/mL | 2.5 ug/mL | N/A (Cipro 2.0 ug/mL) | 1.0 ug/mL | N/A | N/A | 5.0 ug/mL | N/A | 200 ug/mL | 4.0 ug/mL | 1.0 ug/mL |
| 15 | Gegia19 | Proportion concentration method | 30 μg/mL |  | 40 μg/mL | 2.0 μg/mL |  |  |  | 10 μg/mL |  |  | 0.5 μg/mL |  |

**Supplemental Table 11 (continued)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **No** | **Contact person (ref)** | **Name of culture media (Cultre method)** | **Critical Concentrations of DST for Second-Line Drugs (if available)** | | | | | | | | | | | |
| Kanamycin | Amikacin | Capreomycin | Ofloxacin | Ciprofloxacin | Moxifloxacin | Levofloxacin | Ethionamide | Prothionamide | Cycloserine | Para-aminosalicylic acid | Linezolid |
| 16 | Guglielmetti20,21 | Proportion method | 30 μg/mL | 40 μg/mL | 40 μg/mL | 2.0 μg/mL |  | 2.0 μg/mL |  | 40 μg/mL |  | 30 μg/mL | 0.5 μg/mL | 1.0 μg/mL |
| 17 | Guglielmetti22 | Proportion method | 30 μg/mL | 40 μg/mL | 40 μg/mL | 2.0 μg/mL |  | 2.0 μg/mL |  | 40 μg/mL |  | 30 μg/mL | 0.5 μg/mL | 1.0 μg/mL |
| 18 | Hughes23 | Proportion method pre Jan 2017 - then Hain LPA 2nd line |  | x |  | x |  |  |  | x |  |  |  |  |
| 19 | Isaakidis23,24 | BACTEC MGIT 960 | 2.5 μg/mL | 1.0 μg/mL | 2.5 μg/mL | 2.0 μg/mL |  | 0.5 μg/mL |  | 5.0 μg/mL |  |  | 4.0 μg/mL | 1.0 μg/mL |
| 20 | Jarlsberg25 | MGIT or agar proportion method |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  | BACTEC 460 or MGIT 960 |  | x | x |  |  | x |  | x |  |  |  |  |
| 21 | Kempker26 | Proportion method on Löwenstein-Jensen | x |  | x | x |  |  |  | x |  |  | x |  |
| 22 | Koenig27 |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  | Proportion method on 7H10 agar | 5.0 μg/mL | 1.0 μg/mL | 10 μg/mL | 1.0 or 2.0 μg/mL |  |  |  | 5.0 μg/mL |  | 30 μg/mL | 2.0 μg/mL |  |
| 23 | Koh28,29 | Absolute concentration, on L-J | 30 μg/mL | 30 μg/mL | 40 μg/mL | 2.0 μg/mL |  | 2.0 μg/mL | 2.0 μg/mL |  | 40 μg/mL | 30 μg/mL | 1.0 μg/mL |  |
| 24 | Kuksa30 | Lowenstein Jensen (LJ) | 30.0 μg/mL | 30.0 μg/mL | 40.0 μg/mL | 4.0 μg/mL | - | - | - | 40.0 μg/mL | - | 30.0 μg/mL | 1.0 μg/mL | - |
| 25 | Kvasnovsky31,32 | Indirect method on Middlebrook 7H10 | x | x |  | x | x |  |  | x |  |  |  |  |
| 26 | Lange33 | BACTEC MGIT 960 |  | x | x | x |  | x |  | x |  | x | x | x |
|  |  | proportion method on L-J |  |  |  |  |  |  |  |  |  |  |  |  |
| 27 | Laniado-Laborin34 | MGIT | 6.0 g/mL | 1.5 g/mL | 3.0 g/mL |  |  | 0.25 g/mL or 2.0 μg/mL | 0.5-2.0 μg/mL | 5.0 g/mL |  | 60 g/mL | 8.0 mg/mL |  |
| 28 | Leung35,36 | Absolute concentration method on LJ, linezolid in MGIT. | 16 μg/mL | 8 μg/mL | 32 μg/mL | 2.4 μg/mL |  |  |  | 56 μg/mL |  | 28 μg/mL | 1 μg/mL | 1 μg/mL |
| 29 | Marks37 | See Footnote A | x | x | x | x | x | x | x | x | x | x | x | x |
| 30 | Migliori38,39 | BACTEC MGIT 960 | x | x | x | x |  | x | x | x |  | x | x | x |
|  |  | Molecular LPA |  |  |  |  |  |  |  |  |  |  |  |  |
| 31 | Migliori (BDQ)40 | BACTEC MGIT 960 | x | x | x | x |  | x | x | x |  | x | x | x |
| 32 | Milanov41 |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  | BACTEC MGIT 960 | 5.0 µg/mL | 1.0 µg/mL | 2.5 µg/mL | 2.0 µg/mL |  |  |  |  |  |  |  |  |
| 33 | Ndjeka42 | BACTEC MGIT 960 |  |  |  |  |  |  |  |  |  |  |  |  |
| 34 | Ndjeka43 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 35 | O’Donnell44 | Modified proportional growth method on 7H11 agar | x | x |  | x |  |  |  | x |  |  |  |  |

**Supplemental Table 11 (continued)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **No** | **Contact person (ref)** | **Name of culture media (Cultre method)** | **Critical Concentrations of DST for Second-Line Drugs (if available)** | | | | | | | | | | | |
| Kanamycin | Amikacin | Capreomycin | Ofloxacin | Ciprofloxacin | Moxifloxacin | Levofloxacin | Ethionamide | Prothionamide | Cycloserine | Para-aminosalicylic acid | Linezolid |
| 36 | Palmero45 | Solid media proportions method | x | x | x | x |  |  |  | x |  | x | x |  |
|  |  | MIC determination in liquid medium |  |  |  |  |  | x |  |  |  |  |  | x |
| 37 | Podewils46 | Indirect method on Middlebrook 7H11 | x | x |  | x | x |  | x |  |  |  |  |  |
| 38 | Riekstina/Leimane47 | Lowenstein Jensen | 30 μg/mL | 30 μg/mL | 40 μg/mL | 4.0 μg/mL |  |  |  | 40 μg/mL |  | 30 μg/mL | 1.0 μg/mL |  |
|  |  | MIGIT | 2.5 μg/mL | 1.0 μg/mL | 2.5 μg/mL | 2.0 μg/mL |  | 0.5 μg/mL | 2.0 μg/mL |  |  |  |  | 1.0 μg/mL |
| 39 | Rodrigues48 | Not available |  |  |  |  |  |  |  |  |  |  |  |  |
| 40 | Seo49 | Not available |  |  |  |  |  |  |  |  |  |  |  |  |
| 41 | Seung50 | Not available |  |  |  |  |  |  |  |  |  |  |  |  |
| 42 | Shim29,51 | Absolute concentration method, using Lowenstein-Jensen medium | x | x | x | x |  | x | x |  | x | x | x |  |
| 43 | Singla52 | Absolute concentration on Lowenstein-Jensen medium | x | x | x | x |  |  |  | x |  | x | x |  |
