I. Shorter regimens for MDR-TB (PICO 3)

Author(s): Ahmad Khan F, Hamid Salim MA, Schwoebel V, Trébucq A, DuCros P, Casas E, Falzon D, Menzies D (10 November 2015)

Question: Standardized shorter regimens compared to conventional longer regimens for the treatment of MDR-TB (all cases; regardless of pyrazinamide or fluoroquinolone susceptibility)

Setting: Among patients who had no history of previous treatment with second-line drugs; shorter regimens refer to those lasting up to 12 months; longer regimens last 18 months or more. Note that the "conventional longer regimens" group pools data from studies that differ in the combination and number of drugs, in the duration of treatment, and in the use of a standardized versus an individualized approach. Hence the pooled estimates do not necessarily reflect the outcomes associated with the regimen recommended in the 2011 WHO Guidelines for the programmatic management of drug-resistant tuberculosis.

Bibliography: Results for shorter regimens from aggregate meta-analysis combining preliminary data from three series *(1–3)*, with data from three published studies *(4–6)*. Results for conventional longer regimens from aggregate meta-analysis using data from 31 studies of conventional MDR regimens *(7)*.

(1) Médecins Sans Frontières Swaziland, preliminary outcomes, unpublished data. (2) Médecins Sans Frontières Uzbeksitan, preliminary outcomes, unpublished data. (3) Trébucq A, Schwoebel V, Ghislain Koura K, Roggi A, Rieder HL. Observational study on the evaluation of the tolerance and effectiveness of a short 9 months treatment for multidrug resistant tuberculosis patients: preliminary report for the World Health Organization. The International Union Against Tuberculosis and Lung Diseases (UNION). October 16 2015. (4) Aung KJ, Van Deun A, Declercq E, Sarker MR, Das PK, Hossain MA, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis. 2014;18(10):1180–7. (5) Piubello A, Harouna SH, Souleymane MB, Boukary I, Morou S, Daouda M, et al. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. Int J Tuberc Lung Dis. 2014;18(10):1188–94. (6) Kuaban C, Noeske J, Rieder HL, Aït-Khaled N, Abena Foe JL, Trébucq A. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. Int J Tuberc Lung Dis. 2015;19(5):517–24. (7) Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):1212.

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT			
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	STANDARDIZED SHORTER REGIMENS	CONVENTIONAL LONGER REGIMENS	RELATIVE (95% CL)	ABSOLUTE (95% CL)	QUALITY	IMPORTANCE
Treatment success versus failure/relapse (assessed with: indirect comparison of two aggregate data meta-analyses (one of shorter regimens and one of longer regimens)[a]												
37[b]	observational studies	very serious	serious	not serious	serious	strong association all plausible residual confounding would reduce the demonstrated effect	1008/1033 (97.6%)[c]	4033/4639 (86.9%)[d]	not estimable[e]	[e]	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/relapse/death (assessed with: indirect comparison of two aggregate data meta-analyses (one of shorter regimens and one of longer regimens)[a]												
37[b]	observational studies	very serious	serious	not serious	serious	strong association all plausible residual confounding would reduce the demonstrated effect	1008/1116 (90.3%)[f]	4033/5850 (68.9%)[g]	not estimable[e]	[e]	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/relapse/death/loss to follow-up (assessed with: indirect comparison of two pooled individual patient meta-analyses)[a]												
37[b]	observational studies	very serious	serious	not serious	serious	strong association all plausible residual confounding would reduce the demonstrated effect	1008/1205 (83.7%)[h]	4033/7665 (52.6%)[i]	not estimable[e]	[e]	⨁◯◯◯ VERY LOW	CRITICAL

CLs: confidence limits; RE: random effects

[a] In the shorter regimen meta-analysis, data on relapse were only available from the published studies (references 4–6); in the conventional regimen studies relapse was ascertained in 14 cohorts overall (reference 7).

[b] Six studies of shorter regimens, 31 studies of conventional regimens.