| 44 | Skrahina53 | Solid - Lowenstein Jensen (absolute concentration method) | 30.0 µg/mL | 30.0 µg/mL | 40.0 µg/mL |  |  | 1.0 µg/mL | 2.0 µg/mL |  |  | 30.0 µg/mL | 1.0 µg/mL | NA |
|  |  | Liquid - MGIT (proportion method) | 2.5 µg/mL | 1.0 µg/mL | 2.5 µg/mL |  |  | 0.25/1.0 µg/mL | 1.0 µg/mL |  |  | NA | 4.0 µg/mL | 1.0 µg/mL |
| 45 | Smith54 | Proportion method | 5.0 μg/mL | 4.0 μg/mL | 10.0 μg/mL | 2.0 μg/mL |  |  |  | 10.0 μg/mL |  |  | 2.0 μg/mL |  |
| 46 | TMC207-C20855,56 |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  | Agar proportion method | 6.0 μg/mL |  | 10 μg/mL | 2.0 μg/mL |  |  |  | 10.0 μg/mL |  |  | 8.0 μg/mL |  |
| 47 | TMC207-C20957 |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  | Agar proportion method | 6.0 μg/mL |  | 10 μg/mL | 2.0 μg/mL |  |  |  | 10.0 μg/mL |  |  | 8.0 μg/mL |  |
| 48 | Udwadia58 | MGIT 960 | x | x | x | x |  | x |  | x |  |  |  |  |
| 49 | van der Werf59 | Absolute concentration and MGIT | x | x | x |  | x | x |  |  | x | x | x | x |
| 50 | Vasilyeva60 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 51 | Viiklepp61 | MIGIT Liquid media | x | x | x | x |  | x |  |  | x | x | x | x |
|  |  | MTBDR Sl -molecular method |  |  |  |  |  |  |  |  |  |  |  |  |
| 52 | Yim/Kwak62 | Absolute concentration on L-J | 40 μg/mL | 30 μg/mL | 40 μg/mL | 2.0 μg/mL |  | 2.0 μg/mL | 2.0 μg/mL | 40 μg/mL | 40 μg/mL | 30 μg/mL | 1.0 μg/mL |  |

Footnotes: A: Agar or BACTECT/MIGIT. kanamycin: agar 79%, Bactec 18%. amikacin: agar 79%, Bactec 12%. capreomycin: agar 71%, Bactec 23%, MGIT 4%. levofloxacin: Bactec 78%, MGIT 22%. moxifloxacin: Bactec 94%. ethionamide: agar 81%, Bactec 12%, MGIT 4%. para-amino salicylic acid: agar 97%, Bactec 2%. cycloserine: agar 97%, Bactec 1%. clofazimine: Bactec 100%.

**Supplemental Table 12. Daily drug dosages for 1st line drugs and injectables**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **No** | **Contact person (ref)** | **First-line drugs** | | | **Injectables** | | | | | | | | |
| Isoniazid | Rifampin | Ethambutol | Streptomycin | | Kanamycin | | Amikacin | | Capreomycin | |
| 1 | Ahmad1 |  |  | 25 mg/kg/day |  | |  | | 15-20 mg/kg/day | | 15-20 mg/kg/day | |
| 2 | Ahuja2 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day | | 12-18 mg/kg/day | | 15-20 mg/kg/day | | 15-20 mg/kg/day | |
| 3 | Anderson3 | NA | NA | NA | NA | | NA | | NA | | NA | |
| 4 | Bang4 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day | | 12-18 mg/kg/day | |  | | 15-20 mg/kg/day | |
|  |  | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day | | 12-18 mg/kg/day | | 15-20 mg/kg/day | | 15-20 mg/kg/day | |
| 5 | Barkane5 |  |  | 1.5 - 2.0 mg/day |  | |  | | 750 – 1000 mg/day | | 750 – 1000 mg/day | |
| 6 | Barry (Korea) 6,7 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day first 2 months, then 15 mg/kg/day | 5-10 mg/kg/day | | 15 mg/kg 5x/week until culture conversion, then 15mg/kg 3x/week | |  | | 15 mg/kg 5x/week until culture conversion, then 15mg/kg 3x/week | |
| 7 | Barry/Flood (Calif)8 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day | | 12-18 mg/kg/day | | 15-20 mg/kg/day | | 15-20 mg/kg/day | |
| 8 | Bonnet9 | 5mg/Kg/day max 300mg/day | 10mg/Kg/day max 600mg/days | 15mg/Kg/Day max 1200mg/day |  | | 15mg/Kg/day max 1g/day | | 15mg/Kg/day | |  | |
| 9 | Brode10 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day |  | |  | |  | | 8-15 mg/kg/day | |
| 10 | Brust11 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day |  | | 12-18 mg/kg/day | | 15-20 mg/kg/day | |  | |
| 11 | Cegielski12,13 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day | | 12-18 mg/kg/day | | 15-20 mg/kg/day | | 15-20 mg/kg/day | |
| 12 | Chan (Denver)14 | 5 mg/kg/d | 10 mg/kg/d (max: 600 mg) | 15-25 mg/kg/d | 5 mg/kg (max 300 mg) | | 15 mg/kg/day (max: 1 g) | | 15 mg/kg/day (max 1 g) | | 15 mg/kg/day (max 1 g) | |
| 13 | Dheda15-17 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day | | 12-18 mg/kg/day | | 15-20 mg/kg/day | | 15-20 mg/kg/day | |
| 14 | Fox18 |  |  | 20 mg/kg/day | N/A | | 15-20 mg/kg/day | | 15-20 mg/kg/day | | 15-20 mg/kg/day | |
| 15 | Gegia19 | 4-6 mg/kg/day |  | 15-25 mg/kg/day |  | |  | |  | |  | |
| 16 | Guglielmetti20,21 | 3-5 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day | | 12-18 mg/kg/day | |  | | 10- 15 mg/kg/day, | |
| 17 | Guglielmetti22 | 3-5 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day | | 12-18 mg/kg/day | |  | | 10- 15 mg/kg/day, | |
| 18 | Hughes23 | 4-6 mg/kg/day | 10-20 mg/kg/day | 15-20 mg/kg/day |  | |  | | 15-20 mg/kg/day | | 15-20 mg/kg/day | |
| 19 | Isaakidis23,24 | 4-6 mg/kg/day |  | 15-25 mg/kg/day |  | |  | | 15-20 mg/kg/day | | 15-20 mg/kg/day | |
| 20 | Jarlsberg25 |  | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day | | 12-18 mg/kg/day | |  | | 15-20 mg/kg/day | |
| 21 | Kempker26 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day |  | |  | | 15-20 mg/kg/day | |  | |
| 22 | Koenig27 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day |  | | Don't use in MDRTB | | 15 mg/kg/day | |  | |
| 23 | Koh28,29 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day | | 15-20 mg/kg/day | | 15-20 mg/kg/day | | 15-20 mg/kg/day | |
| 24 | Kuksa30 |  |  | 1.5 - 2.0 mg/day |  | |  | | 750 – 1000 mg/day | | 750 – 1000 mg/day | |
| 25 | Kvasnovsky31,32 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-20 mg/kg/day |  | 15 mg/kg/day | | 15 mg/kg/day | | 15 mg/kg/day | |
| 26 | Lange33 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day | 12-18 mg/kg/day | |  | | 15-20 mg/kg/day | |
| 27 | Laniado-Laborin34 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day |  | | 15-20 mg/kg/day | | 15-20 mg/kg/day | |
| 28 | Leung35,36 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day | 12-18 mg/kg/day | | 15-20 mg/kg/day | | 15-20 mg/kg/day | |
| 29 | Marks37 |  |  |  |  |  | |  | |  | |
| 30 | Migliori38,39 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day | 12-18 mg/kg/day | | 15-20 mg/kg/day | | 15-20 mg/kg/day | |

**Supplemental Table 12 (continued)**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **No** | **Contact person (ref)** | **First-line drugs** | | | **Injectables** | | | |
| Isoniazid | Rifampin | Ethambutol | Streptomycin | Kanamycin | Amikacin | Capreomycin |
| 31 | Migliori (BDQ)40 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day | 12-18 mg/kg/day | 15-20 mg/kg/day | 15-20 mg/kg/day |
| 32 | Milanov41 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day |  | 12-18 mg/day/kg | 15-20 mg/kg/day | 15-20 mg/kg/day |
| 33 | Ndjeka42 |  |  | 15-20 mg/kg/day |  |  | 15-20 mg/kg/day |  |
| 34 | Ndjeka43 |  |  |  |  |  |  |  |
| 35 | O’Donnell44 |  |  |  |  |  |  |  |
| 36 | Palmero45 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day | 12-18 mg/kg/day | 15-20 mg/kg/day | 15-20 mg/kg/day |
| 37 | Podewils46 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day |  | 12-18 mg/kg/day | 15-20 mg/kg/day | 15-20 mg/kg/day |
| 38 | Riekstina/Leimane47 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day |  | 15-20 mg/kg/day | 15-20 mg/kg/day |
| 39 | Rodrigues48 | 4-6 mg/kg/dia | 15-25 mg/kg/day | 20-30mg/kg/dia | 12-18mg/kg/dia | Not available | 15-20mg/kg/dia | 15-20mg/kg/dia |
| 40 | Seo49 |  |  |  |  |  |  |  |
| 41 | Seung50 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day |  |  | 15-20 mg/kg/day |  |
| 42 | Shim29,51 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-30 mg/kg/day | 5-10 mg/kg/day |  | 15-20 mg/kg/day |  |
| 43 | Singla52 |  |  |  |  |  | 15-20 mg/kg/day | 15-20 mg/kg/day |
| 44 | Skrahina53 | 0,6 g | 1,2 g | 2,0 g | NA | NA | NA | NA |
| 45 | Smith54 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day | 12-18 mg/kg/day | 15-20 mg/kg/day | 15-20 mg/kg/day |
| 46 | TMC207-C20855,56 |  |  | 15-25 mg/kg/day |  | 12-18 mg/kg/day | 15-20 mg/kg/day | 15-20 mg/kg/day |
| 47 | TMC207-C20957 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day |  | 12-18 mg/kg/day | 15-20 mg/kg/day | 15-20 mg/kg/day |
| 48 | Udwadia58 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day |  | 15-20 mg/kg/day | 15-20 mg/kg/day |
| 49 | van der Werf59 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day |  | 7.5 mg/kg/day | 7.5 mg/kg/day |
| 50 | Vasilyeva60 |  |  |  |  |  |  |  |
| 51 | Viiklepp61 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day | 12-18 mg/kg/day | 15-20 mg/kg/day | 15-20 mg/kg/day |
| 52 | Yim/Kwak62 | 4-6 mg/kg/day | 8-12 mg/kg/day | 15-25 mg/kg/day | 5-10 mg/kg/day | 12-18 mg/kg/day | 15-20 mg/kg/day | 15-20 mg/kg/day |

**Supplemental Table 13: Daily drug dosages for fluoroquinolones and other core second line agents**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **No** | **Contact person (ref)** | **Quinolones** | | | | **Other core second line agents** | | | |
| Ofloxacin | Moxifloxacin | Cifprofloxacin | Gatifloxacin | Ethionamide/  prothionamide | Cycloserine/  terizidone | Para-amino salicylic acid | Clofazimine |
| 1 | Ahmad1 | 15-20 mg/kg/day |  | 7.5-10 mg/kg/day | 15-20 mg/kg/day | 15-20 mg/kg/day | 150 mg/kg/day |  | 15-20 mg/kg/day |
| 2 | Ahuja | 15-20 mg/kg/day | 400-800 mg/day | 750-1000 mg/day | 500-750 mg/day | 500-750 mg/day | 8 g/day | 100 mg/day | 500-750 mg/day |
| 3 | Anderson3 | NA | NA | NA | NA | NA | NA | NA | NA |
| 4 | Bang4 | 15-20 mg/kg/day | 600 mg/day |  | 500-750 mg/day | 500-750 mg/day | 8 g/day |  | 500-750 mg/day |
|  |  | 15-20 mg/kg/day |  | 750-1000 mg/day | 400 mg/day |  |  |  |  |
| 5 | Barkane5 | 800 mg/day | 400 mg/day | - | - | 500 - 750 mg/day | 500 - 750 mg/day | 8000 mg/day | - |
| 6 | Barry (Korea)6,7 | 15 mg/kg 5x/week until culture conversion, then 15mg/kg 3x/week |  | 750 mg/day | 400 mg/day 600mg/day if fluoroquinolone, but moxifloxacin MIC < 2 | 500-750 mg/day | 500-750 mg/day | 8 g/day |  |