[c] Unweighted proportion; weighted proportion from RE meta-analysis: 97.6% (95% CLs: 92.4%–99.2%).

[d] Unweighted proportion; weighted proportion from RE meta-analysis: 91.2% (95% CLs: 86.1%–94.6%).

[e] Due to methodological differences in the studies the relative and absolute risks are not shown. The shorter MDR-TB regimens dataset consists of recently conducted studies – some ongoing – in which patients were carefully selected, and all data were prospectively collected as part of a research protocol. Patients were uniformly treated with a standardized regimen. In contrast, studies with conventional longer regimens dataset were on average older, and many were retrospective series, and many used data collected for clinical purposes. The large majority of patients in the conventional regimens group received individualized therapy, with many regimens that differed from one another in number and type of drugs used, and the duration of treatment.

[f] Unweighted proportion; weighted proportion from RE meta-analysis: 90.3% (95% CLs: 87.8%–92.4%).

[g] Unweighted proportion; weighted proportion from RE meta-analysis: 78.3% (95% CLs: 71.2%–84%).

[h] Unweighted proportion; weighted proportion from RE meta-analysis: 83.7% (95% CLs: 79.2%–87.4%).

[i] Unweighted proportion; weighted proportion from RE meta-analysis: 61.7% (95% CLs: 53.1%–69.6%).

Author(s): Ahmad Khan F, Hamid Salim MA, Schwoebel V, Trébucq A, DuCros P, Casas E, Falzon D, Menzies D (10 November 2015)

Question: Standardized shorter regimens compared to conventional longer regimens for the treatment of MDR-TB (pyrazinamide susceptible; fluoroquinolone susceptible)

Setting: Among patients who had no history of previous treatment with second-line drugs; shorter regimens refer to those lasting up to 12 months; longer regimens last 18 months or more. Note that the "conventional longer regimens" group pools data from studies that differed in the combination and number of drugs, in the duration of treatment, and in the use of a standardized versus an individualized approach. Hence the pooled estimates do not necessarily reflect the outcomes associated with the regimen recommended in the 2011 WHO Guidelines for the programmatic management of drug-resistant tuberculosis.

Bibliography: Results for shorter regimens from individual patient data meta-analysis of unpublished *(1,2)* and published *(3)* data. Results for conventional longer regimens from individual patient data meta-analysis using data from study *(4)*.

(1) Médecins Sans Frontières Swaziland, preliminary outcomes, unpublished data. (2) Médecins Sans Frontières Uzbeksitan, preliminary outcomes, unpublished data. (3) Aung KJ, Van Deun A, Declercq E, Sarker MR, Das PK, Hossain MA, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis. 2014;18(10):1180–7. (4) Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):1212.

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	STANDARDIZED SHORTER REGIMENS	CONVENTIONAL LONGER REGIMENS	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse (assessed with: indirect comparison of two pooled individual patient data meta-analyses)[a]												
26[b]	observational studies	very serious	serious	not serious	serious	strong association all plausible residual confounding would reduce the demonstrated effect dose response gradient[c]	121/121 (100.0%)[d]	890/979 (90.9%)[e]	not estimable[f]	[f]	⨁◯◯◯ VERY LOW	CRITICAL

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	STANDARDIZED SHORTER REGIMENS	CONVENTIONAL LONGER REGIMENS	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death (assessed with: indirect comparison of two pooled individual patient data meta-analyses)[a]												
26[b]	observational studies	very serious	serious	not serious	serious	strong association all plausible residual confounding would reduce the demonstrated effect dose response gradient[c]	121/125 (96.8%)[g]	890/1119 (79.5%)[h]	not estimable[f]	[f]	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/relapse/death/loss to follow-up (assessed with: indirect comparison of two pooled individual patient data meta-analyses)[a]												
26[b]	observational studies	very serious	serious	not serious	serious	strong association all plausible residual confounding would reduce the demonstrated effect dose response gradient[c]	121/132 (91.7%)[i]	890/1666 (53.4%)[j]	not estimable[f]	[f]	⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; RE: random effects

[a] In the shorter regimen individual patient meta-analysis, data on relapse were only available in the Bangladesh series, in which six patients experienced treatment failure and three others relapsed.