| 7 | Barry/Flood (Calif)8 | 15-20 mg/kg/day | 400-800 mg/day | 750-1000 mg/day | 400 mg/day | 500-750 mg/day | 250 or 500 mg/day | usually 6 g/day | 200-300 mg/day (2 first months) then 100 mg/day |
| 8 | Bonnet9 | 15mg/Kg/day | 800mg once daily | 750mg once daily | 400mg once daily | 750-1000 mg/day | 1g/day | 4-6g /day |  |
| 9 | Brode10 |  |  |  | 400 mg/day | 500-750 mg/day | 500-750 mg/day | 8 g/day | 100 mg/day |
| 10 | Brust11 |  |  |  |  | 500-750 | Cs 500-750 mg/day | 8 g/day |  |
| 11 | Cegielski12,13 | 15-20 mg/kg/day | 15-20 mg/kg/day | 750-1000 mg/day | 400 mg/day | 500-750 mg/day | 500-750 mg/day | 8 g/day | 200-300 mg/day X 2mos, then 100 mg/day |
| 12 | Chan (Denver) 14 | 15 mg/kg (max: 1 g) | Not used anymore | 750-1000 mg/day | 400 mg/day 800 mg/day if fluoroquinolone, but moxifloxacin MIC < 2 | 500 to 750 mg/day | 250-500 mg | 8-12 g/day | 100-200 mg/day |
| 13 | Dheda15-17 | 15-20 mg/kg/day |  | 750-1000 mg/day | 400 mg/day | 500-750 mg/day | 500-750 mg/day | 8 g/day | 200-300 mg/day X2 mos then 100 mg/day |
| 14 | Fox18 | N/A | 400 mg/day | N/A | N/A | 500-750 mg/day | 500-750 mg/day | 12 g/day | 100-150 mg/day |
| 15 | Gegia19 | 15-20 mg/kg/day |  | 750-1000 mg/day | 400 mg/day | 500-750 mg/day | 500-750 mg/day | 8 g/day | 300 mg/day |
| 16 | Guglielmetti20,21 | 10-15 mg/kg/day |  | 750-1000 mg/day | 400 mg/day 800 mg/day if fluoroquinolone, but moxifloxacin MIC < 2 | 500-750 mg/day | 500 mg/day | 8 to 12 g/day | 100 mg/day |
| 17 | Guglielmetti22 | 10-15 mg/kg/day |  | 750-1000 mg/day | 400 mg/day 800 mg/day if fluoroquinolone, but moxifloxacin MIC < 2 | 500-750 mg/day | 500 mg/day | 8 to 12 g/day | 100 mg/day |
| 18 | Hughes23 | 15-20 mg/kg/day |  | 750-1000 mg/day | 400 mg/day | 15-20 mg/kg/day | 750 mg/day | 8 g/day | 100 mg/day |
| 19 | Isaakidis23,24 | 15-20 mg/kg/day |  | 750-1000 mg/day | 400 mg/day | 500-750 mg/day | 500-750 mg/day | 8 g/day | 200-300 mg/day X2 months, then 100 mg/day |
| 20 | Jarlsberg25 | 15-20 mg/kg/day |  | 750-1000 mg/day | 400 mg/day | 500-750 mg/day | 500-750 mg/day | 6-8 g/day |  |
| 21 | Kempker26 | 15-20 mg/kg/day |  | 750-1000 mg/day | 400 mg/day | : 500-750 mg/day | 750 or 1000 mg/day | 8 g/day |  |
| 22 | Koenig27 | 15 mg/kg/day |  | 750-1000 mg/day | 400 mg/day | 500-750 mg/day | 500-750 mg/day | 8 g/day |  |
| 23 | Koh28,29 | 15-20 mg/kg/day |  | 750-1000 mg/day | 400 mg/day | 500-750 mg/day | Cs: 500-750 mg/day | 10 g/day |  |
| 24 | Kuksa30 | 800 mg/day | 400 mg/day | - | - | 500 - 750 mg/day | 500 - 750 mg/day | 8000 mg/day | - |

**Supplemental Table 13 (continued)**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **No** | **Contact person (ref)** | **Quinolones** | | | | | | **Other core second line agents** | | | |
| (Ofx) | | (Mfx) | (Cfz) | | (Gfx) | Eto/Pto | Cs/Trd | PAS | Cfz |
| 25 | Kvasnovsky31,32 | | 15 mg/kg/day |  | 750-1000 mg/day | | 400 mg/day | 500-750 mg/day | 500-750 mg/day | 8 -12g/day |  | |
| 26 | Lange33 | | 15-20 mg/kg/day |  | 750-1000 mg/day | | 400 mg/day | 500-750 mg/day | 500-750 mg/day | 13g iv | 100 mg/day | |
| 27 | Laniado-Laborin34 | | 15-20 mg/kg/day |  | 750 mg max dose | | 400-600 mg/day | : 500 mg max dose, | 500 mg max dose | 8 g max dose |  | |
| 28 | Leung35,36 | | 15-20 mg/kg/day |  | 750-1000 mg/day | | 400 mg/day | 500-750 mg/day once daily | Cs: 500-750 mg/day once daily | 2 g/10kg in 2 divided doses | 100 mg/day | |
| 29 | Marks37 | |  |  |  | |  |  |  |  |  | |
| 30 | Migliori38,39 | | 15-20 mg/kg/day |  | 750-1000 mg/day | | 400 mg/day | 500-750 mg/day | 500-750 mg/day | 8 g/day in 2 divided doses | 200-300 mg/day X2 months, then 100 mg/day | |
| 31 | Migliori (BDQ)40 | | 15-20 mg/kg/day |  | 750-1000 mg/day | | 400 mg/day | 500-750 mg/day | 500-750 mg/day | 8 g/day | 200-300 mg/day X 2 months then 100 mg/day | |
| 32 | Milanov41 | | 15-20 mg/kg/day |  | 750-1000 mg/day | | 400 mg/day | 500-750 mg/day | 500-750 mg/day | 8 g/day |  | |
| 33 | Ndjeka42 | | 15-20 mg/kg/day |  | 750-1000 mg/day | | 400 mg/day | 500-750 mg/day | 500-750 mg/day | 8 g/day | 100 mg/day | |
| 34 | Ndjeka43 | |  |  |  | |  |  |  |  |  | |
| 35 | O’Donnell44 | |  |  |  | |  |  |  |  |  | |
| 36 | Palmero45 | | 15-20 mg/kg/day |  | 750 mg/day | | 400 mg/day | 15 mg/kg/day | 15 mg/kg/day | 15 mg/kg/day | 100 mg/day | |
| 37 | Podewils46 | | 15-20 mg/kg/day |  | 500 mg/day | | 400 mg/day | 500-750 mg/day | 500-750 mg/day | 8 g/day | 200-300 mg/day X 2 months then 100 mg/day | |
| 38 | Riekstina/Leimane47 | | 15-20 mg/kg/day |  | 750-1000 mg/day | | 400 mg/day | 500-750 mg/day | 750 mg/day | 8 g/day |  | |
| 39 | Rodrigues48 | | Not available | 400mg/dia | 10-15mg/kg/dia | | Not available | 15-20mg/kg/dia | 250 a 1000mg/dia | 8g/dia | 100mg/dia | |
| 40 | Seo49 | |  |  |  | |  |  |  |  |  | |
| 41 | Seung50 | |  |  | 750-1000 mg/day | |  |  | 500-750 mg/day | 8 g/day |  | |
| 42 | Shim29,51 | | 15-20 mg/kg/day | 10-15 mg/kg/day |  | | 400 mg/day | 500-750 mg/day | 500-750 mg/day | 8 g/day |  | |
| 43 | Singla52 | | 15-20 mg/kg/day |  | 750-1000 mg/day | | 400 mg/day | 500-750 mg/day | 500-750 mg/day | 8 g/day | 200-300 mg/day X 2 months then 100 mg/day) | |
| 44 | Skrahina53 | | 0.8 g | 0.4 g | 1.0 g | | NA | 0.75 g | 0.75 g | 8.0 g | 0.2 g - 1 month  Then - 0.1 g | |
| 45 | Smith54 | | 15-20 mg/kg/day |  | 750-1000 mg/day | | 400 mg/day | 500-750 mg/day | 500-750 mg/day | 8 g/day | 200-300 mg/day X 2 months then 100 mg/day | |
| 46 | TMC207-C20855,56 | | 15-20 mg/kg/day | 800 mg/day | 500-750 mg/day | 400 mg/day | | 500-750 mg/day | 500-750 mg/day | 8 g/day | 100 mg/day |
| 47 | TMC207-C20957 | | 15-20 mg/kg/day | 800 mg/day | 500-750 mg/day | 400 mg/day | | 500-750 mg/day | 500-750 mg/day | 8 g/day | 100 mg/day |
| 48 | Udwadia58 | | 15-20 mg/kg/day |  | 750-1000 mg/day | 400 mg/day 800 mg/day if fluoroquinolone, but moxifloxacin MIC < 2 | | 500-750 mg/day | 500-750 mg/day | 150-200 mg/kg/day | 200-300 mg/day X 2 months then 100 mg/day |
| 49 | van der Werf59 | | 15-20 mg/kg/day |  |  | 400 mg/day | | 500-750 mg/day | 500-750 mg/day | 8 g/day | 100 mg/day |
| 50 | Vasilyeva60 | |  |  |  |  | |  |  |  |  |
| 51 | Viiklepp61 | | 15-20 mg/kg/day |  | 750-1000 mg/day | 400 mg/day | | 500-750 mg/day | 500-750 mg/day | 8 g/day |  |
| 52 | Yim/Kwak62 | | 15-20 mg/kg/day |  | 750-1000 mg/day | 400 mg/day | | 500-750 mg/day | 500-750 mg/day | 8 g/day |  |

**Supplemental Table 14. Daily drug dosage for other agents**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **No** | **Contact person (ref)** |  | | | | | |  | |
| Linezolid | Amoxicillin-clavulanic acid | | High-dose isoniazid | Bedaquiline | Delamanid | Other | |
| 1 | Ahmad1 | 600-1200 mg/day | 1500/375 mg/day | |  |  |  | Clarithromycin: 1000 mg/day | |
| 2 | Ahuja2 | NA |  | | 900 mg/day |  |  |  | |
| 3 | Anderson3 | 600 mg/day | NA | |  |  |  |  | |
| 4 | Bang4 | 300-600 mg/day |  | |  |  |  |  | |
| 5 | Barkane5 | 600 - 1200 mg/day | 1500/375 mg/day | | - | 400 mg/day for 14 days followed by 200 mg/day TWQ | 100 mg/day twice a day | Clarithromycin: 1000 mg/day  Imipenem-cilastatin see in appendix | |
| 6 | Barry (Korea)6,7 | 600mg/day, then 300 mg/day after several months | 80 mg/kg/day | |  |  |  |  | |
| 7 | Barry/Flood (Calif)8 |  | 2000mg amoxicillin/125mg clavulanate BID | |  | 400 mg/day first 2 weeks, then 200mg/day |  |  | |
| 8 | Bonnet9 | 600 mg BID (2011-2012). 600 mg/day from 2013. |  | |  |  |  |  | |
| 9 | Brode10 |  | Only with carbapenems  875/125 mg BID or 500/125 TID | |  | 400 mg/day x 2 weeks then 200 mg TIW |  | Clarithromycin: 500 mg BID.  Imipenem: 500 mg TID until 2012, then 1000 mg BID, | |
| 10 | Brust11 | 600 mg/day |  | |  |  |  |  | |
| 11 | Cegielski12,13 | 600 mg/day | 80 mg/kg/day | |  |  |  |  | |
| 12 | Chan (Denver) 14 | 600 mg/day | Only with Carbapenems | | 900-1500 mg 2-3 times per week | 400 mg/day X 2 weeks, then 200 mg thrice weekly | 100 mg BID | Imipenem-cilastatin 1 g BID | |
| 13 | Dheda15-17 |  | 80 mg/kg/day | | 10 mg/kg/day |  |  |  | |
| 14 | Fox18 | 600 mg/day | N/A | | 800 mg three times weekly | N/A | N/A |  | |
| 15 | Gegia19 | 600 mg/day, |  | |  |  |  |  | |
| 16 | Guglielmetti20,21 | 600 mg/day | Only with carbapenem | | according to therapeutic drug monitoring | 400 mg/day X2 weeks, then 200 mg thrice weekly) | 100 mg BID | Imipenem 1g TID | |
| 17 | Guglielmetti22 | 600 mg/day | Only with carbapenem | | according to therapeutic drug monitoring | 400 mg/day X2 weeks, then 200 mg thrice weekly) | 100 mg BID | Imipenem 1g TID | |
| 18 | Hughes23 | 600 mg/day |  | | 600-900 mg/day | 400 mg/day X2 weeks then 200 mg thrice weekly | 100 mg BID |  | |
| 19 | Isaakidis23,24 | 600 mg/day | 80 mg/kg/day | |  |  |  |  | |
| 20 | Jarlsberg25 |  |  | |  |  |  |  | |
| 21 | Kempker26 | 600 mg/day | 80 mg/kg/day | |  |  |  |  | |
| 22 | Koenig27 | 300 mg/day. (600 mg for 15% of patients) |  | | 15 mg/kg/day (max 900mg/day) | 400 mg/day x 2 weeks then 200 mg TIW |  |  | |
| 23 | Koh28,29 | 600 mg/day | 625 mg TID | | 16-20 mg/kg/day |  |  | Clarithromycin: 100 mg/day | |
| 24 | Kuksa30 | 600 - 1200 mg/day | 1500/375 mg/day | | - | 400 mg/day for 14 days followed by 200 mg/day TWQ | 100 mg/day twice a day | Clarithromycin : 1000 mg/day  Imipenem-cilastatin see in appendix | |
| 25 | Kvasnovsky31,32 | 600 mg/day |  | |  |  |  |  | |
| 26 | Lange33 | 300-600 mg/day | 80 mg/kg/day | | 16-20 mg/kg/day |  |  |  | |
| 27 | Laniado-Laborin34 | 600 mg/day X2 months, then 600mg 5X/week |  | | 900 mg max dose |  |  |  | |
| 28 | Leung35,36 |  |  | | 10-15 mg/kg 3 times per week |  |  |  | |
| 29 | Marks37 | 600 mg/day |  | |  |  |  |  | |
| 30 | Migliori38,39 |  |  |  | |  |  | | Meropenem 1 g TID, Imipenem 500 mg QID plus amoxicillin-clavulanic acid 1.2 g three times daily. |
| 31 | Migliori (BDQ)40 | 600 mg/day | Only with Carbapenems |  | | 400 mg/day X 2 weeks then 200mg alternate days | 100mg BID | |  |
| 32 | Milanov41 | 600 mg/day | 80 mg/kg/day |  | |  |  | |  |