[b] Three studies of shorter regimens; 23 studies of conventional regimens.

[c] Dose-response gradient refers to the inverse relationship observed between increasing resistance and decreasing effectiveness of treatment.

[d] Confidence limits could not be computed using meta-analytical methods. Exact binomial 95%CLs: 97.0%–100%.

[e] Unweighted proportion; weighted proportion from RE meta-analysis: 94.5% (95% CLs: 88.9%–97.4%).

[f] Due to methodological differences in the studies the relative and absolute risks are not shown. The shorter MDR-TB regimens dataset consists of recently conducted studies – some ongoing – in which patients were carefully selected, and all data were prospectively collected as part of a research protocol. Patients were uniformly treated with a standardized regimen. In contrast, studies with conventional longer regimens dataset were on average older, and many were retrospective series, and many used data collected for clinical purposes. The large majority of patients in the conventional regimens group received individualized therapy, with many regimens that differed from one another in number and type of drugs used, and the duration of treatment.

[g] Unweighted proportion; weighted proportion from RE meta-analysis: 96.8% (95% CLs: 77.3%–99.6%).

[h] Unweighted proportion; weighted proportion from RE meta-analysis: 83.5% (95% CLs: 75.7%–89.2%).

[i] Unweighted proportion; weighted proportion from RE meta-analysis: 91.7% (95% CLs: 73.9%–97.7%).

[j] Unweighted proportion; weighted proportion from RE meta-analysis: 68.2% (95% CLs: 56.2%–78.1%).

Author(s): Ahmad Khan F, Hamid Salim MA, Schwoebel V, Trébucq A, DuCros P, Casas E, Falzon D, Menzies D (10 November 2015)

Question: Standardized shorter regimens compared to conventional longer regimens for the treatment of MDR-TB (pyrazinamide susceptible; fluoroquinolone resistant)

Setting: Among patients who had no history of previous treatment with second-line drugs; shorter regimens refer to those lasting up to 12 months; longer regimens last 18 months or more. Note that the "conventional longer regimens" group pools data from studies that differed in the combination and number of drugs, in the duration of treatment, and in the use of a standardized versus an individualized approach. Hence the pooled estimates do not necessarily reflect the outcomes associated with the regimen recommended in the 2011 WHO Guidelines for the programmatic management of drug-resistant tuberculosis.

Bibliography: Results for shorter regimens from individual patient data meta-analysis of unpublished *(1)* and published *(2)* data. Results for conventional longer regimens from individual patient data meta-analysis using data from study *(3)*.

(1) Médecins Sans Frontières Swaziland, preliminary outcomes, unpublished data. (2) Aung KJ, Van Deun A, Declercq E, Sarker MR, Das PK, Hossain MA, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis. 2014;18(10):1180–7. (3) Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):1212.

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	STANDARDIZED SHORTER REGIMENS	CONVENTIONAL LONGER REGIMENS	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse (assessed with: indirect comparison of two pooled individual patient data meta-analyses)[a]												
18[b]	observational studies	very serious	serious	not serious	serious	strong association all plausible residual confounding would reduce the demonstrated effect dose response gradient[c]	12/14 (85.7%)[d]	72/95 (75.8%)[e]	not estimable[f]	[f]	⨁◯◯◯ VERY LOW	CRITICAL

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	STANDARDIZED SHORTER REGIMENS	CONVENTIONAL LONGER REGIMENS	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death (assessed with: indirect comparison of two pooled individual patient data meta-analyses)[a]												
18[b]	observational studies	very serious	serious	not serious	serious	strong association all plausible residual confounding would reduce the demonstrated effect dose response gradient[c]	12/15 (80.0%)[g]	72/120 (60.0%)[h]	not estimable[f]	[f]	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/relapse/death/loss to follow-up (assessed with: indirect comparison of two pooled individual patient data meta-analyses)[a]												
18[b]	observational studies	very serious	serious	not serious	serious	strong association all plausible residual confounding would reduce the demonstrated effect dose response gradient[c]	12/18 (66.7%)[i]	72/155 (46.5%)[j]	not estimable[f]	[f]	⨁◯◯◯ VERY LOW	CRITICAL

CLs: confidence limits; RE: random effects

[a] Fluoroquinolone resistance was an exclusion criterion for enrolment into MSF's Uzbekistan shorter regimen cohort. In the above individual patient meta-analyses for the shorter regimens, each group consists of 1 patient from the Swaziland cohort with the remainder consisting of patients from the Bangladesh study (13 for success versus failure; 14 for success versus failure or death; and 17 for success versus failure, death, or loss to follow-up). In the shorter regimen individual patient meta-analysis, data on relapse were only available in the Bangladesh series.

[b] Two studies of shorter regimens; 16 studies of conventional regimens.

[c] Dose-response gradient refers to the inverse relationship observed between increasing resistance and decreasing effectiveness of treatment.

[d] Unweighted proportion; weighted proportion from FE meta-analysis: 85.7% (95% CLs: 53.5%-96.9%).

[e] Unweighted proportion; weighted proportion from RE meta-analysis: 55.7% (95% CLs: 40.8%-69.8%).

[f] Due to methodological differences in the studies the relative and absolute risks are not shown. The shorter MDR-TB regimens dataset consists of recently conducted studies – some ongoing – in which patients were carefully selected, and all data were prospectively collected as part of a research protocol. Patients were uniformly treated with a standardized regimen. In contrast, studies with conventional longer regimens dataset were on average older, and many were retrospective series, and many used data collected for clinical purposes. The large majority of patients in the conventional regimens group received individualized therapy, with many regimens that differed from one another in number and type of drugs used, and the duration of treatment.

[g] Unweighted proportion; weighted proportion from FE meta-analysis: 80.0% (95% CLs: 50.0%–94.1%).

[h] Unweighted proportion; weighted proportion from RE meta-analysis: 64.4% (95% CLs: 49.6%–76.9%).

[i] Unweighted proportion; weighted proportion from FE meta-analysis: 66.7% (95% CLs: 41.1%–85.2%).

[j] Unweighted proportion; weighted proportion from RE meta-analysis: 56.1% (95% CLs: 40.7%–70.4%).

Author(s): Ahmad Khan F, Hamid Salim MA, Schwoebel V, Trébucq A, DuCros P, Casas E, Falzon D, Menzies D (10 November 2015)

Question: Standardized shorter regimens compared to conventional longer regimens for the treatment of MDR-TB (pyrazinamide resistant; fluoroquinolone susceptible)

Setting: Among patients who had no history of previous treatment with second-line drugs; shorter regimens refer to those lasting up to 12 months; longer regimens last 18 months or more. Note that the "conventional longer regimens" group pools data from studies that differed in the combination and number of drugs, in the duration of treatment, and in the use of a standardized versus an individualized approach. Hence the pooled estimates do not necessarily reflect the outcomes associated with the regimen recommended in the 2011 WHO Guidelines for the programmatic management of drug-resistant tuberculosis.

Bibliography: Results for shorter regimens from individual patient data meta-analysis of unpublished *(1,2)* and published *(3)* data. Results for conventional longer regimens from individual patient data meta-analysis using data from study *(4)*.

(1) Médecins Sans Frontières Swaziland, preliminary outcomes, unpublished data. (2) Médecins Sans Frontières Uzbeksitan, preliminary outcomes, unpublished data. (3) Aung KJ, Van Deun A, Declercq E, Sarker MR, Das PK, Hossain MA, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis. 2014;18(10):1180–7. (4) Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):1212.