**Supplemental Table 14 (continued)**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **No** | **Contact person (ref)** |  | | | | | |  |
| Linezolid | Amoxicillin-clavulanic acid | High-dose isoniazid | Bedaquiline | Delamanid | | Other |
| 33 | Ndjeka42 | >50 kg: 600 mg/day; <50 kg: 300 mg/day |  |  | 400 mg/day X 2 weeks then 200mg alternate days |  |  | |
| 34 | Ndjeka43 |  |  |  |  |  |  | |
| 35 | O’Donnell44 |  |  |  |  |  |  | |
| 36 | Palmero45 | 600 mg/day | Only with Carbapenems | 10 mg/kg/day | 400 mg/day X 2 weeks then 200mg alternate days |  | Meropenem: 2 g IV diluted q8 h until sputum culture is negative, then 1 g q8H IV diluted | |
| 37 | Podewils46 |  |  |  |  |  |  | |
| 38 | Riekstina/Leimane47 | 600 mg/day | 80 mg/kg/day |  |  |  |  | |
| 39 | Rodrigues48 | 600mg/dia | 80mg/kg/dia 2X | 15-20mg/kg/dia | Not available | Not available | Imipenem = 1000mg/dia | |
| 40 | Seo49 |  |  |  |  |  |  | |
| 41 | Seung50 |  |  |  |  |  |  | |
| 42 | Shim29,51 | 600 mg/day | 20-30 mg/kg/day | 15-20 mg/kg/day |  |  | Clarithromycin 15-20 mg/kg/day | |
| 43 | Singla52 | 600 mg BID, or: 600 mg/day | 625 mg TID 1000 mg BID |  |  |  |  | |
| 44 | Skrahina53 | 0.6 g | 2.0 g | NA | 0.4 g - 14 days  Then - 0.2 g 3 times per week | 0.2 g | Clarithromycin: 1.0 g  Imipenem 2.0  Clofazimine 0.2 – 2 months, then - 0.1 g | |
| 45 | Smith54 | 600 mg/day | 80 mg/kg/day in 2 divided doses |  |  |  |  | |
| 46 | TMC207-C20855,56 | 600 mg/day | max 2000 mg/day | 600-900 mg/day | 400 mg/day X 2 weeks then 200mg alternate days |  |  | |
| 47 | TMC207-C20957 | 600 mg/day | max 2000 mg/day | 600-900 mg/day | 400 mg/day X 2 weeks then 200mg alternate days |  |  | |
| 48 | Udwadia58 | 600 mg/day, |  |  |  |  |  | |
| 49 | van der Werf59 | 300 mg BID |  |  |  |  |  | |
| 50 | Vasilyeva60 |  |  |  |  |  |  | |
| 51 | Viiklepp61 | 600 mg/day | 80 mg/kg/day in 2 divided doses |  | 400 mg/day X 2 weeks then 200mg alternate days |  |  | |
| 52 | Yim/Kwak62 | 600 mg/day | 80 mg/day in 2 divided doses | 900 mg/day |  |  |  | |

**Supplemental Table 15. Patient support during MDR treatment – Hospitalization and directly observed therapy**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Hospitalization** | | | **Directly observed therapy** | | | |
| **No** | **Contact person**  **(ref)** | **Routine?**  **Yes/No** | | **Duration of Hospitalization** | **Yes/No** | **Where: CB= Community based/ HF=Health facility based** | **Who: Family/Friend, HCW=Health Care Workers** | **% on directly observed therapy during ambulatory TB treatment** |
| 1 | Ahmad1 | No | | All patients were treated on an ambulatory basis | Yes | HF | HCW |  |
| 2 | Ahuja2 | Yes | | Aim to get people home as soon as possible | Yes | CB, HF | HCW |  |
| 3 | Anderson3 | No | | If infectious and facilities for isolation not available at home, or for clinical indications. | Yes, but not all | HF | HCW | 40% |
| 4 | Bang4 | Yes | | NA | Yes | CB, HF | Family/Friend, HCW | N/A |
| 5 | Barkane5 | No | | Till Ss conversion to negative | Yes | HF | HCW |  |
| 6 | Barry (Korea)6,7 | Yes | | Hospitalization is required at least 2 weeks. | Yes |  |  | about 50% |
| 7 | Barry/Flood (Calif)8 | No | |  | Yes | CB, HF | HCW | >95% |
| 8 | Bonnet9 | Yes | | The entire intensive phase | Yes | CB | HCW | >80% |
| 9 | Brode10 | Yes | | Until culture conversion | Yes | CB | HCW | 70% |
| 10 | Brust11 | Yes | | Duration of intensive phase | No |  |  | none |
| 11 | Cegielski12,13 | Yes and No | | In Estonia, Latvia, Russia, South Africa, and Masan, South Korea, most patients were hospitalized to initiate treatment but in the other countries very few were hospitalized. | Yes and No | CB, HF | HCW | 70% full DOT, 23% partial DOT, 7% no DOT |
| 12 | Chan (Denver) 14 |  | |  |  |  |  |  |
| 13 | Dheda15-17 | Yes | | All patients were admitted until culture conversion, or death. | Yes | HF | HCW | 70-90 % during the intensive phase |
| 14 | Fox18 | Yes | | Variable, according to sputum culture conversion. Typically at least two months. | Yes | HF | HCW | 100 |
| 15 | Gegia19 | Yes | | Average 6 month | Yes | HF | HCW | 80% |
| 16 | Guglielmetti20,21 | Yes | | Until culture conversion | Yes | CB, HF | HCW | selected patients only |
| 17 | Guglielmetti22 | Yes | | Until culture conversion | Yes | CB, HF | HCW | selected patients only |
| 18 | Hughes23 | No | | Only if clinically unstable and unable to attend clinic daily. | Yes | HF | HCW | First 6 months |
| 19 | Isaakidis23,24 | No | |  | Yes | CB, HF | Family/Friend, HCW | 20% |
| 20 | Jarlsberg25 | No | |  | Yes | CB, HF | HCW, Smartphone based DOT | 80% |
| 21 | Kempker26 | Yes | | Until sputum smear or culture conversion and clinical improvement. | Yes | HF | HCW | 100% |
| 22 | Koenig27 | Yes | | 3-6 months | Yes | CB, HF | HCW | 86% DOT |
| 23 | Koh28,29 | No | | At initiation of treatment for at least 2 weeks. | Yes and No |  |  | none |