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	STANDARDIZED SHORTER REGIMENS	CONVENTIONAL LONGER REGIMENS	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse (assessed with: indirect comparison of two pooled individual patient data meta-analyses)[a]												
26[b]	observational studies	very serious	serious	not serious	serious	strong association all plausible residual confounding would reduce the demonstrated effect dose response gradient[c]	90/96 (93.8%)[d]	840/962 (87.3%)[e]	not estimable[f]	[f]	⨁◯◯◯ VERY LOW	CRITICAL

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	STANDARDIZED SHORTER REGIMENS	CONVENTIONAL LONGER REGIMENS	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/deaths (assessed with: indirect comparison of two pooled individual patient data meta-analyses)[a]												
26[b]	observational studies	very serious	serious	not serious	serious	strong association all plausible residual confounding would reduce the demonstrated effect dose response gradient[c]	90/100 (90.0%)[g]	840/1075 (78.1%)[h]	not estimable[f]	[f]	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/relapse/deaths/loss to follow-up (assessed with: indirect comparison of two pooled individual patient data meta-analyses)[a]												
26[b]	observational studies	very serious	serious	not serious	serious	strong association all plausible residual confounding would reduce the demonstrated effect dose response gradient[3]	90/107 (84.1%)[i]	840/1392 (60.3%)[j]	not estimable[f]	[f]	⨁◯◯◯ VERY LOW	CRITICAL

CLs: confidence limits; RE: random effects

[a] In the shorter regimen individual patient meta-analysis, data on relapse were only available in the Bangladesh series.

[b] Three studies of shorter regimens; 23 studies of conventional regimens.

[c] Dose-response gradient refers to the inverse relationship observed between increasing resistance and decreasing effectiveness of treatment.

[d] Unweighted proportion; weighted proportion from RE meta-analysis: 93.5% (95% CLs: 40.4%–99.7%).

[e] Unweighted proportion; weighted proportion from RE meta-analysis: 90.1% (95% CLs: 83.5%–94.2%).

[f] Due to methodological differences in the studies the relative and absolute risks are not shown. The shorter MDR-TB regimens dataset consists of recently conducted studies – some ongoing – in which patients were carefully selected, and all data were prospectively collected as part of a research protocol. Patients were uniformly treated with a standardized regimen. In contrast, studies with conventional longer regimens dataset were on average older, and many were retrospective series, and many used data collected for clinical purposes. The large majority of patients in the conventional regimens group received individualized therapy, with many regimens that differed from one another in number and type of drugs used, and the duration of treatment.

[g] Unweighted proportion; weighted proportion from RE meta-analysis: 88.8% (95% CLs: 47.3%–98.6%).

[h] Unweighted proportion; weighted proportion from RE meta-analysis: 81.4% (95% CLs: 71.6%–88.4%).

[i] Unweighted proportion; weighted proportion from RE meta-analysis: 83.3% (95% CLs: 27.3%–98.5%).

[j] Unweighted proportion; weighted proportion from RE meta-analysis: 64.0% (95% CLs: 53.0%–73.8%).

Author(s): Ahmad Khan F, Hamid Salim MA, Schwoebel V, Trébucq A, DuCros P, Casas E, Falzon D, Menzies D (10 November 2015)

Question: Standardized shorter regimens compared to conventional longer regimens for the treatment of MDR-TB (pyrazinamide resistant; fluoroquinolone resistant)

Setting: Among patients who had no history of previous treatment with second-line drugs; shorter regimens refer to those lasting up to 12 months; longer regimens last 18 months or more. Note that the "conventional longer regimens" group pools data from studies that differed in the combination and number of drugs, in the duration of treatment, and in the use of a standardized versus an individualized approach. Hence the pooled estimates do not necessarily reflect the outcomes associated with the regimen recommended in the 2011 WHO Guidelines for the programmatic management of drug-resistant tuberculosis.

Bibliography: Results for shorter regimens from one published study *(1)*. Results for conventional longer regimens from individual patient data meta-analysis using data from study *(2)*.

(1) Aung KJ, Van Deun A, Declercq E, Sarker MR, Das PK, Hossain MA, Rieder HL. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis. 2014;18(10):1180–7. (2) Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):1212.[a]

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	STANDARDIZED SHORTER REGIMENS	CONVENTIONAL LONGER REGIMENS	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse (assessed with: indirect comparison of two pooled individual patient data meta-analyses)[b]												
19[c]	observational studies	very serious	serious	not serious	very serious[d]	strong association all plausible residual confounding would reduce the demonstrated effect dose response gradient[e]	19/26 (73.1%)[f]	81/112 (72.3%)[g]	not estimable[h]	[h]	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/relapse/death (assessed with: indirect comparison of two pooled individual patient data meta-analyses)[b]												

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	STANDARDIZED SHORTER REGIMENS	CONVENTIONAL LONGER REGIMENS	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
19[c]	observational studies	very serious	serious	not serious	very serious[d]	strong association all plausible residual confounding would reduce the demonstrated effect dose response gradient[e]	19/28 (67.9%)[i]	81/137 (59.1%)[j]	not estimable[h]	[h]	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/relapse/death/loss to follow-up (assessed with: indirect comparison of two pooled individual patient data meta-analyses)[b]												
19[c]	observational studies	very serious	serious	not serious	very serious[d]	strong association all plausible residual confounding would reduce the demonstrated effect dose response gradient[e]	19/32 (59.4%)[k]	81/193 (42.0%)[l]	not estimable[h]	[h]	⨁◯◯◯ VERY LOW	CRITICAL

CLs: confidence limits; RE: random effects

[a] In the study by Aung, et al. *(1)* reporting results from the same Bangladesh cohort, high-level gatifloxacin-resistance (defined as MIC≥2mg/mL) was associated with unsuccessful treatment, but not low-level gatifloxacin-resistance. In the above table, all persons in the short regimen group had ofloxacin-resistant MDR-TB, and amongst these, high-level gatifloxacin resistance was documented in 15; low-level gatifloxacin-resistance in 13; and gatifloxacin MIC was not measured in 4.

[b] In the shorter regimen individual patient meta-analysis, all data are from Bangladesh (i.e. no patients from Swaziland or Uzbekistan).

[c] One study of shorter regimens; 18 studies of conventional regimens.

[d] Confidence limits are wide for shorter regimen; all shorter regimen results are from one study only (Aung, et al.), and few patients involved.

[e] Dose-response gradient refers to the inverse relationship observed between increasing resistance and decreasing effectiveness of treatment.

[f] Unweighted proportion; exact binomial 95% CLs: 52.2%–87.1%.

[g] Unweighted proportion; weighted proportion from RE meta-analysis: 59.4% (95% CLs: 41.2%–75.3%).

[h] Due to methodological differences in the studies the relative and absolute risks are not shown. The shorter MDR-TB regimens dataset consists of recently conducted studies – some ongoing – in which patients were carefully selected, and all data were prospectively collected as part of a research protocol. Patients were uniformly treated with a standardized regimen. In contrast, studies with conventional longer regimens dataset were on average older, and many were retrospective series, and many used data collected for clinical purposes. The large majority of patients in the conventional regimens group received individualized therapy, with many regimens that differed from one another in number and type of drugs used, and the duration of treatment.

[i] Unweighted proportion; exact binomial 95% CLs: 47.6%–84.1%.

[j] Unweighted proportion; weighted proportion from FE meta-analysis: 59.1% (95% CLs: 50.6%–67.1%).

[k] Unweighted proportion; exact binomial 95% CLs: 40.6%–76.3%.

[l] Unweighted proportion; weighted proportion from RE meta-analysis: 49.9% (95% CLs: 30.6%–69.2%).