| 24 | Kuksa30 | No | | Till Ss conversion to negative | Yes | HF | HCW |  |
| 25 | Kvasnovsky31,32 | Yes | | XDR TB – until completion of intensive phase of treatment and >2 consecutive negative sputum samples. | Yes |  |  | Many patients received DOT others were seen monthly |
| 26 | Lange**33** | | Yes |  | Yes |  | Highly variable | N/A |
| 27 | Laniado-Laborin34 | | No |  | Yes | CB | HCW | 100% |
| 28 | Leung35,36 | | Yes | 2-8 weeks | Yes | HF | HCW | >90% |
| 29 | Marks37 | | Yes | Average 2 months | Yes |  |  | Average >90% |
| 30 | Migliori38,39 | | Yes | 60 to 90 days | Yes | CB, HF | HCW | 80%+ |
| 31 | Migliori (BDQ)40 | | Yes | median (IQR)) 179 (92–280) days | Yes | CB, HF | HCW |  |
| 32 | Milanov41 | | Yes | Average 8 months | Yes | HF | HCW |  |
| 33 | Ndjeka42 | |  |  |  |  |  |  |
| 34 | Ndjeka43 | |  |  |  |  |  |  |
| 35 | O’Donnell44 | | Yes | It is routine for XDR-TB not MDR-TB. Current median inpatient time is ~2 months. | Yes | CB | Family/Friend |  |

**Supplemental Table 15 (continued)**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Hospitalization** | | | **Directly observed therapy** | | | |
| **No** | **Contact person**  **(ref)** | **Routine?**  **Yes/No** | | **Duration of Hospitalization** | **Yes/No** | **Where: CB= Community based/ HF=Health facility based** | **Who: Family/Friend, HCW=Health Care Workers** | **% on directly observed therapy during ambulatory treatment** |
| 36 | Palmero45 | | Yes | Initial phase for XDR (6-8 months) For MDR, ambulatory or short admission (<2 months). | Yes | HF | Only when patients are admitted | None |
| 37 | Podewils46 | | No |  | Yes | HF |  | 100% |
| 38 | Riekstina/Leimane47 | | Yes | until stable smear conversion | Yes | HF | HCW | 100% |
| 39 | Rodrigues48 | | No | All patients were treated on an ambulatory basis | yes | Community based | HCW | 3-5X/week |
| 40 | Seo49 | |  |  |  |  |  |  |
| 41 | Seung50 | | Yes | to begin treatment, and many throughout the full course of treatment. | Yes |  |  |  |
| 42 | Shim29,51 | | No | for at least 2 weeks. | Yes and No |  |  | PPM (private-public mix cooperation) nurses take care of the patients. |
| 43 | Singla52 | | Yes | Median 1 month | Yes | HF | HCW | none |
| 44 | Skrahina53 | | Yes | 93-653 (fact.) | Yes | HF | HCW | 100% |
| 45 | Smith54 | | Yes | 159/161 were hospitalized at time of enrollment | Yes |  |  | 100% |
| 46 | TMC207-C20855,56 | | NA |  | Yes | HF | HCW | 100% |
| 47 | TMC207-C20957 | | NA |  | Yes | HF | HCW | 100% |
| 48 | Udwadia58 | | No | no | Yes | CB | Family/Friend | 80% |
| 49 | van der Werf59 | | Yes | Median: 92 days (IQR 61–154, maximum 512) | Yes | CB, HF | HCW | N/A |
| 50 | Vasilyeva60 | |  |  |  |  |  |  |
| 51 | Viiklepp61 | | Yes | Usually 60 days, | Yes | HF | HCW | 90-100% |
| 52 | Yim/Kwak62 | | Yes |  | Yes and No |  |  | none |

**Supplemental Table 16.** **Summary of quality assessment of 52 datasets/studies included in the analysis**­­­­­

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **No** | **Contact person (ref)** | **Sampling method** | | **Info on second-line injectable sensitivity** | | **Info on fluoroquinolone** | **Participation rate** | **Lost to follow-up rate** | | **Outcome definition** | | | **Info on age** | | | **Info on HIV** | | **Info on TB treatment history** | **Quality** |
| 1 | Ahmad1 | Census | | 100.0% | | 100.0% | 96.8% | 1.7% | | Laserson | | | 100.0% | | | 100.0% | | 100.0% | High |
| 2 | Ahuja2 | Random | | 92.4% | | 92.4% | 100.0% | 19.0% | | Laserson | | | 100.0% | | | 80.0% | | 100.0% | High |
| 3 | Anderson3 | Census | | 100.0% | | 100.0% | 100.0% | 12.4% | | Neither Laserson/WHO | | | 100.0% | | | 100.0% | | 90.5% | High |
| 4 | Bang4 | Census | | 96.6% | | 93.1% | 96.7% | 17.2% | | Laserson | | | 100.0% | | | 100.0% | | 100.0% | High |
| 5 | Barkane5 | Census | | 100% | | 100% | 100% | 15.6% | | Laserson | | | 100% | | | 100% | | 100% | High |
| 6 | Barry (Korea)6,7 | RCT | | 100.0% | | 100.0% | 92.7% | 10.5% | | Laserson | | | 100.0% | | | 100.0% | | 100.0% | High |
| 7 | Barry/Flood (Calif)8 | Unclear | | 98.4% | | 95.2% | 100.0% | 4.8% | | WHO 2013 | | | 98.4% | | | 100.0% | | 100.0% | Moderate |
| 8 | Bonnet9 | Census | | 93.3% | | 93.3% | 100.0% | 41.3% | | Laserson | | | 100.0% | | | 11.5% | | 98.6% | High |
| 9 | Brode10 | Census | | 100.0% | | 100.0% | 100.0% | 0.0% | | Laserson | | | 100.0% | | | 100.0% | | 100.0% | High |
| 10 | Brust11 | Census | | 100.0% | | 100.0% | 100.0% | 24.1% | | Laserson | | | 99.3% | | | 57.8% | | 98.5% | Moderate |
| 11 | Cegielski12,13 | Census | | 92.8% | | 92.2% | 60.1% | 19.8% | | Laserson | | | 100.0% | | | 68.3% | | 98.2% | High |
| 12 | Chan (Denver) 14 | Census | | 100.0% | | 100.0% | 100.0% | 26.7% | | Laserson | | | 100.0% | | | 80.0% | | 100.0% | High |
| 13 | Dheda15-17 | | Census | | 100.0% | 100.0% | 61.5% | | 4.7% | | Laserson | | | 99.1% | | | 100.0% | 93.5% | High |
| 14 | Fox18 | | Census | | 93.1% | 96.6% | 100% | | 3.4% | | WHO 2013 | | | 100% | | | 100% | 100% | High |
| 15 | Gegia19 | | Census | | 100.0% | 100.0% | 100.0% | | 21.8% | | Laserson | | | 100.0% | | | 72.9% | 100.0% | High |
| 16 | Guglielmetti20,21 | | Census | | 100.0% | 100.0% | 100.0% | | 11.1% | | WHO 2013 | | | 100.0% | | | 100.0% | 100.0% | High |
| 17 | Guglielmetti22 | | Census | | 100.0% | 100.0% | 100.0% | | 10% | | WHO 2013 | | | 100.0% | | | 100.0% | 90.0% | High |
| 18 | Hughes23 | | Census | | 94.9% | 94.9% | 100.0% | | 25.4% | | Laserson | | | 100.0% | | | 100.0% | 100.0% | High |
| 19 | Isaakidis23,24 | | Census | | 96.7% | 95.4% | 100.0% | | 11.8% | | Laserson | | | 100.0% | | | 100.0% | 98.0% | High |
| 20 | Jarlsberg25 | | Census | | 96.4% | 96.4% | 100.0% | | 3.6% | | Laserson | | | 100.0% | | | 92.9% | 100.0% | High |
| 21 | Kempker26 | | Census | | 100.0% | 100.0% | 94.9% | | 32.7% | | Laserson | | | 100.0% | | | 94.7% | 100.0% | High |
| 22 | Koenig27 | | Census | | 96.3% | 93.3% | 100.0% | | 6.1% | | Laserson | | | 99.4% | | | 100.0% | 100.0% | High |
| 23 | Koh28,29 | | Census | | 100.0% | 100.0% | 100.0% | | 13.4% | | WHO 2013 | | | 100.0% | | | 100.0% | 100.0% | High |
| 24 | Kuksa30 | | Census | | 100% | 100% | 100% | | 15% | | Laserson | | | 100% | | | 100% | 100% | High |
| 25 | Kvasnovsky31,32 | | Census | | 100.0% | 100.0% | 100.0% | | 11.5% | | Laserson | | | 100.0% | | | 96.9% | 100.0% | High |
| 26 | Lange33 | | Census | | 94.0% | 96.7% | 100.0% | | 20.1% | | Laserson | | | 100.0% | | | 99.5% | 98.4% | High |
| 27 | Laniado-Laborin34 | | Census | | 100.0% | 100.0% | 100.0% | | 13.5% | | Laserson | | | 100.0% | | | 100.0% | 100.0% | High |
| 28 | Leung35,36 | | Census | | 100.0% | 100.0% | 100.0% | | 19.9% | | Laserson | | | 100.0% | | | 100.0% | 100.0% | High |
| 29 | Marks37 | | Random | | 92.3% | 91.5% | 100.0% | | 12.3% | | Neither Laserson/WHO | | | 100.0% | | | 85.4% | 100.0% | High |
| 30 | Migliori38,39 | | Census | | 96.6% | 96.6% | Unclear | | 10.9% | | WHO 2013 | | | 100.0% | | | 98.1% | 99.3% | High |
| 31 | Migliori (BDQ)40 | | Census | | 97.0% | 100.0% | Unclear | | 3.7% | | WHO 2013 | | | 100.0% | | | 99.3% | 100.0% | High |
| 32 | Milanov41 | | Census | | 94.0% | 94.0% | 100.0% | | 2.0% | | Laserson | | | 100.0% | | | 100.0% | 100.0% | High |
| 33 | Ndjeka42 | | Unclear | | 78.2% | 81.2% | Unclear | | 21.1% | | Laserson | | | 100.0% | | | 95.5% | 0.0% | Low |
| 34 | Ndjeka43 | | Census | | 100.0% | 100.0% | 100.0% | | 18.5% | | Laserson/WHO | | | 100.0% | | | 100.0% | 100.0% | Low |
| 35 | O’Donnell44 | | Census | | 100.0% | 100.0% | 100.0% | | 13.2% | | Laserson | | | 100.0% | | | 93.9% | 93.9% | High |
| 36 | Palmero45 | | Census | | 100.0% | 100.0% | 100.0% | | 22.2% | | WHO 2013 | | | 100.0% | | | 100.0% | 100.0% | High |
| 37 | Podewils46 | | Census | | 91.0% | 91.2% | 100.0% | | 15.2% | | Laserson | | | 100.0% | | | 55.6% | 100.0% | High |
| 38 | Riekstina/Leimane47 | | Census | | 100.0% | 100.0% | 100.0% | | 14.7% | | Laserson | | | 100.0% | | | 94.0% | 100.0% | High |
| 39 | Rodrigues48 | | Census | | 87.0% | 85.0% | 100.0% | | 10.0% | | Laserson | | | 100.0% | | | 98.0% | 100.0% | High |
| 40 | Seo49 | | Census | | 100.0% | 100.0% | 100.0% | | 16.0% | | Laserson | | | 100.0% | | | 100.0% | 100.0% | High |
| 41 | Seung50 | | Census | | 80.2% | 80.2% | 100.0% | | 1.4% | | Unclear | | | 100.0% | | | 0% | 88.7% | High |
| 42 | Shim29,51 | | Census | | 100.0% | 100.0% | 86.4% | | 8.2% | | WHO 2013 | 100.0% | | | 40% | | | 100.0% | High |
| 43 | Singla52 | | Census | | 100.0% | 100.0% | 100.0% | | 13.8% | | Laserson | 100.0% | | | 100.0% | | | 100.0% | High |
| 44 | Skrahina53 | | Census | | 100.0% | 100.0% | 100.0% | | 1.0% | | WHO 2013 | 100.0% | | | 99.0% | | | 100.0% | High |
| 45 | Smith54 | | Census | | 100.0% | 100.0% | 100.0% | | 21.5% | | Laserson | 100.0% | | | 100.0% | | | 98.5% | High |
| 46 | TMC207-C20855,56 | | RCT | | 84.8% | 84.8% | 82.5% | | 28.8% | | Laserson | 100.0% | | | 100.0% | | | 100.0% | High |
| 47 | TMC207-C20957 | | Census | | 76.1% | 76.1% | 93.1% | | 15.2% | | Laserson | 100.0% | | | 96.5% | | | 100.0% | Moderate |
| 48 | Udwadia58 | | Census | | 100.0% | 100.0% | 100.0% | | 27.8% | | Laserson | 100.0% | | | 44.4% | | | 100.0% | High |
| 49 | van der Werf59 | | Census | | 100.0% | 98.2% | 100.0% | | 13.4% | | Laserson | 100.0% | | | 92.0% | | | 96.4% | High |
| 50 | Vasilyeva60 | | Census | | 94.4% | 94.4% | 100% | | 16% | | WHO 2013 | 100% | | | 100% | | | 100% | High |
| 51 | Viiklepp61 | | Census | | 100.0% | 100.0% | 100.0% | | 11.7% | | Laserson | 100.0% | | | 99.7% | | | 100.0% | High |
| 52 | Yim/Kwak62 | | Census | | 100.0% | 100.0% | 100.0% | | 4.9% | | WHO 2013 | 100.0% | | | 100.0% | | | 100.0% | High |

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